NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD NOVEMBRE 2020

Acad Pediatr. 2020;20:1148-56.

DISPARITIES IN MENTAL AND BEHAVIORAL HEALTH TREATMENT FOR CHILDREN AND YOUTH IN IMMIGRANT FAMILIES.
Rosenberg J, Rosenthal MS, Cramer LD, et al.

Background and Objective: Children and youth in immigrant families (CIF)ΓÇöchildren and youth with at least 1 foreign-born parentΓÇöface unique psychosocial stressors. Yet little is known about access to mental and behavioral health (MBH) services for CIF. Among US CIF and non-CIF with MBH problems, we assessed access to MBH treatment.

Methods: We used the National Survey of Children's Health-2016, a nationally representative survey of predominantly English- or Spanish-speaking US parents. The sample included 2- to 17-year-olds whose parent reported at least 1 MBH problem. The primary outcome was prior-year receipt of MBH treatment (counseling, medication, or both).

Results: Of 50,212 survey respondents, 7164 reported a current MBH problem (809 CIF and 6355 non-CIF). The majority of CIF were Hispanic/Latinx (56% CIF vs 13% non-CIF, P < .001). CIF were less likely than non-CIF to have an Attention Deficit Hyperactivity Disorder (ADHD) diagnosis (35% vs 59%, P < .001) and less likely to have received MBH medication and/or counseling (61% vs 71%, P = .02). This difference was pronounced for receiving medication (32% vs 50%, P < .001). When controlling for multiple covariates, differences in any MBH treatment were no longer statistically significant (adjusted odds ratios 0.76, 95% confidence interval 0.52ΓÇô1.11), while the odds of receipt of medication remained significantly lower for CIF (adjusted odds ratios 0.61, 95% confidence interval 0.42Γ Çô0.88).

Conclusions: Among children and youth with at least 1 parent-reported MBH problem, CIF, compared with non-CIF, were less likely to receive MBH treatment, specifically medication. This may be explained, in part, by differences in the proportion of CIF and non-CIF diagnosed with ADHD

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

Acta Paediatr Int J Paediatr. 2020.

HIGH PREVALENCE OF NEURODEVELOPMENTAL PROBLEMS IN ADOLESCENTS ELIGIBLE FOR BARIATRIC SURGERY FOR SEVERE OBESITY.

Bjork A, Bjork A, ahlgren J, et al.

Aim: To assess the prevalence of neurodevelopmental problems in adolescents with severe obesity and their associations with binge eating and depression.

Methods: Data were collected at inclusion in a randomised study of bariatric surgery in 48 adolescents (73% girls; mean age 15.7 ± 1.0 years; mean body mass index 42.6 ± 5.2 kg/m^2). Parents completed questionnaires assessing their adolescents' symptoms of attention-deficit/hyperactivity disorder and autism spectrum disorder and reported earlier diagnoses. Patients answered self-report questionnaires on binge eating and depressive symptoms.

Results: The parents of 26/48 adolescents (54%) reported scores above cut-off for symptoms of the targeted disorders in their adolescents, but only 15% reported a diagnosis, 32% of adolescents reported binge eating, and 20% reported symptoms of clinical depression. No significant associations were found between neurodevelopmental problems and binge eating or depressive symptoms. Only a third of the adolescents reported no problems in either area.

Conclusion: Two thirds of adolescents seeking surgical weight loss presented with substantial mental health problems (reported by themselves or their parents). This illustrates the importance of a multi-professional approach and the need to screen for and treat mental health disorders in adolescents with obesity

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Addictive Behaviors Reports. 2020;12.

ARE NON-ABSTINENT REDUCTIONS IN WORLD HEALTH ORGANIZATION DRINKING RISK LEVEL A VALID TREATMENT TARGET FOR ALCOHOL USE DISORDERS IN ADOLESCENTS WITH ADHD?

Mitchell HM, Park G, Hammond CJ.

Introduction: Abstinence from drinking represents the primary treatment target for alcohol use disorders (AUD) in youth, but few adolescents who engage in problematic drinking seek treatment. A reduction in World Health Organization (WHO) drinking risk level has been established as valid and reliable non-abstinent treatment target for AUD in adults but remains unstudied in youth.

Methods: The present study used data from the NIDA-CTN-0028 trial to examine associations between reductions in WHO drinking risk level and changes in global functioning and attention-deficit hyperactivity disorder (ADHD) symptoms during treatment in a sample of adolescents (ages 13-18 years) with ADHD and comorbid substance use disorder (SUD) (n = 297, 61% with AUD) receiving a 16-week intervention that combined ADHD pharmacotherapy (OROS-methylphenidate vs. placebo) and drug-focused cognitive-behavioral therapy.

Results: Shifts in drinking risk level during treatment were highly variable in adolescents treated for ADHD/SUD, and influenced by AUD diagnostic status. In the total sample, 15% of participants had a 2-level or greater reduction in WHO drinking risk level, with 59% and 24% showing no change or an increase in risk-level during treatment respectively. Achieving at least a 2-level change in WHO drinking risk level during treatment was associated with greater reduction in ADHD symptoms and better functional outcomes.

Conclusions: These findings parallel the adult AUD literature and provide preliminary support for the use 2-level reductions in WHO risk levels for alcohol use as a clinically valid non-abstinent treatment outcome for youth with ADHD and comorbid AUD

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American Journal of Perinatology. 2020.

MATERNAL HYPOTHYROIDISM INCREASES THE RISK OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN THE OFFSPRING.

Peltier MR, Fassett MJ, Chiu VY, et al.

Objective This study aimed to determine if hypothyroidism prior to, or during, pregnancy increases the risk of attention-deficit hyperactivity disorder (ADHD) in the child and how the association may be modified by preterm birth, sex of the child, and race-ethnicity.

Study Design Data were abstracted from linked maternal-child medical records. Incidence rate differences (IRDs), adjusted hazard ratios (aHRs), and their 95% confidence intervals (CIs) were estimated to evaluate the association of maternal hypothyroidism with childhood ADHD risk. Stratified analyses were used to evaluate whether the association is affected by timing of first diagnosis, gestational age at birth (term vs. preterm), sex, and race-ethnicity.
Results Hypothyroidism diagnosed prior to (IRD = 1.30), or during (IRD = 0.59) pregnancy increases the risk of ADHD in the children (aHR = 1.27; 95% CI: 1.15, 1.41, and 1.17; 95% CI: 1.00, 1.38). The association was strongest when diagnosed during the first trimester (IRD = 0.97 and aHR = 1.28; 95% CI: 1.04, 1.58). For children born preterm, there was significantly increased risk of ADHD if their mothers were diagnosed prior to (IRD = 3.06 and aHR = 1.43; 95% CI: 1.09, 1.88), but not during pregnancy. The effect of maternal hypothyroidism on increased risk of ADHD was stronger for boys (IRD = 1.84 and aHR = 1.26; 95% CI: 1.14, 1.40) than it was for girls (IRD = 0.48 and aHR = 1.19; 95% CI: 1.01, 1.40) and for Hispanic children (IRD = 1.60 and aHR = 1.45; 95% CI: 1.25, 1.68) compared with other race ethnicities.
Conclusion Exposure to maternal hypothyroidism during the periconceptual period significantly increases the risk of ADHD and that the association varies with gestational age at delivery, child sex, and race-ethnicity. Key Points Maternal hypothyroidism increases the risk of ADHD diagnosis in the offspring. The association of maternal hypothyroidism with childhood ADHD was influenced by timing of diagnosis. Strength of the association was strongest in preterm born infants, boys, and Hispanic children

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ANAE Approche Neuropsychol Apprentiss Enfant. 2020;32:453-61.

CLINICAL ISSUES OF NEUROPSYCHOLOGICAL ASSESSMENT OF EXECUTIVE FUNCTIONS IN CHILDREN WITH ADHD.

Schoentgen B.

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders. However, its symptomatology, also exhibited in other biological or psychological problems, may delay or disturb diagnostic sensitivity and weaken the precocity and effectiveness of care. The child's neuropsychological examination, and more particularly the executive functioning, constitutes a key cog in the understanding of his cognitive, affective and behavioral profile. This examination is also a necessary prerequisite in optimizing care through more specific addressing and should facilitate the essential coordination of the child's environment (family, school, health professionals)

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Appl Neuropsychol Child. 2020 Oct;9:314-22.

DIFFERENCES IN PERFORMANCE ON THE TEST OF VARIABLES OF ATTENTION BETWEEN CREDIBLE VS NONCREDIBLE INDIVIDUALS BEING SCREENED FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Harrison AG, Armstrong IT.

Measuring performance validity in Attention Deficit Hyperactivity Disorder (ADHD) assessments is essential, with multiple studies identifying how easily young adults can feign symptoms on self-report measures. Few methods, however, exist to identify such feigning when it occurs. While some clinicians include computerized tests of attention (e.g., Test of Variables of Attention [TOVA]) when assessing for possible ADHD, it is unclear how symptom exaggerators perform, and whether the TOVA Symptom Exaggeration Index (SEI) adequately identifies performance-based exaggeration when it occurs. Using archival data from a university-based ADHD screening clinic we investigated the performance of 245 late adolescents/emerging adults. Three groups were created: (1) Good effort but not ADHD (n = 183); (2) Good effort and diagnosed ADHD (n = 13); and (3) suspect effort (n = 49), based on final diagnosis and performance on an existing validity measure. Results showed clearly that those with suspect effort performed more poorly than the other two groups on all but second-half commission errors on the TOVA. Similar to Nicholls et al., the suspect effort group showed significantly subaverage (i.e., greater than two standard deviations below the mean) scores in Omission errors; in this replication, however, this was true for both the first and second half of the test. Response time variability was similarly exaggerated, with the suspect effort group again returning extreme scores in both halves of the test. Suspect effort students were indistinguishable from those with genuine ADHD when looking solely at self-reported symptoms; however, embedded symptom validity measures on an ADHD rating scale discriminated well between groups. Overall, results support the use of the TOVA as an

embedded performance validity measure in the assessment of late adolescents/emerging adults and support previous findings that symptom report alone cannot distinguish credible from noncredible ADHD presentation

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Appl Neuropsychol Child. 2020 Oct;9:307-13.

TEST OF VARIABLES OF ATTENTION PERFORMANCE AMONG ADHD CHILDREN WITH CREDIBLE VS NON-CREDIBLE PVT PERFORMANCE.

Nicholls CJ, Winstone LK, DiVirgilio EK, et al.

The assessment of effort is a crucial step in the evaluation of children and adolescents who present with symptoms of an Attention-Deficit/Hyperactivity Disorder (ADHD). Studies with adults have found that a large percentage of individuals claiming to have ADHD fail performance validity measures. In children, failure on PVT measures is associated with lower scores on a wide array of neuropsychological measures. The current study examined the performance of 50 children diagnosed with ADHD on the basis of whether they passed (N = 25) versus failed (N = 25) a standalone PVT, on the Test of Variables of Attention (TOVA), the Wisconsin Card Sorting Test - 64 (WCST) and the Tower of London: Drexel (TOL). Subjects who failed one or more PVTs scored significantly below those who passed, on the Omission scores of the TOVA and on several dimensions of the WCST. No significant differences were found on the TOL scores. Specifically, subjects who failed PVTs scored more than two standard deviations below the mean on the first half TOVA Omission errors score, whereas those who passed PVTs scored within the Average range. It is proposed that first half Omission scores on the TOVA may represent an embedded measure of effort.

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Arch Pediatr. 2020.

TIME KNOWLEDGE IMPAIRMENTS IN CHILDREN WITH ADHD.

De la Charie A, Delteil F, Labrell F, et al.

Background: A large number of studies have shown time perception impairment and reaction time (RT) variability in children with attention deficit hyperactivity disorder (ADHD), and have discussed the causes of such difficulties. However, very few studies have investigated time knowledge (i.e., the correct representation and use of time units) in children with ADHD.

Methods: We evaluated time knowledge in 33 children with ADHD, aged 8ΓÇô12 years, who had consulted a reference center for learning disabilities in Paris, matched for age and gender with 33 typically developing (TD) children. We used a simple questionnaire-based survey and neuropsychological tests for cognitive and attentional skills.

Results: The acquisition of time knowledge was delayed in children with ADHD compared with TD children ($P < 0.01$). At the end of primary school, children with ADHD obtained time knowledge scores that were close to those of TD children at the beginning of primary school. In children with ADHD, time knowledge was significantly related to the working memory index ($P < 0.05$), but not to ADHD presentation (with or without hyperactivity).

Conclusion: This study shows time knowledge impairment in children with ADHD, and paves the way for new screening tests and rehabilitation focused on time knowledge and time-related skills, in order to improve patient care and autonomy

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Arch Pediatr. 2020.

COMPARATIVE ANALYSIS OF THE WISC-IV IN A CLINICAL SETTING: ADHD VS. NON-ADHD.

Unnal D, et al.

Background: The Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) is a useful tool for revealing differences in cognitive ability. Using the WISC-IV, the study investigated the intelligence profile of Turkish children diagnosed with ADHD and compared their profile with that of a non-ADHD clinical sample.

Method: On the basis of the records of 257 drug-na+»ve patients (6ΓÇô12 years of age), ADHD (n = 154) and non-ADHD (n = 103) clinical groups were compared with respect to sociodemographic variables and WISC-IV scores.

Results: The non-ADHD clinical group had higher full scale, index, and subtest scores, except for their scores in the Comprehension subtest. The scores on Working Memory, Processing Speed Indices, Similarities, and Matrix Reasoning subtests were especially lower in the ADHD group than in the non-ADHD group. The Similarities, Matrix Reasoning, and Digit Span subtests classified 83% of the children as having ADHD and identified 43.7% of the non-ADHD clinical controls.
Conclusion: In our study, we found differences in the WISC-IV profiles of the Turkish patients with ADHD. Moreover, the WISC-IV profile of the non-ADHD clinical group was different than that of the ADHD group. More prospective studies with larger groups of ADHD patients and further evaluations of executive function deficits can help clinicians better understand the differences in WISC-IV profiles

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Asian J Psychiatry. 2021;55.

THE COMPARISON OF COOL AND HOT EXECUTIVE FUNCTIONS PROFILES IN CHILDREN WITH ADHD SYMPTOMS AND NORMAL CHILDREN.

Shakehnia F, Amiri S, Ghamarani A.

The study aimed to compare cool and hot executive functions profiles in children with ADHD symptoms and normal children. The statistical population consisted of all boys with ADHD symptoms and normal children in elementary school in Isfahan. In causal-comparative study, 200 participants were selected by multi-stage random sample method. Data were collected from Children Symptoms Inventory (CSI-4), Behavior Rating Inventory of Executive Function (BRIEF) and demographic inventory. Data were analyzed by using an analysis of covariance and Kruskal-Wallis test. There is significant difference between groups mean in variable of executive functions and all of their subscales ($P < 0.05$). Results from paired comparisons showed that in comparison with both subgroups of predominantly inattentive and predominantly hyperactive/ impulsive, combined subgroup indicate more damage to executive functions and all of subscales. In addition, subgroups of HD and AD are damaged more than normal group in executive functions and their subscales. Subgroups of HD and AD did not show any significant difference in inhibition, shifting and emotional control subscales (BRI). However, there were significant differences in initiation, monitoring, planning/organizing of materials subscales and total executive function. Negative mean difference in some variables indicates that in comparison with HD, AD has more problems in these subscales (MCI) and total executive function. Performing such studies can help to understand the underlying causes of treatment that has not been addressed so far in relation to this disorder and facilitate the establishment of optimal mechanisms and methods in treatment and standardization of psychological treatments

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Assessment. 2020 Dec;27:1748-57.

STRUCTURE OF ADHD/ODD SYMPTOMS IN SPANISH PRESCHOOL CHILDREN: DANGERS OF CONFIRMATORY FACTOR ANALYSIS FOR EVALUATION OF RATING SCALES.

Molina J, Servera M, Burns GL.

Confirmatory factor analysis (CFA) is often used to evaluate attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptom ratings by parents and teachers. An ADHD-inattention (IN), ADHD-hyperactivity/impulsivity (HI), and ODD three-factor model is usually the best model. Acceptable CFA models, however, can hide symptoms with poor convergent and discriminant validity. To demonstrate this issue, CFA models (i.e., cross-loadings set to zero) along with exploratory CFA models (i.e., cross-loadings allowed) were applied to parent (n = 308) and teacher (n = 258) ratings of ADHD/ODD symptoms with Spanish preschool children (Mage = 4.78, SD = .84, 56% boys). While the three-factor CFA model provided an acceptable-fit with moderate to substantial symptom-factor loadings, the three-factor exploratory CFA model, however, found a large number of the symptoms failed to show convergent and discriminant validity. These outcomes argue for the use of exploratory CFA procedures in the initial evaluation of ADHD/ODD rating scales

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Autism. 2020.

QUALIFICATION FOR UPPER SECONDARY EDUCATION IN INDIVIDUALS WITH AUTISM WITHOUT INTELLECTUAL DISABILITY: TOTAL POPULATION STUDY, STOCKHOLM, SWEDEN.

Stark I, Liao P, Magnusson C, et al.

This study used the Stockholm Youth Cohort, a total population cohort (N = 364,957), to describe patterns and predictors of qualification for upper secondary education, defined by passing graduation grades in core compulsory school subjects in contemporary young individuals diagnosed with autism spectrum disorders without intellectual disability (n = 6138). At the expected age for graduation, 16 years, 29% (adjusted rate difference 95% confidence interval (28.0ΓÇô30.0)) fewer autistic than non-autistic individuals were qualified for upper secondary education (57% and 86%, respectively). Comorbid attention-deficit hyperactivity disorder further increased this difference. Within the group of autistic students without intellectual disability, female sex and lower family income were associated with non-qualification for upper secondary education. The proportion of students with autism without intellectual disability who qualified for upper secondary education increased at age 20. These findings underline the need for improved support for students with a diagnosis of autism without intellectual disability in mainstream education. Lay abstract: Obtaining a quality education is important for any individualΓÇÖs chances of leading a healthy and thriving life. Currently, educational policies in many countries underscore the rights of students with autism to be educated in mainstream schools. While there is some knowledge on school outcomes among students with autism from older studies, little is known about rates of qualification for upper secondary education among children with autism in mainstream schools today. This lack of knowledge is problematic since autism is diagnosed more widely, and prior evidence may not be relevant for individuals with autism and their families today. Using Swedish registers, we therefore examined this in a study including all children and young people in Stockholm County in 2001 through 2011. We found that about two thirds of children with autism without intellectual disability qualified for upper secondary education at the expected age, in comparison with about nine in ten among typically developing peers. We also found that girls with autism had further difficulties obtaining such qualification than boys and that those who were additionally diagnosed with attention-deficit hyperactivity disorder were particularly at risk of non-qualification. Finally, students with autism without intellectual disability had a greater chance of completing compulsory education if given an extended period to graduate. These findings underline the need for supportive interventions for children with autism during compulsory school. They may also challenge the inclusive education policy adopted by majority of western countries, at least in the wake of addressing special needs in mainstream schooling

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Biol Psychiatry. 2020.

DIETARY QUALITY AND DIETARY INFLAMMATORY POTENTIAL DURING PREGNANCY AND OFFSPRING EMOTIONAL AND BEHAVIORAL SYMPTOMS IN CHILDHOOD: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS OF FOUR EUROPEAN COHORTS.

Polanska K, Kaluzny P, Aubert AM, et al.

Background: The impact of maternal diet during pregnancy on child neurodevelopment is of public health and clinical relevance. We evaluated the associations of dietary quality based on the Dietary Approaches to Stop Hypertension (DASH) score and dietary inflammatory potential based on the energy-adjusted Dietary Inflammatory Index (E-DII) score during pregnancy with emotional and behavioral symptoms of offspring at 7 to 10 years of age.

Methods: Individual participant data for 11,870 mother-child pairs from four European cohorts participating in the ALPHABET project were analyzed. Maternal antenatal DASH and E-DII scores were generated from self-completed food frequency questionnaires. Symptoms of depression and anxiety, aggressive behavior, and attention-deficit/hyperactivity disorder in children were assessed using mother-reported tests and classified within the normal or borderline/clinical ranges using validated cutoffs. Adjusted odds ratios were determined by multivariable logistic regression models and aggregated by the two-level individual participant data meta-analysis method.

Results: Higher maternal DASH scores (indicating better dietary quality) were associated with lower risk of depressive and anxiety symptoms, aggressive behavior symptoms, and attention-deficit/hyperactivity disorder symptoms within the borderline/clinical ranges: odds ratio [OR] 0.97, 95% confidence interval [CI], 0.95-0.99; OR 0.97, 95% CI, 0.94-0.99; OR 0.97, 95% CI, 0.95-0.98, per one-unit DASH score increase,

respectively. For depression and anxiety, aggressive behavior, and attention-deficit/hyperactivity disorder symptoms, a one-unit increase in E-DII scores (a more proinflammatory diet) was associated with a 7% increased risk of all three analyzed emotional and behavioral symptoms: OR 1.07, 95% CI, 1.03-1.11; OR 1.07, 95% CI, 1.02-1.13; OR 1.07, 95% CI, 1.01-1.13, respectively.
Conclusions: Our findings suggest that a maternal low-quality and proinflammatory diet may increase the risk of emotional and behavioral symptoms in children

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BMC Med Genomics. 2020;13.

PSYCHOMOTOR DEVELOPMENT AND ATTENTION PROBLEMS CAUSED BY A SPLICING VARIANT OF CNKSR2.

Zhang Y, Yu T, Li N, et al.

Background: Mutations in CNKSR2 have been described in patients with neurodevelopmental disorders characterized by childhood epilepsy, language deficits, and attention problems. The encoded protein plays an important role in synaptic function.
Case presentation: Whole-exome sequencing was applied to detect pathogenic variants in a patient with clinical symptoms of psychomotor development, attention deficit, poor logical thinking ability, and an introverted personality, but without epilepsy or any significant electroencephalogram changes. Genetic study revealed a splicing mutation (c.1904 + 1G > A) and RT-PCR revealed aberrant splicing of exon 16, leading to a reading-frame shift and a truncated protein in the PH domain.
Conclusions: This is the first report of a splicing variant of CNKSR2, and the unique clinical features of this pedigree will help extend our understanding of the genetic and phenotypic spectra of CNKSR2-related disorders

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Brain Dev. 2020.

PREDICTORS OF ADHD PERSISTENCE IN ELEMENTARY SCHOOL CHILDREN WHO WERE ASSESSED IN EARLIER GRADES: A PROSPECTIVE COHORT STUDY FROM ISTANBUL, TURKEY.

Gokce S, Yazgan Y, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorders among school-age children worldwide. In a more recent follow-up study, Biederman et al. found that 78% of children diagnosed with ADHD between the ages of 6–17 years continued to have a full (35%) or a partial persistence after eleven years.
Objective: In this study, it was aimed to identify the factors contributing to the persistence of ADHD symptoms in elemantary school children who were prospectively assessed both in their earlier and upper grades.
Methods: The sample was drawn from a previous community-based study where ADHD symptoms in 3696 first/or second graders were examined in regard to their school entry age. Two years after, the families of the children that participated in the initial study were called by phone and invited to a re-evaluation session. Among those who were reached, 154 were consequently eligible and were assessed with Swanson, Nolan and Pelham questionnaire (SNAP-IV), Conners rating scales (CRS) and the Kiddie schedule for affective disorders and schizophrenia (K-SADS).
Results: Of the 154 children, 81 had been evaluated to have probable ADHD by the initial interview. Among these 81 children, 50 (61.7%) were indeed diagnosed with ADHD after two years. Initial scores of the teacher reported SNAP-IV inattention subscale predicted the ADHD diagnosis after two years, with an odds ratio of 1.0761 (p = 0.032, Wald: 4.595).
Conclusions: Our results suggest that high inattention symptom scores reported by the teacher in the earlier grades, might predict an ADHD diagnosis in upper grades

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Brain Impairment. 2020.

DOES TRANSCRANIAL DIRECT CURRENT STIMULATION AFFECT SELECTIVE VISUAL ATTENTION IN CHILDREN WITH LEFT-SIDED INFANTILE HEMIPLEGIA? A RANDOMIZED, CONTROLLED PILOT STUDY.

Alharbi RA, Aloyuni SA, Kashoo F, et al.

Objective: Infantile hemiplegia due to brain injury is associated with poor attention span, which critically affects the learning and acquisition of new skills, especially among children with left-sided infantile hemiplegia (LSIH). This study aimed to improve the selective visual attention (SVA) of children with LSIH through transcranial direct current stimulation (tDCS).

Methods: A total of 15 children participated in this randomized, double-blinded, pilot study; of them, 10 experienced LSIH, and the remaining 5 were healthy age-matched controls. All the children performed the Computerized Stroop Color-Word Test (CSCWT) at baseline, during the 5th and 10th treatment sessions, and at follow-up. The experimental (n = 5) and control groups (n = 5) received tDCS, while the sham group (n = 5) received placebo tDCS. All three groups received cognitive training on alternate days, for 3 weeks, with the aim to improve SVA.

Results: Two-way repeated measures analysis of variance (ANOVA) showed a statistically significant change in the mean scores of CSCWT between time points (baseline, 5th and 10th sessions, and follow-up) within-subject factor, group (experimental, sham) between-subject factor and interaction (time points X group) ($p < 0.005$). Furthermore, a one-way repeated measures ANOVA showed significant differences between time point ($p < 0.005$) for the experimental and control group but not the sham group.

Conclusion: These pilot results suggest that future research should be conducted with adequate samples to enable conclusions to be drawn

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Brain Sciences. 2020;10:1-11.

DEVELOPMENTAL LANGUAGE DISORDER: WAKE AND SLEEP EPILEPTIFORM DISCHARGES AND CO-MORBID NEURODEVELOPMENTAL DISORDERS.

Dlouha O, Prihodova I, Skibova J, et al.

Developmental language disorder (DLD) is frequently associated with other developmental diseases and may lead to a handicap through adolescence or adulthood. The aim of our retrospective study was to characterize DLD subgroups, their etiological factors and clinical comorbidities, and the role of epileptiform discharges in wake and sleep recordings. Fifty-five children (42 male, mean age 6.2 -¦ 1.4 years, range 4ΓÇô9 years) were included in the present study and underwent phoniatric, psychologic, neurologic, as well as wake and nocturnal electroencephalography (EEG) or polysomnography (PSG) examinations. A receptive form of DLD was determined in 34 children (63.0%), and an expressive form was found in 20 children (37.0%). Poor cooperation in one child did not permit exact classification. DLD children with the receptive form had significantly lower mean phonemic hearing (79.1% -¦ 10.9) in comparison with those with the expressive form (89.7% -¦ 6.2, $p < 0.001$). A high amount of perinatal risk factors was found in both groups (50.9%) as well as comorbid developmental diseases. Developmental motor coordination disorder was diagnosed in 33 children (61.1%), and attention deficit or hyperactivity disorder was diagnosed in 39 children (70.9%). Almost one half of DLD children (49.1%) showed abnormalities on the wake EEG; epileptiform discharges were found in 20 children (36.4%). Nocturnal EEG and PSG recordings showed enhanced epileptiform discharges, and they were found in 30 children (55.6%, $p = 0.01$). The wake EEG showed focal discharges predominantly in the temporal or temporo-parieto-occipital regions bilaterally, while in the sleep recordings, focal activity was shifted to the fronto-temporo-central areas ($p < 0.001$). Almost all epileptiform discharges appeared in non-rapid eye movement (NREM) sleep. A close connection was found between DLD and perinatal risk factors, as well as neurodevelopmental disorders. Epileptiform discharges showed an enhancement in nocturnal sleep, and the distribution of focal discharges changed

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Brain Topogr. 2020 Nov;33:733-50.

INVESTIGATION OF BRAIN FUNCTIONAL NETWORKS IN CHILDREN SUFFERING FROM ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Dini H, Ghassemi F, Sendi M.

ADHD defects the recognition of facial emotions. This study assesses the neurophysiological differences between children with ADHD and matched healthy controls during a face emotional recognition task. The study also explores how brain connectivity is affected by ADHD. Electroencephalogram (EEG) signals were recorded from 64 scalp electrodes. Event-related phase coherence (ERPCOH) method was applied to pre-processed signals, and functional connectivity between any pair of electrodes was computed in different frequency bands. A logistic regression (LR) classifier with elastic net regularization (ENR) was trained to classify ADHD and HC participants using the functional connectivity of frequency bands as a potential biomarker. Subsequently, the brain network is constructed using graph-theoretic techniques, and graph indices such as clustering coefficient (C) and shortest path length (L) were calculated. Significant intra-hemispheric and the inter-hemispheric discrepancy between ADHD and healthy control (HC) groups in the beta band was observed. The graph features indicate that the clustering coefficient is significantly higher in the ADHD group than that in the HC group. At the same time, the shortest path length is significantly lower in the beta band. ADHD's brain networks have a problem in transferring information among various neural regions, which can cause a deficiency in the processing of facial emotions. The beta band seems better to reflect the differences between ADHD and HC. The observed functional connectivity and graph differences could also be helpful in ADHD investigations

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Cereb Cortex. 2020;30:6083-96.

INVESTIGATION OF PSYCHIATRIC AND NEUROPSYCHOLOGICAL CORRELATES OF DEFAULT MODE NETWORK AND DORSAL ATTENTION NETWORK ANTICORRELATION IN CHILDREN.

Owens MM, Yuan DK, Hahn S, et al.

The default mode network (DMN) and dorsal attention network (DAN) demonstrate an intrinsic "anticorrelation" in healthy adults, which is thought to represent the functional segregation between internally and externally directed thought. Reduced segregation of these networks has been proposed as a mechanism for cognitive deficits that occurs in many psychiatric disorders, but this association has rarely been tested in pre-adolescent children. The current analysis used data from the Adolescent Brain Cognitive Development study to examine the relationship between the strength of DMN/DAN anticorrelation and psychiatric symptoms in the largest sample to date of 9- to 10-year-old children (N=6543). The relationship of DMN/DAN anticorrelation to a battery of neuropsychological tests was also assessed. DMN/DAN anticorrelation was robustly linked to attention problems, as well as age, sex, and socioeconomic factors. Other psychiatric correlates identified in prior reports were not robustly linked to DMN/DAN anticorrelation after controlling for demographic covariates. Among neuropsychological measures, the clearest correlates of DMN/DAN anticorrelation were the Card Sort task of executive function and cognitive flexibility and the NIH Toolbox Total Cognitive Score, although these did not survive correction for socioeconomic factors. These findings indicate a complicated relationship between DMN/DAN anticorrelation and demographics, neuropsychological function, and psychiatric problems

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Child Abuse Negl. 2021;112.

DEFINING THE ROLE OF EXPOSURE TO ACES IN ADHD: EXAMINATION IN A NATIONAL SAMPLE OF US CHILDREN.

Walker CS, Walker BH, Brown DC, et al.

Background: Clinical presentations of ADHD vary according to biological and environmental developmental influences. An emerging field of research has demonstrated relationships between exposure to adverse childhood experiences (ACEs) and ADHD prevalence, particularly in high-risk samples. However, research examining the combined role of traditional risk factors of ADHD and ACEs is limited, and reliance on high-risk samples introduces sampling bias.

Objective: To examine the influence of ACEs on ADHD diagnosis using a large, nationally representative sample of US children. Participants and setting: Nationally representative samples (2017 and 2018) of 40,075 parents from the National Survey of Children's Health (NSCH).
Methods: We conducted logistic regression models to examine the association of ACEs and ADHD diagnosis, controlling for child and parent demographic variables and other risk factors.
Results: Exposure to ACEs was significantly associated with parent-reported ADHD diagnosis, controlling for known parental and child-risk factors of ADHD. The association followed a gradient pattern of increased ADHD prevalence with additional exposures. Compared to children with no ACEs, the odds of an ADHD diagnosis were 1.39, 1.92, and 2.72 times higher among children with one, two and three or more ACEs. The ACE most strongly associated with the odds of ADHD was having lived with someone with mental illness closely followed by parent/guardian incarceration.
Conclusions: Results further strengthen the evidence that ACEs exposure is associated with increased ADHD prevalence. Clinicians should assess ACEs in the diagnosis of ADHD. Furthermore, results of the study lend support to the efforts of agencies (both institutional and state-level) promoting routine screening of ACEs in children

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Child Adolesc Ment Health. 2020.

LIFETIME DEPRESSIVE AND CURRENT SOCIAL ANXIETY ARE ASSOCIATED WITH PROBLEMATIC INTERNET USE IN ADOLESCENTS WITH ADHD: A CROSS-SECTIONAL STUDY.

Demirtaf OO, Alnak A, et al.

Aim: To evaluate the relationships between problematic internet use (PIU) and psychiatric comorbid disorders and internet use habits in a clinical sample of adolescents with attention-deficit/hyperactivity disorder (ADHD).
Method: This cross-sectional study included 95 adolescents with ADHD. Problematic behaviors and symptoms related to internet use were evaluated via Young's Internet Addiction Scale (YIAS), and subjects with a YIAS score of ≥50 were categorized as PIU while those with a score of <50 were defined as normal internet use (NIU). The two groups were compared with respect to demographics and psychometric tests. While psychiatric disorders were examined by a semistructured instrument, self-report and parent-report scales were used to assess other individual and clinical characteristics of participants.
Results: 33.7% (n = 32) of the participants were determined to have PIU. There was no gender (p =.058) or age (p =.426) difference between the PIU and NIU groups. Current presence of social phobia (p =.035) and history of major depressive disorder (p =.006) were more frequent in the PIU group than the NIU group. Multivariable regression analysis revealed that PIU was independently associated with online gaming (OR: 2.375, 95% CI: 1.532–3.681), e-mail use (OR: 1.864, 95% CI: 1.170–2.971), social networking (OR: 1.834, 95% CI: 1.156–2.910), and Social Phobia Scale for Children and Adolescents (SPSCA) score (OR: 1.058, 95% CI: 1.020–1.098).
Conclusion: PIU may be common among adolescents with ADHD. The severity of social phobia and particular online activities (playing online games, e-mailing, social networking) may be associated with a higher risk of PIU in adolescents with ADHD

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Child Adolesc Ment Health. 2020.

PRESENTING PROBLEM PROFILES FOR ADOLESCENTS WITH ADHD: DIFFERENCES BY SEX, AGE, RACE, AND FAMILY ADVERSITY.

Coxe S, Sibley MH, Becker SP.

Background: Adolescents with attention-deficit/hyperactivity disorder (ADHD) experience developmentally distinct challenges from children and adults with ADHD. Yet no work in this age group identifies treatment-related phenotypes that can inform treatment matching, development of tailored treatments, and screening efforts.
Method: This study uses Latent Profile Analysis to detect unique presenting problem profiles among adolescents with ADHD and to test whether these profiles differ by key individual characteristics (age, sex, race, family adversity level). Participants were 854 ethnically diverse adolescents (ages 10-17) from the

ADHD Teen Integrative Data Analysis Longitudinal (TIDAL) dataset who were assessed at clinical referral. Parent, adolescent, and teacher ratings, educational testing, and school records measured eight key presenting problems at intake.
Results: A three-profile solution emerged. ADHD simplex (63.7%) was characterized by a mix of the ADHD-Inattentive and ADHD-Combined subtypes, moderate impairment levels, and infrequent comorbidities. ADHD-á+-áinternalizing (11.4%) was characterized by higher likelihood of comorbid anxiety and/or depression. The disruptive/disorganized ADHD (24.9%) profile was characterized by severe organization, time management, and planning (OTP) problems, the ADHD-Combined subtype, and frequent disruptive behavior at school. Age did not vary across these phenotypes. More females were present in the ADHD-á+-áinternalizing phenotype; males were more likely to be found in the disruptive/disorganized ADHD phenotype. Higher family adversity and African American race were associated with the disruptive/disorganized ADHD phenotype.
Conclusions: Adolescents with ADHD demonstrate varying presenting problem phenotypes that vary by sex, family adversity, and race/ethnicity. Consideration of these phenotypes may inform treatment matching and efforts to improve screening among under-diagnosed groups

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Child Neuropsychol. 2020.

DEVELOPMENTAL TRAJECTORY OF SUBTLE MOTOR SIGNS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A LONGITUDINAL STUDY FROM CHILDHOOD TO ADOLESCENCE.

Crasta JE, Zhao Y, Seymour KE, et al.

This study examined the developmental trajectory of neurodevelopmental motor signs among boys and girls with attention-deficit/hyperactivity disorder (ADHD) and typically-developing (TD) children. Seventy children with ADHD and 48 TD children, aged 8ΓÇô17-áyears, were evaluated on at least two time-points using the Physical and Neurological Assessment of Subtle Signs (PANESS). Age-related changes in subtle motor signs (overflow, dysrhythmia, speed) were modeled using linear mixed-effects models to compare the developmental trajectories among four subgroups (ADHD girls and boys and TD girls and boys). Across visits, both boys and girls with ADHD showed greater overflow, dysrhythmia, and slower speed on repetitive motor tasks compared to TD peers; whereas, only girls with ADHD were slower on sequential motor tasks than TD girls. Developmental trajectory analyses revealed a greater reduction in overflow with age among boys with ADHD than TD boys; whereas, trajectories did not differ among girls with and without ADHD, or among boys and girls with ADHD. For dysrhythmia and speed, there were no trajectory differences between the subgroups, with all groups showing similar reductions with age. Children with ADHD show developmental trajectories of subtle motor signs that are consistent with those of TD children, with one clear exception: Boys with ADHD show more significant reductions in overflow from childhood to adolescence than do their TD peers. Our findings affirm the presence of subtle motor signs in children with ADHD and suggest that some of these signs, particularly motor overflow in boys, resolve through adolescence while dysrhythmia and slow speed, may persist

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Child Neuropsychol. 2020.

A RETROSPECTIVE INVESTIGATION OF THE ADDED CLINICAL VALUE OF SCT SYMPTOMS ON NEUROPSYCHOLOGICAL ASSESSMENTS IN YOUTH WITH ADHD.

Barakat M, Mashmoushi R, Oghgassian G, et al.

Some researchers believe that Sluggish Cognitive Tempo (SCT) should be its own psychiatric disorder. However, despite the abundance of literature describing its possible symptoms, evidence of its clinical impact on cognitive tests and some clinical comorbidities is still weak. This retrospective study aimed to analyze the added clinical value of exploring SCT symptoms prior to a neuropsychological assessment in a youth population diagnosed with an Attention-Deficit/Hyperactivity Disorder (ADHD). For this purpose, we used linear regressions to examine the association between different test results and SCT, as well as logistic regressions to examine the association between the existence of different diagnoses and SCT in a group of 295 ADHD patients [73 females, 24.7%], aged between 6 and 18-áyears [Mean (SD): 9.91 (3.12)]. Our results showed that parent-reported SCT symptoms did not help predict neuropsychological test outcomes. In

addition, they did not predict Specific Learning Disorder (SLD) or Developmental Coordination Disorder (DCD), nor anxiety and depression when we controlled for age, Vanderbilt inattention and hyperactivity subscales, autism spectrum disorder, and intellectual disability. These results requestion the added-value of screening for SCT in similar clinical neuropsychological settings

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Child Psychiatry Hum Dev. 2020 Oct;51:813-26.

COMORBID INTERNALIZING AND EXTERNALIZING SYMPTOMS AMONG CHILDREN WITH ADHD: THE INFLUENCE OF PARENTAL DISTRESS, PARENTING PRACTICES, AND CHILD ROUTINES.

McRae E, Stoppelbein L, O'Kelley S, et al.

Emotional/behavioral concerns are common among children with ADHD. Familial factors (e.g., parental adjustment, parenting behaviors) are linked to the presence of comorbid internalizing/externalizing symptoms among children with ADHD. The purpose of the present study was to evaluate a model that includes multiple familial variables and their direct and indirect effects on child emotional and behavioral problems among children with ADHD. Participants included parents of children (6–12 years of age; M = 8.87, SD = 1.92) with a diagnosis of ADHD (N = 300). Participants completed measures of child emotional/behavioral concerns, parental distress, routines, and parenting behaviors. Path analyses revealed direct effects for parental distress, parent behavior and routines on child adjustment, after controlling for the other variables. A significant indirect relation between parental distress, routines, and externalizing behavior was observed. These findings highlight one specific path through which parental distress appears to influence specific behavioral concerns that are commonly observed in children with ADHD

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Chin J Contemp Pediatr. 2020;22:1178-82.

INTELLIGENCE STRUCTURE AND CLINICAL FEATURES OF SCHOOL-AGE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SPECIFIC LEARNING DISORDER.

Yue XJ, Wang CX, Li HH, et al.

Objective To study the intelligence structure and clinical features of children with attention deficit hyperactivity disorder (ADHD) and specific learning disorder (SLD).

Methods A retrospective analysis was performed on 88 school-age children with ADHD. According to the presence or absence of SLD, they were divided into two groups: simple ADHD group with 45 children and ADHD+SLD group with 43 children. Intelligence structure and clinical features were compared between the two groups.

Results Compared with the simple ADHD group, the ADHD+SLD group had significantly lower verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), and full intelligence quotient (FIQ) ($P<0.05$), significantly lower scores of VIQ factors (including information, similarities, arithmetic, and recitation) ($P<0.05$), and significantly lower scores of PIQ factors (including picture completion, picture arrangement, block design, and object assembly) ($P<0.05$). The development of SLD was negatively correlated with FIQ, VIQ, and PIQ. It was also negatively correlated with the scores of intelligence structure factors (including information, similarities, arithmetic, recitation, picture completion, picture arrangement, block design, and object assembly) ($P<0.05$).

Conclusions Children with ADHD and SLD have poorer FIQ, VIQ, and PIQ than those with ADHD alone, which mainly manifests as the weak abilities of most intelligence structure factors. It is necessary to pay attention to the management and intervention of SLD in school-age children with ADHD

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Clin Psychopharmacol Neurosci. 2020;18:469-83.

NUTRITIONAL NEUROSCIENCE AS MAINSTREAM OF PSYCHIATRY: THE EVIDENCE-BASED TREATMENT GUIDELINES FOR USING OMEGA-3 FATTY ACIDS AS A NEW TREATMENT FOR PSYCHIATRIC DISORDERS IN CHILDREN AND ADOLESCENTS.

Chang JPC, Su KP.

Omega-3 polyunsaturated fatty acids (or omega-3 PUFAs, n-3 PUFAs) are essential nutrients throughout the life span. Recent studies have shown the importance of n-3 PUFAs supplementation during prenatal and

perinatal period as a potential protective factor of neurodevelopmental disorders. N-3 PUFAs have been reported to be lower in youth with attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and major depressive disorder (MDD). N-3 PUFAs supplementation has shown potential effects in the improvement of clinical symptoms in youth with ADHD, ASD, and MDD, especially those with high inflammation or a low baseline n-3 index. Moreover, it has been suggested that n-3 PUFAs had positive effects on lethargy and hyperactivity symptoms in ASD. For clinical application, the following dosage and duration are recommended in youth according to available randomized controlled trials and systemic literature review: (1) ADHD: a combination of eicosapentaenoic acid (EPA) docosahexaenoic acid (DHA) 750 mg/d, and a higher dose of EPA (1,200 mg/d) for those with inflammation or allergic diseases for duration of 16-24 weeks; (2) MDD: a combination of a EPA DHA of 1,000-2,000 mg/d, with EPA:DHA ratio of 2 to 1, for 12-16 weeks; (3) ASD: a combination of EPA DHA of 1,300ΓêÆ1,500 mg/d for 16-24 weeks as add-on therapy to target lethargy and hyperactivity symptoms. The current review also suggested that n-3 index and inflammation may be potential treatment response markers for youth, especially in ADHD and MDD, receiving n-3 PUFA

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Clin Psychopharmacol Neurosci. 2020;18:553-61.

ASSOCIATIONS AMONG HIGH RISK FOR SLEEP-DISORDERED BREATHING, RELATED RISK FACTORS, AND ATTENTION DEFICIT/HYPERACTIVITY SYMPTOMS IN ELEMENTARY SCHOOL CHILDREN.

Kim KM, Kim JH, Kim D, et al.

Objective: Habitual snoring is a common problem in children. We evaluated the association between a high risk for sleep-disordered breathing and attention deficit/hyperactivity symptoms.

Methods: Parents of 13,560 children aged 6 to 12 years responded to questionnaires including items on habitual snoring and the Korean attention deficit/hyperactivity disorder rating scale. The snoring score comprised the number of yes responses to habitual-snoring items, and a high risk for sleep-disordered breathing was defined as a snoring score 2.

Results: The odds ratio (OR) of a high risk for sleep-disordered breathing was significantly higher in boys (OR = 1.47; p ∩+£ 0.001), overweight children (OR = 2.20; p 0.001), and children with current secondhand-smoking exposure (OR = 1.38; p 0.001). The Korean attention deficit/hyperactivity disorder rating scale score increased significantly with the snoring score (0 vs. 1, B = 1.56, p 0.001; 0 vs. 2, B = 2.44, p 0.001; 0 vs. 3, B = 2.48, p 0.001; 0 vs. 4, B = 3.95; p 0.001).

Conclusion: Our study confirms several risk factors of sleep-disordered breathing, namely male sex, overweight, and exposure to tobacco smoking, and found a positive association between habitual snoring and attention deficit/hyperactivity symptoms

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CNS Spectr. 2020.

CURRENT AND FUTURE NONSTIMULANTS IN THE TREATMENT OF PEDIATRIC ADHD: MONOAMINE REUPTAKE INHIBITORS, RECEPTOR MODULATORS, AND MULTIMODAL AGENTS.

Cutler AJ, Mattingly GW, Jain R, et al.

Attention-deficit/hyperactivity disorder (ADHD), the single most common neuropsychiatric disorder with cognitive and behavioral manifestations, often starts in childhood and usually persists into adolescence and adulthood. Rarely seen alone, ADHD is most commonly complicated by other neuropsychiatric disorders that must be factored into any intervention plan to optimally address ADHD symptoms. With more than 30 classical Schedule II (CII) stimulant preparations available for ADHD treatment, only three nonstimulants (atomoxetine and extended-release formulations of clonidine and guanfacine) have been approved by the FDA, all of which focus on modulating the noradrenergic system. Given the heterogeneity and complex nature of ADHD in most patients, research efforts are identifying nonstimulants which modulate pathways beyond the noradrenergic system. New ADHD medications in clinical development include monoamine reuptake inhibitors, monoamine receptor modulators, and multimodal agents that combine receptor agonist/antagonist activity (receptor modulation) and monoamine transporter inhibition. Each of these pipeline ADHD medications have a unique chemical structure and differ in their pharmacologic profiles in terms of molecular targets and mechanisms. The clinical role for each of these agents will need to be explored

with regard to their potential to address the heterogeneity of individuals struggling with ADHD and ADHD-associated comorbidities. This review profiles alternatives to Schedule II (CII) stimulants that are in clinical stages of development (Phase 2 or 3). Particular attention is given to viloxazine extended-release, which has completed Phase 3 studies in children and adolescents has been accepted for review by the FDA with a target action date in late 2020

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Dev Med Child Neurol. 2020.

WHAT ARE THE EFFECTS OF SOCIAL SKILLS TRAINING ON CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER? A COCHRANE REVIEW SUMMARY WITH COMMENTARY.

Ferrario I.

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Dev Med Child Neurol. 2020.

ELEMENTARY VISUOSPATIAL PERCEPTION DEFICIT IN CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Pisella L, Vialatte A, Martel M, et al.

Aim: To assess the prevalence of elementary visuospatial perception (EVSP) deficit in children with neurodevelopmental disorders.

Method: Using a screening test designed and validated to measure dorsal EVSP ability, 168 children (122 males, 46 females; mean age 10y [SD 1y 10mo], range 4y 8mo-16y 4mo) diagnosed with developmental coordination disorder (DCD), specific learning disorder (SLD), attention-deficit/hyperactivity disorder (ADHD), and/or oral language disorder were compared with a group of 184 typically developing children. We also tested 14 children with binocular vision dysfunction and no neurodevelopmental disorder.

Results: Children with SLD scored below the interquartile range of typically developing children as frequently (59%) as children with DCD, but only 5% were severely impaired (i.e. scored as outliers). Children with DCD were the most severely impaired (22% of outliers), even more so when they exhibited a co-occuring disorder. Children with language disorder and those with binocular vision dysfunction scored similarly to the group of typically developing children.

Interpretation: These results confirm the importance of assessing EVSP in the clinical evaluation of children with neurodevelopmental disorders, in particular those presenting with DCD or SLD

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Dev Med Child Neurol. 2020.

AUTISM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH CEREBRAL PALSY: HIGH PREVALENCE RATES IN A POPULATION-BASED STUDY.

Phlman M, Gillberg C, Himmelmann K.

Aim: To assess a total population of school-age children with cerebral palsy (CP) for autism and attention-deficit/hyperactivity disorder (ADHD) with a view to determining their prevalence and to relate findings to motor function, intellectual disability, and other associated impairments.

Method: Of 264 children, born between 1999 and 2006, from the CP register of western Sweden, 200 children (109 males, 91 females, median age at assessment 14y, range 7ΓÇô18y) completed comprehensive screening and further neuropsychiatric clinical assessments.

Results: Ninety children (45%) were diagnosed with autism, ADHD, or both, 59 (30%) were diagnosed with autism, and 60 (30%) were diagnosed with ADHD. Intellectual disability was present in 51%. Two-thirds had autism, ADHD, and/or intellectual disability. In regression models, autism was mainly predicted by intellectual disability (odds ratio [OR]=4.1) and ADHD (OR=3.2), and ADHD was predicted by intellectual disability (OR=2.3) and autism (OR=3.0). Autism was more common in children born preterm (OR=2.0). Gross motor function was not associated with autism. ADHD prevalence was low in children with severe motor impairment, possibly due to diagnostic limitations.

Interpretation: Autism and ADHD were common in this population of children with CP and were mainlyindependent of motor severity and CP type. The strongest predictor of autism/ADHD was intellectual disability. Assessment for autism and ADHD is warranted as part of the evaluation in CP

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Diving Hyperb Med. 2020 Dec;50:399-404.

CHILDREN AND DIVING, A GUIDELINE.

Buwalda M, Querido AL, van Hulst RA.

Scuba diving is an increasingly popular recreational activity in children and adolescents. During the dive medical examination aspects of human physiology, anatomy, and psychology, that differ between adults and children, deserve our special attention. For example, lack of mental maturity, diminished Eustachian tube function and heat loss can pose problems during diving. It is important that children who wish to take up scuba diving are seen by a dive physician, with extra attention to Eustachian tube function. In children, asthma, bronchial hyperreactivity, pulmonary hypertension, and right-to-left shunts are contra-indications for scuba diving. Attention deficit hyperactivity disorder is a relative contra-indication. This article provides a review of the current literature and presents recommendations for recreational diving in children and adolescents. These recommendations are based solely on 'expert' opinion and were accepted by the Dutch Society of Diving and Hyperbaric Medicine in 2020

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Encephale. 2020.

HOW TO IMPROVE IN FRANCE ADHD TRANSITION SUPPORT FROM CHILDHOOD TO ADULTHOOD.

Fourneret P, Zimmer L, Rolland B.

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Environ Sci Pollut Res Int. 2021 Jan;28:1370-80.

ASSOCIATION BETWEEN POSTNATAL SECOND-HAND SMOKE EXPOSURE AND ADHD IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Huang A, Wu K, Cai Z, et al.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which is caused by the interplay of genetic and environmental risk factors such as second-hand smoke (SHS). The association between postnatal exposure to SHS and ADHD risk in children was still inconclusive. We performed a systematic review and meta-analysis to explore the definite association. We searched for relevant studies from PubMed, Embase, Ovid, and Web of Science databases up to January 2020. We used random effect models to calculate pooled odds ratio (OR) with 95% confidence interval (CI). Subgroup analyses and sensitive analyses were also performed to solve the heterogeneity. According to our inclusion criteria, 9 studies including 6 cross-sectional studies, 2 cohort studies, and 1 case-control study were included in the final analysis. Postnatal exposure to SHS increased the risk of ADHD in children (OR: 1.60; 95% CI: 1.37-1.87). Children who exposed to SHS were found a slight risk for conduct problems (OR: 1.33, 95% CI: 1.00-1.77). Among the studies which used cotinine as a biomarker for SHS exposure, a lower pooled OR (OR=1.16, 95% CI=1.01, 1.33) was observed between cotinine and ADHD in children. Our meta-analysis results suggested that SHS exposure may be a risk factor for ADHD. We also found that SHS exposure may be associated with some adverse behavioral outcomes. More prospective studies should be conducted to confirm the relationship between SHS exposure and ADHD in children

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Epilepsy Behav. 2020.

UTILITY OF EEG ON ATTENTION DEFICITΓÇôHYPERACTIVITY DISORDER (ADHD).

Mahmoud MB, Ali NB, Fray S, et al.

Objective: The aim of our study was to analyze electrophysiological findings in patient with Attention Deficit Hyperactivity Disorder (ADHD) by electroencephalography (EEG) recording, estimate the prevalence of epilepsy in ADHD population and assess its clinical characteristics.

Methods: We conducted a retrospective and analytic study that concerned children with ADHD, followed for at least two-years in the Tunisian National Center for School and University Medicine (NCSUM). All patients recruited underwent at the diagnosis of ADHD, neurological examination and EEG recording in the department of Neurology of Charles Nicolle Hospital. Medical data including family history, ictal semiology and ADHD features were assessed.

Results: Thirty patients were enrolled in our study. Mean age was 12.27 years with a sex ratio of 3.28. Mean age at diagnosis of ADHD was 6.6 years. Attention Deficit Hyperactivity Disordercombined subtype was seen in 18/30 patients, Hyperactive/ Impulsive subtype in 7/30 patients and Inattentive subtype in 5/30 patients. Epilepsy-disease was reported in 20% (Seizures preceded the diagnosis of ADHD in 3/6 cases and appeared after an average of 3.67 years in 3/6 cases). Mean age of seizure onset was 7 years. Seizure-types were generalized (motor 4/6 cases, absence-type (1/6 case)) and focal (1/6 case). Electroencephalography revealed Epileptiform discharges in 30% with frontal and left dominance. Interictal discharges were significantly associated with younger age of onset (p: 0.02), inattentive subtype (p: 0.04) and intellectual disability (p: 0.04). These discharges was not associated with epilepsy.
Conclusion: Our results have shown that epileptiform discharges could be used as risk factor for seizures and cognitive impairment which may influence outcome in ADHD population

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Epilepsy Behav. 2020;113.

ASSOCIATION BETWEEN LACK OF FUNCTIONAL CONNECTIVITY OF THE FRONTAL BRAIN REGION AND POOR RESPONSE INHIBITION IN CHILDREN WITH FRONTAL LOBE EPILEPSY.

Ueda R, Kaga Y, Takeichi H, et al.

Purpose: We investigated the relationship between electroencephalographic (EEG) functional connectivity and executive function in children with frontal lobe epilepsy (FLE).
Methods: We enrolled 24 children with FLE (mean age, 11.0 years; 13 boys) and 22 sex-, age-, and intelligence-matched typically developing children (TDC) to undergo 19-channel EEG during light sleep. We estimated functional connectivity using the phase lag index (PLI) that captures the synchronization of EEG. We also performed continuous performance tests (CPTs) on the children and obtained questionnaire responses on attention deficit hyperactivity disorder and oppositional defiant disorder (ODD).
Results: The average gamma PLI was lower in the FLE group than in the TDC group, especially between long-distance frontoparietal pairs, between interhemispheric frontal pairs, and between interhemispheric parietotemporal pairs. Gamma PLIs with long-distance frontoparietal and interhemispheric frontal pairs were positively associated with inattention, ODD scores, omission error, and reaction time in the FLE group but not in the TDC group. Conversely, they were negatively associated with age, hyperactivity score, and commission error.
Conclusions: A lack of functional connectivity of the frontal brain regions in children with FLE was associated with poor response inhibition

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Epilepsy Res. 2021;169.

EVALUATION OF PSYCHIATRIC COMORBIDITY IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH EPILEPSY: A CASE-CONTROL STUDY.

Ahmed GK, Darwish AM, Khalifa H, et al.

Objective: Attention deficit/hyperactivity disorder (ADHD) is a developmental disorder caused by structural and functional brain abnormalities as well as genetic and environmental factors. ADHD symptoms are commonly observed in individuals with epilepsy. A few studies have reported a pattern of behavioral problems in children with combined epilepsy and ADHD. We aimed to evaluate comorbid behavioral problems and mental health concerns among children with epilepsy with ADHD and without ADHD including autism spectrum disorder, anxiety, depression, somatic problems, oppositional defiant disorder, and conduct disorder.
Methods: A total of 100 children aged between 6 and 11 years were recruited and categorized into 1 of 5 groups (20 child/group): (1) epilepsy, (2) epilepsy with ADHD, (3) ADHD with electroencephalogram (EEG) changes, (4) ADHD without EEG changes, and (5) healthy control. The scales used in our study included the Childhood Autism Spectrum Test (CAST) to screen autism spectrum conditions and related social and communication conditions, Conners Parent Rating Scale (CPRS) to assess ADHD and other comorbid behavioral and social-emotional difficulties, and Children Behavior Checklist (CBCL) to evaluate behavior problems.

Results: The CAST scale score showed no significant difference among the studied groups. Regarding the Conners-3 scale, the combined type of ADHD was predominant in the ADHD with EEG changes group and the ADHD with epilepsy group, while hyperactive ADHD was predominant in the ADHD without EEG changes group. The ADHD with EEG changes group and the ADHD with epilepsy group had equally high clinical rating scores for CBCL in internalizing and externalizing problems. There was a significant difference in the profile of all Diagnostic and Statistical Manual of Mental Disorders (DSM-5) scales of CBCL among the studied groups.
Conclusion: This is the first study to use EEG in patients with ADHD in comparison with epilepsy. ADHD with epilepsy is closely related to ADHD with EEG changes regarding psychiatric comorbidity in terms of anxiety, depression, somatic problems, oppositional defiance problems, and conduct problems

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Eth Human Psychol Psychiatry. 2020;22:31-48.

THE ONLINE NURTURED HEART APPROACH TO PARENTING: A RANDOMIZED STUDY TO IMPROVE ADHD BEHAVIORS IN CHILDREN AGES 6-8.

Nuno VL, Wertheim BC, Murphy BS, et al.

Objectives: To evaluate the efficacy of the Nurtured Heart Approach (NHA) to improve attention deficit hyperactivity disorder (ADHD) behaviors in children.
Methods: In 2017, we conducted a trial among parents (n = 104) with children ages 6–8 years diagnosed with ADHD/at risk for a diagnosis. Participants were randomly selected, but not blinded, to the immediate (NHA) or delayed (control) group. The NHA training was held online over 6 weeks.
Results: The NHA group (−7.0 ± 8.1), but not the control group (0.2 ± 6.6), reported a decrease in inattention (p <.001). The NHA group (−7.9 ± 9.3), but not the control group (−0.5 ± 7.3), reported a decrease in hyperactivity/impulsivity (p <.001).
Conclusions: The study provides preliminary data of the NHA's potential to improve ADHD related behaviors

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Eur Child Adolesc Psychiatry. 2020.

PREDICTING DELINQUENT BEHAVIOR IN YOUNG ADULTS WITH A CHILDHOOD DIAGNOSIS OF ADHD: RESULTS FROM THE COLOGNE ADAPTIVE MULTIMODAL TREATMENT (CAMT) STUDY.

Breuer D, von Wirth E, Mandler J, et al.

The aim of this study was to investigate which factors predict lifetime reports of delinquent behavior in young adults who had received adaptive multimodal treatment of attention-deficit/hyperactivity disorder (ADHD) starting at ages 6ΓÇô10-áyears. Participants were reassessed 13ΓÇô24-áyears (M = 17.6, SD = 1.8) after they had received individualized ADHD treatment in the Cologne Adaptive Multimodal Treatment Study (CAMT). Their behavior was classified as non-delinquent (n = 34) or delinquent (n = 25) based on self-reports regarding the number of police contacts, offenses, and convictions at follow-up. Childhood variables assessed at post-intervention (e.g., externalizing child behavior problems, intelligence, and parenting behavior) that were significantly associated with group membership were entered as possible predictors of delinquency in a Chi-squared automatic interaction detector (CHAID) analysis. Delinquent behavior during adolescence and adulthood was best predicted by (a) meeting the symptom count diagnostic criteria for conduct disorder (CD) according to parent ratings, in combination with a nonverbal intelligence of IQ Γëñ 106 at post-intervention, and (b) delinquent behavior problems (teacher rating) at post-intervention. The predictor variables specified in the CHAID analysis classified 81% of the participants correctly. The results support the hypothesis that a childhood diagnosis of ADHD is only predictive of delinquent behavior if it is accompanied by early conduct behavior problems. Low nonverbal intelligence was found to be an additional risk factor. These findings underline the importance of providing behavioral interventions that focus on externalizing behavior problems to children with ADHD and comorbid conduct problems

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Eur J Neurosci. 2020 Nov;52:4356-69.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: AN EVENT-RELATED POTENTIAL STUDY OF WORKING MEMORY.

Arjona Valladares A, Gómez CM, Rodríguez-Martínez EI, et al.

Working memory (WM) impairments have been frequently observed as an important feature of attention-deficit/hyperactivity disorder (ADHD). Event-related potential (ERP) differences between ADHD and healthy controls (HC) would be expected during WM task performance. Especially, the so-called slow wave (SW), which is related to the retention process, might present amplitude differences in ADHD. In this ERP study participated twenty-nine ADHD children and adolescents and thirty-four HC. WM performance was assessed using the Working Memory Test Battery for Children (WMTB-C), and ERPs were analyzed with a Delayed Match-To-Sample (DMTS) task. ADHD sample showed worse behavioral performance in both WMTB-C and DMTS task, and higher SW amplitude during the retention phase of the DMTS task. Additionally, the principal component analysis indicated that the scores on the component explaining the centro-parietal SW were significantly different between ADHD subjects and HC. The observed impaired neurophysiological activity during the encoding and retention periods in ADHD, which would be the origin of the behavioral deficits in WM task performance, might be reflecting a delayed maturation of the neural processes underlying the centro-parietal SW. (PsycInfo Database Record (c) 2020 APA, all rights reserved)

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Eur J Neurosci. 2020.

NEURAL GENERATORS INVOLVED IN VISUAL CUE PROCESSING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Zarka D, Leroy A, Cebolla AM, et al.

Event-related potentials (ERP) studies report alterations in the ongoing visuo-attentional processes in children with attention-deficit/hyperactivity disorder (ADHD). We hypothesized that the neural generators progressively recruited after a cue stimulus imply executive-related areas well before engagement in executive processing in children with ADHD compared to typically developed children (TDC). We computed source localization (swLORETA) of the ERP and ERSP evoked by the Cue stimulus during a visual Cue-Go/Nogo paradigm in 15 ADHD compared to 16 TDC. A significant difference in N200/P200 amplitude over the right centro-frontal regions was observed between ADHD and TDC, supported by a stronger contribution of the left visuo-motor coordination area, premotor cortex, and prefrontal cortex in ADHD. In addition, we recorded a greater beta power spectrum in ADHD during the 80ΓÇô230-áms interval, which was explained by increased activity in occipito-parieto-central areas and lower activity in the left supramarginal gyrus and prefrontal areas in ADHD. Successive analysis of the ERP generators (0ΓÇô500-áms with successive periods of 50-áms) revealed significant differences beginning at 50-áms, with higher activity in the ventral anterior cingulate cortex, premotor cortex, and fusiform gyrus, and ending at 400Γ Çô500-áms with higher activity of the dorsolateral prefrontal cortex and lower activity of the posterior cingulate cortex in ADHD compared to TDC. The areas contributing to ERP in ADHD and TDC differ from the early steps of visuo-attentional processing and reveal an overinvestment of the executive networks interfering with the activity of the dorsal attention network in children with ADHD

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P.045 IMPROVING ADHD SCREENING AND DIAGNOSIS FOR GIRLS: NEW CUT-OFF SCORES FOR THE WORLD HEALTH ORGANIZATION ADHD SELF-REPORT FOR ADOLESCENTS (ASRS-A) .

Fernandez-Quintana A, Vadlin S, Nilsson KW, et al.

Introduction: Although ADHD is more prevalent among boys than girls [1] and gender leads to a different symptom profile [2], both groups experience the same negative consequences [3] and benefit from early diagnosis [4]. Most studies have focused on boys with ADHD [5]. Therefore, there is an urgent need for suitable screening and diagnostic tools to identify affected girls.

Aims: To establish adequate clinical cut-off points of the ASRS-A total score for the detection and identification of ADHD in girls referred to Child and Adolescent Psychiatry (CAP). To analyze differences in psychometric properties and clinical utility of the ASRS-A by sex.

Method: Sixty-seven girls aged 12-18 years referred to CAP in two Swedish towns (Vasteras and Sala) were studied. Participants were interviewed with the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS) and completed the ASRS-A. Receiver operating characteristic (ROC) analyses were used to identify two clinical cut-offs; a screening cut-off (maximum possible sensitivity with at least 50% specificity), and a diagnostic cut-off (maximum possible specificity with at least 50% sensitivity). The results were compared to a sample of 44 boys aged 12-18 years old referred to the same CAMHS department. In the sample of boys, a screening and a diagnostic cut-off scores were established according to the same criteria as for girls.
Results: Mean age 15.9 years, SD=1.39. According to K-SADS, 27 girls (40.29%) met the diagnostic criteria for ADHD. Mean ARSR-A score 34.61 points (score range 0-72). A high reliability was noted (Cronbach's alpha=0.915). Area Under the Curve (AUC) for ASRS-A 0.804 (95% CI= 0.69-0.91). The screening cut-off score of 30 yielded a sensitivity of 81.5%, specificity 50%, Positive Predictive Value (PPV) of 52.37% (95% CI=43.45% to 61.14%), Negative Predictive Value (NPV) of 80.01% (95% CI=63.11% to 90.35%), accuracy 62.68% (95% CI=50.01% to 74.20%), Positive Likelihood Ratio (LR+) 1.63 (95% CI=1.14 to 2.33), Negative Likelihood Ratio (LR-) 0.37 (95% CI=0.16 to 0.87). The diagnostic cut-off ΓëÑ44 points showed a specificity of 92.5%, sensitivity 51.9%, PPV 82.35% (95% CI=59.69% to 93.63%), NPV 74.01% (95% CI=65.59% to 80.96%), accuracy 76.12%, LR+ 6.91 (95% CI=2.19 to 21.78), LR- 0.52 (95% CI=0.35 to 0.78). Sample of boys: mean age 15.41 years, ADHD prevalence 68.18%, Cronbach's alpha 0.89, AUC 0.70 (95% CI=0.52 to 0.88). A comparison of statistical measures by sex is summarized in the following table
Conclusion: The ASRS-A could be used as a screening tool in specialty treatment settings and appears to have better psychometric properties in girls than in boys. The screening cut-off (30 points) correctly identified over 80% of girls with ADHD. The diagnostic cut-off (ΓëÑ44 points) increased the probability of an ADHD-diagnosis with over 40 percentage points. Further studies in larger samples are warranted to validate these findings. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S35-S36.

P.051 EFFECTS OF GUM CHEWING AND REPETITIVE MOTOR ACTIVITY ON SUSTAINED ATTENTION IN ADULT PATIENTS WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Can KC, Tugba EOK.

Introduction and Objective: Attention Deficit-Hyperactivity Disorder is a clinical syndrome characterized by persistent inattention, hyperactivity and impulsivity. ADHD in adults has different clinical manifestations compared to children and adolescents such that attention problems, difficulty in focusing, social and professional adaptation problems and interpersonal relationship problems are more prominent. Recent studies have associated gum chewing with increased attention and decreased level of stress among healthy subjects [1]. Few studies have reported an association between repetitive motor activity and improved academic performance of students in classroom settings [2,3]. The present study aimed to evaluate the effects of gum chewing and repetitive motor activity on attention in adult ADHD patients and to compare them with healthy volunteers.
Method: Thirty ADHD patients aged between 18 and 45 years and 30 healthy volunteers who were matched with age and total educational time of the patients were included in this study. For the diagnosis of ADHD, the Diagnostic Interview for ADHD in Adults (DIVA 2.0) was performed. Hamilton Depression Scale, Adult ADHD Self-Report Scale, Wender Utah Rating Scale, Hyperfocusing Scale, State- Trait Anxiety Inventory were used for clinical evaluation. In order to measure participants' attentional performances, the modified Continuous Performance Test was administered once for each three conditions; gum chewing (with a sugar-free, odorless and aroma-free gum), repetitive motor activity (repetitively by pressing a drum pedal) and neutral condition. The order of the three conditions was randomized for each participant. At the end of each condition, participants were asked to score their anxiety and attention levels on a visual analog scale. For each condition, the number and mean reaction times of correct target responses were calculated. A 2 (Group: ADHD and Healthy Control) x 3 (Task: Neutral, Gum Chewing and Repetitive Motor Activity) mixed-design repeated measures ANOVA was performed.
Results: It was found that participants reaction times to the correct targets were significantly reduced in both active conditions compared to the neutral condition ($F(2,57) = 4.04$ $p = .02$). The average reaction times were shortened in both groups for active conditions when evaluated in groups. However, this change was not within the limits of statistical significance ($F(2,57) = .26$ $p = .76$). In addition, the significant difference between

the scores of subjective anxiety and attention levels in the neutral condition between the groups disappeared in the chewing gum condition. The statistical significance for the correct target response counts between the groups in the neutral condition was lost in the chewing gum condition.
Conclusion: In this study, it was found that both gum chewing and repetitive motor activity had a positive effect on the attention performance of both groups, but this effect was not different for the ADHD group than the healthy control group in both active conditions. Gum chewing and repetitive motor activity can be used as easily accessible intervention tools for improving attention. No conflict of interest

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EUR NEUROPSYCHOPHARMACOL. 2020;40:S31-S32.
P.047 WHITE MATTER MICROSTRUCTURE AND ATTENTION-DEFICIT/HYPERACTIVITY SYMPTOMS: CROSS-SECTIONAL AND LONGITUDINAL EFFECTS.
Damatac C, Leenders A, Chauvin R, et al.
Background: Unlike diagnostic categories in attention-deficit/hyperactivity disorder (ADHD), symptoms of the disorder are continuously distributed throughout the population [1,2]. Additionally, ADHD symptom severity tends to change and often reduces over time, throughout childhood and adolescence. Using diffusion magnetic resonance imaging (dMRI), ADHD has been associated with white matter (WM) microstructural alterations; however, dimensional analyses of symptom severity show inconsistent results and rarely include more than one dMRI timepoint [3,4]. As an individual with ADHD develops into adulthood, symptom remission may be underpinned by WM normalization. In a large, longitudinal cohort, we first cross-sectionally investigated the association of symptom dimension severity with WM microstructure, and then examined how the effect develops over time.
Methods: Clinical and MRI data were obtained from 654 participants (322 unaffected, 258 affected, 74 subthreshold; age 7-29 years, mean=17.41, SD=3.66). Follow-up data were acquired on average 3.73 years later (SD=0.5years) in a subset of 118 people (53 unaffected, 43 affected, 22 subthreshold; age 12-29 years, mean=20.61, SD=3.38). We applied automated global probabilistic tractography [5] on 18 major WM pathways. We used linear mixed-effects regression models to test associations of symptom score and symptom change over time with global brain and tract-specific FA. All models incorporated age, sex, MRI acquisition site, and head motion as fixed effects and family membership as random effect. Global models also included tract as fixed effect and subject as random effect. Cross-sectional models also included acquisition wave as fixed effect. Longitudinal models additionally included baseline symptom score and age at both timepoints. Symptom remission was calculated by subtracting baseline symptom score from follow-up score. Tract-specific model P-values were Bonferroni-corrected for number of tracts (PFWE=Px18).
Results: Cross-sectional Global models indicated effects of hyperactivity-impulsivity (HI) and inattention (IA) scores (PHI=0.031,td=-0.026; PIA=0.030,td=-0.026) on FA, and significant interaction effects with tract (both P<0.007). There was no association between global FA and categorical ADHD diagnosis. Tract-specific models showed a negative association between right cingulum angular bundle (rCAB) FA and HI severity (PFWE=0.045, td=-0.107). Longitudinal Less combined (HI+IA) symptom remission had a positive effect on follow-up global FA (P=0.048, td=0.044). Conversely, baseline FA was not associated with prospective symptom remission. There were no interaction effects with tract, so we did not test tract-specific models.
Conclusions: This is the first time global probabilistic tractography has been applied to an ADHD dataset of this size. Our cross-sectional findings indicate that dimensional symptom severity is more sensitive to subtle differences in FA than are diagnostic categories. FA associations with ADHD are not uniformly distributed across WM tracts and the rCAB in particular may play a role in symptoms of hyperactivity and impulsivity. Our longitudinal results indicate a counterintuitive direction of effect: less symptom remission is associated with increased FA at follow-up. Yet, this is consistent with previous findings in an overlapping sample at a younger age-range [4]. Reduction in FA does not predict, but follows a change in symptoms. Therefore, decreased FA may be the downstream result of brain maturation or reorganization in widespread brain regions, resulting in less overall stimulation of WM tracts. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S29-S30.

P.044 MENTAL HEALTH IN CHILDREN OF PARENTS WITH ADHD: CURRENT KNOWLEDGE AND FUTURE RESEARCH OPPORTUNITIES.

Fernandez-Quintana A, Nilsson KW, Olofsdotter S.

Introduction: About 2.5% of adults in the general population have Attention Deficit Disorder with Hyperactivity (ADHD) [1]. Children of parents with ADHD are at high risk of suffering from mental health concerns. At least one third of fathers who have ADHD will have children who also will be diagnosed with ADHD [2]. Aims: To provide an up-to-date outline of psychopathology in children of parents with ADHD. To identify knowledge gaps and find directions for future research.

Method: A search was conducted in PubMed, MEDLINE and PsycInfo databases for MeSH terms: ADHD, child och impaired parents, Attention Deficit and Disruptive Behavior Disorders, Substance-Related Disorders. Keywords: children, parents with mental illness, addicted parents or parental addiction.

Results: ADHD is a highly heritable disorder. Having both a father and/or a mother with ADHD is associated with an increased risk of severe ADHD in their children, more family conflicts and less family cohesion [3]. However, children's ADHD symptomatology appears to be more persistent when their mother has ADHD. No significant difference in children's risk of ADHD has been found when comparing parents with remitted ADHD versus parents with persistent ADHD in adulthood [4]. It has been estimated that up to 43% of children of parents with ADHD can develop ADHD themselves [5]. These children also have a higher risk of developing other mental health concerns such as autism and affective disorders. Furthermore, it is possible that a number of children have a parent with undiagnosed ADHD, which reduces the family's chances of getting adequate help. The prevalence of ADHD symptoms in parents of children with autism is higher than in the general population, whether or not parents meet the diagnostic criteria for ADHD. In adults, ADHD is frequently associated with a myriad of comorbid psychiatric diseases. Therefore, many parents with ADHD have psychiatric comorbidity (primarily with mood and anxiety disorders, substance use disorder and personality disorders). Children of parents with psychiatric comorbidity tend to have a worse prognosis than children of parents with one psychiatric diagnosis. Children of parents with ADHD and substance use syndrome are at even greater risk of ADHD themselves. Moreover, children of parents with ADHD and substance misuse are at higher risk of developing substance use disorder, depression, post-traumatic stress disorder, antisocial personality syndrome and other behavioral disorders. The risk is higher if both parents abuse drugs and if the children have a long-term exposure to parents' substance misuse. In addition, having a mother with substance use syndrome increases the children's risk of alcohol abuse as young adults, whether or not the children have ADHD.

Conclusion: A paucity of literature into children of parents with ADHD remains. Further research is needed into the impact of ADHD in fathers on childrens' mental health. The high rates of psychiatric comorbidity among patients with ADHD lead to an increasing need for studies on children of parents with dual diagnosis and other psychiatric comorbidity. Specifically, little is known about the mental health of children whose parents are drug users or have a personality disorder in combination with ADHD. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S77-S78.

P.125 ATTENTION DEFICIT HYPERACTIVITY DISORDER MODULATES THE ASSOCIATION BETWEEN GENETIC LIABILITY TO AUTISM AND SUBCORTICAL STRUCTURE.

Bussu G, Pons VT, Beckmann C, et al.

Background: Autism Spectrum Disorder (ASD) is a heterogeneous disorder, characterized by high individual variability in neuroanatomical outcomes. Despite imaging studies have highlighted the role of specific subcortical structures in ASD, there is no clear neuroanatomy of ASD [1], rather high variation which is likely to be modulated by the interaction of genetic and environmental factors. Research into the genetics of ASD suggests a complex polygenic architecture for the disorder [2]. Polygenic scores for ASD (PS-ASD) measure the cumulative genetic loads for ASD at an individual level, allowing the investigation of the genetic link between predisposition to ASD and brain structure.

Objectives: We investigate the association between polygenic scores for ASD and subcortical volumes in individuals with and without an ASD diagnosis. Given the high genetic overlap between ASD and attention-deficit/hyperactivity disorder (ADHD), we also explored potential effects of ADHD comorbidity on this association. Methods: First, polygenic scores for ASD were computed on 343 ASD cases and 241 typically

developing (TD) controls from the EU-AIMS Longitudinal European Autism Project (LEAP [3]). Next, subcortical volumes were obtained from T1-weighted Magnetic Resonance Imaging (MRI) scans collected on 670 individuals using automatic subcortical segmentation. After quality control, subsequent analyses were performed on 348 individuals between 7 and 31 years of age (240 males), from four different outcome groups: typically developed individuals (TD, n=137), ASD cases (n=176), individuals with intellectual disability but not ASD (ID-controls, n=9), and ASD cases with intellectual disability (ID-ASD, n=26). For each subcortical structure, we performed linear mixed-effect modelling with bilateral volume as outcome variable and PS-ASD as predictor of interest, yielding to 8 models. Subcortical volumes were corrected for intra-cranial volume. We included sex, ASD diagnosis, ADHD comorbidity, age and full-scale intelligence quotient (fsIQ) as confounding factors, and scanning site as random-effect term. Finally, we used false-discovery-rate (FDR, q<=0.05) to correct for multiple comparisons.

Results: There was a significant interaction effect between PS-ASD and ADHD comorbidity on bilateral volumes of amygdala (t(336)=2.49, p=0.01), globus pallidus (t(338)=2.66, p=0.01), and nucleus accumbens (t(337)=2.10, p=0.04). In particular, higher PS-ASD was linked to smaller amygdala and globus pallidus in individuals without ADHD (ps=0.03), and to larger nucleus accumbens in individuals with ADHD (p=0.02). However, significance was not retained after FDR-correction for the nucleus accumbens, and the effect was only marginally significant for amygdala and globus pallidus (ps=0.053).

Conclusions: Findings suggest that alterations in subcortical volumes might be causally associated with genetic predisposition to ASD. ADHD comorbidity modulates this association, likely due to the complex genetic overlap between the disorders. Given the role of frontostriatal circuits in reward and motivation in both disorders, we conceptualize that increased cumulative effect of common genetic variants linked to ASD leads to structural alterations of amygdala and globus pallidus, which may lead to diminished motivation to attend to social stimuli, in turn influencing social development and resulting in the ASD social phenotype. The investigation of genetic covariance with neuroanatomical alterations in ASD and ADHD might be crucial to understand the biological underpinnings of the high comorbidity between these disorders. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S34-S35.

P.050 HEMODYNAMIC RESPONSE TO METHYLPHENIDATE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: FIRST ADMINISTRATION, TITRATION PHASE AND ASSOCIATIONS WITH CLINICAL SEVERITY.

Grazioli S, Rosi E, Bacchetta A, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a prevalence of about 5% in children. ADHD is characterized by lack of self-regulation and presence of deficits in organizing behaviors in response to emotional stimuli [1]. Methylphenidate (MPH) is one of the most effective and frequently prescribed psychostimulant drugs for ADHD [2], however, a possible predictive utility of brain hemodynamic data related to MPH administration and its relation to clinical symptomatology - in a longitudinal framework - is still not clear. To address these questions we used Near Infrared Spectroscopy (NIRS) technology, a useful non-invasive optical technique that allows to investigate the effect of psychopharmacological treatment on cortical hemodynamics.

Aims: Aim 1: To evaluate whether any hemodynamic changes induced by first MPH administration at wave 2 (W2) would predict changes in hemodynamic activation in frontal areas at wave 3 (W3, titration phase). Aim 2: To analyze possible associations between hemodynamic and clinical data before (wave 1, W1) and after (W3) MPH administration.

Methods: **Study design**: 20 children with ADHD underwent a three-waves study and 25 typically developing peers were recruited at W1 as a control group. At W2 children with ADHD received first MPH administration and at W3 they reached the titration phase. At each phase children performed - during NIRS recording - an emotional continuous performance task with visual stimuli of different emotional content: faces expressing positive, negative or neutral emotions or no face condition (distorted) [3]. Clinical data were collected at W1 and W3 through Child Behaviour Checklist/6-18 (CBCL/6-18) and Conners' Parent Rating Scale-Revised (CPRS-R) [4,5].

Statistical analyses: Aim 1) We aimed at finding a linear relationship between the difference between NIRS activation at W2 and W1 (Delta1) and W3 and W2 (Delta2), for each subject, task condition and brain region. Aim 2) Lastly, to address relationships between brain hemodynamics and clinical data across time, we

investigated Spearman linear correlations between the Delta1 and clinical symptomatology indexes at W1 and between Delta2 and clinical data at W3.
Results: Significant linear regression and Spearman linear correlations results are depicted in the table below.
Conclusions: Our study results suggest that hemodynamic changes in right prefrontal region probably induced by first MPH administration could predict hemodynamic changes related to MPH titration phase. These biological indexes could be associated to clinical evidences related not only to core ADHD symptoms but also to affective correlates. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S356.

P.633 SO MANY FORMULATIONS, SO LITTLE CONCENTRATION: HOW MANY MODIFICATIONS DO WE NEED UNTIL FINDING THE OPTIMAL TREATMENT FOR CHILDHOOD ADHD?

Garran RP, et al.

Background: attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children, and its prevalence is increasing. It is presented with a very heterogeneous dysfunctional pattern, making sometimes difficult to discern the appropriate treatment in each patient. Furthermore, medications used to treat ADHD may cause side effects like insomnia or decreased appetite that mimic symptoms of depression. Psychiatric comorbidity predicts more severe and persistent symptoms and poorer short-term outcomes. The objective of this study is to assess the number of changes that had to be made to find the optimal treatment.
Methods: we present a descriptive retrospective study performed on a sample of patients aged less than 18 years-old, with the main diagnosis of ADHD according to ICD-10 treated at the Child and Adolescent Psychiatry Unit of the Virgen Macarena Hospital in Seville, during the period from 04/01/2017 to 04/01/2019. Strategies of change or drug combination were considered as treatment modifications but dose adjustments were not included as a new treatment variation.
Results: this study included 46 patients aged 12.59 -¦ 3.26 years-old. Most of the patients (60.1%) presented comorbidities with other psychiatric pathology. The most prevalent psychiatric comorbidity was conduct disorder (39.1%). The most used initial psychopharmacological treatment was methylphenidate (88.1%), followed by atomoxetine (5.5%). The majority of patients (58.7%) required a modification of the treatment initially prescribed, 23.9% a second, 17.4% a third and 8.5% a fourth. The most frequent adjustment was the switch to another methylphenidate format (43.2%), along with other alternatives such as the combination with guanfacine (14.8%) or atomoxetine (11.1%). On average, 2.4 -¦ 1.32 treatment variations were required.
Discussion: the goal of ADHD treatment is not only to improve the symptoms, but also the comorbidity and functionality of the patient. Stimulant treatment for ADHD is one of the best studied medications in children and adolescents. Most of the guidelines consider methylphenidate as the first line of pharmacological treatment and if the clinical response is inadequate or insufficient, the formulation of the treatment should be changed or another alternative drug should be looked for. Comorbidities, poor compliance or intolerances could affect to the effectiveness of the treatment and sometimes, it is necessary to try several lines of medication until finding the most adequate one. A family member's history of mental health problems and their responses to treatments may guide not only diagnosis, but also treatment of the child. Untreated ADHD can cause stress and low self-esteem because of negative feedback and interactions from others that are a result of hyperactivity, impulsivity and inattention that negatively affect social interactions. Since every treatment consideration depends on a risk/benefit analysis, the patients and their parents should fully understand short and long-term risks as well as benefits compared to non-treatment of ADHD. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S223-S224.

P.390 SLEEP EEG CYCLIC ALTERNATING PATTERN ALTERATIONS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A META-ANALYSIS OF CURRENT LITERATURE.

Biancardi C, Sesso G, Faraguna U, et al.

Background: Sleep alterations are a common finding in children with Attention Deficit and Hyperactivity Disorder (ADHD) [1], as revealed by subjective and objective reports, indicating higher sleep fragmentation and instability and reduced recovery function of sleep [2]. However, only few significant differences in the macrostructure of the sleep EEG have emerged between ADHD and healthy children (HC) [2, 3]. On the other hand, NREM cyclic alternating pattern (CAP) represents a microstructural EEG marker of unstable sleep and is closely related with sleep recovery function [4]. Thus, recent studies have investigated CAP in ADHD although showing conflicting results. To achieve a more robust evidence about the actual usefulness of CAP as a parameter for objective assessment of disordered sleep in ADHD, we performed a meta-analysis of the available literature.

Methods: A systematic search was performed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria [5] and was conducted on two electronic databases (PubMed and Scopus), from inception to February 2020. We included clinical studies aimed at evaluating the sleep CAP in patients with ADHD compared to HC. Hedges' g effect sizes and standard errors for each CAP parameter of each included study were estimated either from means and standard deviations or from p–values of independent statistics. We performed 23 meta-analyses according to the CAP parameters that were investigated in all meta-analyzed studies. The Cochrane Q test and the I2 index were applied for heterogeneity evaluation, and either fixed effects or random effects models were used to compute standardized mean differences (SMD).

Results: We retrieved 426 abstracts (after removing duplicates) using our search strategy and included three studies in the meta-analysis. Overall, study samples included a total of 109 subjects (ADHD: 62, HC: 47; age range: 6 – 13 years; Intelligence Quotient > 70). The following 23 parameters of CAP were meta-analyzed: total CAP rate in NREM, N1, N2 and N3 sleep (percentage of NREM, N1, N2 and N3 sleep time occupied by CAP sequences); CAP A1, A2 and A3 rates in NREM sleep (percentage of NREM sleep time occupied by CAP A1, A2 and A3 sequences); CAP A1, A2 and A3 indexes (number of A1, A2 and A3 phases per hour of NREM, N1, N2 and N3 sleep); duration of A and B phases; number and duration of CAP sequences. Of the 23 meta-analyses, only three showed significant differences between patients and controls. Particularly, compared to HC, ADHD patients showed significantly lower total CAP rate in N2 sleep (SMD = –0.96, 95% CI = –1.73 to –0.19), CAP A1 rate in NREM sleep (SMD = –0.69, 95% CI = –1.09 to –0.30), and CAP A1 index in N2 sleep (SMD = –1.15, 95% CI = –2.28 to –0.03).

Conclusions: Our results provide specific CAP variables (total rate in N2, A1 rate in total NREM, A1 index in N2) as possible biomarkers, measurable through standardized scoring of EEG microstructure, for assessing sleep fragmentation and instability in children with ADHD. No conflict of interest

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Eur Neuropsychopharmacol. 2020;40:S26-S27.

P.039 CELL TYPE-SPECIFIC DNA METHYLATION IS ASSOCIATED WITH CHILDHOOD ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS.

Meijer M, Klein M, Franke B, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of 5% in children [1]. Both genetic and environmental adversities, such as early life stress, play an important role in the onset of ADHD. The interplay between genome and environment can be studied via DNA methylation of CpG sites, which is thought to influence gene expression levels and, ultimately, behaviour [2]. Here, we performed a methylome-wide association study (MWAS) of ADHD symptoms (N=583 children, age<16 years with mean age 13.5, 50% boys) in an American longitudinal cohort called the Great Smoky Mountain Study (GSMS) [3]. Associations of sequencing-based DNA methylation levels in whole blood of the majority of 28 million CpG sites in the human genome were calculated for parent-rated ADHD symptoms via linear regression using the RaMWAS R package [4]. The model included covariates for age and squared age, sex, ethnicity, blood cell type, smoking, socioeconomic status, trauma, technical batch effects, and four principal components to account for remaining major sources of unmeasured variation. Results on bulk cells did not show any methylome-wide significant hits (q-value<0.05). With the use of epigenomic deconvolution, MWAS

was performed on specific blood cell types. For robustness, the cohort was randomly divided in three sub-cohorts and results were meta-analysed. This study identified the first 2, 24, and 16 methylome-wide significant hits for ADHD (q-value<0.05) in T cells, monocytes, and granulocytes, respectively. Overlapping hits were found in non-coding regions of the genome. Enriched Gene Ontology (GO) terms in top hits per cell type (p-value<1*10-5) identified metallopeptidase, ribonuclease, and endonuclease activity for T cells. Differentially methylated genes in monocytes were enriched for calcium ion binding and channel activity, and granulocytes showed enrichment of DNA methylation in genes related to neuropeptide receptor activity. We then expanded the linear model to study the specific effects of two variables. First, since previous studies showed a possible interaction between ADHD and sex in DNA methylation levels [5], we examined the effect of sex by including it as an interaction term. This led to the identification of significant hits in bulk cells (q-value<0.05), with the most significantly differentially methylated sites located in genes involved in cell-cell adhesion, calcium signaling, and protein kinases. Second, stress is thought to be an environmental risk factor for the development of ADHD and the participants in the current cohort were selected based on high levels of perceived stress. Therefore, we tested whether stress plays a role in DNA methylation levels associated with ADHD by adding perceived trauma as an interaction term in the linear model. Significant hits were identified in monocytes and granulocytes (q-value<0.05). Here, top hits were involved in calcium channel signaling, and migration of neuronal cells. Interestingly, GO term enrichment showed a possible involvement of steroid hormone receptor signaling genes in monocytes. Replication and further analysis of these preliminary results should reveal the possible biological role of blood cell type-specific DNA methylation markers in childhood ADHD symptoms. No conflict of interest

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Front Human Neurosci. 2020;14.

ASSESSING FINE-GRANULARITY STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Wang P, Jiang X, Chen H, et al.

Attention deficit hyperactivity disorder (ADHD) was considered to be a disorder with high heterogeneity, as various abnormalities were found across widespread brain regions in recent neuroimaging studies. However, remarkable individual variability of cortical structure and function may have partially contributed to these discrepant findings. In this work, we applied the Dense Individualized and Common Connectivity-Based Cortical Landmarks (DICCCOL) method to identify fine-granularity corresponding functional cortical regions across different subjects based on the shape of a white matter fiber bundle and measured functional connectivities between these cortical regions. Fiber bundle pattern and functional connectivity were compared between ADHD patients and normal controls in two independent samples. Interestingly, four neighboring DICCCOLs located close to the left parietooccipital area consistently exhibited discrepant fiber bundles in both datasets. The left precentral gyrus (DICCCOL 175, BA 6) and the right anterior cingulate gyrus (DICCCOL 321, BA 32) had the highest connection number among 78 pairs of abnormal functional connectivities with good cross-sample consistency. Furthermore, abnormal functional connectivities were significantly correlated with ADHD symptoms. Our studies revealed novel fine-granularity structural and functional alterations in ADHD

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EXPLORING THE NEURAL STRUCTURES UNDERLYING THE PROCEDURAL MEMORY NETWORK AS PREDICTORS OF LANGUAGE ABILITY IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sanjeevan T, Hammill C, Brian J, et al.

Introduction: There is significant overlap in the type of structural language impairments exhibited by children with autism spectrum disorder (ASD) and children with attention deficit hyperactivity disorder (ADHD). This similarity suggests that the cognitive impairment(s) contributing to the structural language deficits in ASD and ADHD may be shared. Previous studies have speculated that procedural memory deficits may be the shared cognitive impairment. The procedural deficit hypothesis (PDH) argues that language deficits can be explained by differences in the neural structures underlying the procedural memory network. This hypothesis is based

on the premise that the neural structures comprising the procedural network support language learning. In this study, we aimed to test the PDH in children with ASD, ADHD, and typical development (TD). Methods: One hundred and sixty-three participants (ages 10-21): 91 with ASD, 26 with ADHD, and 46 with TD, completed standardized measures of cognitive and language ability as well as structural magnetic resonance imaging. We compared the structural language abilities, the neural structures underlying the procedural memory network, and the relationship between structural language and neural structure across diagnostic groups.
Results: Our analyses revealed that while the structural language abilities differed across ASD, ADHD, and TD groups, the thickness, area, and volume of the structures supporting the procedural memory network were not significantly different between diagnostic groups. Also, several neural structures were associated with structural language abilities across diagnostic groups. Only two of these structures, the inferior frontal gyrus, and the left superior parietal gyrus, are known to be linked to the procedural memory network.
Conclusions: The inferior frontal gyrus and the left superior parietal gyrus, have well-established roles in language learning independent of their role as part of the procedural memory system. Other structures such as the caudate and cerebellum, with critical roles in the procedural memory network, were not associated with structural language abilities across diagnostic groups. It is unclear whether the procedural memory network plays a fundamental role in language learning in ASD, ADHD, and TD

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Frontiers in Pediatrics. 2020;8.

PARENT AND TEACHER TRAINING INCREASES MEDICATION ADHERENCE FOR PRIMARY SCHOOL CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Zheng X, Shen L, Jiang L, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common neurobiological disorder for which effective and safe medication is recommended as first-line treatment. However, many parents and teachers do not believe that ADHD is a disorder or do not accept medication treatment in China. Treatment is often short term or intermittent. Our study aimed to investigate the clinical effect of employing a 4-week, session-based training for both parents and teachers in improving medication adherence for primary school children with ADHD.
Methods: From January 2018 to December 2018, a total of 5,118 primary school children were screened. Among 211 children diagnosed with ADHD, 116 were assigned to the intervention group and 95 to the control group. This study provided systematic training for parents and teachers in the intervention group. The training consisted of education about the disorder and ADHD behavioral intervention for both parents and teachers as well as classroom management techniques for just the teachers. A cluster randomized controlled trial (RCT) was conducted to investigate the effect of this training at 6 months follow-up. The study determined medication adherence using a questionnaire and scoring with a rating scale at baseline and at the 6 month follow-up endpoint. The questionnaire was self-report.
Results: The study population had a relatively low rate of attention deficit hyperactivity disorder (4.1%) compared to the generally accepted prevalence. After the training, more parents and teachers believed that ADHD is a neurobiological disorder and that medication is the first line treatment. At 6 months follow-up, the Medication Adherence Report Scale (MARS) score for the intervention group was 22.8 -¦ 0.75 and 16.5 -¦ 1.63 for the control group ($t = 5.217$, $P < 0.01$). Based on parents' reports and medical records, 82 children (70.69%) were continuously taking medication for 6 months in the intervention group, while only 35 children (36.84%) were doing so in the control group. In the intervention group, the mean SNAP-IV score was 1.98 -¦ 0.42 at baseline but 0.99 -¦ 0.31 at 6-month follow-up. In the control group, the mean SNAP-IV score was 1.89 -¦ 0.47 at baseline but 1.37 -¦ 0.42 at 6-months follow-up ($F = 2.67$, $P = 0.009$). Factors influencing medication adherence for children with ADHD were parent's beliefs, teacher's beliefs, socioeconomic status, adverse effect, insurance coverage, gender, and trust of the medical system.
Conclusions: Our findings indicate that comprehensive training programs improve the understanding of ADHD and medication adherence for both children's parents and teachers, providing a promising approach for improving clinical efficacy for children with ADHD

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Front Psychiatry. 2020;11.

SERUM LEVELS OF VITAMIN A AND VITAMIN D AND THEIR ASSOCIATION WITH SYMPTOMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Li HH, Yue XJ, Wang CX, et al.

Objective: To measure levels of vitamin A (VA) and vitamin D (VD) and the symptomatic association of their co-deficiencies on attention deficit hyperactivity disorder (ADHD) in Chinese children (6-9 years).

Methods: Eighty-two children (69 boys and 13 girls; mean age = 7.1 -¦ 0.9 years at the time of the diagnosis) with ADHD were recruited as ADHD group. A total of 106 healthy children were recruited as the healthy control (HC) group. Serum levels of retinol and 25-hydroxyvitamin D (25(OH)D) of all children were evaluated using high-performance liquid chromatography (HPLC) and HPLC-tandem mass spectrometry. The Swanson, Nolan, and Pelham IV Rating Scale (SNAP-IV) was employed to assess the clinical symptoms of ADHD.

Results: Children suffering from ADHD had significantly reduced serum levels of retinol and 25(OH)D compared with those of HCs, and the prevalence of VA deficiency and VD deficiency were higher in children suffering from ADHD. Serum concentrations of 25(OH)D and retinol were linked closely with the presence or absence of ADHD after adjustment for age, body mass index, season of blood sampling, and sun exposure. Serum concentrations of 25(OH)D and retinol showed a negative correlation with the total scores of SNAP-IV. Children with ADHD as well as VA and VD co-deficiency had increased SNAP-IV total scores and ADHD inattention subscale scores.

Conclusion: VA deficiency and VD deficiency in children with ADHD were increased in comparison with that in HCs. VA and VD co-deficiency associated with ADHD symptom severity. Attention should be paid to regular testing of VA levels and VD levels. However, the mechanism of VA and VD in ADHD needs to be further studied. Interventional studies on VA and VD supplementation are recommended to further verify the relationship between VA and VD co-deficiency and ADHD

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Front Psychiatry. 2020;11.

TRACKING INHIBITORY CONTROL IN YOUTH WITH ADHD: A MULTI-MODAL NEUROIMAGING APPROACH.

Tremblay LK, Hammill C, Ameis SH, et al.

Background: A decreased ability to inhibit a speeded motor response is a well-studied deficit in Attention Deficit Hyperactivity Disorder (ADHD), and has been proposed as an endophenotype. Inhibitory control has been assessed reliably with the Stop Signal Task (SST) and is associated with prior documented differences in regional brain function using f-MRI. Here, we advance on these findings by examining their structural connectivity and white matter integrity with the goal of identifying a network underlying a core cognitive deficit in ADHD.

Methods: Healthy controls (N=16) and youth diagnosed with ADHD (N=60) were recruited through the Province of Ontario Neurodevelopmental Disorders Network (POND) and the Hospital for Sick Children. An f-MRI activation difference map was co-registered with each participantΓÇÖs white matter imaging data, representing the specific network nodes where ADHD youth diverged significantly from controls while performing the SST. Probabilistic tractography was applied from these nodes, and white matter integrity indices such as fractional anisotropy (FA) within the tracts of interest were contrasted between the groups and correlated with SST output measures, including the measure of inhibitory control, the stop signal reaction time (SSRT).

Results: The tracts that connected the network nodes belonged primarily to the inferior fronto-occipital fasciculus (IFOF) and cingulum. ADHD subjects showed trend differences in FA compared to controls between right inferior frontal gyrus (IFG) and right superior temporal gyrus (P= 0.09), right IFG and right posterior cingulate (P= 0.01), right anterior cingulate to posterior cingulate (p= 0.08), and between left middle temporal gyrus (BA 39) and left posterior cingulate (P=0.02). A trend correlation was found between radial diffusivity within IFG to STG white matter (IFOF) and SSRT.

Conclusions: We identified potential white matter tracts related to deficient inhibitory control, elucidating the brain mechanisms of an important cognitive deficit in ADHD. These findings could be integrated into future endophenotypic biomarker studies, incorporating altogether brain structure, function, and behavior for future studies of ADHD and other psychiatric conditions that exhibit this deficit

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Front Psychol. 2020 Nov;11.

REGULATION-FOCUSED PSYCHOTHERAPY FOR CHILDREN (RFP-C): ADVANCES IN THE TREATMENT OF ADHD AND ODD IN CHILDHOOD AND ADOLESCENCE.

Di Giuseppe M, Prout TA, Rice T, et al.

In recent years the authors developed a novel, manualized, time-limited psychodynamic treatment approach for children who present with disruptive behaviors and emotional dysregulation, like Oppositional Defiance Disorder, named Regulation-Focused Psychotherapy for Children. RFP-C conceptualizes children's externalizing behaviors as expressions of maladaptive defense mechanisms formulated as the products of developmental delays in the implicit emotion regulation system

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Indian Journal of Public Health Research and Development. 2020;11:83-87.

EFFECT OF VESTIBULAR STIMULATION ON LANGUAGE SKILLS OF CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Jegadeesan T, Nagalakshmi P.

Aim: The purpose of the study was to evaluate the effect of vestibular stimulation on language in children with Attention Deficit and Hyperactivity Disorder.

Methodology: Total of 30 subjects with Attention deficit and hyperactivity disorder, 15 in experimental group and 15 in control group with age of 4 to 6 years participated in this study. Both control and experimental groups were assessed using The Bzoch-League Receptive-Expressive Emergent Language Scale (Reels) for the measurement of language skills in children.

Result: Statistical significant is present (t = 3.8) in the experimental group with regard to effectiveness of vestibular stimulation on language skills among ADHD children.

Concusion: The conclusion of this study indicates that the vestibular stimulation activities are effective in improving language skills in ADHD children

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Indian Journal of Public Health Research and Development. 2020;11:72-77.

DEVELOPMENT AND VALIDATION OF JEGADEESAN AND MAIMOONA IMPULSIVITY PARENT RATING SCALE (JAM-IPRS) FOR ADHD CHILDREN.

Renuchitra R, Ajmal M, Jegadeesan T.

Aim: The aim of this study is to develop and validate the Jegadeesan and Maimoona Impulsivity Parent Rating Scale (JAM-IPRS) among ADHD Children.

Objectives To generate the scale items through focus group discussion. To identify the appropriateness and relevance of the items through subject matter Expert Rating. To establish the psychometric properties of developed scale. To develop norms for developed scale. To translate the scale items in a two vernacular languages Tamil and Malayalam

Methodology: Formulation of 42 statements was done with focus group discussion. The statements are sent to 50 experts in the field of Occupational Therapy, Speech Therapy, Psychologist and Special Educator for validating the items. Total of 42 items are validated by the experts. A total of 60 samples (30 normal subjects and 30 impulsive subjects) were selected for the field trial/ main study those who were under occupational therapy management at the age range between 5-13 years residing Kerala (Malappuram and Thrissur) and Tamilnadu (Erode and Komarapalayam). Samples were selected by using convenient sampling method. Socio-demographic data sheet prepared by investigators were used for collecting information regarding the name of the child, number of siblings, birth order, type of family, parental occupation and parental education.

Conclusion: From the statistical analysis the assessment's Cronbach alpha value is +¦ = 0.68 to 0.72 which shows the assessment tool has good internal consistency, reliability. The expert validation was done and got

good relevance or content validity for all the scale items. The Test-Retest Reliability of developed scale is 0.725. Hence Jegadeesan and Maimoona Impulsivity Parent Rating Scale(JAM-IPRS) can be used to identify the level of impulsivity for ADHD children

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Infant Ment Health J. 2020.

COMMUNICATION BETWEEN INFANT BOYS AND THEIR MOTHERS WITH ADHD SYMPTOMS.

Karagianni E, Papaeliou CF, Maniadaki K, et al.

Aim: This preliminary longitudinal study examined timing features and type of interaction between infant boys and their mothers with attention deficit hyperactivity disorder (ADHD) symptoms.

Method: Ten infants and their mothers with ADHD symptoms and 10 control dyads were video recorded at home during free play interactions when infants were 2-, 4-, 6-, and 9-month old. Microanalysis of the video recordings was carried out to assess synchronization, turn-taking, and type of interaction. Infants temperament was also assessed.

Results: ADHD dyads showed shorter synchronization at 2 months and shorter duration of Joint Attention. Partial least squares regression analysis revealed that infant's ability for Joint Attention is predicted mainly by duration of maternal behavior as well as by earlier forms of communication, that is, protoconversations.

Conclusion: The data from our preliminary study suggest that-mothers with ADHD symptoms may have difficulties maintaining their behavior for enough time possibly due to the core symptoms of the disorder, that is, inattention, hyperactivity, and impulsivity. This maternal deficit seems to affect temporal coordination with their infants and maybe the development of more complex forms of interaction. Clinical implications of these findings are also discussed

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Int J Psychol. 2020 Dec;55:973-82.

CROSS-LATERALISATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND MOTOR SKILL PERFORMANCE.

Musalek M, Scharoun Benson SM, Lejcarova A, et al.

Cross-lateralisation and increased motor difficulties have been reported in children with attention-deficit/hyperactivity disorder (ADHD). Nevertheless, the question of how crossed (i.e. mixed preference) or uncrossed (i.e. same side preference) lateralisation impacts motor performance in children with ADHD has yet to be examined. In this study, previously validated observational measures of hand and foot preference were used to identify right-handed children with ADHD who display cross- (nÂ =Â 29) and uncross-lateralisation (nÂ =Â 31). An uncross-lateralised typically developing (TD) group (nÂ =Â 32) was also identified, and included as a control. Motor performance was assessed with seven valid and reliable fine and gross motor tasks performed with both preferred and non-preferred limbs. Group, task and sex-related effects were examined. Findings revealed that male (but not female) cross-lateralised children with ADHD performed significantly worse, respectively, in two of the fine motor tasks (spiral tracing [pâ€‰<â€‰.01], and dot filling [pâ€‰<â€‰.05]). Results suggest that cross-lateralised hand and foot preference may affect complex motor skills in male children with ADHD. Furthermore, characteristics of ADHD may manifest differently in male and female children. Findings highlight the importance of considering both hand and foot preference when targeting motor interventions for children with ADHD

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Int Clin Psychopharmacol. 2020.

MANAGEMENT OF ANXIETY DISORDERS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A NARRATIVE REVIEW.

Golubchik P, Weizman A.

Anxiety disorders are common comorbidities of attention deficit/hyperactivity disorder (ADHD) and conversely, ADHD is prevalent among anxious youths. A variety of treatments, both psychopharmacological and nonpsychopharmacological, are used to manage combined ADHD/anxiety disorder. This article aims to review the literature on the treatment of ADHD with comorbid anxiety disorders, and make evidence-based recommendations for clinical practice. In most cases, when ADHD is the primary condition, stimulants are

the first-line of treatment, frequently resulting not only in improvement in ADHD symptoms but also alleviating the symptoms of the comorbid anxiety disorder. Stimulant treatment is relatively safe and well-tolerated in ADHD with comorbid anxiety disorder. When the stimulant administration does not attenuate the severity of the comorbid anxiety disorder, a treatment that targets specifically the anxiety disorder should be added. This recommendation, however, might be challenged by the impressive efficacy of atomoxetine for both the ADHD and anxiety disorder symptoms. Adjunctive cognitive-behavior therapy for anxiety disorder symptoms is strongly recommended and is considered superior to medication alone. Other options include adding pharmacological treatment for the anxiety symptoms. In moderate and severe cases of comorbid Ads, selective serotonin reuptake inhibitors can be added to the stimulants, with the required caution

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Int J Environ Res Public Health. 2020;17:1-14.

THEORY OF MIND IN ADHD. A PROPOSAL TO IMPROVE WORKING MEMORY THROUGH THE STIMULATION OF THE THEORY OF MIND.

Lavigne R, Gonzalez-Cuenca A, Romero-Gonzalez M, et al.

The aim of this study was to investigate the relationships between Theory of Mind (ToM), Working Memory (WM), and Verbal Comprehension (VC). Performance of these variables was evaluated in 44 elementary students (6ΓÇô12 years) diagnosed with ADHD. Their performance in all variables was collected through the Neuropsychological Battery (NEPSY-II) and the Wechsler Intelligence Scale for Children IV. The results showed that fifty percent of the participants were below the 25th percentile in ToM and that this low performance was not related to age. In addition, analyses showed statistically significant relationships between WM, VC, and ToM. Analysis of the effect of WM and VC on ToM showed that only WM explained the variance in participant performance in ToM. These results led us to raise the need to include ToM among the skills to be stimulated in programs for the treatment of ADHD, accompanying other skills related to social adaptation that are usually included in such programs. Likewise, considering that ToM implies putting into practice skills such as considering different points of view, attending to relevant aspects of the context, making decisions, inferring mental states, and predicting behaviors, we believe that through the stimulation of ToM, WM would also be stimulated

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Int J Environ Res Public Health. 2020;17:1-17.

MATERNAL FERRITIN LEVELS DURING PREGNANCY AND ADHD SYMPTOMS IN 4-YEAR-OLD CHILDREN: RESULTS FROM THE INMA-INFANCIA Y MEDIO AMBIENTE (ENVIRONMENT AND CHILDHOOD) PROSPECTIVE BIRTH COHORT STUDY.

Santa-Marina L, Lertxundi N, Andiarena A, et al.

Erritin status during prenatal brain development may influence the risk of attention deficit and hyperactivity disorder (ADHD) symptoms in childhood. We investigated the association of maternal ferritin in pregnancy and ADHD-like symptoms in offspring. A total of 1095 mother-child pairs from three birth cohorts of the INMA Project (Spain) were studied. Maternal plasma ferritin in pregnancy was measured at 11.57 weeks of gestation. Children's ADHD-like symptoms at ages 4-5 years were assessed using the ADHD Rating Scale-IV. The count model of the zero-inflated Poisson regression model showed a significant inverse association between ferritin (continuous variable) and inattention, β = -0.19 (-0.32, -0.07), for boys. Comparing ferritin level by tertiles, significant differences were observed between the first tertile ([1.98, 20.92]) and the second ([20.92, 38.79]) and third tertiles ([38.79, 216.5]) (mg/L).The number of symptoms was lower for those in the third tertile, β = -0.3 (-0.55, -0.5), and for those in the second one, β = -0.37 (-0.6, -0.14). The model stratification by sex also showed this inverse association for boys only, β = -0.21 (-0.34, -0.08). No associations were found between ferritin level and hyperactivity or total ADHD symptoms. High ferritin levels during pregnancy show a protective association with child inattentive-type ADHD symptoms

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Ir J Psychol Med. 2020.

ROLLING OUT A MINDFULNESS-BASED STRESS REDUCTION INTERVENTION FOR PARENTS OF CHILDREN WITH ADHD: A FEASIBILITY STUDY.

Rice R, Ni Bhearra A, Kilbride K, et al.

Background: Attention-deficit/Hyperactivity Disorder (ADHD) is the single most frequent reason for attendance at Child and Adolescent Mental Health Services (CAMHS) in Ireland. Research has suggested that parents of children with ADHD experience more parenting stress than parents of non-clinical controls, yet routine treatment for ADHD rarely addresses parental well-being. Mindfulness-based interventions (MBIs) have been found to result in a reduction in parental stress.
Method: An adapted Mindfulness-Based Stress Reduction (MBSR) intervention was delivered to parents (n = 23) of children with ADHD recruited from CAMHS and ADHD Ireland.
Results: Following the intervention a significant improvement was documented within the social relationships domain of quality of life (WHOQOL-BREF) and a significant reduction on the child hyperactivity scale of the Strengths and Difficulties (SDQ) questionnaire.
Conclusion: This pilot study suggests that an MBSR intervention is both feasible and effective for parents whose children have ADHD. Larger scale studies need to be conducted before inclusion in routine CAMHS

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J Clin Psychiatry. 2020 Dec;81.

PATERNAL DEPRESSION AS A RISK FACTOR FOR NEURODEVELOPMENTAL DISORDERS IN OFFSPRING: IMPLICATIONS FOR MATERNAL DEPRESSION AND ITS TREATMENT DURING PREGNANCY.

Andrade C.

Many but not all studies suggest that gestational exposure to antidepressant drugs is associated with an increased risk of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in offspring. All of these studies have been observational in design, and observational research may suggest but cannot establish cause-effect relationships. In this context, a recent, large, population-based, observational study found that exposure to maternal depression before, during, or after pregnancy was each associated with an increased risk of ASD as well as ADHD. Strikingly, the same finding was obtained for paternal depression, as well, with mostly similar values for risk. If paternal depression before, during, or after pregnancy can increase the risk of ASD and ADHD in the offspring, it suggests that genetic variables, or environmental adversities engendered by behaviors related to paternal depression, may drive the risk for the adverse neurodevelopmental outcomes; some data exist to support this view. An understanding of these possibilities allows greater room for flexibility when considering the prescription of antidepressant drugs to depressed pregnant women

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J Law Med. 2020 Dec;28:282-88.

ADOLESCENT DRIVERS - ARE WE DOING ENOUGH?

Beran RG.

The minimum eligible driving age in Australia is 15 years 9 months, in the Australian Capital Territory, and 16 years elsewhere in the country. Approval to drive mandates: appropriate age; completing computer-generated testing; and monitored Graduated Licensing Schemes. The National Road Safety Strategy 2011-2020, released by the Australian Transport Council, either has been or is being implemented, including sponsorship of the Australasian College of Road Safety and establishing Cabinet representation for road safety. Factors include: driving ability; developmental factors; personality; demographics; general environment; and driving environment. The Graduated Licensing process has counted driver inexperience, but immaturity and peer pressure remain additional considerations. Complementing Graduated Licensing, parental and respected directives and guidance are essential to minimise negative peer pressure. Specific counselling and other targeted interventions may also assist. Attention Deficit Hyperactivity Disorder or adolescent epilepsy demand appropriate management to facilitate driving in accordance with the AUSTROADS Guidelines. A composite targeted approach is required to deal with adolescent road fatalities and injuries

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JMIR Mental Health. 2020;7.

USING MOBILE ELECTROENCEPHALOGRAPHY AND ACTIGRAPHY TO DIAGNOSE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: CASE-CONTROL COMPARISON STUDY.

Chu KC, Lu HK, Huang MC, et al.

Background: Children with attention-deficit/hyperactivity disorder (ADHD), a neurobehavioral disorder, display behaviors of inattention, hyperactivity, or impulsivity, which can affect their ability to learn and establish proper family and social relationships. Various tools are currently used by child and adolescent psychiatric clinics to diagnose, evaluate, and collect information and data. The tools allow professional physicians to assess if patients need further treatment, following a thorough and careful clinical diagnosis process.

Objective: We aim to determine potential indicators extracted from a mobile electroencephalography (EEG) device (Mindset; NeuroSky) and an actigraph (MotionWatch 8; CamNtech) and to validate them for diagnosis of ADHD. The 3 indicators are (1) attention, measured by the EEG; (2) meditation, measured by the EEG; and (3) activity, measured by the actigraph.

Methods: A total of 63 participants were recruited. The case group comprised 40 boys and 9 girls, while the control group comprised 5 boys and 9 girls. The groups were age matched. The test was divided into 3 stages-pretest, in-test, and posttest-with a testing duration of 20 minutes each. We used correlation analysis, repeated measures analysis of variance, and regression analysis to investigate which indicators can be used for ADHD diagnosis.

Results: With the EEG indicators, the analysis results show a significant correlation of attention with both hit reaction time (RT) interstimulus interval (ISI) change (r=-0.368; P=.003) and hit standard error (SE) ISI change (r=-0.336; P=.007). This indicates that the higher the attention of the participants, the smaller both the hit RT change and the hit SE ISI change. With the actigraph indicator, confidence index (r=0.352; P=.005), omissions (r=0.322; P=.01), hit RT SE (r=0.393; P=.001), and variability (r=0.351; P=.005) were significant. This indicates that the higher the activity amounts, the higher the impulsive behavior of the participants and the more target omissions in the continuous performance test (CPT). The results show that the participants with ADHD present a significant difference in activity amounts (P<0.001). The actigraph outperforms the EEG in screening ADHD.

Conclusions: When the participants with ADHD are stimulated under restricted conditions, they will present different amounts of activity than in unrestricted conditions due to participants' inability to exercise control over their concentration. This finding could be a new electronic physiological biomarker of ADHD. An actigraph can be used to detect the amount of activity exhibited and to help physicians diagnose the disorder in order to develop more objective, rapid auxiliary diagnostic tools

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J Bras Psiquiatr. 2020;69:247-54.

A CASE-CONTROL STUDY ABOUT AUTISM SPECTRUM DISORDER AND FAMILIAR HISTORY OF MENTAL DISORDERS.

Cezar IAM, Maia FA, Mangabeira G, et al.

Objective: To investigate the association between ASD and cooccurrences of psychiatric disorders among relatives of children/adolescents from northern Minas Gerais, Brazil.

Methods: A case-control study was performed, consisting of 248 individuals with ASD (cases) and 886 neurotypical controls. A semi-structured questionnaire and the multiple logistic regression model were adopted in the data analysis. To estimate the magnitude of associations, the crude and adjusted odds ratio (OR) was used.

Results: There was a positive and significant association between ASD and the presence of relatives with: any psychiatric disorder (OR: 3.68; 95% confidence interval [95%CI]: 2.68-5.05), with ASD (OR: 3,37; 95%CI: 2.09-5.43), with ADHD (OR: 2.19; 95%CI: 1.41-3.39) and epilepsy (OR: 1.91; 95%CI: 1.20-2.98).

Conclusion: This study suggests that children/adolescents with ASD have a higher chance of family history of psychiatric disorders, especially ASD, ADHD and epilepsy. These findings may have important implications for both Clinical Psychiatry and Public Health, as they can be used to form a clinical profile of people with psychiatric disorders who are at risk of having a family member with ASD

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J Abnorm Child Psychol. 2020 Oct;48:1265-77.

HETEROGENEOUS TRAJECTORIES OF PROBLEMATIC ALCOHOL USE, DEPRESSIVE SYMPTOMS, AND THEIR CO-OCCURRENCE IN YOUNG ADULTS WITH AND WITHOUT CHILDHOOD ADHD.

Wang FL, Pedersen SL, Devlin B, et al.

[Correction Notice: An Erratum for this article was reported in Vol 48(11) of Journal of Abnormal Child Psychology (see record [rid]2020-67861-001[/rid]). In the originally published article, the title of the article as a heading on the first page of the introduction was included, but this should be deleted. The corrected first paragraph is presented in the erratum.] Abstract The literature is inconsistent regarding whether childhood ADHD confers risk for adulthood problematic alcohol use, depressive symptoms, and their co-occurrence. These inconsistencies could be due to meaningful heterogeneity in the adulthood outcomes of children with ADHD that were obscured in traditional group-based analyses. The current study tested this possibility, as well as the contribution of adulthood ADHD symptom persistence, in order to clarify long-term risk in this population. Children diagnosed with ADHD and demographically-similar children without ADHD were followed longitudinally into adulthood and repeatedly assessed on heavy drinking, alcohol problems, and depressive symptoms from ages 21–29 (84.1% White (not Hispanic); 86.9% male; 51.2% childhood ADHD; 14.7% adulthood-persistent ADHD; N = 320). Group-based multi-trajectory modeling identified six groups with different combinations of trajectories across these variables. Heterogeneous longitudinal outcomes for those with ADHD were found. Some children with ADHD showed increased risk as typically predicted, with a higher likelihood of membership in a group with stable-moderate alcohol outcomes and stable-severe depression (adulthood persistent ADHD also predicted this group), whereas some children with ADHD were more likely to belong to a group with virtually no alcohol outcomes and low depression. Additionally, adulthood persistent ADHD predicted membership in a group with stable-severe alcohol outcomes and stable-moderate depression. Given the severity associated with co-occurring alcohol and depressive disorders, studies of early risk and protective factors and long-term outcomes for these disparate trajectory patterns are needed, particularly for those with childhood and persisting ADHD

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J Abnorm Child Psychol. 2020 Nov;48:1425-37.

DO PARENTS' ADHD SYMPTOMS AFFECT TREATMENT FOR THEIR CHILDREN? THE IMPACT OF PARENTAL ADHD ON ADHERENCE TO BEHAVIORAL PARENT TRAINING FOR CHILDHOOD ADHD.

Friedman LM, Dvorsky MR, McBurnett K, et al.

Nearly half of all youth with Attention-Deficit Hyperactivity Disorder (ADHD) have at least one parent who also meets criteria for the disorder, and intergenerational ADHD is a significant risk factor for poor outcomes following evidence-based behavioral parent training (BPT) programs. Given that BPT is predicated on consistent parental involvement, symptoms of ADHD in parents may be a significant barrier to effective engagement with BPT treatment. In the present investigation, we examine the effect of parental ADHD symptoms on BPT treatment engagement for children with ADHD-predominantly inattentive presentation (N = 148, ages 7–11). We examine the following parent- and clinician-rated treatment engagement domains: between-session skill adherence, in-session participation, perceived skill understanding, treatment-engagement attitudes, and session attendance. Parent- and clinician-rated between-session adherence was the only treatment engagement domain related significantly to parental ADHD symptoms. This finding was robust and remained even after accounting for symptoms of parental anxiety and depression, child ADHD symptom severity, and various sociodemographic factors (parental education level, household income, employment status, and being a single parent). These findings suggest that targeting parental ADHD symptoms in the context of parenting interventions may be a promising approach for improving adherence and treatment outcomes for BPT interventions

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J Abnorm Child Psychol. 2020 Oct;48:1251-64.

SUBGROUPS OF CHILDHOOD ADHD BASED ON TEMPERAMENT TRAITS AND COGNITION: CONCURRENT AND PREDICTIVE VALIDITY.

Goh PK, Lee CA, Martel MM, et al.

Efforts to parse ADHD's heterogeneity in the DSM system has generally relied on subtypes, or presentations, based on different symptom combinations. Promising recent work has suggested that biologically-relevant and clinically predictive subgroups may be identified via an alternative feature set based on either a) temperament traits or b) executive function measures. Yet, the potential additive ability of these domains for specifying ADHD sub-phenotypes remains unknown. We thus sought to determine whether temperament traits and executive function, together, could facilitate a more nuanced and clinically meaningful subgrouping of children with ADHD. Participants included 828 children aged 7–11 years (62% with ADHD, 38% female). Latent profile and community detection analyses using both temperament and cognitive input features provided support for a primarily temperament-based three-subgroup solution (i.e., 'Mild,' 'Irritable,' and 'Surgent'), although the distinction between Surgent and Mild subgroups may have been better explained as an ADHD symptom severity effect. There was also evidence of a five-subgroup solution, in which cognitive measures differentiated the Surgent subgroup into those with and without cognitive impairment. Cognitive measures also appeared to differentiate the Irritable subgroup based on severity, although differences in resulting subgroups appeared better explained via differences in negative affect and shyness. Subgroups within the five-subgroup solution meaningfully differed with respect to concurrent comorbidity. The utility of the five-subgroup solution for predicting comorbid diagnoses 2 years later was more limited. Additional work is needed to fully characterize the integration of cognitive and affective functioning in ADHD and their overlapping or additive value for clinical prediction

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J Abnorm Child Psychol. 2020 Nov;48:1439-53.

INTEGRATING TOBACCO PREVENTION SKILLS INTO AN EVIDENCE-BASED INTERVENTION FOR ADOLESCENTS WITH ADHD: RESULTS FROM A PILOT EFFICACY RANDOMIZED CONTROLLED TRIAL.

Corona R, Dvorsky MR, Romo S, et al.

Adolescents with attention-deficit/hyperactivity disorder (ADHD) are at high risk for tobacco use, but tobacco use prevention strategies are not regularly incorporated into evidence-based ADHD interventions. We conducted a pilot randomized-controlled trial to determine the feasibility of integrating tobacco use prevention skills into a behavioral treatment for ADHD and to provide preliminary efficacy data comparing a combined (ADHD + tobacco) intervention (N = 40) to an ADHD only intervention (N = 23) on tobacco risk outcomes. Sixty-three adolescents (72% male; 13–17 years) with ADHD and their caregivers were randomly assigned to condition and families were masked to condition. Parent and adolescent ratings were collected at baseline, immediate post-intervention, and at 3- and 9-month follow-up assessments. The combined intervention was (1) implemented with high fidelity (94%), (2) well received by parents and adolescents as evidenced by high levels of treatment attendance (82%) and satisfaction with the intervention, and (3) associated with parent- and adolescent-reported reductions in tobacco use risk. Relative to the ADHD intervention, the combined intervention buffered against increases in tobacco risk, including reduced intentions to smoke and maladaptive social normative beliefs, and increased parental control, family cohesion, and family communication about substance use. Effect sizes at post-treatment were in the small to moderate range. Overall, this study provides preliminary support for a parent-adolescent behavioral treatment supplemented with family-based tobacco prevention strategies. This approach targets families already in treatment for ADHD, reducing barriers that occur when families attend multi-session prevention programs in addition to ADHD treatment

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J Adolesc Health. 2020.

INVESTIGATING NEUROCOGNITIVE FUNCTIONING IN YOUTHS WITH EXTERNALIZING DISORDERS FROM THE PHILADELPHIA NEURODEVELOPMENTAL COHORT.

Honrath P, Kohls G, Moore TM, et al.

Purpose: Disruptive behavior disorders (DBD) and attention-deficit/hyperactivity disorder (ADHD) are externalizing disorders that frequently co-occur but also have distinct clinical characteristics. Identifying distinct neurocognitive phenotypes may help optimizing individual diagnosis and treatment of both disorders.
Methods: Using data from 6,517 children and adolescents from the Philadelphia Neurodevelopmental Cohort, we investigated diagnostic group (i.e., typically developing, DBD, ADHD, DBD + ADHD) and sex differences across various neurocognitive functions, as well as co-occurring psychiatric symptoms, while adjusting for various confounding factors.
Results: Neurocognitive deficits were associated with ADHD but not DBD. Co-occurring DBD in both girls and boys with ADHD did not appear to have an additive deteriorating effect on neurocognitive functioning. Task-specific sex differences were observed but did not interact with diagnostic group.
Conclusions: The findings of this study suggest that neurocognitive deficits in DBD seem to be largely driven by co-occurring ADHD and this applies equally to both sexes

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J Child Adolesc Ment Health. 2020;32:119-29.

INTERNALISING COMORBIDITIES IN PRIMARY SCHOOL CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): SEX AND AGE DIFFERENCES.

Mphahlele RM, Pillay B, Meyer A.

Objectives: Studies suggest that females with ADHD display more symptoms of anxiety and depression than their male counterparts. This study attempted to determine comorbid anxiety and depression in children with ADHD. Further, we aimed to establish whether there are sex and age differences in the expression of comorbid symptoms.
Method: The Beck Anxiety Inventory and Beck Depression scale from the Beck Youth Inventory were administered to 216 participants (108 with ADHD and 108 matched controls without ADHD symptoms). Participants included children aged 6 to 15 years, resident in the Limpopo Province of South Africa. The groups were compared for comorbid anxiety and depression symptoms and analysed as a function of sex and age.
Results: The ADHD group showed significantly more symptoms of anxiety and depression than the neurotypical control group. However, no sex differences were observed in the expression of anxiety symptoms. Nonetheless, girls did show significantly higher levels of depression than boys. No age differences were detected in respect of anxiety symptoms.
Conclusion: Children with ADHD displayed more symptoms of anxiety and depression compared to controls without ADHD. Age and sex did not affect anxiety symptoms, however girls showed more symptoms of depression than boys

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J Child Adolesc Psychopharmacol. 2020;30:580-89.

EFFICACY AND SAFETY OF MULTILAYER, EXTENDED-RELEASE METHYLPHENIDATE (PRC-063) IN CHILDREN 6-12 YEARS OF AGE WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A LABORATORY CLASSROOM STUDY.

Childress AC, Brams MN, Cutler AJ, et al.

Objective: To determine the safety and efficacy of PRC-063, a once-daily, multilayer, extended-release (ER) formulation of methylphenidate (MPH) hydrochloride, in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children in a randomized, double-blind, parallel group, dose-optimized, placebo-controlled phase 3 study.
Methods: Boys and girls aged 6-12 years diagnosed with ADHD were enrolled. During a 6-week, open-label, dose-optimization phase, subjects began treatment at 25 mg/day of PRC-063 and were titrated until an optimal dose (maximum 85 mg/day) was reached. During the double-blind period, subjects were randomized to receive treatment with their optimal dose of PRC-063 or placebo for 1 week. Efficacy was assessed in a laboratory classroom setting on the final day of the double-blind treatment using the Swanson, Kotkin, Agler,

M-Flynn, and Pelham (SKAMP) Rating Scale and Permanent Product Measure of Performance (PERMP). Safety was assessed measuring adverse events (AEs), vital signs, and electrocardiograms.
Results: The study was completed by 147 subjects. In the primary efficacy analysis, significant improvements were demonstrated with PRC-063 versus placebo ($p < 0.0001$) when SKAMP-Combined scores were averaged over the 13-hour full-day laboratory classroom (least squares mean difference = -8.6, 95% confidence interval = -10.6 to -6.6). Mean average PERMP-Total scores were also significantly improved with PRC-063 versus placebo at all time points postdose ($p < 0.01$). The onset of treatment effect was present by 1-hour postdose (the first time point measured) and duration of efficacy was up to and including 13 hours postdose. AEs reported in 5% of subjects during the dosing optimization period were decreased appetite, abdominal pain upper, affect lability, weight decreased, headache, irritability, and insomnia.
Conclusions: PRC-063 was effective in improving attention and reducing symptoms of ADHD versus placebo and had a rapid onset and extended duration of effect. AEs were consistent to those reported with other ER MPH treatments

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J Child Psychol Psychiatry. 2020 Oct;61:1160-68.

IMPACT OF SLEEP RESTRICTION ON AFFECTIVE FUNCTIONING IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Becker SP, Tamm L, Epstein JN, et al.

Background: Shortened sleep and affective disturbances are both prevalent in adolescents with attention-deficit/hyperactivity disorder (ADHD), yet the causal link between these domains has not been examined. This study investigated whether shortened sleep duration is causally linked to affective functioning in adolescents with ADHD.
Methods: Participants were 48 adolescents (75% male) aged 14–17 years with ADHD who successfully completed a three-week sleep protocol using an experimental crossover design. The protocol included a phase stabilization week, followed, in randomized counterbalanced order, by one week of sleep restriction (6.5 hr in bed) and one week of sleep extension (9.5 hr in bed). Sleep was monitored with objective actigraphy, and all participants included in this study obtained = 1 hr actigraphy-measured sleep duration during extension compared to restriction. Parents and adolescents provided daily ratings of positive and negative affect during the extension and restriction conditions. Ratings of affect, internalizing symptoms, and emotion regulation were collected at laboratory visits conducted at the end of each week.
Results: Both parents and adolescents reported greater depressive symptoms and lower positive affect during restriction compared to extension. Parents also reported greater negative affect and emotion dysregulation among adolescents during sleep restriction than extension. No effects were found for parent- or adolescent-reported anxiety symptoms or for adolescent-reported emotion regulation or negative affect.
Conclusions: Findings from this study provide the first evidence that shortened sleep duration is a causal contributor to the affect and mood disturbances frequently experienced by adolescents with ADHD, particularly as observed by parents. Targeting sleep may be important to reduce affective disturbances in adolescents with ADHD

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J Child Psychol Psychiatry. 2020 Nov;61:1173-83.

RESEARCH REVIEW: THE STRENGTH OF THE GENETIC OVERLAP BETWEEN ADHD AND OTHER PSYCHIATRIC SYMPTOMS— A SYSTEMATIC REVIEW AND META-ANALYSIS.

Andersson A, Tuvblad C, Chen Q, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) frequently co-occurs with other psychiatric disorders. Twin studies have established that these co-occurrences are in part due to shared genetic risks. However, the strength of these genetic overlaps and the potential heterogeneity accounted for by type of psychiatric symptoms, age, and methods of assessment remain unclear. We conducted a systematic review to fill this gap.
Methods: We searched PubMed, PsycINFO, Embase, and Web of Science until March 07, 2019. Genetic correlations (rg) were used as effect size measures.

Results: A total of 31 independent studies fulfilled the inclusion criteria. The pooled estimates showed that the associations between ADHD and other psychiatric symptoms were partly explained by shared genetic factors, with a pooled genetic correlation of 0.50, 95% confidence interval: 0.46–0.60. The genetic correlations (rg) between ADHD and externalizing (rg = .49 [0.37–0.61]), internalizing (rg = .50 [0.39–0.69]), and neurodevelopmental (rg = .56 [0.47–0.66]) symptoms were similar in magnitude. The genetic correlations in childhood and adulthood were rg = .53 (0.43–0.63) and rg = .51 (0.44–0.56), respectively. For methods of assessment, the genetic correlations were also similar in strength, self-reports rg = .52 (0.47–0.58), other informants rg = .55 (0.41–0.69), and combined raters rg = .50 (0.33–0.65).
Conclusions: These findings indicate that the co-occurrence of externalizing, internalizing, and neurodevelopmental disorder symptoms in individuals with ADHD symptoms in part is due to a shared genetic risk

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J Child Psychol Psychiatry. 2020 Nov;61:1234-42.

ASSOCIATIONS BETWEEN ADHD AND EMOTIONAL PROBLEMS FROM CHILDHOOD TO YOUNG ADULTHOOD: A LONGITUDINAL GENETICALLY SENSITIVE STUDY.

Stern A, Agnew-Blais JC, Danese A, et al.

Background: Attention deficit/hyperactivity disorder (ADHD) is associated with emotional problems, and their co-occurrence often leads to worse outcomes. We investigated the developmental associations between ADHD and emotional problems from childhood to early adolescence and examined the genetic and environmental contributions to their developmental link. We further tested whether this developmental association remained across the transition to young adulthood.
Methods: We used data from the Environmental Risk (E-Risk) Longitudinal Twin Study, a cohort of 2,232 British twins. In childhood, ADHD and emotional problems were assessed at ages 5, 7, 10 and 12 with mothers' and teachers' reports. At age 18, we used self-reported symptoms according to DSM-5 criteria for ADHD, and DSM-IV for anxiety and depression.
Results: Longitudinal analyses showed that earlier ADHD was associated with later emotional problems consistently across childhood. However, earlier emotional problems were not associated with later ADHD symptoms. The developmental association between ADHD and later emotional problems in childhood was entirely explained by common genetic factors. Consistent with results in childhood, earlier symptoms of ADHD were associated with later emotional problems during the transition to young adulthood.
Conclusions: Our findings demonstrate that ADHD symptoms are predictors of the development of emotional problems, from childhood up to young adulthood, through shared genetic influences. Interventions targeting ADHD symptoms might prevent the development of emotional problems. Clinicians treating youth with ADHD must be aware of their risk for developing emotional problems and ought to assess, monitor and treat emotional problems alongside ADHD symptoms from childhood to adulthood

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J Clin Diagn Res. 2020;14:VR01-VR05.

STUDY OF IRON PROFILE AND EFFECT OF ORAL IRON SUPPLEMENTATION IN PATIENTS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN RURAL TERTIARY HEALTH CARE CENTRE FROM CENTRAL INDIA: A CASE SERIES.

Ghogare AS, John S, Patil PS, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a neuropsychiatric condition affecting the preschoolers, children, adolescents and adults globally. Dopamine synthesis is dependent on availability of iron in the body and dopamine deficit theory is the widely accepted ADHD causation theory. So, serum iron levels are important to watch out for in patients suffering from ADHD. This article describes six cases to emphasise the importance of diagnosing and treating underlying Iron Deficiency (ID) state with oral iron supplementation for effective management of patients suffering from ADHD. All the six cases which were given oral iron supplementation along with methylphenidate had shown improvement in inattentive domain and in hyperactivity-impulsivity domain at both home as well as school settings. They were given doses of methylphenidate and oral iron supplement as per the recommended body weight. Their parents and teachers were asked to mark the responses on Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) 26 item parent and teacher rating scale respectively. Scores on SNAP-IV were recorded at the first visit and after three

months of treatment. Scores were then evaluated on both occasions for evidence of improvement in ADHD symptoms

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J Clin Child Adolesc Psychol. 2020 Nov;49:912-29.

EXAMINING ODD/ADHD SYMPTOM DIMENSIONS AS PREDICTORS OF SOCIAL, EMOTIONAL, AND ACADEMIC TRAJECTORIES IN MIDDLE CHILDHOOD.

Evans SC, Cooley JL, Blossom JB, et al.

The goal of this article is to investigate the symptom dimensions of oppositional defiant disorder (ODD; irritability, defiance) and attention deficit/hyperactivity disorder (ADHD; inattention, hyperactivity-impulsivity) as predictors of academic performance, depressive symptoms, and peer functioning in middle childhood. Children (N = 346; 51% female) were assessed via teacher-report on measures of ODD/ADHD symptoms at baseline (Grades K–2) and academic performance, depressive symptoms, peer rejection, and victimization on 7 occasions over 4 school years (K–2 through 3–5). Self-report and grade point average data collected in Grades 3–5 served as converging outcome measures. Latent growth curve and multiple regression models were estimated using a hierarchical/sensitivity approach to assess robustness and specificity of effects. Irritability predicted higher baseline depressive symptoms, peer rejection, and victimization, whereas defiance predicted higher baseline peer rejection; however, none of these ODD-related effects persisted 3 years later to Grades 3–5. In contrast, inattention predicted persistently poorer academic performance, persistently higher depressive symptoms, and higher baseline victimization; hyperactivity-impulsivity predicted subsequent peer rejection and victimization in Grades 3–5. In converging models, only inattention emerged as a robust predictor of 3-year outcomes (viz., grade point average, depressive symptoms, peer rejection, and relational victimization). Broadly, ODD dimensions—particularly irritability—may be linked to acute disturbances in social-emotional functioning in school-age children, whereas ADHD dimensions may predict more persistent patterns of peer, affective, and academic problems. By examining all 4 ODD/ADHD symptom dimensions simultaneously, the present analyses offer clarity and specificity regarding which dimensions affect what outcomes, and when. Findings underscore the importance of multidimensional approaches to research, assessment, and intervention

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J Clin Med. 2020;9:1-17.

AUTISM SPECTRUM DISORDER AND DISRUPTIVE BEHAVIOR DISORDERS COMORBIDITIES DELINEATE CLINICAL PHENOTYPES IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER: NOVEL INSIGHTS FROM THE ASSESSMENT OF PSYCHOPATHOLOGICAL AND NEUROPSYCHOLOGICAL PROFILES.

Sesso G, Cristofani C, Berloffa S, et al.

Although childhood-onset psychiatric disorders are often considered as distinct and separate from each other, they frequently co-occur, with partial overlapping symptomatology. Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) commonly co-occur with each other and with other mental disorders, particularly disruptive behavior disorders, oppositional defiant disorder/conduct disorder (ODD/CD). Whether these associated comorbidities represent a spectrum of distinct clinical phenotypes is matter of research. The aim of our study was to describe the clinical phenotypes of youths with ADHD with and without ASD and/or ODD/CD, based on neuropsychological and psychopathological variables. One-hundred fifty-one participants with ADHD were prospectively recruited and assigned to four clinical groups, and assessed by means of parent-reported questionnaires, the child behavior checklist and the behavior rating inventory of executive functions. The ADHD alone group presented a greater impairment in metacognitive executive functions, ADHD+ASD patients presented higher internalizing problems and deficits in Shifting tasks, and ADHD+ODD/CD subjects presented emotional-behavioral dysregulation. Moreover, ADHD+ASD+ODD/CD individuals exhibited greater internalizing and externalizing problems, and specific neuropsychological impairments in the domains of emotional regulation. Our study supports the need to implement the evaluation of the psychopathological and neuropsychological functioning profiles, and to characterize specific endophenotypes for a finely customized establishment of treatment strategies

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J Mol Neurosci. 2020.

UBIQUINONE LEVELS AS A MARKER OF ANTIOXIDANT SYSTEM IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Karagaz YS, et al.

The aims of this study are to compare serum ubiquinone levels in children with attention deficit hyperactivity disorder (ADHD) with healthy controls and to investigate the correlation between ubiquinone levels of children with ADHD and their ADHD symptoms. Twenty-seven children who are 6ΓÇô12-áyears old age with attention deficit hyperactivity disorder having clinically normal intelligence and 23 children with clinically normal intelligence and no psychiatric disorder of similar age and sex who referred to Ankara University School of Medicine Department of Child and Adolescent Psychiatry were included in this study. All children were diagnosed by same researcher using the Semi-Structured Clinical Interview for DSM-IV Scale for Affective Disorders and Schizophrenia Interview for School Children-Now and for the Life-Long Version (K-SADS-PL). Parents and teachers of the children completed the Conners Parent Rating Scale Revised Long Form (CPRS-LF) and Conners Teacher Rating Scale Revised Long Form (CTRS-LF). There were no statistically significant differences regarding the age, gender, and sociodemographic data of the groups. Serum ubiquinone levels of the ADHD group were significantly lower than the control group. We did not find any correlation between ubiquinone levels and clinical values. Since ubiquinone levels are lower in children with ADHD compared with controls, we suggest that decreased antioxidant levels may play a role in ADHD pathogenesis by disrupting oxidative balance

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J Neurodevelopmental Disord. 2020;12.

MEDICATIONS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN INDIVIDUALS WITH OR WITHOUT COEXISTING AUTISM SPECTRUM DISORDER: ANALYSIS OF DATA FROM THE SWEDISH PRESCRIBED DRUG REGISTER.

Johansson V, Sandin S, Chang Z, et al.

Background: Clinical studies found that medication for attention-deficit/hyperactivity disorder (ADHD) is effective in coexisting autism spectrum disorder (ASD), but current research is based on small clinical studies mainly performed on children or adolescents. We here use register data to examine if individuals with ADHD and coexisting ASD present differences in the prescribing patterns of ADHD medication when compared to individuals with pure ADHD.

Methods: Data with information on filled prescriptions and diagnoses was retrieved from the Swedish Prescribed Drug Register and the National Patient Register. We identified 34,374 individuals with pure ADHD and 5012 individuals with ADHD and coexisting ASD, aged between 3 and 80 years. The first treatment episode with ADHD medications (2 filled prescriptions within 90 days) and daily doses of methylphenidate during a 3-year period was measured. Odds ratios (ORs) were calculated for the likelihood of being prescribed ADHD medication in individuals with and without ASD and Wilcoxon rank-sum test was used to compare group differences in dose per day.

Results: Individuals with ADHD and coexisting ASD were less likely to start continuous treatment with ADHD medication (ADHD 80.5%; ADHD with ASD 76.2%; OR, 0.80; 95% confidence interval, 0.75-0.86), were less likely to be prescribed methylphenidate, and were more commonly prescribed second line treatments such as dexamphetamine, amphetamine, or modafinil. No group difference was observed for atomoxetine. In adults with ADHD and coexisting ASD, methylphenidate was prescribed in lower daily doses over three years as compared to individuals with pure ADHD.

Conclusions: The findings indicate that there are differences in the medical treatment of individuals with or without ASD. If these differences are due to different medication responses in ASD or due to other factors such as clinicians perceptions of medication effects in patients with ASD, needs to be further studied

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J Pediatr Psychol. 2020 Oct;45:1074-83.

MINDFUL PARENTING BEHAVIORS AND EMOTIONAL SELF-REGULATION IN CHILDREN WITH ADHD AND CONTROLS.

Evans S, Bhide S, Quek J, et al.

Objective: Mindfulness is defined as paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally and these behaviors can be applied to parenting. Thus far, it is not understood whether

mindful parenting (MP) differs in parents of children with and without attention-deficit/hyperactivity disorder (ADHD), and how MP relates to other parenting practices and children's self-regulation.
Methods: This study examined the relationships between MP, parenting behaviors and children's self-regulation in 120 families with child ADHD (85% male; mean age = 11.93) and 105 control families (62% male; mean age = 11.98). Parents completed measures of MP (Interpersonal Mindfulness in Parenting Scale), parenting behaviors (parenting warmth, consistency, and anger assessed with the Longitudinal Study of Australian Children measures), psychological distress (Kessler 6), and children's self-regulation (Social Skills Improvement System—self-control subscale).
Results: When compared with controls, parents of children with ADHD reported significantly lower MP. Higher MP was associated with lower levels of parent psychological distress, higher levels of parenting warmth and consistency, lower levels of parenting anger, and higher child emotion self-regulation in both groups. In mediation analyses, MP was indirectly associated with child emotion self-regulation through lower parenting anger, with the model accounting for 55% of the variance in child self-regulation.
Conclusions: MP is a useful construct for understanding parent behaviors, and children's emotion self-regulation

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J Psychopathol Behav Assess. 2020.
THE ACCURACY OF RETROSPECTIVE RECALL OF CHILDHOOD ADHD: RESULTS FROM A LONGITUDINAL STUDY.
von Wirth E, Mandler J, Breuer D, et al.
Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset condition that may continue into adulthood. When assessing adult patients, clinicians usually rely on retrospective reports of childhood symptoms to evaluate the age-of-onset criterion. Since inaccurate symptom recall may impede the diagnosis and treatment of ADHD, knowledge about the factors influencing retrospective reports is needed. This longitudinal study investigated (a) the accuracy of retrospective symptom ratings by adult participants with a childhood diagnosis of ADHD (self-ratings) and parents or significant others (proxy ratings), and (b) the influence of current ADHD symptom severity and ADHD-associated impairments on retrospective symptom ratings. Participants (N-á= 55) were members of the Cologne Adaptive Multimodal Treatment (CAMT) study who had been referred and treated for ADHD in childhood and were reassessed in adulthood (average age 27-áyears). ParticipantsΓÇÖ retrospective self-ratings were substantially lower than, and did not correlate with, parentsΓÇÖ ADHD symptom ratings provided at study entry, while retrospective symptom ratings provided by proxy respondents correlated moderately with parentsΓÇÖ childhood ratings. In addition, participants were more likely to underreport childhood symptoms (79%) and more frequently denied the presence of three or more childhood symptoms (17%) compared to proxy respondents (65% underreporting, 10% false-negative recall). Proxy respondentsΓÇÖ symptom recall was best predicted by childhood ADHD, while participantsΓÇÖ symptom recall was best predicted by current ADHD symptom severity. ADHD-associated impairments were not correlated with symptom recall after controlling for childhood ADHD. Together, these findings suggest a recall bias in adult patients and question the validity of retrospective reports, even in clinical samples

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J Psychopharmacol. 2020.
PHARMACOTHERAPY OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN INDIVIDUALS WITH AUTISM SPECTRUM DISORDER: A SYSTEMATIC REVIEW OF THE LITERATURE.
Joshi G, Wilens T, Firmin ES, et al.
Aim: To assess the empirical evidence for the treatment of attention deficit/hyperactivity disorder (ADHD) in populations with autism spectrum disorder (ASD).
Methods: A systemic PubMed, PsychINFO, Embase, and Medline database search of peer-reviewed literature was conducted. Included in the review were controlled trials published in English with sample sizes Γ®¥10 participants examining the safety and efficacy of anti-ADHD medication in ASD populations. Data was extracted on relevant variables of study design, demographics, associated psychopathology, medication dose, efficacy, and tolerability.

Results: Nine controlled trials met the inclusion and exclusion criteria: five with methylphenidate, three with atomoxetine, and one with guanfacine. Sample sizes ranged from 10 to 128 with 430 children participating across all the trials. In all the trials, treatment response was significantly superior to placebo. However, almost all trials assessed only hyperactivity, and most included only participants with intellectual disability with high levels of irritability. None of the trials distinguished agitation from hyperactivity. The response on hyperactivity for methylphenidate and atomoxetine was less than that observed in the neurotypical population; however, the response for guanfacine surpassed results observed in neurotypical populations. Treatment-emergent mood lability (i.e. mood dysregulation and mood-related adverse events) was frequently associated with methylphenidate and guanfacine treatments. Worse treatment outcomes were associated with individuals with lower intellectual capability compared with those with higher IQs.
Conclusions: here is a scarcity of controlled trials examining ADHD treatments in ASD populations, particularly in intellectually capable individuals with ASD and in adults. Response to ADHD medications in ASD were adversely moderated by the presence of intellectual disability and mood lability

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J Am Acad Child Adolesc Psychiatry. 2017;56:436-44.

IMPACT OF A COMMON GENETIC VARIATION ASSOCIATED WITH PUTAMEN VOLUME ON NEURAL MECHANISMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Xu B, Jia T, Macare C, et al.

Objective In a recent genomewide association study of subcortical brain volumes, a common genetic variation at rs945270 was identified as having the strongest effect on putamen volume, a brain measurement linked to familial risk for attention-deficit/hyperactivity disorder (ADHD). To determine whether rs945270 might be a genetic determinant of ADHD, its effects on ADHD-related symptoms and neural mechanisms of ADHD, such as response inhibition and reward sensitivity, were explored.
Method A large population sample of 1,834 14-year-old adolescents was used to test the effects of rs945270 on ADHD symptoms assessed through the Strengths and Difficulties Questionnaire and region-of-interest analyses of putamen activation by functional magnetic resonance imaging using the stop signal and monetary incentive delay tasks, assessing response inhibition and reward sensitivity, respectively.
Results There was a significant link between rs945270 and ADHD symptom scores, with the C allele associated with lower symptom scores, most notably hyperactivity. In addition, there were sex-specific effects of this variant on the brain. In boys, the C allele was associated with lower putamen activity during successful response inhibition, a brain response that was not associated with ADHD symptoms. In girls, putamen activation during reward anticipation increased with the number of C alleles, most significantly in the right putamen. Remarkably, right putamen activation during reward anticipation tended to negatively correlate with ADHD symptoms.
Conclusion These results indicate that rs945270 might contribute to the genetic risk of ADHD partly through its effects on hyperactivity and reward processing in girls

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J Am Acad Child Adolesc Psychiatry. 2020.

DOUBLE-BLIND PLACEBO-CONTROLLED RANDOMIZED CLINICAL TRIAL OF NEUROFEEDBACK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH 13-MONTH FOLLOW-UP.

Arnold LE, Arns M, Barterian J, et al.

Objective: To determine whether theta/beta-ratio (TBR) electroencephalographic biofeedback (neurofeedback [NF]) has a specific effect on attention-deficit/hyperactivity disorder (ADHD) beyond nonspecific benefit.
Method: In a 2-site double-blind randomized clinical trial, 144 children aged 7 to 10 years with rigorously diagnosed moderate/severe ADHD and theta/beta-ratio (TBR) 4.5 were randomized 3:2 to deliberate TBR downtraining versus a control of equal duration, intensity, and appearance. Two early dropouts left 142 children for modified intent-to-treat analysis. The control used prerecorded electroencephalograms with the participant's artifacts superimposed. Treatment was programmed via Internet by an off-site statistician-guided co-investigator. Fidelity was 98.7% by trainers/therapists and 93.2% by NF expert monitor. The

primary outcome was parent- and teacher-rated inattention; analysis was mixed-effects regression. Because the expense and effort of NF can be justified only by enduring benefit, follow-ups were integrated.
Results: Blinding was excellent. Although both groups showed significant improvement (p <.001, d = 1.5) in parent/teacher-rated inattention from baseline to treatment end and 13-month follow-up, NF was not significantly superior to the control condition at either time point on this primary outcome (d = 0.01, p =.965 at treatment end; d = 0.23, p =.412 at 13-month follow-up). Responders (Clinical Global Impression-Improvement [CGI-I] = 1Γ 2) were 61% of NF and 54% of controls (p =.36). Adverse events were distributed proportionally between treatments. The 13-month follow-up found nonsignificant improvement from treatment end for NF (d = 0.1), with mild deterioration for controls (d = 0.07). NF required significantly less medication at follow-up (p =.012). Conclusion: This study does not support a specific effect of deliberate TBR NF at either treatment end or 13-month follow-up. Participants will be reassessed at 25-month follow-up.
Clinical trial registration information: Double-Blind 2-Site Randomized Clinical Trial of Neurofeedback for ADHD; https://clinicaltrials.gov/; NCT02251743

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J Am Acad Child Adolesc Psychiatry. 2021;60:61-75.
SYSTEMATIC REVIEW AND META-ANALYSIS: RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDIES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Cortese S, Aoki YY, Itahashi T, et al.
Objective: To conduct a meta-analysis of resting-state functional magnetic resonance imaging (R-fMRI) studies in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and in adults with ADHD to assess spatial convergence of findings from available studies.
Method: Based on a preregistered protocol in PROSPERO (CRD42019119553), a large set of databases were searched up to April 9, 2019, with no language or article type restrictions. Study authors were systematically contacted for additional unpublished information/data. Resting-state functional magnetic resonance imaging studies using seed-based connectivity (SBC) or any other method (non-SBC) reporting whole-brain results of group comparisons between participants with ADHD and typically developing controls were eligible. Voxelwise meta-analysis via activation likelihood estimation with cluster-level familywise error (voxel-level: p < .001; cluster-level: p < .05) was used.
Results: Thirty studies (18 SBC and 12 non-SBC), comprising 1,978 participants (1,094 with ADHD; 884 controls) were retained. The meta-analysis focused on SBC studies found no significant spatial convergence of ADHD-related hyperconnectivity or hypoconnectivity across studies. This nonsignificant finding remained after integrating 12 non-SBC studies into the main analysis and in sensitivity analyses limited to studies including only children or only nonΓÇômedication-na+»ve patients.
Conclusion: The lack of significant spatial convergence may be accounted for by heterogeneity in study participants, experimental procedures, and analytic flexibility as well as in ADHD pathophysiology. Alongside other neuroimaging meta-analyses in other psychiatric conditions, the present results should inform the conduct and publication of future neuroimaging studies of psychiatric disorders

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J Int Neuropsychol Soc. 2020 Nov;26:1019-27.
IS THERE A FUNCTIONAL RELATION BETWEEN SET SHIFTING AND HYPERACTIVITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)?
Irwin LN, Groves NB, Soto EF, et al.
Objective: Replicated evidence indicates that children with attention-deficit/hyperactivity disorder (ADHD) show disproportionate increases in hyperactivity/physical movement when their underdeveloped executive functions are taxed. However, our understanding of hyperactivity's relation with set shifting is limited, which is surprising given set shifting's importance as the third core executive function alongside working memory and inhibition. The aim of this study was to experimentally examine the effect of imposing set shifting and inhibition demands on objectively measured activity level in children with and without ADHD.
Method: The current study used a validated experimental manipulation to differentially evoke set shifting, inhibition, and general cognitive demands in a carefully phenotyped sample of children aged 8–13 years with

ADHD (n = 43) and without ADHD (n = 34). Activity level was sampled during each task using multiple, high-precision actigraphs; total hyperactivity scores (THS) were calculated.
Results: Results of the 2 × 5 Bayesian ANOVA for hyperactivity revealed strong support for a main effect of task (BF10 = 1.79 × 10¹8, p < .001, ² = .20), such that children upregulated their physical movement in response to general cognitive demands and set shifting demands specifically, but not in response to increased inhibition demands. Importantly, however, this manipulation did not disproportionally increase hyperactivity in ADHD as demonstrated by significant evidence against the task × group interaction (BF01 = 18.21, p = .48, ² = .002).
Conclusions: Inhibition demands do not cause children to upregulate their physical activity. Set shifting produces reliable increases in children's physical movement/hyperactivity over and above the effects of general cognitive demands but cannot specifically explain hyperactivity in children with ADHD

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Koomesh. 2020;23:49-55.

EFFECT OF METHYLPHENIDATE ON SLEEP STATUS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Soltanifar A, Soleimani M, Moharari F, et al.
Introduction: Sleep disorders are one of the most important problems in children with attention deficit hyperactivity disorder. Methylphenidate has different effects on the sleep parameters of affected children. The aim of this study was to evaluate the sleep status of children with attention deficit hyperactivity disorder (ADHD) before and after methylphenidate use.
Materials and Methods: This descriptive-analytical study was performed on 34 children (5 to 12 years) diagnosed with ADHD who referred to Ibne-Sina hospital in Mashhad city (Iran). The children were treated with methylphenidate for four weeks. Parents completed sleep status of children before and after the treatment by Children's Sleep Habits Questionnaire (CSHQ). The mean score of children's sleep status in 8 subscales was compared.
Results: The results showed that most of the children were boys (60%) and their mean age was 8.35-¦2.83 years. The mean score of sleep status of children before the treatment was 54.47-¦7.22 and after the treatment with methylphenidate was 50.38-¦6.19 which was significant (P<0.001). The sleep status of children improved after treatment with methylphenidate on the subscales of resistance to sleep (P<0.001), anxiety habits (P=0.001), waking up at night (P=0.002), and daytime sleepiness (P=0.001).
Conclusion: The findings of this study showed that although methylphenidate consumption improves the sleep status of children with attention deficit hyperactivity disorder, it is not effective in all sleep subscales. Conclusively, assessing the child's characteristics and sleep status before starting the treatment can be help to physicians to adjusting the dose to improve child's sleep and using the other methods of improving sleep

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Med Hypotheses. 2020;145.

IS CONTRAST SENSITIVITY A PHYSIOLOGICAL MARKER IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER?
Danmez YE, et al.
Attention-deficit hyperactivity disorder (ADHD) is one of the most common childhood-onset psychiatric disorders. Although the etiology is complex and has not yet been clarified, dopamine is thought to play a role in the etiology. Methylphenidate (MPH) is a psychostimulant drug used as first-line treatment for ADHD and it inhibits dopamine and norepinephrine reuptake transporters. Dopamine also has an effect on retina and contrast sensitivity. Despite evidence indicating the effects of dopamine on contrast sensitivity, the results of studies examining contrast sensitivity in ADHD patients are inconsistent. Also, no studies have been encountered examining the possible effect of MPH on contrast sensitivity. The hypotheses of this study are that children with ADHD who have not used MPH will have lower contrast sensitivity levels than the members of the control group, that contrast sensitivity levels increase after the use of MPH, and that contrast sensitivity is a potential physiological marker for ADHD. The study was conducted with 30 children with ADHD and 30 children without ADHD. Psychiatric evaluations of the participants were conducted with the Schedule for Affective Disorders and Schizophrenia for School Age ChildrenΓÇôPresent and LifetimeΓÇöTurkish version, Conner's Parent Rating ScaleΓÇôRevised Short form and the Turgay DSM-IV-based Child and Adolescent Behavioral Disorders Screening and Rating Scale. Photopic contrast sensitivity was measured using the

Functional Acuity Contrast Test (FACT). Results showed that FACT mean values of the control group were significantly higher than those of the ADHD group (pre-treatment) in all spatial frequencies. In four spatial frequencies (CPD 1.5, 3, 12 and 18), the FACT mean values of the control group were significantly higher than the ADHD group (during the OROS-MPH treatment). At all spatial frequencies, the mean values of the ADHD group during the OROS-MPH treatment were significantly higher than before the OROS-MPH treatment. In conclusion, the present study showed that contrast sensitivity is low in children with ADHD and increases significantly after OROS-MPH medication, but still did not reach the levels of the children without ADHD. Our findings suggest that contrast sensitivity may be a potential physiological marker in ADHD

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Medico-Legal Update. 2020;20:200-05.

ASSESSMENT OF KNOWLEDGE AND ATTITUDES TOWARD ATTENTION DEFICIT/HYPERACTIVITY DISORDERS AMONG PRIMARY SCHOOLS' TEACHERS IN AL-NAJAF CITY.

Al-Amarei HM, Mohamed SH.

Attention deficit/hyperactivity disorder (ADHD) is one of the common emotional, cognitive and behavioral disorder in primary school children and it affects on children socially and academically, welfare . an important role in identify of AD/HD due to their daily contact with students in a range of related situations. Basically, elementary school teachersΓÇÖ need to Knowledge and enhance their positive attitude on pupils with ADHD to create a positive learning environment. Consequently, the present investigator made an insight into the aim of the study as follows: to assess teachersΓÇÖ Knowledge and attitude toward pupils with ADHD and to find out the correlation between knowledge of primary school teachersΓÇÖ regarding ADHD. As well as to find out the relationship between the teachersΓÇÖ knowledge and their demographic data. The study was conducted on at governmental primary schools at Al-Najaf City, Iraq. A total of the (10) governmental primary schools selected randomly from total (253) governmental primary schools in Al-Najaf City. A purposive (non-probability) sample of (70) primary school teachersΓÇÖ were selected from the candidate schools were included in the present study. During the period of 1st September 2018 to 30th May 2019. The data was collected by questionnaire which consisted of two parts, first part consists socio demographic sheet. Second part is about knowledge and attitude which consist of (53) items scale of teachersΓÇÖ knowledge and attitude about children with ADHD . In the present study. Findings revealed a poor in teachersΓÇÖ knowledge of as well as satisfied responses attitude (negative)to pupils with AD/HD among elementary school teachers. Fondly the our main findings indicate that there is a significant positive correlation between the teachersΓÇÖ knowledge and the teachers attitude toward children with AD/HD. And there is a significant relationship between demographic characteristics and do of knowledge for the sample such as: (age,education level, years of experience,main sources of information). Thus, it is recommended for responsible parties to notes the need for greater efforts to provide teacher training specifically in identifying and managing children with ADHD

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Neurosci Behav Physiol. 2020;50:1105-11.

COMBINED INFLUENCES OF GENETIC FACTORS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER ON THE DEVELOPMENT OF DEPENDENCE ON SYNTHETIC CANNABINOIDS.

Gareeva AE, Sharafiev RR, Akhmetova EA, et al.

Objectives. To create a complex model of the individual risk of developing dependence on synthetic cannabinoids taking account of the combined influences of genetic predisposition and attention deficit hypera-ctivity disorder (ADHD).

Materials and methods. A total of 146 male adolescents consuming synthetic cannabinoids and 136 healthy subjects (controls) were observed. Genetic studies assessed cases with the combination of these dependencies with ADHD. DNA was collected and six polymorphic loci of genes of the dopaminergic and serotoninergic systems were determined; results were analyzed using a series of special statistical methods.

Results and conclusions. These data demonstrate the important role of the dopaminergic and serotoninergic systems in the pathogenesis of dependence on psychoactive substances and the significance of changes in the nucleotide sequences of the DRD2, SLC6A3, and HTR2A genes in the development of dependence on synthetic cannabinoids in males with ADHD

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Neurosci Biobehav Rev. 2020.

LONG TERM METHYLPHENIDATE EXPOSURE AND GROWTH IN CHILDREN AND ADOLESCENTS WITH ADHD. A SYSTEMATIC REVIEW AND META-ANALYSIS.

Carucci S, Balia C, Gagliano A, et al.

Background: Methylphenidate (MPH) is an efficacious treatment for ADHD but concerns have been raised about potential adverse effects of extended treatment on growth.

Objectives: To systematically review the literature, up to December 2018, conducting a meta-analysis of association of long-term (> six months) MPH exposure with height, weight and timing of puberty.

Results: Eighteen studies (ADHD n = 4868) were included in the meta-analysis. MPH was associated with consistent statistically significant pre-post difference for both height (SMD = 0.27, 95% CI 0.16-0.38, p < 0.0001) and weight (SMD = 0.33, 95% CI 0.22-0.44, p < 0.0001) Z scores, with prominent impact on weight during the first 12 months and on height within the first 24-30 months. No significant effects of dose, formulation, age and drug-naïve condition as clinical moderators were found. Data on timing of puberty are currently limited.

Conclusions: Long-term treatment with MPH can result in reduction in height and weight. However, effect sizes are small with possible minimal clinical impact. Long-term prospective studies may help to clarify the underlying biological drivers and specific mediators and moderators

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Neurosci Biobehav Rev. 2021;120:236-48.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD), ANTISOCIALITY AND DELINQUENT BEHAVIOR OVER THE LIFESPAN.

Retz W, Ginsberg Y, Turner D, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is closely linked to the development of conduct problems during socialization in early life and to an increased risk for antisocial activities and delinquency over the lifespan. The interaction between ADHD and common comorbid disorders like substance use disorders as well as changing environmental conditions could mediate the course of antisocial and delinquent behavior with increasing age. However, this complex interaction is only partially understood so far. This review presents current knowledge about the association of ADHD with antisociality and the development of delinquent behavior. Thereby, the relationships between ADHD, conduct disorder and antisocial personality disorder in offenders are discussed, as well as the impact of comorbid psychiatric disorders and psychosocial conditions on offending behavior. Also, treatment studies in offender populations with ADHD are presented. Although our understanding of the role of ADHD in the development of criminal behavior has substantially improved during the last two decades, more research is needed to further elucidate the mechanisms generating unfavorable outcomes and to engender adequate treatment strategies for this population at risk. Moreover, more attention is needed on children with conduct problems in order to avoid antisocial or delinquent behaviors over the lifespan

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Nord J Psychiatry. 2020.

THE ROAD TO DIAGNOSIS AND TREATMENT IN GIRLS AND BOYS WITH ADHD□ÇÔGENDER DIFFERENCES IN THE DIAGNOSTIC PROCESS.

Kantzer AK, Gillberg C, et al.

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

Methods: From a consecutive cohort of Child and Adolescent Psychiatric (CAP) outpatients, the medical records of 50 boys and 50 girls (under 18 years of age) with a diagnosis of ADHD were selected by an Excel random numbers generator. Data about referral reason, diagnostic process and treatment were analysed.
Results: Emotional symptoms were more common as a reason for referral to CAP among girls, whereas neurodevelopmental disorders were more common among boys. Compared to the boys, the girls were older at first visit to CAP and at the ADHD diagnosis. The girls had had more visits to the clinic prior to the ADHD diagnostic decision and had more often been prescribed non-ADHD medication both before and after the ADHD diagnosis. The rate of ADHD medication was similar in boys and girls. Girls had more often been admitted to a CAP inpatient care unit prior to the ADHD diagnosis due to acute psychiatric symptoms, and had received more individual psychotherapeutic counselling.
Conclusion: The results highlight the need for broader psychiatric investigations including neuropsychiatric symptoms in girls referred for emotional problems

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Paediatrics and Child Health (Canada). 2020;25:e22.

IMPLEMENTATION OF A DEVELOPMENTAL OUTREACH CLINIC HOUSED WITHIN A FAMILY HEALTH TEAM-PRELIMINARY FINDINGS IN BUILDING A SHARED CARE MODEL FOR CHILDREN AND YOUTH WITH MENTAL HEALTH AND DEVELOPMENTAL DISORDERS.

Young E, Goldfarb R, Green L, et al.

BACKGROUND: At our inner city hospital, we developed a shared care model between family health teams (FHTs), pediatricians and developmental pediatricians to care for children with mental health and developmental disorders. In phase one of our study, 84 FHT members participated in focus groups to inform the development of our clinic. Family physicians described their role as referral agent, long term supporter and healthcare coordinator. They expressed the desire to learn and do more, but noted barriers to providing care, including limited training, lack of service knowledge, limited communication, and cumbersome access to mental health and dual diagnosis services. Phase One was completed and accepted for publication. Phase Two describes the implementation of our clinic using a mixed methods approach and report preliminary findings.
OBJECTIVES: To evaluate the first two years of implementation of the developmental clinic housed within a family health team (FHT) an obtain feedback from members of the shared care model.
DESIGN/METHODS: Mixed methods were used including chart review of all patients referred to the clinic and semi structured interviews with primary care physicians, pediatricians and developmental pediatricians regarding their roles in managing children with developmental and mental health disorders, as well as use and impact of the developmental clinic.
RESULTS: A total of 115 charts were reviewed between Feb 2016 and Jan 2018. Of all patients seen, 34% were female 64% male and 2% transgender. Ages ranged from 1-17 years. Eighty-one percent had an existing diagnosis and were referred for re-assessment while 43% received a new diagnosis: ASD (72%), ADHD (11%), GDD (11%), learning disorder (3%), Anxiety (1%), Other (1%). There was an 8% no show rate. Providers endorsed improved communication through use of a shared EMR for documentation and messaging, and improved service knowledge through availability of a pediatric service navigator who also used EMR to document service and funding applications. Longer term follow up, namely the roles and responsibilities of pediatrics vs. developmental pediatrics vs. primary care remained unclear.
CONCLUSION: Implementation of the shared care model for this population with primary care is feasible, and does address some stated barriers to care, including improved communication, increased service knowledge, and provision of reassessments. Further areas to develop include clarifying the roles and responsibilities of the different healthcare providers of children with mental health and developmental disorders, and determining what is needed for long-term follow up and transitional care

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Pediatrics. 2020;146:590.

IMPROVEMENT IN FUNCTIONAL IMPAIRMENT DURING THE EARLY MORNING AND LATE AFTERNOON/EVENING BOOKENDS OF THE DAY: DATA FROM TWO PHASE 3 TRIALS OF EVENING-DOSED DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE IN CHILDREN WITH ADHD.

DeSousa N, Pliszka S, Wilens T, et al.

Purpose: Evening-dosed HLD200 is a delayed-release and extended-release methylphenidate (DR/ER-MPH) which uses the DELEXIS-« drug delivery technology to delay initial drug release by 8-10 hours, providing onset of treatment effect upon awakening and lasting into the evening. Herein, we report clinician-rated assessments of functional impairment based on parent interview during the early morning and late afternoon/evening in children with attention-deficit/hyperactivity disorder (ADHD) from two pivotal, multicenter, phase 3 trials of DR/ER-MPH.

Methods: HLD200-107 (NCT02493777) was a placebo-controlled laboratory classroom trial in children (6-12 years) with ADHD. DR/ER-MPH was titrated to an optimal dose (20-100 mg/d) and dosing time (8:00 PM -¦ 1.5 h) over a 6-week open-label period. Participants were then randomized 1:1 to double-blind, treatment-optimized DR/ER-MPH or placebo for 1 week. Functional impairment in the early morning and late afternoon/evening was assessed using two validated clinician-rated instruments based on parent interview. The Before School Functioning Questionnaire (BSFQ) measured early morning functional impairment during the open-label period. The Parent Rating of Evening and Morning Behavior, Revised, morning subscale (PREMB-R AM) and evening subscale (PREMB-R PM) measured functional impairment during the bookends of the day during the double-blind period. HLD200-108 (NCT02520388) was a 3-week, randomized, double-blind, placebo-controlled, forced-dose titration trial in children (6-12 years) with ADHD that evaluated DR/ER-MPH (40-80 mg/d) with dosing time adjustments (8:00 PM -¦ 1.5 h) permitted. Functional impairment was assessed by BSFQ, PREMB-R AM, and PREMB-R PM. Results: In HLD200-107, the intention-to-treat (ITT) population comprised 117 participants (DR/ER-MPH, n=64; placebo, n=53). Following the open-label period, the mean optimized dose was 66.2 mg and the most common prescribed dosing time was 8:00 PM. Mean (SD) BSFQ score decreased from 40.7 (10.28) at baseline to 7.3 (6.45) at Week 6. Following randomization, one week of double-blind DR/ER-MPH treatment significantly improved functional impairment versus placebo in the early morning (least-squares [LS] mean PREMB-R AM: 0.9 vs 2.7; P<0.001) and the late afternoon/evening (LS mean PREMB-R PM: 6.1 vs 9.3; P=0.003). In HLD200-108, the ITT population comprised 161 participants (DR/ER-MPH, n=81; placebo, n=80). Mean DR/ER-MPH dose after 3 weeks of treatment was 68.1 mg and the most common prescribed dosing time was 8:00 PM. Three weeks of treatment with DR/ER-MPH significantly improved functional impairment in the early morning and late afternoon/evening versus placebo (LS mean BSFQ: 18.7 vs 28.4; P<0.001; LS mean PREMB-R AM: 2.1 vs 3.6; P<0.001; LS mean PREMB-R PM: 9.4 vs 12.2; P=0.002). In both studies, no serious treatment-related adverse events (TEAEs) were reported and TEAEs were consistent with those expected for methylphenidate.

Conclusion: Evening-dosed DR/ER-MPH was well tolerated and demonstrated significant improvements versus placebo in early morning and late afternoon/evening functional impairment in two pivotal studies of children with ADHD, as measured by two validated scales

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Pediatrics. 2020;146:592.

IMPROVEMENTS IN EARLY MORNING AND LATE AFTERNOON/EVENING FUNCTIONAL IMPAIRMENT WITH DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE IN CHILDREN WITH ADHD: POST HOC ANALYSIS OF 2 VALIDATED SCALES BY NORM-REFERENCED CUT-OFFS.

Incledon B, Faraone S, Wilens T, et al.

Purpose: In a pivotal phase 3 trial in children (6-12 years) with attention-deficit/hyperactivity disorder (ADHD), evening-dosed HLD200, a delayed-release and extended-release methylphenidate (DR/ER-MPH), significantly improved ADHD symptoms and reduced functional impairment versus placebo (PBO), the latter measured by two validated rating scales-the Before School Functioning Questionnaire (BSFQ) and the Parent Rating of Evening and Morning Behavior Scale-Revised (PREMB-R). Recently, age-adjusted cut-offs for the BSFQ and the PREMB-R morning (PREMB-R AM) and evening (PREMB-R PM) subscales were determined from a sample of 1200 representative US youth (6-17 years) to define severity levels of functional impairment: screening risk (80th percentile), mild (90th percentile), moderate (93rd percentile), and severe (98th percentile). In this post hoc analysis, the age-adjusted, norm-referenced cut-offs were applied to BSFQ,

PREMB-R AM, and PREMB-R PM outcomes to help interpret the changes in functional impairment severity with DR/ER-MPH and PBO treatment that were reported in the trial (NCT025203880).
Methods: Total BSFQ, PREMB-R AM, and PREMB-R PM scores were evaluated using the age-adjusted, norm-referenced cut-offs to determine the severity of functional impairment at baseline and following 3 weeks of treatment. Proportions and distributions of participants meeting each norm-referenced cut-off at baseline and Week 3 were compared between treatment groups. Proportions of participants with any severity of functional impairment that "normalized" (ie, below screening risk) after 3 weeks of treatment were also determined. Results: Most participants at baseline were at or above screening risk for functional impairment by norm-referenced cut-offs in DR/ER-MPH and PBO groups (BSFQ: 98% and 96%, PREMB-R AM: 86% and 77%, PREMB-R PM: 94% and 91%, respectively). After 3 weeks, improvements in functional impairment were more pronounced with DR/ER-MPH versus PBO. Of participants with functional impairment of any severity at baseline, a greater proportion achieved "normalized" scores with DR/ER-MPH versus PBO (BSFQ: 66% vs 39%, PREMB-R AM: 72% vs 40%, PREMB-R PM: 43% vs 26%, respectively).
Conclusion: In this post hoc analysis, 3 weeks of DR/ER-MPH treatment resulted in more pronounced improvements across all severity levels of functional impairment and more participants achieving "normalized" scores on BSFQ, PREMB-R AM, and PREMB-R PM versus PBO

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Pediatrics. 2020;146:78-79.

OBESITY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) -WHEN EPIDEMICS COLLIDE: A LONGITUDINAL STUDY OF BODY MASS INDEX (BMI) PATTERNS IN PEDIATRIC PATIENTS WITH ADHD TREATED WITH STIMULANT MEDICATION.

Lewis JM, Nease C.

Purpose ADHD and obesity are common and often comorbid conditions in pediatric populations. While research has demonstrated that treatment of ADHD with stimulant medication typically results in a concomitant (and often appropriate) decrease in BMI, the prevalence of weight gain during treatment is a potentially underestimated and poorly understood issue.
Methods Data were obtained from the electronic health records of pediatric patients receiving effective stimulant therapy for the treatment of ADHD from 2009 to 2013. Patients were diagnosed and treated by one behavioral pediatrician following current American Academy of Pediatrics guidelines. Additional diagnoses of anxiety, adjustment disorder, disruptive behavior disorder and the concurrent use of guanfacine or antidepressant medications was performed by the same pediatrician during the 2 year time interval. Body mass index (BMI) values were recorded from the onset of treatment at 3-6 month intervals over a 2 year follow up period. Chi-squared and odds ratio tests were conducted to test whether likelihood of weight gain varied by initial BMI, medication type, ADHD subtype, demographic variables, comorbidities, and concurrent medications.
Results Of 265 total patients, 27.1% (n=72) showed an increase in BMI, with a mean percentile increase of 12.04 over 2 years of follow up in this group. Children diagnosed at ages 8-10 years (OR 1.95) and 11-13 years (OR 4.71) showed a significantly higher odds of weight gain (Figure). Patients with BMIs in the obese range at diagnosis showed a significantly lower odds of weight gain (OR 0.18). Odds of weight gain did not significantly differ based on gender, insurance status, ADHD subtype, comorbidities, or concurrent medications (Table).
Conclusions These findings demonstrate that children who begin stimulant treatment for ADHD in late childhood and particularly early adolescence are at an increased risk for weight gain. Obesity at initial diagnosis may be protective against excessive weight gain over the first 2 years of stimulant treatment

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Pediatrics. 2020;146:595-97.

POSITIVE ASSOCIATION OF DEPRESSION, ANXIETY, AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN YOUTH WITH CONGENITAL HEART DISEASE: A CROSS-SECTIONAL COMPARATIVE STUDY.

Gonzalez VJ, Lopez KN, Kimbro R, et al.

Purpose: Depression and anxiety in older adolescents and adults with complex congenital heart disease (CHD) has been well described. Additionally, studies report higher rates of ADHD in children with complex

CHD. These data are lacking for younger and simple CHD patients. The goal of our study was to characterize anxiety/depression and ADHD in children with all types of CHD compared to those without CHD.
Methods: Data was obtained using electronic medical records between 2011-2016 from a large tertiary care pediatric hospital. Inclusion criteria were youth < 18 years old with at least one inpatient encounter. Our primary predictor variable was having a simple or complex CHD diagnosis. Other predictor variables included age, sex, race/ethnicity, and insurance type. Our primary outcome variable was having an ICD-9 or 10 diagnosis and/or medication prescribed for depression/anxiety or ADHD. Logistic regression analyses (using Stata version 15) were used to predict depression/anxiety, ADHD, or having both conditions for CHD and non-CHD patients.
Results: We identified 250,214 unique patients and a total of 6,690 patients with CHD. Demographics of CHD patients were largely < 10 years old (90%), male (54%), and had complex CHD (58%). Overall, 24% (n=1,607) of children with CHD had anxiety and/or depression compared to 4% (n=9,558) of non-CHD youth. A total of 2% (n=101) of children with CHD had ADHD compared to 1% (n=2,157) of non-CHD youth. As children aged, they were more likely to have a diagnosis of depression and/or anxiety (OR 1.14; 95% CI 1.13-1.14), or ADHD (OR 1.16; 95% CI 1.15-1.17). Compared to those without CHD, children with simple CHD had a 3.5 times higher odds of ADHD (OR 3.50; 95% CI 2.88-4.25); children with complex CHD had a 4.5 times higher odds of ADHD (OR 4.52; 95% CI 3.90-5.24); and males with CHD were 1.7 times more likely to have ADHD (OR 1.72; 95% CI 1.60-1.84). Compared to children without CHD, children with simple CHD had a 6 times higher odds of depression and/or anxiety (OR 6.31; 95% CI 5.67-7.03) and children with complex CHD were 11 times more likely to have depression and/or anxiety (OR 11.05; 95% CI 10.16-12.03).
Conclusion: Youth with CHD were found to have higher odds of ADHD compared to non-CHD youth, which was most pronounced in those with complex CHD. Regardless of CHD complexity, youth with CHD were found to have much higher odds of depression and/or anxiety than youth without CHD, with significantly higher odds found in patients with complex CHD. Screening for depression, anxiety, and ADHD should be considered in young patients with CHD, as they appear to have higher odds of these diagnoses and/or medications compared to their non-CHD peers

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Pediatrics. 2020 Oct;146.

CHILDREN'S RELATIVE AGE AND ADHD MEDICATION USE: A FINNISH POPULATION-BASED STUDY.

Vuori M, Martikainen JE, Koski-Pirilä A, et al .

Objectives: The youngest children in a classroom are at increased risk of being medicated for attention-deficit/hyperactivity disorder (ADHD). We examined the association between children's birth month and ADHD medication rates in Finland.
Methods: Using a population-based study, we analyzed ADHD medication use among children born in 2005 to 2007. Cases (n = 7054) were identified from the first purchase of medication for ADHD. Cox proportional hazard models and hazard ratios (HRs) were examined by birth month and sex. Finnish children start first grade in the year of their seventh birthday. The cutoff date is December 31.
Results: Risk of ADHD medication use increased throughout the year by birth month (ie, January through April to May through August to September through December). Among boys born in September to December, the association remained stable across cohorts (HR: 1.3; 95% confidence interval [CI]: 1.1-1.5). Among girls born in September to December, the HR in the 2005 cohort was 1.4 (95% CI: 1.1-1.8), whereas in the 2007 cohort it was 1.7 (95% CI: 1.3-2.2). In a restricted follow-up, which ended at the end of the year of the children's eighth birthday, the HRs for boys and girls born in September to December 2007 were 1.5 (95% CI: 1.3-1.7) and 2.0 (95% CI: 1.5-2.8), respectively.
Conclusions: Relative immaturity increases the likelihood of ADHD medication use in Finland. The association was more pronounced during the first school years. Increased awareness of this association is needed among clinicians and teachers

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PLoS ONE. 2020;15.

A NOVEL QUANTITATIVE ELECTROENCEPHALOGRAPHY SUBTYPE WITH HIGH ALPHA POWER IN ADHD: ADHD OR MISDIAGNOSED ADHD?

Byeon J, Choi TY, Won GH, et al.

This study investigated quantitative electroencephalography (QEEG) subtypes as auxiliary tools to assess Attention Deficit Hyperactivity Disorder (ADHD). A total of 74 subjects (58 male and 16 female) were assessed using the Korean version of the Diagnostic Interview Schedule for Children Version IV and were assigned to one of three groups: ADHD, ADHD-Not Otherwise specified (NOS), and Neurotypical (NT). We measured absolute and relative EEG power in 19 channels and conducted an auditory continuous performance test. We analyzed QEEG according to the frequency range: delta (1ΓÇô4 Hz), theta (4ΓÇô8 Hz), slow alpha (8ΓÇô10 Hz), fast alpha (10ΓÇô13.5 Hz), and beta (13.5ΓÇô30 Hz). The subjects were then grouped by WardΓÇÖs method of cluster analysis using the squared Euclidian distance to measure dissimilarities. We discovered four QEEG clusters, which were characterized by: (a) elevated delta power with less theta activity, (b) elevated slow alpha relative power, (c) elevated theta with deficiencies of alpha and beta relative power, and (d) elevated fast alpha and beta absolute power. The largest proportion of participants in clusters (a) and (c) were from the ADHD group (48% and 47%, respectively). Conversely, group (b) mostly consisted of the participants from the NOS group (59%), while group (d) had the largest proportion of participants from the NT group (62%). These results indicate that children with ADHD does not neurophysiologically constitute a homogenous group. We also identified a new subtype with increased alpha power in addition to those commonly reported in ADHD. Given the QEEG characteristics with increased alpha power, we should consider the possibility that this subtype may be caused by childhood depression. In conclusion, we believe that these QEEG subtypes of ADHD are expected to provide valuable information for accurately diagnosing ADHD

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PLoS ONE. 2020;15.

COMPUTER-BASED INHIBITORY CONTROL TRAINING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): EVIDENCE FOR BEHAVIORAL AND NEURAL IMPACT.

Meyer KN, Santillana R, Miller B, et al.

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed psychological disorder of childhood. Medication and cognitive behavioral therapy are effective treatments for many children; however, adherence to medication and therapy regimens is low. Thus, identifying effective adjunct treatments is imperative. Previous studies exploring computerized training programs as supplementary treatments have targeted working memory or attention. However, many lines of research suggest inhibitory control (IC) plays a central role in ADHD pathophysiology, which makes IC a potential intervention target. In this randomized control trial (NCT03363568), we target IC using a modified stop-signal task (SST) training designed by NeuroScouting, LLC in 40 children with ADHD, aged 8 to 11 years. Children were randomly assigned to adaptive treatment (n = 20) or non-adaptive control (n = 20) with identical stimuli and task goals. Children trained at home for at least 5 days a week (about 15m/day) for 4-weeks. Relative to the control group, the treatment group showed decreased relative theta power in resting EEG and trending improvements in parent ratings of attention (i.e. decreases in inattentive behaviors). Both groups showed improved SST performance. There was not evidence for treatment effects on hyperactivity or teacher ratings of symptoms. Results suggest training IC alone has potential to positively impact symptoms of ADHD and provide evidence for neural underpinnings of this impact (change in theta power; change in N200 latency). This shows promising initial results for the use of computerized training of IC in children with ADHD as a potential adjunct treatment option for children with ADHD

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2020.

POTENTIAL DISTURBANCE OF METHYLPHENIDATE OF GONADAL HORMONES OR PUBESCENT DEVELOPMENT IN PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A TWELVE-MONTH FOLLOW-UP STUDY.

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

Several animal or case reports have demonstrated that methylphenidate (MPH) disrupts endogenous gonadal hormones and interferes with the pubescent development of children with attention-deficit/hyperactivity disorder (ADHD). Therefore, this prospective study examined the changes in gonadal hormones and pubescent development in children with ADHD undergoing 12-month MPH treatment. We recruited 146 patients with ADHD (mean age: 8.9 years, 76.7% males) and 70 healthy controls (mean age: 9.2 years, 65.7% males). Blood samples were obtained to measure the serum levels of sex hormone-binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, testosterone, free testosterone, and prolactin in each child. The sex maturation of ADHD patients was evaluated using the Tanner Stage. Patients with ADHD (107 received MPH treatment and 39 were under natural observation) were followed up for 12 months, and we re-examined hormone levels and Tanner Stage at the endpoint. During a 12-month follow-up for all ADHD patients, the serum levels of SHBG and progesterone significantly decreased, while LH, FSH, and free-testosterone levels significantly increased. However, the duration, drug formulations, and doses of the MPH treatment did not significantly influence gonadal hormone trends or changes of Tanner Stage. This study provides evidence about gonadal hormone trends and pubescent development in children with ADHD who receive long-term MPH treatment in natural settings. We suggest that MPH treatment at usual doses does not significantly alter gonadal function trends in ADHD patients over the course of one year

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Psychoanalytic Psychotherapy. 2020.

GRIPPED BY THE CHAOS: A PSYCHOANALYTICALLY-INFORMED QUALITATIVE EXPLORATION OF ADOLESCENT ADHD.

Clancy J, OΓÇÖConnor J, Ni Mhaolain C.

Attention deficit hyperactivity disorder (ADHD) in adolescence has largely been overlooked in the literature in terms of the experience of those so diagnosed. In clinical practice there is an understanding that this population experiences profoundly painful interpersonal difficulties, but at an empirical level the experience of the adolescent is poorly understood. In this psychoanalytically-informed qualitative study, five adolescents, aged 16ΓÇô17, with a diagnosis of ADHD took part in three interviews. The material was analysed in keeping with the psychoanalytically-informed method. Three inter-related themes emerged: not being able to let out difficult emotion, which reflected participants struggle with overwhelming and unmanageable affect; (un)soothing experience with self and other, which described the relationship between care-seeking and care-giving behaviours in the lives of these youths; and being in and out of control, which relates to the complex relationship that participants have with self-control as well as the control of others. In the lives of these adolescents, the search for containment in interpersonal relationships is explored, as well as a discussion of a substitute for soothing in the absence of a good enough object in early interactions

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Psychoneuroendocrinology. 2021;125.

L-CYSTINE IS ASSOCIATED WITH THE DYSCONNECTIVITY OF THE DEFAULT-MODE NETWORK AND SALIENCE NETWORK IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wang LJ, Lin LC, Lee SY, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. Distributed dysconnectivity within both the default-mode network (DMN) and the salience network (SN) has been observed in ADHD. L-cystine may serve as a neuroprotective molecule and signaling pathway, as well as a biomarker of ADHD. The purpose of this study was to explore whether differential brain network connectivity is associated with peripheral L-cystine levels in ADHD patients. We recruited a total of 31 drug-na+»ve patients with ADHD (mean age: 10.4 years) and 29 healthy controls (mean age: 10.3 years) that underwent resting state functional magnetic resonance imaging scans. Functional connectomes were generated for each subject, and we examined the cross-sectional group difference in functional connectivity (FC) within and between DMN and SN. L-cystine plasma levels were determined using high-performance chemical

isotope labeling (CIL)-based liquid chromatography-mass spectrometry (LC-MS). Compared to the control group, the ADHD group showed decreased FC of dorsal DMN (p = 0.031), as well as decreased FC of precuneus-post SN (p = 0.006) and ventral DMN-post SN (p = 0.001). The plasma L-cystine levels of the ADHD group were significantly higher than in the control group (p = 0.002). Furthermore, L-cystine levels were negatively correlated with FC of precuneus-post SN (r = 0.404, p = 0.045) and ventral DMN-post SN (r = 0.540, p = 0.007). The findings suggest that decreased synergies of DMN and SN may serve as neurobiomarkers for ADHD, while L-cystine may be involved in the pathophysiology of network dysconnectivity. Future studies on the molecular mechanism of the cystine-glutamate system in brain network connectivity are warranted

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Sinapse. 2019;19:6-16.

HOW DO CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER SLEEP?

Andrade JV, Gomes C, Sousa P, et al.

Introduction: Sleep disorders are frequently associated with neurodevelopment pathologies, such as attention deficit hyperactivity disorder (ADHD).

Methods: An observational, transversal and analytic study was conducted through the analysis of anonymous survey applied to caregivers of patients with ADHD from 6 to 17 years of age, followed in a Development Consult of a level II hospital. We studied the sociodemographic characteristics, personal data, sleep habits and disorders. For statistical treatment we used SPSS-« software to test associations between variables, statistical significance p<0.05.

Results: Two hundred children and adolescents were enrolled, 72% male, median age of 12 years -¦ 2.8. They were classified as ADHD combined type (46%), inattentive type (49%) and hyperactive-impulsive type (5%) and medicated in 96% with methylphenidate. Sleep disorder was referred by 91% of the parents and more frequently associated to ADHD combined type (p=0.018), particularly the presence of parasomnias (p=0.017). About 73% of the sample referred insomnia, more frequent in the male gender (p=0.012) and 33% referred day hypersomnia that affected daily life activities. Parents of children and adolescents with sleep disorders were worried about this topic (p=0.008). Only in 13% of the cases, parents had the opportunity to address this issue with the physician.

Conclusion: We noticed that sleep disorders in children and adolescents with ADHD in our sample were higher than those reported in the literature and in about a third of the cases affects the daily life activities. We noticed that this topic is not addressed in the child-¦s health surveillance appointments. It is important to change this approach, as sleep disturbance has a significant impact in the quality of life of these patients

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Sleep. 2020;43.

ACOUSTIC CLOSED-LOOP STIMULATION DURING SLEEP IMPROVES CONSOLIDATION OF REWARD-RELATED MEMORY INFORMATION IN HEALTHY CHILDREN BUT NOT IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Prehn-Kristensen A, Ngo HVV, Lentfer L, et al.

Study Objectives: Slow oscillations (SO) during slow-wave sleep foster the consolidation of declarative memory. Children with attention-deficit hyperactivity disorder (ADHD) display deficits in the sleep-associated consolidation of declarative memory, possibly due to an altered function of SO. The present study aimed at enhancing SO activity using closed-looped acoustic stimulation during slow-wave sleep in children with ADHD.

Methods: A total of 29 male children (14 with ADHD; aged 8-12 years) participated in a double-blind, placebo-controlled study trial. Children spent two experimental nights in a sleep lab, one stimulation night and one sham night. A declarative learning task (word-pair learning) with a reward condition was used as a primary outcome. Secondary outcome variables were a procedural memory (serial reaction time) and working memory (WM; n-back) task. Encoding of declarative and procedural memory took place in the evening before sleep. After sleep, the retrieval took place followed by the n-back task.

Results: The stimulation successfully induced SO activity during sleep in children with and without ADHD. After stimulation, only healthy children performed better on high-rewarded memory items (primary outcome).

In contrast, there were indications that only children with ADHD benefitted from the stimulation with respect to procedural as well as WM performance (secondary outcome).
Conclusions: We were able to show that the acoustic closed-loop stimulation can be applied to enhance SO activity in children with and without ADHD. Our data indicate that SO activity during sleep interacts with subsequent memory performance (primary outcome: rewarded declarative memory; secondary outcome: procedural and WM) in children with and without ADHD

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Technology and Disability. 2020;32:243-53.

INNOVATIVE TECHNOLOGICAL ADVANCEMENTS TO IMPROVE COGNITIVE AND SOCIAL SKILLS OF STUDENTS WITH NEURODEVELOPMENTAL DISORDERS.

Manta O, Androutsou T, Anastasiou A, et al.

BACKGROUND: A major concern that is being increasingly addressed in modern educational environments is the ability to present equal accessibility opportunities to students with neurodevelopmental conditions and disorders as for typically developing children. OBJECTIVE: The main objective of the paper is to employ innovative technological advancements merged with evidence-based practices in order to teach, improve and generalise social skills for children with neurodevelopmental disorders, specifically children with High Functioning Autism (HFA) as well as children with Attention Deficit Disorder (ADD).
METHODS: The development of a personalized solution adapted to the needs of each student is proposed. The platform will be composed of three main modules (Content Management, Emotional Analysis and Personalization). The target group is students of the Primary Years Program and Middle Years Program.
EXPECTED RESULTS: Improved communicational and interactional capability of people with disabilities and facilitate social innovation; more affordable technologies and products that support interactions for people with disabilities, and new generation of services that are highly adaptable and personalisable to individual contexts.
CONCLUSIONS: In order to achieve the optimum output/result of the system the procedure need to be implemented and reviewed by all involved parties

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Career Dev Q. 2020 Dec;68:288-301.

DYSFUNCTIONAL CAREER THOUGHTS AND PERCEIVED QUALITY OF PARENTAL RELATIONSHIPS IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Dipeolu A, Hargrave S, Leierer SJ, et al.

Attention-deficit/hyperactivity disorder (ADHD) is known to cause significant difficulties in interpersonal relationships. Empirical research in career development has demonstrated that close, supportive relationships are associated with positive vocational behaviors (Kenny et al., 2018). We examined dysfunctional career thoughts and perceived quality of parental relationships in high school students with ADHD. One hundred two adolescents (76 boys, 26 girls) with ADHD responded to measures of career thoughts and interpersonal relationship quality. Preliminary exploratory analysis, using multiple linear regression, showed that male participants' dysfunctional career thoughts were statistically significantly related to their relationships with their mothers. For female participants, relationships with fathers represented an area for further exploration. Results suggest that career professionals can enhance positive outcomes of decision-making and problem-solving issues in adolescence with additional focus on relational interventions. Future research should incorporate the influence of gender and race/ethnicity on crucial relationships and focus on paternal relationships using cognitive information processing–based interventions with this population

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Trends in Psychiatry and Psychotherapy. 2020;42:340-47.

DOES ADHD WORSEN INHIBITORY CONTROL IN PRESCHOOL CHILDREN BORN VERY PREMATURE AND/OR WITH VERY LOW BIRTH WEIGHT?

Lacerda BC, Martinez SBS, Franz AP, et al.

Introduction: Deficits in executive functioning, especially in inhibitory control, are present in children born very premature and/or with very low birth weight (VP/VLBW) and in children with attention-deficit/ hyperactivity disorder (ADHD). Objective: To evaluate whether ADHD imposes additional inhibitory control (IC) deficits in preschoolers born VP/VLBW.

Methods: 79 VP/VLBW (4 to 7 years) children were assessed for ADHD using the Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version (K-SADS-PL). IC was measured with Conners Kiddie Continuous Performance Test (K-CPT 2) and the Behavior Rating Inventory of Executive Function Preschool Version (BRIEF-P).

Results: No significant differences were found between ADHD (n = 24) and non-ADHD children (n = 55) for any of the measures (p = 0.062 to p = 0.903). Both groups had deficits in most K-CPT 2 scores compared to normative samples, indicating poor IC and inconsistent reaction times.

Conclusions: ADHD does not aggravate IC deficits in VP/VLBW children. Either neuropsychological tasks and parent reports of executive functions (EFs) may not be sensitive enough to differentiate VP/VLBW preschoolers with and without ADHD, or these children's EFs are already so impaired that there is not much room for additional impairments imposed by ADHD

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Turkish Journal of Pediatric Disease. 2020;14:302-09.

NEUROPSYCHOLOGICAL TESTS FOR DIFFERENTIAL DIAGNOSIS OF ADHD AND ADHD WITH DYSLEXIA.

Hakelekli F, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) and dyslexia are two prominent disorders seen in referrals to the child psychiatry clinics because of poor academical success. It may be difficult to distunguish two disorders, however, this differential diagnosis is essential in order to provide the correct treatment. Main objective of this study is to analyze and compare the neuropsychological components of ADHD and ADHD with dyslexia.

Material and Methods: This study consists of 53 children referred to Children's Hospital with poor academical success and completed neuropsychological tests for the differential diagnosis of suspected ADHD with/out dyslexia. After the evaluation, subjects were divided into two groups as ADHD and ADHD with dyslexia. Sociodemographics and neuropsychological test results were compared.

Results: Despite being clinically overlapping, compared to ADHD group, ADHD with dyslexia had a predominance of girls, lower score in WISC-R similarities subtest, higher score of picture completion; higher ratio of late reaction times in first and second domains Stroop test and a poorer reading rate.

Conclusion: This study suggests significant differences between ADHD and ADHD with dyslexia which may be of help to the clinician. It also points out the importance of assessment of WISC-R subtests individually and reaction time probably due to decreased processing speed in ADHD with dyslexia

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Turk J Pediatr. 2020;62:970-78.

SENSORY PROFILE, FERRITIN AND ZINC LEVELS IN PRESCHOOL-AGED CHILDREN WITH SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Celen Yoldaf T, Huri M, et al.

Background. Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders and has a big impact on the well-being of children. The disorder can lead to noticeable functional limitations for children and bio-ecological factors also contribute to symptoms of ADHD. We aimed to investigate the associations between ADHD symptoms and some related bio-ecological factors including serum ferritin, zinc levels and sensory processing in preschool-aged children.

Methods. Twenty-two children who had been referred to the division of Developmental Pediatrics because of ADHD symptoms and 22 participants from the general pediatric outpatient clinics were included in the study. The symptoms of ADHD were evaluated with Conners Parent Rating Scale-Revised Short form.

Complete blood count, serum ferritin and zinc levels were also evaluated. A blind occupational therapist implemented sensory processing measurements. The characteristics of each participant such as prematurity, perinatal complications, developmental practices and sociodemographic data were also considered.
Results. Sensory processing measurement analysis revealed that all Sensory Profile scores were significantly lower in the children with ADHD symptoms compared to the control group indicating that the child shows the behavior more than desired. The low level of zinc (p=0.026, OR=6.153, 95% CI= 1.247-30.362) and the presence of perinatal complications (p=0.045, OR=10.864, 95% CI=1.059-111.499) increased the risk of ADHD symptoms. We could not find an association for ferritin levels in our study.
Conclusions. The evaluation of zinc level and sensory profile parallel to other strategies can be recommended during the management of ADHD symptoms in preschool children

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World Journal of Gastroenterology. 2020;26:6626-37.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND GASTROINTESTINAL MORBIDITY IN A LARGE COHORT OF YOUNG ADULTS.

Kedem S, Yust-Katz S, Carter D, et al.

BACKGROUND Although the association of attention deficit hyperactivity disorder (ADHD) with psychiatric disorders is well known, its association with somatic diseases is unclear. Only few studies have investigated the gastrointestinal (GI) morbidity in adult patients with ADHD.
AIM To measure gastrointestinal comorbidity and its burden on healthcare in young adults with ADHD. METHODS The cohort included subjects aged 17-35 years recruited to the Israel Defense Forces in 2007-2013, 33380 with ADHD and 355652 without (controls). The groups were compared for functional and inflammatory conditions of the gastrointestinal tract and clinic and specialist visits for gastrointestinal symptoms/disease during service (to 2016). Findings were analyzed by generalized linear models adjusted for background variables.
RESULTS Compared to controls, the ADHD group had more diagnoses of functional gastrointestinal disorders (referred to as FGID), namely, dyspepsia [odds ratio (OR): 1.48, 95% confidence interval (CI): 1.40-1.57, P < 0.001], chronic constipation (OR: 1.64, 95%CI: 1.48-1.81, P < 0.001), and irritable bowel syndrome (OR: 1.67, 95%CI: 1.56-1.80, P < 0.001) but not of organic disorders (inflammatory bowel disease, celiac disease). They had more frequent primary care visits for gastrointestinal symptoms [rate ratio (RR): 1.25, 95%CI: 1.24-1.26, P < 0.001] and referrals to gastrointestinal specialists (RR: 1.96, 95%CI: 1.88-2.03, P < 0.001) and more episodes of recurrent gastrointestinal symptoms (RR: 1.29, 95%CI: 1.21-1.38, P < 0.001). Methylphenidate use increased the risk of dyspepsia (OR: 1.49, 95%CI: 1.28-1.73, P < 0.001) and constipation (OR: 1.42, 95%CI: 1.09-1.84, P = 0.009).
CONCLUSION ADHD in young adults is associated with an excess of FGID and increased use of related health services. Research is needed to determine if an integrative approach treating both conditions will benefit these patients and cut costs

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Z Kinder- Jugendpsychiatr Psychother. 2020;1-9.

ADHERENCE TO GUIDELINES IN THE DIAGNOSIS AND TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS IN ROUTINE CARE: A REPRESENTATIVE SURVEY.

Sonneck A, et al.

Objective: The study evaluated guideline adherence in the current routine care of children and adolescents with Attention Deficit-/Hyperactivity Disorder (ADHD) in various groups of healthcare providers nationwide.
Method: N = 275 providers from all relevant groups of a Germany-wide random sample (specialists in pediatric and adolescent medicine, child and adolescent psychiatry and psychotherapy, child and adolescent psychotherapists and all Social Pediatric Centers, outpatient departments of child and adolescent psychiatric clinics and behavioral therapy training institutes) participated in an online interview.
Results: The recommendations in the guidelines were implemented on average in 75-100 % of the patients. Exceptions were those of teacher/educator exploration and school interventions. Questionnaires on diagnostics and follow-up or psychotherapeutic interventions were applied comparatively rarely, in about 50

% of the patients. Differences between provider groups and correlations with sociodemographic variables were analyzed at the level of the adherence indices.
Conclusions: Overall, the participants reported high guideline adherence. We found a high similarity of the data in different care segments within the care providers. Differences in self-reports of the various care groups stimulate considerations of the roles in the care process with ADHD patients

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What are the effects of social skills training on children with attention-deficit/hyperactivity disorder? A Cochrane Review summary with commentary

IRENE FERRARIO

ISICO (Italian Scientific Spine Institute), Milan, Italy.

The aim of this commentary is to discuss, from a rehabilitation perspective, the published Cochrane Review 'Social skills training for attention deficit hyperactivity disorder (ADHD) in children aged 5 to 18 years'[1] by Storebø et al., under the direct supervision of Cochrane Developmental, Psychosocial and Learning Problems Group. This Cochrane Corner is produced in agreement with *Developmental Medicine & Child Neurology* by Cochrane Rehabilitation.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder and the main symptoms include problems with attention, impulsiveness, and hyperactivity. ADHD is characterized by difficulties in the domains of attentional and cognitive functions (e.g. problem solving, planning, sustained attention, response inhibition, and working memory), emotional regulation, and social skills (e.g. social incompetence, and disruptive and rule violating behavior).[2,3] An ADHD diagnosis can be made if symptoms of excessive inattention, hyperactivity, and impulsivity that cause impairment in functioning or development are present before the age of 12 years.[4,5] Pharmacological treatment can be administered to manage the symptoms of the condition but can rarely solve the difficulties that these children encounter with social interactions. Social skills training is designed to improve and maintain the individual's social skills and prevent or alleviate social difficulties by focusing on problem-solving, control of emotions, and verbal and nonverbal communication. Social skills training aims to teach children social norms, social rules, and expectation of others; by social modeling and behavioral practice, participants observe and repeat the skills until they become more generalized.[6] This Cochrane Review[1] searched for evidence of the effects of social skills training in ADHD.

This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD008223, https://doi.org/10.1002/14651858.CD008223.pub3 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. The views expressed in the summary with commentary are those of the Cochrane Corner author and do not represent the Cochrane Library or Wiley.

SOCIAL SKILLS TRAINING FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AGED 5 TO 18 YEARS[1]

What is the aim of this Cochrane Review?

The aim of this Cochrane Review[1] was to assess the effects of social skill training on children and adolescents with ADHD.

What was studied in the Cochrane Review?

Children and adolescents between the ages of 5 and 17 years were assessed in this review. All participants were diagnosed with ADHD using tools based on the international Diagnostic and Statistical Manual of Mental Disorders (DSM), the International Classification of Disease, Tenth Revision, or a cut-off score from the Conners' Rating Scales. Most of the trials were conducted in outpatient clinics in the USA, Asia, and Europe. The interventions studied (duration range: 5wks–2y) were based on a cognitive behavioral model and included treatments such as social and life skills training, cognitive behavioral therapy, multimodal behavioral/psychosocial therapy, and meta-cognitive training. The intervention was compared to no intervention or a waiting-list control group, with or without pharmacological treatment. The primary outcomes studied were social skills, emotional competencies, and general behavior, either at home or in school. The secondary outcomes studied were core ADHD symptoms (inattention, impulsivity, and hyperactivity), school performance and grades, satisfaction with treatment, and adverse events. The outcomes were assessed using a variety of validated scales rated by children's teachers, parents, or observers.

Up-to-dateness of the Cochrane Review

The review authors searched for randomized clinical trials (RCTs) up to July 2018 on CENTRAL, MEDLINE, Embase, PsycINFO, four other databases, and two trials registers. They also searched nine conference proceedings for potentially relevant abstracts and contacted experts in the field for information about unpublished or ongoing RCTs.

What are the main results of the Cochrane Review?

The review included 25 RCTs (with 2690 participants). The primary analyses were conducted on teacher-rated

rather than parent-rated outcomes, as these are considered more reliable and less prone to systematic errors (arising, for example, from a lack of blinding).

The findings of the review are listed below.

Social skills

The intervention may have little to no effect on social skills as rated either by teachers (standardized mean difference [SMD] 0.11, 95% confidence interval [CI] −0.00 to 0.22; 11 RCTs, 1271 participants) or parents (SMD 0.19, 95% CI 0.06–0.32; 15 RCTs, 1609 participants) at the end of treatment, but the evidence is very uncertain.

Emotional competencies

The intervention may have little to no effect on teacher-rated emotional competencies at the end of treatment (SMD −0.02, 95% CI −0.72 to 0.68; two RCTs, 129 participants), but the evidence is very uncertain.

General behavior

The intervention may result in little to no difference in teacher-rated general behavior at the end of treatment (SMD −0.06, 95% CI −0.19 to 0.06; eight RCTs, 1002 participants), but the certainty of the evidence is low. Social skills training may improve parent-rated general behavior at the end of treatment (SMD −0.38, 95% CI −0.61 to −0.14; eight RCTs, 995 participants), but the evidence is very uncertain.

Core ADHD symptoms

The intervention may reduce ADHD symptoms as rated by both teachers (SMD −0.26, 95% CI −0.47 to −0.05; 14 RCTs, 1379 participants) and parents (SMD −0.54, 95% CI −0.81 to −0.26; 11 RCTs, 1206 participants) at the end of treatment, but the evidence is very uncertain. The studies did not report any serious or non-serious adverse events.

How did the authors conclude on the evidence?

The authors concluded that the current evidence is insufficient to determine whether social skills training is beneficial for children with ADHD. All included trials presented with methodological issues, such as an overestimation of benefits and underestimation of harms, and the quality of the evidence was assessed as low and very low. Furthermore, the interventions were difficult to compare due to their heterogeneity.

What are the implications of the Cochrane evidence for practice in rehabilitation?

This Cochrane Review[1] highlights the uncertainty around the effectiveness of social skill training on the social skills of children with ADHD. Due to the questionable evidence, it is not possible to conclude whether these kinds of interventions work or not. In their everyday practice, clinicians should consider their clinical expertise and best practice guidelines, and be aware of how they recommend these interventions because families need as much information as possible to be able to make an informed decision.

When interpreting these findings, clinicians should note that the studies included in the review[1] had several methodological limitations; for example, the lack of blinding of personnel introduced a high risk of bias in the outcome assessment. Furthermore, most of the included trials had small sample sizes leading to a high risk of random errors. These issues should be addressed by future well-designed RCTs assessing the effectiveness of social skills training programs. Such studies should include adolescents as well as children, and should be designed according to the SPIRIT statement[7] and reported according to the CONSORT statement,[8] to reduce the risk of publication bias.

ACKNOWLEDGEMENTS

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REFERENCES

1. Storebø OJ, Elmose Andersen M, Skoog M, et al. Social skills training for attention deficit hyperactivity disorder (ADHD) in children aged 5 to 18 years. *Cochrane Database Syst Rev* 2019; **6**: CD008223.
2. Pasini A, Paloscia C, Alessandrelli R, et al. Attention and executive functions profile in drug naive ADHD subtypes. *Brain Dev* 2007; **29**: 400–8.
3. Landau S, Milich R, Widiger TA. Conditional probabilities of child interview symptoms in the diagnosis of attention deficit disorder. *J Child Psychol Psychiatry* 1991; **32**: 501–13.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 5th ed. Washington, DC: American Psychiatric Publishing, 2013.
5. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical Descriptions and Diagnostic, Guidelines. Geneva: World Health Organization, 1992.
6. Almerie MQ, Okba Al Marhi M, Jawoosh M, et al. Social skills programmes for schizophrenia. *Cochrane Database Syst Rev* 2015; **2015**: CD009006.
7. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; **158**: 200–7.
8. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**: c332.

P.050
Hemodynamic response to methylphenidate in children with attention deficit hyperactivity disorder: first administration, titration phase and associations with clinical severity

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Introduction: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a prevalence of about 5% in children. ADHD is characterized by lack of self-regulation and presence of deficits in organizing behaviors in response to emotional stimuli [1]. Methylphenidate (MPH) is one of the most effective and frequently prescribed psychostimulant drugs for ADHD [2], however, a possible predictive utility of brain hemodynamic data related to MPH administration and its relation to clinical symptomatology - in a longitudinal framework - is still not clear. To address these questions we used Near Infrared Spectroscopy (NIRS) technology, a useful non-invasive optical technique that allows to investigate the effect of psychopharmacological treatment on cortical hemodynamics.
Aims: *Aim 1*: To evaluate whether any hemodynamic changes induced by first MPH administration at wave 2 (W2) would predict changes in hemodynamic activation in frontal areas at wave 3 (W3, titration phase).

Aim 2: To analyze possible associations between hemodynamic and clinical data before (wave 1, W1) and after (W3) MPH administration.
Methods: *Study design:* 20 children with ADHD underwent a three-waves study and 25 typically developing peers were recruited at W1 as a control group. At W2 children with ADHD received first MPH administration and at W3 they reached the titration phase. At each phase children performed - during NIRS recording - an emotional continuous performance task with visual stimuli of different emotional content: faces expressing positive, negative or neutral emotions or no face condition (distorted) [3]. Clinical data were collected at W1 and W3 through Child Behaviour Checklist/6-18 (CBCL/6-18) and Conners' Parent Rating Scale-Revised (CPRS-R) [4,5].

Statistical analyses: Aim 1) We aimed at finding a linear relationship between the difference between NIRS activation at W2 and W1 (Delta1) and W3 and W2 (Delta2), for each subject, task condition and brain region. Aim 2) Lastly, to address relationships between brain hemodynamics and clinical data across time, we investigated Spearman linear correlations between the Delta1 and clinical symptomatol-

ogy indexes at W1 and between Delta2 and clinical data at W3.

Results: Significant linear regression and Spearman linear correlations results are depicted in the table below.

Linear regression analyses. IV = Independent variable DV = Dependent variable	Standardized regression coefficient	p = Model p value R-sq = R-squared value
IV = Delta1, Positive condition, right prefrontal. DV = Delta2, Positive condition, right prefrontal.	0.828	$p = 0.03$ R-sq = 0.513
IV = Delta1, Neutral condition, right prefrontal. DV = Delta2, Neutral condition, right prefrontal.	0.840	$p = 0.018$ R-sq = 0.587
IV = Delta1, Distorted condition, right prefrontal. DV = Delta2, Distorted condition, right prefrontal.	1.068	$p = 0.001$ R-sq = 0.730
Spearman linear correlation. CV = Clinical variable NV = NIRS variable	**Correlation coefficient**	**p value**
CV = Anxiety/Depression at W1. NV = Delta1, Distorted condition, right prefrontal.	-0.633	0.008
CV = Social Problems at W1. NV = Delta1, Distorted condition, right prefrontal.	-0.616	0.011
CV = Attention Problems at W1. NV = Delta1, Distorted condition, right prefrontal.	-0.516	0.041
CV = Dysregulation Profile at W1. NV = Delta1, Distorted condition, right prefrontal.	-0.620	0.01
CV = ADHD index at W3. NV = Delta1, Distorted condition, right prefrontal.	-527	0.044

Conclusions: Our study results suggest that hemodynamic changes in right prefrontal region probably induced by first MPH administration could predict hemodynamic changes related to MPH titration phase. These biological indexes could be associated to clinical evidences related not only to core ADHD symptoms but also to affective correlates.

No conflict of interest

References

[1] Shaw, P., Stringaris, A., Nigg, J., Leibenluft, E., 2014. Emotion Dysregulation in Attention Deficit Hyperactivity Disorder. American Journal of Psychiatry 171, 276-293. doi:10.1176/appi.ajp.2013.13070966.

[2] Greenhill, L.L., Pliszka, S., Dulcan, M.K., 2001. Summary of the practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. Journal of the American Academy of Child & Adolescent Psychiatry 40, 1325-1355. doi:10.1097/00004583-200111000-00020.

[3] Soloff, P.H., White, R., Omari, A., Ramaseshan, K., Diwadkar, V.A., 2015. Affective context interferes with brain responses during cognitive processing in borderline personality disorder: fMRI evidence. Psychiatry Research 233, 23-35. doi:10.1016/j.pscychresns.2015.04.006.

[4] Achenbach, T.M., Rescorla, L.A., 2001. Manual for the ASEBA school-age forms and profiles. University of Vermont, Research Center for Children, Youth, and Families. Burlington.

[5] Conners, C.K., 1997. Conners' Rating Scales—Revised: User's Manual; Multi-Health Systems, Incorporated: North Tonawanda, NY, USA.

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Sleep EEG cyclic alternating pattern alterations in attention deficit hyperactivity disorder: a meta-analysis of current literature

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Background: Sleep alterations are a common finding in children with Attention Deficit and Hyperactivity Disorder (ADHD) [1], as revealed by subjective and objective reports, indicating higher sleep fragmentation and instability and reduced recovery function of sleep [2]. However, only few significant differences in the macrostructure of the sleep EEG have emerged between ADHD and healthy children (HC) [2, 3]. On the other hand, NREM cyclic alternating pattern (CAP) represents a microstructural EEG marker of unstable sleep and is closely related with sleep recovery function [4]. Thus, recent studies have investigated CAP in ADHD although showing conflicting results. To achieve a more robust evidence about the actual usefulness of CAP as a parameter for objective assessment of disordered sleep in ADHD, we performed a meta-analysis of the available literature.
Methods: A systematic search was performed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria [5] and was conducted on two electronic databases (PubMed and Scopus), from inception

to February 2020. We included clinical studies aimed at evaluating the sleep CAP in patients with ADHD compared to HC. Hedges' g effect sizes and standard errors for each CAP parameter of each included study were estimated either from means and standard deviations or from p-values of independent statistics. We performed 23 meta-analyses according to the CAP parameters that were investigated in all meta-analyzed studies. The Cochrane Q test and the I2 index were applied for heterogeneity evaluation, and either fixed effects or random effects models were used to compute standardized mean differences (SMD).

Results: We retrieved 426 abstracts (after removing duplicates) using our search strategy and included three studies in the meta-analysis. Overall, study samples included a total of 109 subjects (ADHD: 62, HC: 47; age range: 6 – 13 years; Intelligence Quotient $>$ 70). The following 23 parameters of CAP were meta-analyzed: total CAP rate in NREM, N1, N2 and N3 sleep (percentage of NREM, N1, N2 and N3 sleep time occupied by CAP sequences); CAP A1, A2 and A3 rates in NREM sleep (percentage of NREM sleep time occupied by CAP A1, A2 and A3 sequences); CAP A1, A2 and A3 indexes (number of A1, A2 and A3 phases per hour of NREM, N1, N2 and N3 sleep); duration of A and B phases; number and duration of CAP sequences. Of the 23 meta-analyses, only three showed significant differences between patients and controls. Particularly, compared to HC, ADHD patients showed significantly lower total CAP rate in N2 sleep (SMD = -0.96, 95% CI = -1.73 to -0.19), CAP A1 rate in NREM sleep (SMD = -0.69, 95% CI = -1.09 to -0.30), and CAP A1 index in N2 sleep (SMD = -1.15, 95% CI = -2.28 to -0.03).

Conclusions: Our results provide specific CAP variables (total rate in N2, A1 rate in total NREM, A1 index in N2) as possible biomarkers, measurable through standardized scoring of EEG microstructure, for assessing sleep fragmentation and instability in children with ADHD.

No conflict of interest

References

[1] Cortese, S., 2015. Sleep and ADHD: what we know and what we do not know. Sleep Medicine 16, 5–6.
[2] Cortese, S., Faraone, S.V., Konofal, E., Lecendreux, M., 2009. Sleep in children with Attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. Journal of the American Academy of Child & Adolescent Psychiatry 48, 894–908.
[3] Díaz-Román, A., Hita-Yáñez, E., Buela-Casal, G., 2016. Sleep characteristics in children with Attention deficit hyperactivity disorder: systematic review and meta-analyses. Journal of Clinical Sleep Medicine 12, 747–756.
[4] Parrino, L., Ferri, R., Bruni, O., Terzano, M.G., 2012. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Medicine Reviews 16, 27–45.
[5] Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine. this issue https://doi.org/10.1371/journal.pmed.1000097 .

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OPINION
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Regulation-Focused Psychotherapy for Children (RFP-C): Advances in the Treatment of ADHD and ODD in Childhood and Adolescence

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INTRODUCTION

Externalizing behaviors are among the most common problems of childhood and affect many aspects of psychological development (Wilens et al., 2002; Liu, 2004). Children with oppositional defiant disorder (ODD) are at higher risk for developing emotional disorders as well as conduct disorder and antisocial personality disorder in adulthood, especially when they receive inadequate psychological support (Rutter et al., 2006; Stringaris and Goodman, 2009; Diamantopoulou et al., 2010; Reef et al., 2010; Hudson et al., 2018).

Parental stress, depression, and anxiety are elevated among parents of children with ODD as compared to those with typical developmental patterns (Katzmann et al., 2018; Lin et al., 2019; Manti et al., 2019). For many years, behavioral parent training (BPT) approaches, including Parent Management Training (PMT), have been the primary treatment option for children with ODD because of their robust evidence base for children with externalizing behaviors (Serketich and Dumas, 1996; Brestan and Eyberg, 1998; Kazdin and Weisz, 1998). All BPT interventions rely on traditional cognitive behavioral strategies in working primarily with the parent, and include behavioral modeling, rewards, reinforcement, and developmentally-appropriate consequences for misbehavior (Webster-Stratton, 1994; Eyberg and Bussing, 2010). A limitation associated with behavioral parent programs is elevated attrition rates for vulnerable populations affected by factors, such as low socioeconomic status, ethnic minority status, low parental functioning, high maternal stress, low parental motivation, and high child symptom severity (Kazdin, 1990; Werba et al., 2006; Fernandez and Eyberg, 2009; Lanier et al., 2011; Granero et al., 2015). Attrition in behavioral parent training may also be due to common parental attributions about where the problem resides—within the child (Baden and Howe, 1992; Bickett et al., 1996; Prout et al., 2015). Parents may feel that since the treatment approach is through the parents, they are implicitly responsible for the child's maladaptive behavior, and may avoid sustained engagement in the treatment to unburden themselves of heightened feelings of responsibility or blame. Finally, behavioral approaches usually do not directly identify, address, or engage with the underlying emotions in the child, which can become dysregulated. An inability to effectively address and engage with these emotions can lead to persistent oppositional behaviors.

In recent years, L.H., T.R., and T.A.P. developed a novel, manualized, time-limited psychodynamic treatment approach for children who present with disruptive behaviors and emotional dysregulation named Regulation-Focused Psychotherapy for Children (RFP-C; Hoffman and Rice, 2016). RFP-C conceptualizes children's externalizing behaviors as expressions of

maladaptive defense mechanisms formulated as the products of developmental delays in the implicit emotion regulation system (Rice and Hoffman, 2014). RFP-C targets the strengthening of the child's implicit emotional regulation system through direct work on the child's maladaptive defenses and provides psychoeducation and empathic support to parents of the child in distress. Throughout 16 individual play therapy sessions and four parent meetings, the clinician increases understanding that all behavior, especially disruptive behavior, has meaning in the service of emotional and behavioral regulation (Prout et al., 2019a). This insight leads to a decreased need and reliance to act on the distressing emotions (e.g., less need for disruptive behaviors) and an increased ability to tolerate, work through, and talk about the feelings that previously needed to be warded off. In addition, parents are relieved of the burden of feeling heightened responsibility as the locus of the child's problems. The clinician joins the parent and the child as a system all directly working toward improvement. The efficacy of RFP-C has been demonstrated in an initial pilot study (Prout et al., 2019b) and promising preliminary data from a recent randomized controlled trial of the intervention (Di Giuseppe et al., 2020c; Prout, 2020).

ASSESSMENT OF DEFENSE MECHANISMS IN CHILDREN

Defined as unconscious operations that protect the self from the awareness of feelings and thoughts of internal conflicts and external stressors (Vaillant, 1992; MacGregor and Olson, 2005; American Psychiatric Association, 2013), defense mechanisms play a key role in RFP-C. This therapeutic approach is based on the observation, interpretation, and developing awareness of child defense mechanisms either activated "in session" or reported in the patient narratives (Perry et al., 2020). The accuracy of defense mechanism assessment becomes essential for successfully addressing immature defensive patterns and fostering adaptive implicit emotion regulation (Di Giuseppe et al., 2019, 2020a). Despite progress in defense mechanism assessment in adults (Bond et al., 1989; Perry, 1990; Perry and Henry, 2004; Di Giuseppe et al., 2014, 2020b), only a few measures assess defenses in children (Cramer, 1991; Laor et al., 2001; Nimroody et al., 2019). None of these utilize an empirically-derived, observer-rated methodology that can be applied to psychotherapy sessions.

To fill the lack of empirical measures for child defense mechanisms assessment, one of the authors (M.D.G.), developed the Q-sort version of the Perry's Defense Mechanisms Rating Scale (DMRS-Q; Di Giuseppe et al., 2014) for clinical use. Our aim is to create a new computerized observer-rated measure for assessing defense mechanisms in children, the Defense Mechanisms Rating Scale—Q-Sort for Children (DMRS-QC), based on the theoretical background of the DMRS-Q. This will be the first attempt to provide an empirical instrument consistent with the definitions and hierarchical organization of defense mechanisms (Vaillant, 1992; American Psychiatric Association, 1994; Perry and Henry, 2004). Analyzing defense mechanisms in action in RFP-C has the potential to promote identification of the defensive profile of children with disruptive behaviors, as well as the changes that underlie successful RFP-C treatment outcome. The DMRS-QC will provide an effective and easy-to-use measure for examining defense mechanisms in children across a wide range of treatment modalities.

TRAINING IN RFP-C

One of the advantages of RFP-C is the ease with which it can be applied. As any other evidence-based psychotherapy, RFP-C requires a specific training for its reliable use.

The training includes didactic instruction, a competency quiz, and attendance at several supervision sessions. RFP-C therapists learn how to focus on behavioral, non-verbal, verbal, and play disruptions as evidence of defense mechanisms in action. Attention is also paid to the importance of the therapeutic relationship as a vehicle for therapeutic intervention. The recognition of specific defensive patterns and their underlying regulation function during the session allow the RFP-C therapist to efficiently address the implicit emotion regulation strategies and enhance changes in the child overall defensive maturity. Thus, the knowledge of definitions and functions of defense mechanisms is a crucial part of the RFP-C training.

DISCUSSION

Preliminary validation studies on the efficacy of RFP-C in treating ODD children have found that the treatment provides relief from symptoms of ODD and an increase in overall emotion regulation (Prout et al., 2019b; Prout, 2020). In working with parents, therapists help them in observing, reflecting and understanding the triggers which provoke the child's disruptive behavior. Parents can then reflect of more effective ways of addressing the triggers. Working with children who have ODD allows them to find new ways of thinking about their emotions and behaviors as a defensive response to anger, frustration, and fear. Throughout the therapeutic relationship children experience positive social relationships where unpleasant feelings can be thought about and not only acted upon.

Initially formulated in New York City as a collaboration among faculty from three institutions, The New York Psychoanalytic Society and Institute, The Icahn School of Medicine at Mount Sinai, and most importantly at the Ferkauf Graduate School of Psychology where the randomized controlled trial has been conducted, RFP-C is now practiced by many practitioners, who have had various exposures to the principles of RFP-C across the United States. Close collaboration with one of the authors (M.D.G.) has allowed us to expand the dissemination of this manualized psychotherapy to Italy, where the Center for Regulation Focused Psychotherapy for Children will begin to offer official RFP-C training in the near future.

AUTHOR CONTRIBUTIONS

MD conceived the idea and made a significant contribution by drafting the manuscript. All authors critically revised the manuscript and approved the final version to be published.

REFERENCES

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders. 4th Edn.* Washington, DC: American Psychiatric Association.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders. 5th Edn.* Washington, DC: American Psychiatric Association.

Baden, A. D., and Howe, G. W. (1992). Mothers' attributions and expectancies regarding their conduct disordered children. *J. Abnorm. Child Psychol.* 20, 467–485. doi: 10.1007/BF00916810

Bickett, L. R., Milich, R., and Brown, R. T. (1996). Attributional styles of aggressive boys and their mothers. *J. Abnorm. Child Psychol.* 24, 457–472. doi: 10.1007/BF01441568

Bond, M., Perry, J. C., Gautier, M., Goldenberg, M., Oppenheimer, J., and Simand, J. (1989). Validating the self-report of defense styles. *J. Pers. Disord.* 3, 101–112.

Brestan, E. V., and Eyberg, S. M. (1998). Effective psychosocial treatments of conduct-disordered children and adolescents: 29 years, 82 studies, and 5,272 kids. *J. Clin. Child Psychol.* 27, 180–189. doi: 10.1207/s15374424jccp2702_5

Cramer, P. (Ed.). (1991). "The defense mechanism manual," in *The Development of Defense Mechanisms* (New York, NY: Springer-Verlag), 215–234.

Di Giuseppe, M., Gennaro, A., Lingiardi, V., and Perry, J. C. (2019). The role of defense mechanisms in emerging personality disorders in clinical adolescents. *Psychiatry* 82, 128–142. doi: 10.1080/00332747.2019.1579595

Di Giuseppe, M., Perry, J. C., Conversano, C., Gelo, O. C. G., and Gennaro, A. (2020a). Defense mechanisms, gender and adaptiveness in emerging personality disorders in adolescent outpatients. *J. Nerv. Ment. Dis.* doi: 10.1097/NMD.0000000000001230. [Epub ahead of print].

Di Giuseppe, M., Perry, J. C., Lucchesi, M., Michelini, M., Vitiello, S., Piantanida, A., et al. (2020b). Preliminary validity and reliability of the novel self-report based on the Defense Mechanisms Rating Scales (DMRS-SR-30). *Front. Psychiatry* 11:870. doi: 10.3389/fpsyt.2020.00870

Di Giuseppe, M., Perry, J. C., Petraglia, J., Janzen, J., and Lingiardi, V. (2014). Development of a Q-Sort version of the Defense Mechanism Rating Scales (DMRS-Q) for clinical use. *J. Clin. Psychol.* 70, 452–465. doi: 10.1002/jclp.22089

Di Giuseppe, M., Prout, T. A., Fabiani, M., and Kui, T. (2020c). Defensive profile of parents of children with externalizing problems receiving regulation-focused psychotherapy for children (RFP-C): a pilot study. *Mediterr. J. Clin. Psychol.* 8. doi: 10.6092/2282-1619/mjcp-2515

Diamantopoulou, S., Verhulst, F. C., and van der Ende, J. (2010). Testing developmental pathways to antisocial personality problems. *J. Abnorm. Child Psychol.* 38, 91–103. doi: 10.1007/s10802-009-9348-7

Eyberg, S. M., and Bussing, R. (2010). "Parent-child interaction therapy for preschool children with conduct problems," in *Clinical Handbook of Assessing and Treating Conduct Problems in Youth*, eds R. C. Murrihy, A. D. Kidman, and T. H. Ollendick (New York, NY: Springer), 139–162. doi: 10.1007/978-1-4419-6297-3_6

Fernandez, M. A., and Eyberg, S. M. (2009). Predicting treatment and follow-up attrition in parent-child interaction therapy. *J. Abnorm. Child Psychol.* 37, 431–441. doi: 10.1007/s10802-008-9281-1

Granero, R., Louwaars, L., and Ezpeleta, L. (2015). Socioeconomic status and oppositional defiant disorder in preschoolers: parenting practices and executive functioning as mediating variables. *Front. Psychol.* 6:1412. doi: 10.3389/fpsyg.2015.01412

Hoffman, L., and Rice, T. (2016). *Manual of Regulation-Focused Psychotherapy for Children (RFP-C) With Externalizing Behaviors: A Psychodynamic Approach*. New York, NY: Routledge.

Hudson, J. L., Murayama, K., Meteyard, L., Morris, T., and Dodd, H. F. (2018). Early childhood predictors of anxiety in early adolescence. *J. Abnorm. Child Psychol.* 47, 1121–1133. doi: 10.1007/s10802-018-0495-6

Katzmann, J., Döpfner, M., and Görtz-Dorten, A. (2018). Child-based treatment of oppositional defiant disorder: mediating effects on parental depression, anxiety and stress. *Eur. Child Adolesc. Psychiatry* 27, 1181–1192. doi: 10.1007/s00787-018-1181-5

Kazdin, A. E. (1990). Premature termination from treatment among children referred for antisocial behavior. *Child Psychol. Psychiatry Allied Discipl.* 31, 415–425. doi: 10.1111/j.1469-7610.1990.tb01578.x

Kazdin, A. E., and Weisz, J. R. (1998). Identifying and developing empirically supported child and adolescent treatments. *J. Consult. Clin. Psychol.* 66, 19–36.

Lanier, P., Kohl, P. L., Benz, J., Swinger, D., Moussette, P., and Drake, B. (2011). Parent–child interaction therapy in a community setting: examining outcomes, attrition, and treatment setting. *Res. Soc. Work Pract.* 21, 689–698. doi: 10.1177/1049731511406551

Laor, N., Wolmer, L., and Cicchetti, D. V. (2001). The comprehensive assessment of defensive style: measuring defense mechanisms in children and adolescents. *J. Nerv. Ment. Disord.* 189, 360–368. doi: 10.1097/00005053-200106000-00003

Lin, X., Li, Y., Xu, S., Ding, W., Zhou, Q., Du, H., et al. (2019). Family risk factors associated with oppositional defiant disorder symptoms, depressive symptoms, and aggressive behaviors among chinese children with oppositional defiant disorder. *Front. Psychol.* 10:2062. doi: 10.3389/fpsyg.2019.02062

Liu, J. (2004). Childhood externalizing behavior: theory and implications. *J. Child Adolesc. Psychiatr. Nurs.* 17, 93–103. doi: 10.1111/j.1744-6171.2004.tb00003.x

MacGregor, M. W., and Olson, T. R. (2005). "Defense mechanisms: their relation to personality and health. an exploration of defense mechanisms assessed by the Defense-Q," in *Advances in Psychology Research*, Vol. 36, ed A. Columbus (Hauppauge, NY: Nova Science Publishers), 95–141.

Manti, F., Giovannone, F., and Sogos, C. (2019). Parental stress of preschool children with generalized anxiety or oppositional defiant disorder. *Front. Pediatr.* 7:415. doi: 10.3389/fped.2019.00415

Nimroody, T., Hoffman, L., Christian, C., Rice, T., and Murphy, S. (2019). Development of a defense mechanisms manual for children's Doll Play (DMCP). *J. Infant Child Adolesc. Psychother.* 18, 58–70. doi: 10.1080/15289168.2018.1565005

Perry, J. C. (1990). *Defense Mechanism Rating Scales (DMRS). 5th Edn.* Cambridge, MA: J. C. Perry.

Perry, J. C., Banon, E., and Bond, M. (2020). Change in defense mechanisms and depression in a pilot study of antidepressive medications plus 20 sessions of psychotherapy for recurrent major depression. *J. Nerv. Ment. Dis.* 208, 261–268. doi: 10.1097/NMD.0000000000001112

Perry, J. C., and Henry, M. (2004). "Studying defense mechanisms in psychotherapy using the Defense Mechanism Rating Scales," in *Defense Mechanisms: Theoretical, Research and Clinical Perspectives*, eds U. Hentschel, G. Smith, J. G. Draguns, and W. Ehlers (Amsterdam: Elsevier), 165–192.

Prout, T. A. (2020). "Psychodynamic treatment for children and families: outcomes of a randomized controlled trial of RFP-C," in *Winter Meeting* (New York, NY: American Psychoanalytic Association).

Prout, T. A., Gerber, L. E., Gaines, E., Hoffman, L., and Rice, T. R. (2015). The development of an evidence-based treatment: regulation-focused psychotherapy for children with externalizing disorders. *J. Child Psychother.* 41, 255–271. doi: 10.1080/0075417X.2015.1090695

Prout, T. A., Malone, A., Rice, T., and Hoffman, L. (2019a). Resilience, defenses, and implicit emotion regulation in psychodynamic child psychotherapy. *J. Contemp. Psychother.* 49, 235–244. doi: 10.1007/s10879-019-09423-w

Prout, T. A., Rice, T. R., Murphy, S., Gaines, E., Aizin, S., Sessler, D., et al. (2019b). Why is it easier to get mad than it is to feel sad? Pilot study of regulation focused psychotherapy for children. *Am. J. Psychother.* 72, 2–8. doi: 10.1176/appi.psychotherapy.20180027

Reef, J., Diamantopoulou, S., van Meurs, I., Verhulst, F., and van der Ende, J. (2010). Predicting adult emotional and behavioral problems from externalizing problem trajectories in a 24-year longitudinal study. *Eur. Child Adolesc. Psychiatry* 19, 577–585. doi: 10.1007/s00787-010-0088-6

Rice, T. R., and Hoffman, L. (2014). Defense mechanisms and implicit emotion regulation: a comparison of a psychodynamic construct with one from contemporary neuroscience. *J. Am. Psychoanal. Assoc.* 62, 693–708. doi: 10.1177/0003065114546746

Rutter, M., Kim-Cohen, J., and Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *J. Child Psychol. Psychiatry* 47, 276–295. doi: 10.1111/j.1469-7610.2006.01614.x

Serketich, W. J., and Dumas, J. E. (1996). The effectiveness of behavioural parent training to modify antisocial behaviour in children: a meta-analysis. *Behav. Ther.* 27, 171–186. doi: 10.1016/S0005-7894(96)80013-X

Stringaris, A., and Goodman, R. (2009). Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J. Am. Acad. Child Adolesc. Psychiatry* 48, 404–412. doi: 10.1097/CHI.0b013e3181984f30

Vaillant, G. E. (1992). *Ego Mechanisms of Defense: A Guide for Clinicians and Researchers.* Washington, DC: American Psychiatric Press.

Webster-Stratton, C. H. (1994). "Parent intervention content: typical questions," in *Troubled Families—Problem Children*, eds C. Webster, C. Stratton, and M. Herbert (Chicester: John Wiley and Sons), 237–308.

Werba, B. E., Eyberg, S. M., Boggs, S. R., and Algina, J. (2006). Predicting outcome in parent-child interaction therapy: success and attrition. *Behav. Modif.* 30, 618–646. doi: 10.1177/0145445504272977

Wilens, T. E., Biederman, J., Brown, S., Tanguay, S., Monuteaux, M. C., Blake, C., et al. (2002). Psychiatric comorbidity and functioning in clinically referred preschool children and school-age youths with ADHD. *J. Am. Acad. Child Adolesc. Psychiatry* 41, 262–268. doi: 10.1097/00004583-200203000-00005

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Article

Autism Spectrum Disorder and Disruptive Behavior Disorders Comorbidities Delineate Clinical Phenotypes in Attention-Deficit Hyperactivity Disorder: Novel Insights from the Assessment of Psychopathological and Neuropsychological Profiles

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Abstract: Although childhood-onset psychiatric disorders are often considered as distinct and separate from each other, they frequently co-occur, with partial overlapping symptomatology. Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) commonly co-occur with each other and with other mental disorders, particularly disruptive behavior disorders, oppositional defiant disorder/conduct disorder (ODD/CD). Whether these associated comorbidities represent a spectrum of distinct clinical phenotypes is matter of research. The aim of our study was to describe the clinical phenotypes of youths with ADHD with and without ASD and/or ODD/CD, based on neuropsychological and psychopathological variables. One-hundred fifty-one participants with ADHD were prospectively recruited and assigned to four clinical groups, and assessed by means of parent-reported questionnaires, the child behavior checklist and the behavior rating inventory of executive functions. The ADHD alone group presented a greater impairment in metacognitive executive functions, ADHD+ASD patients presented higher internalizing problems and deficits in Shifting tasks, and ADHD+ODD/CD subjects presented emotional-behavioral dysregulation. Moreover, ADHD+ASD+ODD/CD individuals exhibited greater internalizing and externalizing problems, and specific neuropsychological impairments in the domains of emotional regulation. Our study supports the need to implement the evaluation of the psychopathological and neuropsychological functioning profiles, and to characterize specific endophenotypes for a finely customized establishment of treatment strategies.

Keywords: attention-deficit hyperactivity disorder; autism spectrum disorder; oppositional defiant disorder; conduct disorder; neurodevelopment; disruptive behavior; executive functions; BRIEF; CBCL; children

1. Introduction

Attention deficit and hyperactivity disorder (ADHD) is one of the most frequent reasons for consultation in the context of mental health services for minors, causing significant impairment in various life contexts from childhood to adolescence and adulthood [1–3]. Despite previous attempts to characterize its multifaceted nature, the considerable heterogeneity of its clinical presentations still remains a major subject of debate among clinicians [1]. One of the aspects of this heterogeneity is the comorbidity between ADHD and other psychiatric disorders in at least 60% of patients, mostly other neurodevelopmental conditions—particularly autism spectrum disorders (ASD), intellectual disabilities, Tourette syndrome, and motor coordination disorders [1,4–8]; and disruptive behavior disorders—such as oppositional defiant disorder (ODD) and conduct disorder (CD); but also internalizing disorders—especially anxiety and mood disorders. The coexistence of clinical comorbidities in the context of ADHD represents a serious matter especially in terms of early detection. Consequently, therapeutic interventions are even more challenging to define, with the risk of being less specific and less effective.

The impact of comorbidities in ADHD patients can be substantial. For instance, the severity of ADHD symptomatology is further worsened, in terms of emotional and behavioral problems, when ASD phenotype overlaps along with its adaptive impairment [9–12]. Particularly, these patients exhibit more severe externalizing behaviors, and greater impairments in verbal working memory [10]. A dual diagnosis of ADHD and ASD is now allowed according to the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5) criteria [13], with rates of co-occurrence of up to 42% [14,15]. On the other hand, ADHD children with comorbid ODD and/or CD are characterized by higher rates of learning difficulties and school problems, including neglect, expulsion, and dropouts from school [16,17], and lower performances in visual–motor integration and visuo-spatial tasks [18]. Additionally, they are more prone, in adulthood, to develop drug abuse, and to be engaged in criminal behaviors and antisocial conduct [19,20].

Recent studies have raised the question of whether ADHD with associated comorbidities is merely characterized by an increased symptoms variety with enhanced impairment severity, or it represents a spectrum of distinct phenotypes [21]. Interestingly, the identification of clinical phenotypes is a developing area of research aimed at best characterizing the multifaceted aspect of neurodevelopmental disorders. Current research is focused on the fine investigation of some dimensional constructs, such as executive function (EF) deficits, which are well known to characterize the neuropsychological profiles of affected individuals [21]. Indeed, studies comparing EF in ADHD with different comorbidities have identified specific executive profiles across different clinical phenotypes. It is still unclear, however, whether these neuropsychological difficulties are either trans-diagnostic or specific to that particular clinical entity.

EF deficits in children with ADHD and/or ASD feature some shared characteristics, as shown by a recent meta-analysis by Craig and colleagues [22], including 26 studies that used different assessment measures of EF. Although the results of such studies are not entirely consistent, the authors identified overlapping impairments in EF profiles—for instance, attention deficits significantly higher both in ADHD alone and ADHD+ASD patients. While performances in working memory and fluency tasks did not differ between the clinical groups, inhibition and cognitive flexibility appeared more impaired in ASD and ADHD+ASD children. Therefore, ADHD+ASD group may show a distinct and more severe dysexecutive profile, characterized by the presence of characteristic deficits of both disorders. Additionally, a more recent study by Berenguer and colleagues [23] assessed EF profiles in children with ADHD, ASD, and ADHD+ASD, comparing them with a control group, by means of the Behavior Rating Inventory of Executive Function (BRIEF) scale. Results revealed alterations in most BRIEF variables in all three clinical groups, with the exception of inhibit and material organization subscales, which appeared significantly affected only in the two groups with symptoms of ADHD. Moreover, ADHD alone and ADHD+ASD patients showed higher deficits in the working memory, plan/organize and monitor subscales than ASD group.

On the other hand, EF deficits have also been identified in children with ODD/CD, and they partially overlap with those typically found in ADHD patients [24,25]. Some results suggest that the executive dysfunction of children with ADHD and ODD/CD might be milder than that of children with ADHD alone [26]. Contradictory findings showed, however, that EF profiles of children with ADHD+ODD/CD were impaired, especially in terms of inhibition, more slightly [27] or more severely [28], than those of children with ADHD alone. Another study assessing EF by means of different environmentally valuable tools [29] proved that adolescents with ADHD+ODD/CD are less inclined to identify effective strategies and control behavioral responses, when compared to individuals with ODD/CD only. A study by Qian and colleagues [30] compared participants with ADHD and ADHD+ODD/CD to a healthy control group using the behavior rating inventory of executive function—second version (BRIEF-2) [31], showing that the comorbid group got worse scores in inhibit, shift, and emotional control subscales. Interestingly, Hobson et al. [32] confirmed overlapping profiles in metacognitive EF profile, assessed with standardized performance test, for individuals with ADHD and ODD/CD, who share similar difficulties in tolerating delayed rewards, but showed greater impairment in emotional regulation EF in ODD/CD group. Both the studies suggest that children with ADHD and ODD/CD may present a more pronounced impairment in emotional, rather than in cognitive control. From that perspective, a fairly simplistic but clinically useful distinction among two major dimensions of EF, namely, between "cold" and "hot" EF, has been proposed [33]. While the former are more strictly related to metacognitive skills such as working memory, programming, and organization attitudes, the latter refer to processes underlying the affective modulation of behavioral responses, or in other words, the emotional regulation domain.

Only a few studies have investigated EF profiles among young people with ADHD and comorbid ASD and/or ODD/CD. A recent study by Leno et al. [34] aimed at comparing different EF tasks' performances in three clinical groups by controlling for conduct problems and ADHD symptoms. The authors concluded that only the ADHD+ASD group exhibited reduced inhibition in the go/no-go task, while all three clinical groups demonstrated greater reaction time variability than the control group; similarly, both ADHD+ODD/CD and ADHD+ASD groups showed an increase in impulse responses, whereas no differences could be detected in cognitive flexibility and switch. Finally, a study by Tye and colleagues [35], showed that stronger callous-unemotional traits in children with ASD improve performance in the go/no-go task, highlighting greater skills in inhibition processes.

Based on these findings, we hypothesize that ADHD alone and ADHD with associated comorbidities represent distinct phenotypes, with suitable clusters of psychopathological and neuropsychological features. These psychopathological and neuropsychological indices may be useful not only for differentiating clinical subtypes of patients, but also for identifying specific intervention pathways. To test this hypothesis, the main aim of our preliminary study is to describe the clinical phenotypes of minors with ADHD in its "pure" presentation and with psychiatric comorbidities (ASD and/or ODD/CD), with respect to psychopathological and neuropsychological variables, to highlight similarities and differences among the groups. This study represents one of few literature reports that evaluates clinical phenotypes of children with ADHD+ASD+ODD/CD comorbidity. Furthermore, to the best of our knowledge, this is the first study assessing EF in such a cohort through parental reports, by means of BRIEF-2 questionnaire designed to explore EF of youths in daily contexts, related to everyday life behaviors. Furthermore, the BRIEF-2 inventory finely captures the multidimensional structure of EF, and particularly the distinction between cold (metacognition) and hot (emotional regulation) dimensions.

Therefore, we assessed psychopathological profiles using a dimensional approach for identifying phenotypic domains, representing meaningful variations across multiple domains of behaviors, with two broader dimensions, internalizing and externalizing behaviors [36–38].

2. Experimental Section

2.1. Participants and Diagnostic Procedures

Our study prospectively included 151 drug-naïve participants (137 boys, age range 6–18 years old, mean age 9.51 ± 2.64 years) recruited from March 2019 to December 2019 in the Department of Child and Adolescent Psychiatry of our third level hospital with a nation-wide catchment. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

The diagnoses, based on DSM-5 diagnostic criteria, were made using historical information, and a structured clinical interview, the Italian version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) [39], administered by child psychiatry trainees under the supervision of the senior child psychiatrist. Diagnoses were finally confirmed by consensus of a multidisciplinary board.

The Italian version of the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) [40] was also routinely administered to all patients to assess the intellectual functioning. Moreover, the Italian versions of the Autism Diagnostic Observation Schedule—Second Edition (ADOS-2) [41] and of the Autism Diagnostic Interview—revised (ADI-R) [42] were administered only in those patients for whom an initial diagnosis of ASD according to DSM-5 criteria was discussed. Thus, they were used to assist clinicians in the diagnostic procedure and to either confirm or to question the ASD diagnoses by final consensus of our multidisciplinary team, as routinely performed in the Department according to international guidelines. All assessments were conducted by highly experienced psychologists specialized in child neuropsychological evaluations.

2.2. Inclusion and Exclusion Criteria

Patients were included whether they received a diagnosis of ADHD with or without comorbid ASD, ODD/CD, or both. Other associated psychiatric conditions, such as anxiety and mood disorders and learning disabilities, were accepted but not primarily considered for analytical purposes. Exclusion criteria were as follows: a total WISC-IV IQ score lower than 70 points; younger than 6 years old or older than 18 years old; use of psychoactive medications; neurologic impairments or neurodegenerative conditions. All recruited patients met inclusion criteria and agreed to participate in the study after informed consent was obtained by parents.

2.3. Clinical Groups

We identified four clinical groups in our sample: ADHD alone group, including 64 participants (12.5% girls, mean age 10.02 ± 2.49 years); comorbid ADHD+ASD group (hereinafter referred to as ADHD+ASD group), including 19 participants (5.26% girls, mean age 9.58 ± 2.69 years) who did not fulfill ODD/CD diagnostic criteria; comorbid ADHD+ODD/CD group (hereinafter referred to as ADHD+ODD/CD group), including 43 participants (9.3% girls, mean age 9.37 ± 2.95 years) who did not fulfill ASD diagnostic criteria; comorbid ADHD+ASD+ODD/CD group (hereinafter referred to as ADHD+ASD+ODD/CD group), including 25 participants (4% girls, mean age 8.40 ± 2.24 years) who fulfilled diagnostic criteria for both ODD/CD and ASD. These groups could present other associated psychiatric conditions, i.e., anxiety and mood disorders or learning disabilities.

2.4. Measures

All patients were assessed with the Italian version of the child behavior checklist for ages 6 to 18 years (CBCL-6/18) [43], a 118-item scale, completed by parents, with 8 different syndromes scales, a total problem score, and two broad-band scores designated as internalizing problems and externalizing problems. The reliability coefficients (Cronbach's alpha) were 0.82, 0.81, and 0.82, respectively [43].

The parents of all patients were asked to fill in the Italian version of the BRIEF-2 inventory [31]. The instrument is the updated version of the BRIEF questionnaire and provides a structured

assessment of EF behaviors in everyday life environments, allowing the identification of helpful clinical manifestations in different contexts, i.e., home and school. Designed for ages 5 to 18, BRIEF-2 is available in three versions (parent-report, teacher-report, and self-report). In this study, the parent-reported version was used, which includes 63 items assessing the frequency of occurrence of common behaviors in everyday life settings. BRIEF-2 is a multidimensional measurement that investigates nine factors related to specific EFs: inhibit, self-monitor, shift, emotional control, initiate, working memory, plan/organize, task monitor, organization of materials. Three composite scales are also identifiable: behavioral regulation index (BRI) (including inhibit and self-monitor), emotional regulation index (ERI) (shift and emotional control), and cognitive regulation index (CRI) (initiate, working memory, plan/organize, task monitor, organization of materials). A global executive composite (GEC) score was also computed as the sum of the three composite indexes.

2.5. Statistical Analysis

Statistical analyses were performed by means of MatLab® (MathWorks, Natick, MA, USA) and RStudio® (RStudio Inc., Boston, MA, USA) software. For each clinical variable with a continuous distribution, outliers were defined as observations lying outside the range between (first quartile − 1.5 * interquartile range) and (third quartile + 1.5 * interquartile range) and removed. For each BRIEF-2 subscale-related variable, observations were removed if the corresponding values for either the infrequency or the inconsistency scale were higher than the 99th percentile of normalized data.

The χ^2 test was used to detect significant differences (p-value < 0.05) for clinical and demographic categorial variables, such as gender and clinical comorbidities. When more than 20% of observations had expected frequencies less than 5, Fisher's exact test was performed. Analyses of variance (ANOVA) was conducted to assess significant differences (p-value < 0.05) between clinical and demographic variables with continuous distribution. Homogeneity of variances across groups was checked using Levene's test before applying ANOVA; all variables showed equal variances in the different groups (Levene's test: p-value > 0.05), so that variance homogeneity assumption was reliably satisfied. A Tukey post-hoc test was utilized whenever the ANOVA led to a statistically significant result in order to retrieve significant comparisons between variables.

Finally, we performed a principal component analysis (PCA) with Promax oblique rotation to empirically derive variables that were subsequently compared between clinical groups. All BRIEF-2 and CBCL-6/18 subscale variables were used to conduct the PCA—specifically, the inhibit, self-monitor, emotional control, shift, initiate, working memory, plan/organize, task-monitor, and organization of materials scales of former; and the anxious/depressed, withdrawn/depressed, social problems, somatic complaints and thought problems, attention problems, rule-breaking behavior, and aggressive behavior symptoms scales of the latter. A scree-plot was used to determine the appropriate number of components. Thus, a number (greater than 1) of components was extracted, and component scores for each participant were computed using regression approach. An ANOVA with Tukey's post-hoc test was then conducted to assess significant differences between groups in the continuous data of the three components identified through the PCA.

3. Results

3.1. Clinical and Demographic Characteristics

As shown in Table 1, the four clinical groups did not differ in terms of age or gender. No significant difference emerged in WISC-IV scores, nor in full-scale intelligence quotient, nor in its four composite scores; nonetheless, all four groups scored appreciably lower in working memory and processing speed composites than the verbal comprehension and perceptual reasoning composites. Clinical comorbidities are also reported; as expected, mood disorders were more expressed in the ADHD+ASD+ODD/CD group than the ADHD group only, while anxiety disorders were more prevalent in the ADHD+ASD group than the ADHD only group.

Table 1. Demographic and clinical data.

	ADHD	ADHD+ASD	ADHD+ODD/CD	ADHD+ASD+ODD/CD	*p*-Values
Subjects [a]	64 (42.38)	19 (12.58)	43 (28.48)	25 (16.56)	
Age [b]	10.02 ± 2.49	9.58 ± 2.69	9.37 ± 2.95	8.40 ± 2.24	0.0760
Adolescents [a]	19 (29.69)	6 (31.58)	10 (23.26)	4 (16)	0.5238
Gender [a]	8 (12.5)	1 (5.26)	4 (9.3)	1 (4)	0.6998
WISC-IV					
VCI [b]	104.89 ± 17.41	104.76 ± 17	104.5 ± 14.61	107.32 ± 19.24	0.9440
PRI [b]	99.11 ± 12.76	104.76 ± 17.07	103.82 ± 18.17	107.77 ± 16.19	0.2860
WMI [b]	87.07 ± 13.38	88.07 ± 7.32	88.95 ± 11.53	90.33 ± 17.45	0.8710
PSI [b]	83.56 ± 15.28	83.73 ± 13.97	89.47 ± 18.46	83.1 ± 14.89	0.5470
FSIQ or *GAI* [b]	93 ± 14.98	92.69 ± 17	96.86 ± 16.05	98.94 ± 18.06	0.5440
Comorbidities					
Mood Dis [a]	8 (12.50) *	7 (36.84)	14 (32.56)	13 (52.00) *	0.0011 *
Anxiety Dis [a]	7 (10.94) *	8 (42.11) *	7 (16.28)	8 (32.00)	0.0087 *

Data are presented either as (a) number (percentage) for dichotomous variables or (b) mean ± standard deviation for continuous variables. * *p*-values < 0.05. Abbreviations: VCI = verbal comprehension index; PRI = perceptual reasoning index; WMI = working memory index; PSI = processing speed index; FSIQ = full-scale intelligence quotient; GAI = general ability index; Dis = disorders.

3.2. Child Behavior Checklist

Only one outlier was removed from the analysis in the somatic complaints subscale of the CBCL questionnaire, belonging to the ADHD+ASD+ODD/CD group. No outliers were identified and removed based on interquartile range for all the other CBCL variables. Scores obtained by the four clinical groups and ANOVA statistics in the CBCL are illustrated in Figure 1A–C and Table 2. Significant differences were detected in the externalizing problems scale (Figure 1A) between ADHD+ASD (59.72 ± 8.10) and ADHD+ASD+ODD/CD (67.77 ± 9.62) groups, but no significant differences emerged for the internalizing and the total problems scales, though the mean scores of all four groups exceeded the clinical cut-offs for both.

Table 2. CBCL-6/18 scales.

CBCL – 6/18	ADHD	ADHD+ASD	ADHD+ODD/CD	ADHD+ASD+ODD/CD	F Value	*p*-Values
Internalizing P	62.47 ± 8.59	61.37 ± 11.62	59.95 ± 10.09	62.61 ± 12.75	0.612	0.608
Externalizing P	63.13 ± 9.28	59.72 ± 8.10	65.51 ± 8.69	67.77 ± 9.63	3.222	0.025 *
Total Problems	65.89 ± 7.24	65.22 ± 6.73	65.49 ± 8.09	68.45 ± 8.18	0.896	0.445
Anxious/Dep	62.09 ± 8.09	61.63 ± 9.62	60.88 ± 7.84	63.41 ± 9.72	0.455	0.714
Withdrawn/Dep	63.19 ± 9.73	66.11 ± 10.19	61.56 ± 7.37	65.35 ± 12.07	1.361	0.257
Somatic C	57.90 ± 6.81	56.37 ± 8.17	55.81 ± 5.99	58.48 ± 8.16	1.121	0.343
Social Problems	62.78 ± 7.14	64.84 ± 8.53	62.59 ± 7.66	67.09 ± 7.88	2.239	0.086
Thought P	60.63 ± 7.91	63.16 ± 9.59	60.84 ± 7.47	64.87 ± 9.79	1.814	0.147
Attention P	70.73 ± 8.45	67.53 ± 8.59	66.26 ± 8.55	67.10 ± 7.39	2.786	0.043 *
Rule-Breaking B	61.28 ± 7.51	56.79 ± 5.68	62.98 ± 7.57	62.36 ± 7.91	3.252	0.024 *
Aggressive B	64.78 ± 10.16	61.16 ± 8.85	65.93 ± 10.46	67.61 ± 12.35	1.448	0.231
DP Index	197.94 ± 20.62	190.32 ± 19.90	192.93 ± 23.40	198.64 ± 26.56	0.930	0.428
Affective P	66.05 ± 7.02	63.63 ± 7.54	62.70 ± 8.18	66.30 ± 10.62	1.885	0.135
Anxious P	63.25 ± 7.20	63.58 ± 7.99	62.12 ± 7.54	64.04 ± 9.09	0.380	0.767
Somatic P	55.60 ± 6.47	53.95 ± 6.83	54.72 ± 5.79	54.78 ± 7.15	0.389	0.761
ADHD P	69.09 ± 7.62	65.06 ± 8.24	67.02 ± 7.48	66.22 ± 6.65	1.870	0.137
ODD P	62.63 ± 7.47	59.63 ± 7.68	65.67 ± 8.48	65.43 ± 8.17	3.316	0.022 *
Conduct P	61.63 ± 7.86	56.53 ± 5.89	64.40 ± 8.29	65.09 ± 7.58	5.693	0.001 **
SCT	61.94 ± 7.86	62.72 ± 9.13	57.88 ± 7.27	59.30 ± 7.88	2.922	0.036 *
OCD P	56.69 ± 6.91	59.71 ± 8.82	56.33 ± 7.02	64.14 ± 10.63	5.952	0.001 **
PTSD P	65.40 ± 7.85	65.83 ± 6.44	64.33 ± 7.56	67.32 ± 8.44	0.741	0.529

Data are presented as mean ± standard deviation. * *p*-values < 0.05; ** *p*-values < 0.01. Abbreviations: B = behaviors; C = complaints; Dep = depressed; DP = dysregulation profile; OCD = obsessive compulsive disorder; P = problems; PTSD = post-traumatic stress disorder; SCT = sluggish cognitive tempo.

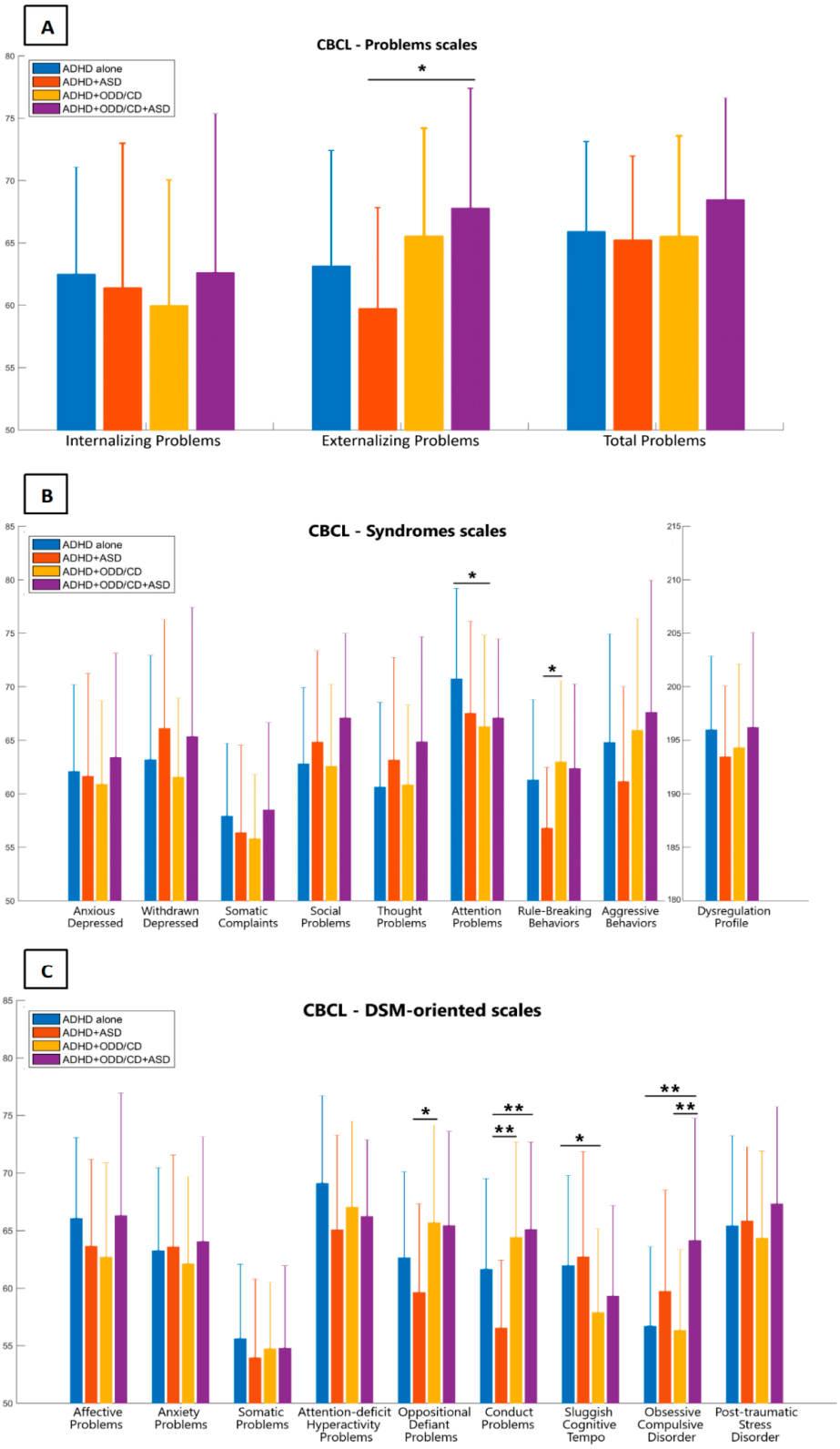

Figure 1. Scores obtained by the four clinical groups in the child behavior checklist questionnaire are illustrated: (**A**) problems scales, (**B**) syndromes scales, and (**C**) DSM-oriented scales are compared between ADHD alone group (blue bars), ADHD+ASD group (red bars), ADHD+ODD/CD group (yellow bars), and ADHD+ASD+ODD/CD group (purple bars). Graphs represent means with standard deviation bars. * p-values < 0.05, ** p-values < 0.01.

As for the syndromes scale (Figure 1B), a significant difference was found in the attention problems scale between ADHD alone (70.73 ± 8.44) and ADHD+ODD/CD groups (66.25 ± 8.55); in the rule-breaking behaviors scale the ADHD+ODD/CD group (62.97 ± 7.57) scored significantly higher than the ADHD+ASD group (56.78 ± 5.68).

As for the DSM-oriented scales (Figure 1C), the ADHD+ODD/CD group scored significantly higher (65.67 ± 8.48) than the ADHD+ASD group (59.63 ± 7.68) in the oppositional-defiant problems scale, and significantly higher (64.39 ± 8.29) than the ADHD+ASD group (56.52 ± 5.89) in the conduct problems scale, as did the ADHD+ASD+ODD/CD group (65.09 ± 7.52).

Finally, significant differences emerged in the sluggish cognitive tempo scale between ADHD alone (62.72 ± 9.13) and ADHD+ODD/CD groups (57.88 ± 7.26), and in the obsessive-compulsive problems scale between ADHD+ASD+ODD/CD (64.13 ± 10.63), and both ADHD alone (56.69 ± 6.91) and ADHD+ODD/CD groups (56.33 ± 7.02).

3.3. Behavior Rating Inventory of Executive Function

No outliers were identified and removed based on BRIEF-2 variables' interquartile ranges. Profiles of the scores obtained by the four clinical groups in the BRIEF-2 scales and ANOVA statistics are shown in Figure 2A,B and Table 3. As for the BRIEF-2 general indexes (Figure 2A), the only significant difference was found for the CRI, with higher scores obtained by ADHD alone group (70.41 ± 10.16) compared to ADHD+ODD/CD group (63.97 ± 11.41). It may be noticed that, although differences did not reach statistical significance, ODD/CD and ADHD+ASD+ODD/CD groups scored the highest in both BRI and ERI, exceeding cut-off values. Similarly, although differences among groups were not significant, all four groups presented elevated scores, exceeding the cut-off values, in the GEC scale.

Table 3. BRIEF-2 scales.

BRIEF-2	ADHD	ADHD+ASD	ADHD+ODD/CD	ADHD+ASD+ODD/CD	F Value	*p*-Values
ERI	63.92 ± 12.95	64.00 ± 11.60	65.16 ± 11.04	69.22 ± 13.10	1.086	0.358
BRI	66.40 ± 13.51	63.76 ± 11.54	70.82 ± 11.53	68.00 ± 11.93	1.562	0.201
CRI	70.42 ± 10.16	64.88 ± 10.30	63.97 ± 11.41	65.57 ± 10.42	3.551	0.016 *
GEC	70.40 ± 11.00	67.59 ± 10.47	68.29 ± 11.73	69.22 ± 12.17	0.426	0.735
Inhibition	66.23 ± 12.37	66.35 ± 10.58	71.82 ± 12.03	68.61 ± 12.34	1.809	0.149
Self-Monitor	60.22 ± 12.55	58.76 ± 12.47	64.39 ± 9.68	64.87 ± 9.06	2.036	0.112
Shift	63.48 ± 12.58	66.00 ± 11.37	59.58 ± 11.69	68.13 ± 14.85	2.408	0.059 §
Emotional C	59.98 ± 13.69	63.76 ± 11.22	68.03 ± 11.25	66.83 ± 12.75	3.698	0.014 *
Initiate	65.15 ± 10.34	64.71 ± 9.80	59.50 ± 9.66	62.43 ± 12.73	2.423	0.059 §
Working M	70.45 ± 9.57	63.82 ± 11.67	64.95 ± 10.70	65.48 ± 8.37	3.705	0.013 *
Plan/Organize	68.02 ± 10.40	63.35 ± 11.17	62.5 ± 11.65	63.09 ± 11.48	2.549	0.050 *
Org of Materials	65.21 ± 11.31	58.82 ± 10.25	58.61 ± 12.70	57.83 ± 12.61	3.802	0.012 *
Task Monitor	65.24 ± 9.01	62.59 ± 10.18	62.52 ± 11.68	59.35 ± 10.10	2.032	0.112

Data are presented as mean ± standard deviation. § *p*-values < 0.06; * *p*-values < 0.05. Abbreviations: C = control; M = memory; Org = organization.

As for the BRIEF-2 subscales (Figure 2B), inhibition, self-monitor, and task monitor subscales did not differentiate the four groups. The ADHD alone group scored significantly higher than the other three groups in working memory, plan/organize, and organization of materials subscales. The initiate subscale score was significantly higher in the ADHD alone group, compared to the ADHD+ODD/CD group, but not compared to the other two groups. The ADHD+ODD/CD group scored significantly higher than the ADHD alone in the emotional control scale, while the ADHD+ASD+ODD/CD group only approached statistical significance.

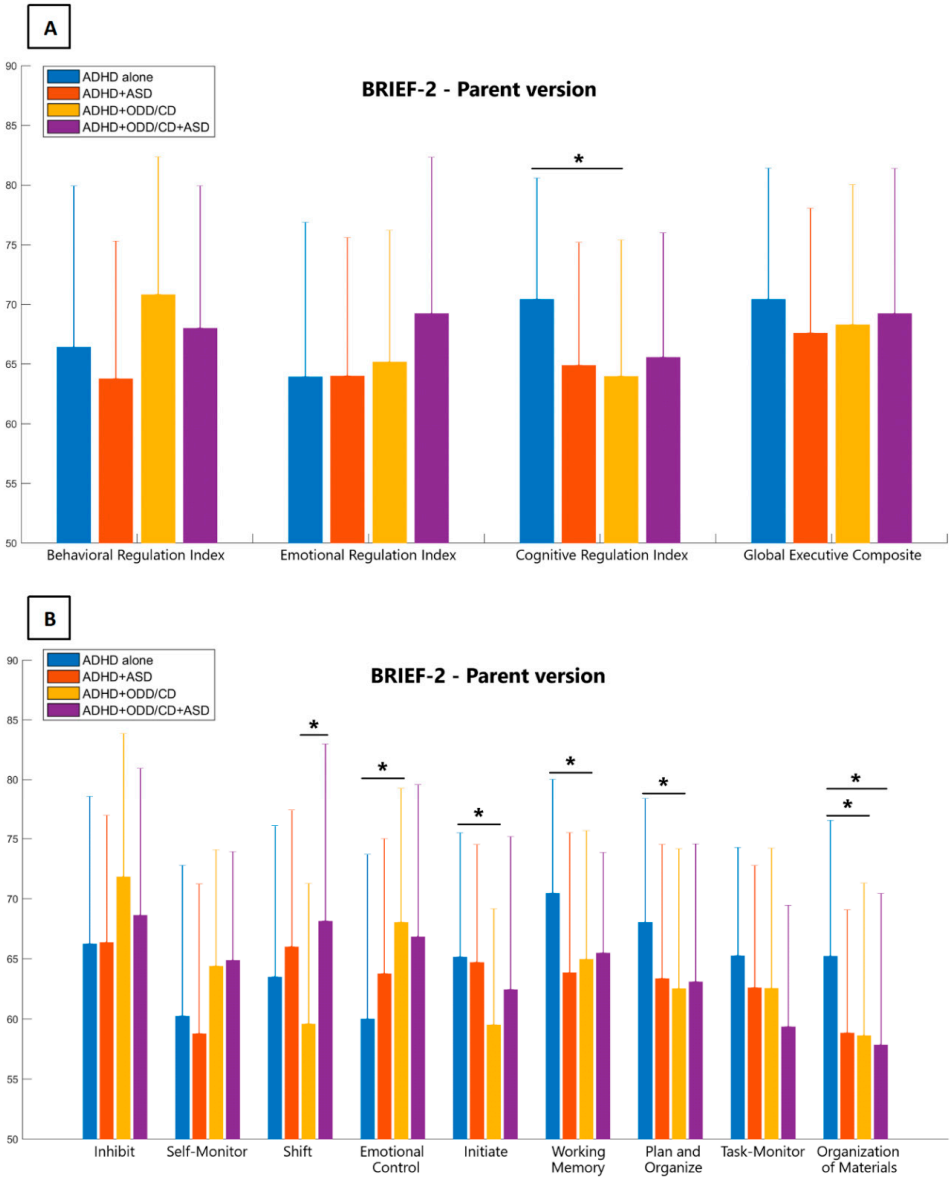

Figure 2. Scores obtained by the four clinical groups in the brief rating inventory of executive functions questionnaire are illustrated: (**A**) global indexes and (**B**) specific subscales are compared between ADHD alone group (blue bars), ADHD+ASD group (red bars), ADHD+ODD/CD group (yellow bars), and ADHD+ASD+ODD/CD group (purple bars). Graphs represent means with standard deviation bars. * p-values < 0.05.

3.4. Principal Component Analysis

The PCA we performed led to a three-component solution explaining 59% of variance. As shown in Table 4, the first rotated component (RC1) included the cognitive regulation-related subscales (initiate, working memory, plan/organize, task-monitor, and organization of Materials) of the BRIEF-2 and the attention problems of the CBCL. The second rotated component (RC2) included the shift subscale of the BRIEF-2 and the internalizing problems-related subscales of the CBCL (anxious/depressed, withdrawn/depressed, social problems, somatic complaints, and thought problems). The third rotated component (RC3) included the behavioral regulation-related subscales (inhibit and self-monitor) and the emotional control subscale of the BRIEF-2, and the externalizing problems-related subscales of the CBCL (rule-breaking behavior and aggressive behavior). High scores represent greater impairment impairments in all variables included in the different components.

Table 4. Principal component analysis.

	RC1	RC2	RC3
BRIEF-2—Plan/Organize	**0.8420**	0.2389	0.1921
BRIEF-2—Task Monitor	**0.8019**	0.0576	0.2487
BRIEF-2—Working Memory	**0.7848**	0.0050	0.1382
BRIEF-2—Organization of Materials	**0.6903**	−0.0165	0.1760
BRIEF-2—Initiate	**0.6900**	0.3306	0.0691
CBCL—Attention Problems	**0.5421**	0.3778	0.2531
CBCL—Anxious/Depressed	0.0162	**0.8254**	0.1641
CBCL—Somatic Complaints	0.2113	**0.7475**	−0.0119
CBCL—Social Problems	0.0169	**0.7259**	0.3128
CBCL—Withdrawn/Depressed	0.1771	**0.7107**	0.1029
CBCL—Thought Problems	0.0625	**0.6922**	0.2486
BRIEF-2—Shift	0.4150	**0.5162**	0.1894
BRIEF-2—Inhibit	0.2657	0.0520	**0.8497**
CBCL—Rule-Breaking Behaviors	0.2006	0.1169	**0.7782**
CBCL—Aggressive Behaviors	0.1491	0.3767	**0.7615**
BRIEF-2—Emotional Control	0.1613	0.3199	**0.6968**
BRIEF-2—Self-Monitor	0.1731	0.1165	**0.6913**
Unadjusted Eigenvalue	6.6114	2.2253	1.7460
Adjusted Eigenvalue	5.9195	1.6879	1.3212
Proportion Variance	0.2151	0.2121	0.1954
Cumulative Variance	0.2151	0.4271	0.6225

Data are presented as *z*-scores. Abbreviations: RC1 = first rotated component; RC2 = second rotated component; RC3 = third rotated component. Component loadings > 0.5 are shown in bold.

As illustrated in Figure 3, the ADHD alone group scored the highest in the RC1 component and significantly differed from the ADHD+ODD/CD and the ADHD+ASD+ODD/CD groups. As for the RC2 component, a significant difference emerged between the ADHD+ASD+ODD/CD and the ADHD+ODD/CD groups, the former scoring higher than the latter. On the contrary, the ADHD+ODD/CD group scored the highest in the RC3 component, significantly differing from the ADHD alone and the ADHD+ASD groups, while the difference approached statistical significance between the ADHD+ASD+ODD/CD and the ADHD groups.

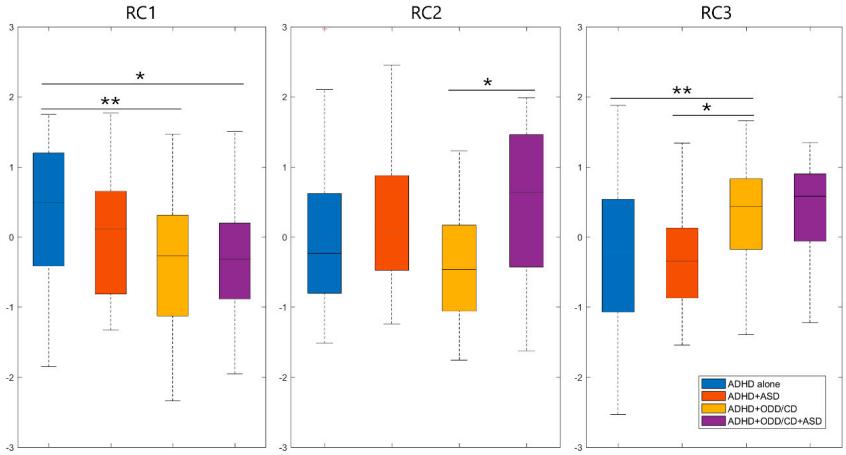

Figure 3. Scores obtained by the four clinical groups in the three components of the principal component analysis, as described in detail in the main text, are illustrated here: (**left**) RC1, (**middle**) RC2, and (**right**) RC3 are compared between ADHD alone group (blue bars), ADHD+ASD group (red bars), ADHD+ODD/CD group (yellow bars), and ADHD+ASD+ODD/CD group (purple bars). Boxplots represent medians and first and third quartiles with minimum/maximum bars. * *p*-values < 0.05, ** *p*-values < 0.01. Abbreviations: RC1 = first rotated component; RC2 = second rotated component; RC3 = third rotated component.

4. Discussion

The main aim of the present study was to identify possible phenotypes of patients with ADHD, ASD, and ODD/CD, based on EF and psychopathological domains, in order to better characterize their diagnostic frameworks. To the best of our knowledge, this is the first study assessing EF through parental reports, by means of the BRIEF-2 questionnaire, in a clinical sample of youth with comorbid conditions.

The BRIEF-2 questionnaire provides a structured assessment of EF behaviors in everyday life environments, by means of a multi-comprehensive assessment of different aspects of child behavior. A large number of world-wide clinical trials and case-control studies are indeed available to derive specific normative data based on age and gender. For these reasons, we chose the BRIEF-2 questionnaire as a valuable instrument for the assessment of EF in our sample.

The four groups in our sample were similar in terms of age, gender, and cognitive abilities. Our analyses demonstrated in the ADHD alone group a specific pattern of impairment in attentive and metacognitive domains, as revealed by CBCL questionnaire and BRIEF-2 inventory (cognitive regulation, working memory, plan/organize, organization of materials, initiate), with greater impairment in the domains of the so-called "cold" EF. These features appear more evident in the ADHD alone group when compared to those associated with comorbid conditions, which seems to support the executive dysfunction theory of ADHD [25,44,45]. Other features (i.e., inhibition, self-monitoring, shift, and task monitoring) do not seem to be affected by comorbidities, as they are indifferently present both in ADHD alone and when it is associated with ODD/CD and/or ASD.

As expected, when ADHD is comorbid with ODD/CD, it is associated not only with attention problems (but not with the sluggish cognitive tempo subscale), but also with rule breaking behavior [16]. Externalizing problems score is not significantly higher in ADHD+ODD/CD compared to ADHD alone and ADHD+ASD groups, and only the association ADHD+ASD+ODD/CD presents a significantly higher externalizing problems score. In contrast, the ADHD+ASD condition is prevalently associated with higher obsessive-compulsive traits and sluggish cognitive tempo, lower scores in rule breaking behaviors and conduct problems, and when associated with ODD/CD, lower shift abilities, compared to ODD/CD without ASD.

The PCA supports these findings. Indeed, the ADHD alone group is associated with the attention problems of CBCL, and with the cognitive regulation-related subscales (initiate, working memory, plan/organize, task-monitor, and organization of materials) of BRIEF-2. The triple comorbidity ADHD+ASD+ODD/CD is associated with both RC2 and RC3. However, the RC2 (internalizing problems-related subscales of CBCL, anxious/depressed, withdrawn/depressed, social problems, somatic complaints, and thought problems, and the shift subscale of BRIEF-2) is prevalently associated with both ADHD+ASD and ADHD+ASD+ODD/CD, with a prevalent contribution of the ASD component. On the other hand, the RC3 (externalizing problems-related subscales of the CBCL; rule-breaking behavior and aggressive behavior, inhibit, and self-monitor; and the emotional control subscale of the BRIEF-2) is prevalently associated with the ADHD+ASD+ODD/CD and ADHD+ODD/CD, with a prevalent contribution of the ODD/CD component.

While the profile of the ADHD+ODD/CD is consistent with previous findings regarding the increased severity of both externalizing symptoms and emotional dysregulation [46–48], the profile of ADHD participants with comorbid ASD is more difficult to interpret, and consistent with the notion that the ADHD+ASD phenotype does not simply reflect the sum of the symptoms of the two disorders [9,49]. Our results suggest that the presence of ASD traits modulates the severity of the externalizing symptoms, further increasing aggressive and shattering behaviors. Indeed, externalizing symptoms are lowest when ASD is associated with ADHD, even compared to ADHD alone, and are highest when ASD is associated with both ADHD and ODD/CD, thereby worsening the externalizing impact of this association. However, in line with previous studies [50], the principal component analysis we performed suggests that the ADHD+ASD+ODD/CD association further increases internalizing

problems (anxiety, mood symptoms, and social problems). Consistently, Cooper at al. (2014) correlated the presence of autistic traits in children with ADHD with a greater severity of behavioral symptoms and anxiety symptoms.

In summary, our study highlighted that, compared to ADHD alone, comorbid ODD/CD and ASD worsen externalizing and internalizing symptoms' severity, and the neuropsychological profile, but with different patterns. ADHD alone appears to be characterized by a more specific impairment of metacognitive ("cold") functioning and attentive capacities. On the other hand, comorbid ODD/CD seems more significantly related to "hot" executive dysfunctions and emotional self-regulation. Less consistent findings have been found regarding the implications of ASD comorbidity, namely, a more selective impairment in shifting, possibly related to their low cognitive flexibility.

Our data are in line with novel approaches to the classical categorical nosographic entities, using dimensional psychopathological and neuropsychological tools, in a transdiagnostic fashion, possibly with supporting evidence from biological markers, to understand the common patterns of neural dysfunction that link apparently different disorders, including ADHD and ASD [51]. Within this framework, defining a new approach to understanding mental illness, the Research Domain Criteria (RDoC) project [52] presented mixed dimensional abnormalities based on brain circuits and connectivity, which are conceptualized as underlying dysfunctions that can contribute to clinically diverging mental disorders, such as ADHD and ASD, as recently shown [53,54]. Our study does not provide biological markers, and dimensional and psychopathological tools were applied to behavioral syndromes according to the "old" DSM-5 categories. This "false assumption" [55] has been limited so far to the extension of this novel approach to child and adolescent psychiatry [56]. However, the intent of RDoC is not to become a new diagnostic classification system, but it may be useful for refining current diagnostic classifications through the lens of fundamental components, i.e., executive functions, that cut across diagnoses [56]. This approach may be also functional for understand the heterogeneity within a single DSM disorder, based on neuropsychological, psychopathological, or temperamental dimensions.

Our study shows, however, a number of limitations. Importantly, a marked discrepancy in the sizes of the four groups, particularly between the ADHD alone group and those associated with comorbid ASD. Furthermore, these groups were not recruited through an age-matching protocol design, though no significant difference in age emerged when comparing them by means of statistical tests. Additionally, we did not include a control group of healthy children. Therefore, future studies with larger age- and sex-matched samples and healthy controls could be carried out to support our results.

Moreover, an ecological parent report-based measure of EF was used in the present study. It should be noted that low correlations have been reported between performance measures and behavioral rating scales of EF in ADHD and ASD research; however, task-based measures capture only limited facets of the EF system in a limited temporal span, while neglecting the integrated multidimensional decisional process related to and based on a priority-based strategic analysis performed by the individual, which is what daily life situations often require. From this perspective, ecological measures are important to foresee the severity of dysfunction in daily life situations experienced by children at home and school, which are important settings wherein parents and teachers assessing the essential expressions of executive functioning may provide a valuable amount of information which could help clinicians in their measurements.

Another limitation of our study is that it did not include the "limited prosocial emotion" specifier. Further research could be performed, including using more participants showing high levels of callous-unemotional traits, in order to possibly identify further phenotypes of ADHD with comorbid disruptive behavior disorders. Similarly, we could not ascertain the presence of subthreshold symptoms within the different clinical domains explored by the K-SADS interview and the ADOS-2 observation; subthreshold symptoms could be usefully considered in a multidimensional perspective in future studies. Unfortunately, we could not provide teacher-rated measures of ADHD symptoms to compare parent reports, though educational observations were performed for all patients. Finally, we did not correct our tests for multiple comparisons, as all comparisons we performed would not survive

such correction with a statistical threshold below 0.001. Nonetheless, given the exploratory nature of our study and the relatively limited sample size, we believed it more convenient to keep all statistically significant comparisons while waiting for future larger studies aimed at corroborating—or invalidating—our results.

5. Conclusions

Our study provides a further contribution to a better understanding of the clinical manifestations of ADHD and comorbidities with ASD and/or ODD/CD, and suggests that specific comorbidities might help in the selection of the treatment strategies. Our findings support the need to associate, within the clinical assessment and diagnostic framework, the evaluation of psychiatric comorbidities and neuropsychological functioning, with more thoroughly characterized specific clinical phenotypes, i.e., by means of standardized neuropsychological tests in clinical settings.

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References

1. Biederman, J.; Faraone, S.V.; Spencer, T.; Wilens, T.; Norman, D.; Lapey, K.A.; Mick, E.; Lehman, B.K.; Doyle, A. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am. J. Psychiatry* **1993**, *150*, 1792–1798. [CrossRef] [PubMed]
2. Klein, R.G.; Mannuzza, S.; Ramos Olazagasti, M.A.; Roizen, E.; Hutchison, J.A.; Lashua, E.C.; Castellanos, F.X. Clinical and functional outcome of childhood attention-deficit/ hyperactivity disorder 33 years later. *Arch. Gen. Psychiatry* **2012**, *69*, 1295–1303. [CrossRef] [PubMed]
3. Mrug, S.; Brooke, B.S.; Hoza, B.; Gerdes, A.C.; Hinshaw, S.P.; Hechtman, L.; Arnold, L.E. Peer rejection and friendships in children with attention-deficit/ hyperactivity disorder: Contributions to long-term outcomes. *J. Abnorm. Child Psychol.* **2012**, *40*, 1013–1026. [CrossRef] [PubMed]
4. Barkley, R.; Fischer, M.; Edelbrock, C.S.; Smallish, L. The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. *J. Am. Acad. Child Adolesc. Psychiatry* **1990**, *29*, 546–557. [CrossRef] [PubMed]
5. Masi, G.; Mucci, M.; Pfanner, C.; Berloffa, S.; Magazù, A.; Perugi, G. Developmental pathways for different subtypes of early-onset bipolarity in youths. *J. Clin. Psychiatry* **2012**, *73*, 1335–1341. [CrossRef] [PubMed]
6. Green, J.L.; Sciberras, E.; Anderson, V.; Efron, D.; Rinehart, N. Association between autism symptoms and functioning in children with ADHD. *Arch. Dis. Child.* **2016**, *101*, 922–928. [CrossRef] [PubMed]
7. Jensen, C.M.; Steinhausen, H.C. Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *ADHD Atten. Deficit Hyperact. Disord.* **2015**, *7*, 27–38. [CrossRef]
8. Gnanavel, S.; Sharma, P.; Kaushal, P.; Hussain, S. Attention deficit hyperactivity disorder and comorbidity: A review of literature. *World J. Clin. Cases* **2019**, *7*, 2420–2426. [CrossRef]
9. Scandurra, V.; Emberti Gialloreti, L.; Barbanera, F.; Scordo, M.R.; Pierini, A.; Canitano, R. Neurodevelopmental Disorders and Adaptive Functions: A Study of Children with Autism Spectrum Disorders (ASD) and/or Attention Deficit and Hyperactivity Disorder (ADHD). *Front. Psychiatry* **2019**, *10*. [CrossRef]
10. Cooper, M.; Martin, J.; Langley, K.; Hamshere, M.; Thapar, A. Autistic traits in children with ADHD index clinical and cognitive problems. *Eur. Child Adolesc. Psychiatry* **2014**, *23*, 23–34. [CrossRef]

11. Maskey, M.; Warnell, F.; Parr, J.R.; Le Couteur, A.; McConachie, H. Emotional and behavioural problems in children with autism spectrum disorder. *J. Autism Dev. Disord.* **2013**, *43*, 851–859. [CrossRef]
12. Yamawaki, K.; Ishitsuka, K.; Suyama, S.; Suzumura, S.; Yamashita, H.; Kanba, S. Clinical characteristics of boys with comorbid autism spectrum disorder and attention deficit/hyperactivity disorder. *Pediatr. Int.* **2020**, *62*, 151–157. [CrossRef]
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; CBS Publishers: New Delhi, India, 2013.
14. Stevens, M.C.; Gaynor, A.; Bessette, K.L.; Pearlson, G.D. A preliminary study of the effects of working memory training on brain function. *Brain Imaging Behav.* **2016**, *10*, 387–407. [CrossRef] [PubMed]
15. Sprenger, L.; Bühler, E.; Poustka, L.; Bach, C.; Heinzel-Gutenbrunner, M.; Kamp-Becker, I.; Bachmann, C. Impact of ADHD symptoms on autism spectrum disorder symptom severity. *Res. Dev. Disabil.* **2013**, *34*, 3545–3552. [CrossRef] [PubMed]
16. Atherton, O.E.; Lawson, K.M.; Ferrer, E.; Robins, R.W. The role of effortful control in the development of ADHD, ODD, and CD symptoms. *J. Pers. Soc. Psychol.* **2019**. [CrossRef] [PubMed]
17. Erskine, H.E.; Norman, R.E.; Ferrari, A.J.; Chan, G.C.K.; Copeland, W.E.; Whiteford, H.A.; Scott, J.G. Long-Term Outcomes of Attention-Deficit/Hyperactivity Disorder and Conduct Disorder: A Systematic Review and Meta-Analysis. *J. Am. Acad. Child Adolesc. Psychiatry* **2016**, *55*, 841–850. [CrossRef] [PubMed]
18. Moffitt, T.E.; Silva, P.A. Self-Reported Delinquency, neuropsychological deficit, and history of attention deficit disorder. *J. Abnorm. Child Psychol.* **1988**, *16*, 553–569. [CrossRef]
19. Barkley, R.; Fischer, M.; Smallish, L.; Fletcher, K. Young adult follow-up of hyperactive children: Antisocial activities and drug use. *J. Child Psychol. Psychiatry Allied Discip.* **2004**, *45*, 195–211. [CrossRef]
20. Sibley, M.H.; Waxmonsky, J.G.; Robb, J.A.; Pelham, W.E. Implications of Changes for the Field: ADHD. *J. Learn. Disabil.* **2013**, *46*, 34–42. [CrossRef]
21. Ter-Stepanian, M.; Grizenko, N.; Cornish, K.; Talwar, V.; Mbekou, V.; Schmitz, N.; Joober, R. Attention and Executive Function in Children Diagnosed with Attention Deficit Hyperactivity Disorder and Comorbid Disorders. *J. Can. Acad. Child Adolesc. Psychiatry* **2017**, *26*, 21–30.
22. Craig, F.; Margari, F.; Legrottaglie, A.R.; Palumbi, R.; de Giambattista, C.; Margari, L. A review of executive function deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. *Neuropsychiatr. Dis. Treat.* **2016**, *12*, 1191–1202. [PubMed]
23. Berenguer, C.; Roselló, B.; Colomer, C.; Baixauli, I.; Miranda, A. Children with autism and attention deficit hyperactivity disorder. Relationships between symptoms and executive function, theory of mind, and behavioral problems. *Res. Dev. Disabil.* **2018**, *83*, 260–269. [CrossRef] [PubMed]
24. Antonini, T.N.; Becker, S.P.; Tamm, L.; Epstein, J.N. Hot and Cool Executive Functions in Children with Attention-Deficit/Hyperactivity Disorder and Comorbid Oppositional Defiant Disorder. *J. Int. Neuropsychol. Soc.* **2015**, *21*, 584–595. [CrossRef]
25. Glenn, A.L.; Remmel, R.J.; Ong, M.Y.; Lim, N.S.J.; Ang, R.P.; Threadgill, A.H.; Ryerson, N.; Raine, A.; Fung, D.; Ooi, Y.P. Neurocognitive characteristics of youth with noncomorbid and comorbid forms of conduct disorder and attention deficit hyperactivity disorder. *Compr. Psychiatry* **2017**, *77*, 60–70. [CrossRef] [PubMed]
26. Schachar, R.; Mota, V.L.; Logan, G.D.; Tannock, R.; Klim, P. Confirmation of an inhibitory control deficit in attention- deficit/hyperactivity disorder. *J. Abnorm. Child Psychol.* **2000**, *28*, 227–235. [CrossRef]
27. Shuai, L.; Wang, Y. Executive function characteristic in boys with attention deficit hyperactivity disorder comorbid learning disabilities. *Beijing Da Xue Xue Bao* **2007**, *39*, 526–530. [PubMed]
28. Van der Meere, J.; Marzocchi, G.M.; De Meo, T. Response inhibition and attention deficit hyperactivity disorder with and without oppositional defiant disorder screened from a community sample. *Dev. Neuropsychol.* **2005**, *28*, 459–472. [CrossRef]
29. Clark, C.; Prior, M.; Kinsella, G.J. Do executive function deficits differentiate between adolescents with ADHD and Oppositional Defiant/Conduct Disorder? A neuropsychological study using the Six Elements Test and Hayling Sentence Completion Test. *J. Abnorm. Child Psychol.* **2000**, *28*, 403–414. [CrossRef]
30. Qian, Y.; Shuai, L.; Cao, Q.; Chan, R.C.K.; Wang, Y. Do executive function deficits differentiate between children with Attention Deficit Hyperactivity Disorder (ADHD) and ADHD comorbid with oppositional defiant disorder? A cross-cultural study using performance-based tests and the behavior rating inventory. *Clin. Neuropsychol.* **2010**, *24*, 793–810. [CrossRef]

31. Gioia, G.A.; Isquith, P.K.; Guy, S.C.; Kenworthy, L.; Baron, I.S. Behavior rating inventory of executive function. *Child Neuropsychol.* **2000**, *6*, 235–238. [CrossRef]
32. Hobson, C.W.; Scott, S.; Rubia, K. Investigation of cool and hot executive function in ODD/CD independently of ADHD. *J. Child Psychol. Psychiatry Allied Discip.* **2011**, *52*, 1035–1043. [CrossRef] [PubMed]
33. Zelazo, P.D.; Carlson, S.M. Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Dev. Perspect.* **2012**. [CrossRef]
34. Carter Leno, V.; Chandler, S.; White, P.; Pickles, A.; Baird, G.; Hobson, C.; Smith, A.B.; Charman, T.; Rubia, K.; Simonoff, E. Testing the specificity of executive functioning impairments in adolescents with ADHD, ODD/CD and ASD. *Eur. Child Adolesc. Psychiatry* **2018**, *27*, 899–908. [CrossRef] [PubMed]
35. Tye, C.; Bedford, R.; Asherson, P.; Ashwood, K.L.; Azadi, B.; Bolton, P.; McLoughlin, G. Callous-unemotional traits moderate executive function in children with ASD and ADHD: A pilot event-related potential study. *Dev. Cogn. Neurosci.* **2017**, *26*, 84–90. [CrossRef] [PubMed]
36. Hudziak, J.J.; Achenbach, T.M.; Althoff, R.R.; Pine, D.S. A dimensional approach to developmental psychopathology. *Int. J. Methods Psychiatr. Res. Int. J. Methods Psychiatr. Res* **2007**, *16*, 16–23. [CrossRef] [PubMed]
37. Achenbach, T.M.; Ivanova, M.Y.; Rescorla, L.A.; Turner, L.V.; Althoff, R.R. Internalizing/Externalizing Problems: Review and Recommendations for Clinical and Research Applications. *J. Am. Acad. Child Adolesc. Psychiatry* **2016**, *55*, 647–656. [CrossRef]
38. Van Dam, N.T.; O'Connor, D.; Marcelle, E.T.; Ho, E.J.; Cameron Craddock, R.; Tobe, R.H.; Gabbay, V.; Hudziak, J.J.; Xavier Castellanos, F.; Leventhal, B.L.; et al. Data-Driven Phenotypic Categorization for Neurobiological Analyses: Beyond DSM-5 Labels. *Biol. Psychiatry* **2017**, *81*, 484–494. [CrossRef]
39. Kaufman, J.; Birmaher, B.; Brent, D.; Rao, U.; Flynn, C.; Moreci, P.; Williamson, D.; Ryan, N. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry* **1997**, *36*, 980–988. [CrossRef]
40. Wechsler, D. *The Wechsler Intelligence Scale for Children—Fourth Edition*; Springer: Berlin, Germany, 2004; ISBN 9780470135389.
41. Lord, C.; Rutter, M.; Di Lavore, P.; Risi, S.; Gotham, K.; Bishop, S. Autism Diagnostic Observation Schedule—Second Edition (ADOS-2). Available online: https://www.wpspublish.com/ados-2-autism-diagnostic-observation-schedule-second-edition (accessed on 22 February 2020).
42. Rutter, M.; LeCouteur, A.; Lord, C. Autism Diagnostic Interview-Revised (ADI-R). Available online: https://www.wpspublish.com/adi-r-autism-diagnostic-interview-revised (accessed on 22 February 2020).
43. Achenbach, T.; Rescorla, L. *Manual for the ASEBA School-Age Forms and Profiles: An Integrated System of Multi-Informant Assessment*; University of Vermont, Research Center for Children, Youth, & Families: Burlington, VT, USA, 2001.
44. Gioia, G.A.; Isquith, P.K.; Retzlaff, P.D.; Espy, K.A. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child Neuropsychol.* **2002**, *8*, 249–257. [CrossRef]
45. Willcutt, E.G.; Doyle, A.E.; Nigg, J.T.; Faraone, S.V.; Pennington, B.F. Validity of the Executive Function Theory of Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. *Biol. Psychiatry* **2005**, *57*, 1336–1346. [CrossRef]
46. Stringaris, A.; Goodman, R. Longitudinal outcome of youth oppositionality: Irritable, headstrong, and hurtful behaviors have distinctive predictions. *J. Am. Acad. Child Adolesc. Psychiatry* **2009**, *48*, 404–412. [CrossRef] [PubMed]
47. Thapar, A.; Harrington, R.; McGuffin, P. Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design. *Br. J. Psychiatry* **2001**, *179*, 224–229. [CrossRef] [PubMed]
48. Drechsler, R.; Zulauf Logoz, M.; Walitza, S.; Steinhausen, H.C. The Relations Between Temperament, Character, and Executive Functions in Children With ADHD and Clinical Controls. *J. Atten. Disord.* **2018**, *22*, 764–775. [CrossRef] [PubMed]
49. Craig, F.; Lamanna, A.L.; Margari, F.; Matera, E.; Simone, M.; Margari, L. Overlap Between Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder: Searching for Distinctive/Common Clinical Features. *Autism Res.* **2015**, *8*, 328–337. [CrossRef] [PubMed]
50. Mansour, R.; Dovi, A.T.; Lane, D.M.; Loveland, K.A.; Pearson, D.A. ADHD severity as it relates to comorbid psychiatric symptomatology in children with Autism Spectrum Disorders (ASD). *Res. Dev. Disabil.* **2017**, *60*, 52–64. [CrossRef]

51. Insel, T.R. The nimh research domain criteria (RDOC) project: Precision medicine for psychiatry. *Am. J. Psychiatry* **2014**, *171*, 395–397. [CrossRef]
52. Cuthbert, B.N. The RDoC framework: Facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry* **2014**, *13*, 28–35. [CrossRef]
53. Di Martino, A.; Zuo, X.N.; Kelly, C.; Grzadzinski, R.; Mennes, M.; Schvarcz, A.; Rodman, J.; Lord, C.; Castellanos, F.X.; Milham, M.P. Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. *Biol. Psychiatry* **2013**, *74*, 623–632. [CrossRef]
54. Kernbach, J.M.; Satterthwaite, T.D.; Bassett, D.S.; Smallwood, J.; Margulies, D.; Krall, S.; Shaw, P.; Varoquaux, G.; Thirion, B.; Konrad, K.; et al. Shared endo-phenotypes of default mode dsfunction in attention deficit/hyperactivity disorder and autism spectrum disorder. *Transl. Psychiatry* **2018**, *8*. [CrossRef]
55. Beauchaine, T.P.; Hinshaw, S.P. RDoC and Psychopathology among Youth: Misplaced Assumptions and an Agenda for Future Research. *J. Clin. Child Adolesc. Psychol.* **2020**, *49*, 322–340. [CrossRef]
56. Garvey, M.; Avenevoli, S.; Anderson, K. The National Institute of Mental Health Research Domain Criteria and Clinical Research in Child and Adolescent Psychiatry. *J. Am. Acad. Child Adolesc. Psychiatry* **2016**, *55*, 93–98. [CrossRef] [PubMed]

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Review article

Long term methylphenidate exposure and growth in children and adolescents with ADHD. A systematic review and meta-analysis

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ABSTRACT

Background: Methylphenidate (MPH) is an efficacious treatment for ADHD but concerns have been raised about potential adverse effects of extended treatment on growth.
Objectives: To systematically review the literature, up to December 2018, conducting a meta-analysis of association of long-term (> six months) MPH exposure with height, weight and timing of puberty.
Results: Eighteen studies (ADHD n = 4868) were included in the meta-analysis. MPH was associated with consistent statistically significant pre-post difference for both height (SMD = 0.27, 95% CI 0.16-0.38, p < 0.0001) and weight (SMD = 0.33, 95% CI 0.22-0.44, p < 0.0001) Z scores, with prominent impact on weight

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growth
puberty

during the first 12 months and on height within the first 24-30 months. No significant effects of dose, formulation, age and drug-naïve condition as clinical moderators were found. Data on timing of puberty are currently limited.

Conclusions: Long-term treatment with MPH can result in reduction in height and weight. However, effect sizes are small with possible minimal clinical impact. Long-term prospective studies may help to clarify the underlying biological drivers and specific mediators and moderators.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders (Polanczyk et al., 2014). It is characterized by two main symptom dimensions, inattention and motor restlessness/impulsivity, which are pervasive and result in significant functional impairments (APA, 2013). According to international guidelines, treatment for ADHD should follow a multimodal approach that combines behavioural and pharmacological treatment (NICE, 2018; Pliszka et al., 2006a; Taylor et al., 2004). The first-choice medication (Taylor et al., 2004) and the most frequently used treatment for ADHD in Europe is Methylphenidate (MPH). Positive effects of methylphenidate and other psychostimulants have been reported in numerous studies and meta-analyses, across a range of outcomes including core ADHD symptoms (Cortese et al., 2018; Coghill et al., 2017; Faraone and Buitelaar, 2010; Storebø et al., 2015). However, their use can be accompanied by a range of adverse effects including elevated blood pressure and heart rate (Hennissen et al., 2017), sleep disturbance, nervousness, reduced appetite, headache and abdominal pain.

Effects on growth are also prominent among these adverse effects. These include weight loss and height gain reduction occurring after extended use (Graham and Coghill, 2008; Cortese et al., 2013; Storebø et al., 2018). Although many studies have measured the effects of clinical treatment with stimulant medications on growth and weight loss, there is as yet no clear consensus as to whether observed changes in growth are related specifically to stimulant medication or to other causes such as the condition of ADHD itself. Furthermore, the overall clinical significance of medication-related reductions in height during development has been questioned (Vitiello, 2008) – with researchers arguing that final adult height should be considered the ultimate index of growth for a correct evaluation (Jensen et al., 2004). The key question for these researchers is whether children treated with medication obtain their expected height as adults, or not (Swanson et al., 2017). Studies providing longitudinal data suggest that stimulants reduce growth in height by as much as 1 cm/year during the first three years of treatment and that this reduction can be clinically significant (Poulton, 2005). Some data suggest that these effects attenuate over time so that final adult stature is not affected by prior stimulant exposure (Faraone et al., 2008; Biederman et al., 2010; Kramer et al., 2000; Peyre et al., 2013). Finally, other authors reported that the height or weight changes might be a natural symptom of ADHD rather than a consequence of medication (Spencer et al., 1996; Hanc and Cieslik, 2008; Swanson et al., 2007). While, on average, reported effects of stimulants on growth appear to be modest, a substantial variability has been observed, with some children seemingly completely unaffected (Biederman et al., 2010; Findling et al., 2009; Zachor et al., 2006), whilst others experience significant growth suppression (Pliszka et al., 2006b; Charach et al., 2006; Zhang et al., 2010; Poulton et al., 2012).

A recent publication by Swanson and the MTA Cooperative Group re-examined children's physical growth for cost-benefit evaluation and revealed that the "*New medicated subgroup*" was, at the 36 months follow up point, 3.04 cm shorter and 2.71 kg lighter than the "*Not medicated group*" with a growth-related cost persisting into adolescence and adulthood. During this last phase of observation, orthogonal comparisons revealed that treated cases were shorter than the untreated cases, indicating that height suppression was correlated to treatment (Swanson et al., 2018).

Earlier detailed reviews (Poulton, 2005; Faraone et al., 2008) substantially confirmed that treatment with stimulants (methylphenidate and amphetamine) in childhood, may reduce expected height and weight when only high quality studies are considered (longitudinal designs analysing changes in z-scores). Studies that failed to detect effects on growth were generally of poor methodological quality. All these reviews, although extensive and very well conducted, did not completely resolve the key issues related to the effects of MPH on growth. They concluded that more work was still needed in order to both clarify the effects of variations in formulation and dosing regime and better understand how individual characteristics moderate MPH effects. Thus, following the European Committee for Medicinal Products for Human Use (European Union, 2009) requesting provision for further safety information about methylphenidate, specifically asking for more data on the long-term effects of MPH on growth and development in children and adolescents, we aimed to perform an update on the topic by exploring the recent most relevant published literature and by conducting a meta-analysis where data were adequate.

Compared to previous searches we aimed to specifically explore the effects of methylphenidate exposure on growth (excluding other stimulant medications when possible), by selecting a reasonable time of treatment exposure (> 6 months) for a mid and long term evaluation. As more than ten years have passed since the extensive review performed by Faraone et al. (2008) was published, our objective was to integrate new evidences of the last ten years with the hypothesis of including more studies with stronger methodologies. This could allow a more precise estimate of pooled effects to be made and an analysis of heterogeneity to be undertaken through sensitivity analyses in order to address the following questions:

- *Is MPH associated with clinically significant reduction in growth in children with ADHD?*
- *Are such effects moderated/predicted by patient's characteristics (baseline auxological parameters, age, gender)?*
- *Do dose and formulation (immediate release vs long acting), length of treatment, previous treatment history or continuous versus non-continuous therapy moderate the effect of MPH on growth?*
- *Does MPH affect the timing of puberty?*
- *Does MPH affect body composition and/or bone metabolism?*

2. Methods

The systematic review was restricted to studies examining the effects of methylphenidate on growth in children and adolescents suffering from ADHD. There was no restriction with regards to ADHD subtype, presence of co-morbid disorders, gender, or socio-economic status of participants.

Since no long-term randomized clinical trials reporting standardized data on growth outcomes are available, for the purpose of this review all observational, open-label, retrospective and prospective study designs, with or without a control group were included.

2.1. Inclusion and Exclusion criteria

Studies were eligible for inclusion in a quantitative analysis if they:

Table 1
Characteristics of the studies included in the quantitative analysis.

Author, year	Study design	N ADHD [completers*] (final FU)	Gender % Male	Type of sample	Controls [completers*]	Age mean ± SD [range]	Med Formulation	MPH Dose mg/d (mg/kg/d) [range]	FU length months (length of treat, m)	Primary outcome measures	Main results
Lisska and Rivkees, 2003	Retrospective	84	81	Drug naïve	87 siblings no ADHD	8.7 ± 2.7	MPH	22.5 ± 7.8 [5-85]	36	Height/ Height velocity Z scores absolute value BMI	Effect on height in both gender, dose correlation in males
Poulton and Cowell, 2003	Retrospective	51	86.2	Drug naïve	-	7.2 ± 1.9 [3.1-11.4]	MPH/AMP	27.5 (1.0 ± 0.24) [10-40]	42 (23)	Height/ weight/ Height velocity Z scores	Effect on height and weight after 6 and 18 months up to 30 months. Effect on height velocity during first 30 months
Bereket et al., 2005	Prospective	72 (14)	71.4	Drug naïve	-	8.12 ± 1.8 [6.47-10.42]	MPH	(0.75)	16	Height/ weight/BMI Z scores	No effects on height, weight and BMI by MPH treatment
Charach et al., 2006	Observational prospective	79 (49)	70.8	Drug naïve	-	8.3 ± 1.5 [6-12]	MPH/AMP (IR e LA)	31.9 (0.6)	60	Height/ weight Z scores	Dose related effect on height and weight. ≥ 1,5 mg/kg/day on weight 1st y ≥2,5 mg/kg/day on height in 4 y
Pliszka et al., 2006b	Retrospective Comparative	113 (42)	80.4	-	66 AMP (21)	8.5 ± 2.1 [7-17]	MPH (IR e LA)	34.8	36 (2.6)	Height/ Weight/BMI Z scores	Weight and BMI loss AMP > MPH, MPH > first 12 months. Mild correlation with cumulative dose for height
Spencer et al., 2006	Observational prospective	407 [178]	82.8	154 No drug naive	-	9.4 ± 1.7 [6-13]	MPH (OROS)	34.3-43.7 (1.1-1.2)	21	Height/ Weight/BMI Z scores Height/ Weight/BMI Deficit Malnutrition Index	Slight height and BMI decrease during first 12 months. Slight weight loss first 5 months Effects > drug naïve, younger ss, continuous treatment
Zachor et al., 2006	Retrospective	81	65.4	-	-	8.5 [5-19]	MPH/AMP	-	36	Height/ Weight Z scores BMI absolute values	Impact on weight > first months up to 24 months. Weight loss related to basal parameters and age (prepuberal). No impact on height in the long term
Faraone and Giefer, 2007	Retrospective	154 [127]	-	57 Drug naïve	-	[6-12]	MPH (MTS)	[6-43.2]	36	Height/ weight/BMI Z scores	Mild effect on height, weight and BMI mostly during

(continued on next page)

Table 1 (*continued*)

Author, year	Study design	N ADHD [completers*] (final FU)	Gender % Male	Type of sample	Controls [completers*]	Age mean ± SD [range]	Med Formulation	MPH Dose mg/d (mg/kg/d) [range]	FU length months (length of treat, m)	Primary outcome measures	Main results
											first 12 months. Relation to dose, drug naïve condit and basal auxol parameters
Swanson et al., 2007	Observational prospective	485 [370]	79	88 Drug naïve *"Newly med"*	260 LNCG	[7.7-9.0]	MPH/AMP	30.3	36	Height/ weight/BMI Z scores	Effect on weight and height. Relation to dose (height) and length of treat (weight and height)
Poulton et al., 2012	Prospective	34 (24)	85.2	Drug naïve	241 DXA at baseline	7.3 ± 1.3 [4.7-9.1]	MPH/AMP (IR e LA)	24.3 ± 6.2 (0.91 ± 0.19)	36	Height/ weight/BMI Z scores	Effect on weight/ height/BMI > first 6 months. Bone maturation deceleration
Durá-Travé et al., 2012	Retrospective	187 (160)	69	-	-	8.14 ± 1.60	MPH (OROS)	[25-55]	48	Height/ weight/BMI Z scores Mean diff between expected and observed values	Effect on weight and height > first 30 months. Effect on weight from 12 moth, on height from 24 month
Germinario et al., 2013	Observational prospective	1758 [590] 296 MPH (90)	87.1	Drug naïve	294 ADHD on ATX	[6-18]	MPH-IR	18.8 ± 10.7 (0.48 ± 0.22)	24	Height/ weight absolute values and percentiles Height Z score	Effect on height ATX > MPH after 12 months
Harstad et al., 2014	Partially retrospective	243 [171]	72.0	-	394	10.2 ± 3.5	MPH/AMP	26.2 ± 10.7	-	Height Z score Peak height velocity (PHV) Adult Height	ADHD = controls and ADHD MED = NO MED for PHV and adult height NO significant decrease on height Z score Positive relation between length of treatment and PVH in males
Powell et al., 2015	Observational retrospective	410	90	Drug naïve			MPH/AMP	9.2 [3.3-17.6]	>72	Height/ weight Z scores	Effect on weight and height with attenuation after 12-47 months but baseline values not reached at 72+ months. Effect dose related
Poulton et al., 2016	Prospective	73 [40]	81	Drug naïve	siblings 35 [22]	7.96 ± 1.82 [4.08 - 11.61]	MPH/AMP (IR e LA)	25.5 ± 8.7 (0.87 ± 0.34)	36	Height/ weight Z scores and height/	Effect on weight and height. Effect on weight > in first 6 months.

(*continued on next page*)

Table 1 (*continued*)

Author, year	Study design	N ADHD [completers*] (final FU)	Gender % Male	Type of sample	Controls [completers*]	Age mean ± SD [range]	Med Formulation	MPH Dose mg/d (mg/kg/d) [range]	FU length months (length of treat, m)	Primary outcome measures	Main results
										weight velocity	Larger doses > effects
Landgren et al., 2017	Retrospective Within subjects design	70	87	-		12 ± 2.4 [8-17]	LA MPH	(0.95) [0.4-2.6]	39	Height/weight/BMI Z scores	Slight impact on height and weight. Baseline height (taller) influenced height at follow up. Larger doses > effects on weight and BMI
Díez-Suárez et al., 2017	Observational retrospective	342	80.13	Drug naïve	-	10.7 ± 3.84 [6-18]	MPH any formulation	59.7 ± 22.9 (1.25 ± 0.40)	27 14-41^	Height/weight/BMI Z scores	Effect on BMI and weight. Effect on height on children 6-12 Effect on height > females, younger and higher doses
Granato et al., 2018	Retrospective	159 [93]	78.5	93 Drug naïve	334	[5.1 -13.8]	MPH	-	30	Height/BMI Z scores	No impact on height Significant decrease in BMI

[completers*] : available growth data; **FU**: Follow up; **SD**: Standard Deviation; **ADHD**: Attention Deficit/Hyperactivity Disorder**; MPH**: Methylphenidate; **IR**: Immediate release; **LA:** Long Acting; **AMP**: amphetamine; **y:** year; **ss:** subjects.
[completers*] : available growth data; **FU**: Follow up; **SD**: Standard Deviation; **ADHD**: Attention Deficit/Hyperactivity Disorder**; LNCG:** Local Normal Comparison Group; **MPH**: Methylphenidate; **IR**: Immediate release; **LA:** Long Acting; **MTS:** Methylphenidate Transdermal Delivery System; **AMP**: amphetamine; **y:** year; **auxol.:** auxological; **condit.**: condition.
[completers*] : available growth data; **FU**: Follow up; **m**: mean; **SD**: Standard Deviation; **ADHD**: Attention Deficit/Hyperactivity Disorder; **MPH**: Methylphenidate; **IR**: Immediate release; **LA:** Long Acting; **AMP**: amphetamine.

- enrolled subjects with a diagnosis of ADHD formulated according to DSM criteria (DSM-III, DSM-III-R or DSM-IV) or of Hyperkinetic Disorder according to the previous ICD system;
- reported a continuous length of treatment of at least six months.
- examined subjects on MPH as a mono-therapy or associated with other stimulant medications when it was not possible to distinguish between the two drugs;
- were written in English;
- reported data on humans.
- Recorded growth parameters and/or data on pubertal maturation in children ($\geq$ 6 and $<$ 12 years) and/or adolescents ($\geq$ 12 and $<$ 18 years) exposed to MPH, using adequate population-based norms for height and weight.

Studies were excluded if:

- they were restricted only to the exposure of the drug in adulthood;
- the effects on growth were related exclusively to psycho-stimulants other than MPH;
- they reported data on animals.

2.1.1. Outcome measures

Only studies clearly reporting Z scores for height and/or weight, expressed as mean and Standard Deviation (SD), baseline (pre) and at the endpoint (post), were included into the quantitative analysis. The outcome measures were the pre–post treatment change in height and weight Z scores related to MPH treatment. Where more than one follow-up measurement was performed within the same study, the outcomes of the longest follow-up were recorded in order to explore measurements of growth parameters over the longest follow-up interval. Where studies included auxological parameters from both MPH and a comparison arm (e.g., not medicated ADHD or typically developmental control group), only the parameters for the medication treatment group were included in the main analysis. A separate analysis was performed including Δ Standard Mean Difference (SMD) in order to compare the medicated and not medicated/non ADHD sample.

When data were available, we also reviewed the changes in body composition (lean tissue, fat masses, fat distribution, bone mineral density, bone turnover) and the onset of pubertal maturation.

2.2. Search strategy

We first searched for the most relevant published reviews on the topic (Faraone et al., 2008; Poulton, 2005; Ptacek et al., 2009, 2014; Rapport and Moffitt, 2002). In a second search we considered individual trials published from the 70 s up to December 2018 and not included in the previous reviews, by using the following research sources (PubMed, MEDLINE via Ovid SP, EMBASE via Ovid SP, PsycINFO via Ovid SP).

The search strategy involved medical subject headings [MeSH] and terms as free text word (see Appendix B including a flow chart of the search strategy Fig. A1).

Articles were all screened by two of the authors (SC, CB) on the basis

Table 2
Studies examining possible clinical correlates.

Study	Outcome measure	N ADHD MPH	FU time		Dose		Length of treatment		Drug holidays		Drug Naïve condition		Gender		Age		Pubertal stage		Basal auxological parameters	
			H	W	H	W	H	W	H	W	H	W	H	W	H	W	H	W	H	W
Lisska and Rivkees, 2003	Z score	84			YES (M)				NO											
Poulton and Cowell, 2003	Z score	51	YES	YES					NO											
Bereket et al., 2005	Z score	72																		
Charach et al., 2006	Z score	49			YES	YES	YES	NO							NO					
Pliszka et al., 2006b	Z score	113			POSS		NO		NO											
Spencer et al., 2006	Z score	178							NO	POSS	NO	YES			YES	NO			NO	NO
Zachor et al., 2006	Z score	81		YES												YES				YES
Faraone and Giefer, 2007	Z score	127	YES	YES	NO	YES		YES			NO	YES							YES	YES
Swanson et al., 2007	Z score	370			YES	YES	YES	YES												
Durá-Travé et al., 2012	Z score	160	YES	YES	NO	NO							NO	NO	NO	NO				
Poulton et al., 2012	Z score	24	YES	YES																
Germinario et al., 2013	Z score	297	YES	YES																
Harstad et al., 2014	PHV	243					YES													
Diez-Suarez et al., 2017	Z score	342			YES	YES	POSS	YES					YES	YES	YES	NO				
Powell et al., 2015	Z score	410			YES	YES							NO	NO	NO	NO			YES	^
Poulton et al., 2016	Z score	73	YES	YES	YES	YES			NO	POSS					YES	YES				YES
Landgren et al., 2017	Z score	70			NO	YES	NO	-					NO	-	NO	-			YES	-
	Percentile																			
Granato et al., 2018	Z score	252		NO																YES

H: height; **W:** weight; **FU:** Follow Up; **M:** males; **POSS:** possible; **PHV:** Peak Height Velocity; ^ = Patients with decrease in relative weight within the first 12 months experienced a more profound relative weight loss.; patients with weight loss in the first year experienced a more serious relative height deficit.

of title and abstract. Assessment of articles for final inclusion was based on full text review. Discrepancies were resolved by consensus between the two authors and, in case of disagreement, a third author (AZ) acted as arbitrator.

From each paper the following data were extracted into an Excel file:

- Characteristics of the studies: year of publication, location, study design, sample size, diagnostic criteria;
- Characteristics of study participants: sex distribution, mean and range of age, number of growth data information, whether ADHD were medication naïve at baseline or previously exposed to ADHD medications;
- Characteristics of medication: mean and range doses, formulation, length and continuity of treatment;
- Primary and secondary outcome measurement and time of outcome measurements.

2.2.1. Data analysis

A quantitative analysis was conducted for those studies which clearly reported Z scores for height and/or weight expressed as mean and SD at baseline and after methylphenidate treatment. The outcome of the latest follow-up was recorded. A pre–post within-group design was used to meta-analyse medication effects on height and weight. Data were analysed using RevMan 5.3 (http://ims.cochrane.org.revman). Given the heterogeneity of sample characteristics and design in the included studies, individual effect sizes (ES) were calculated by using a random effects model and expressed as SMD with 95% confidence intervals. ES of about 0.3 represents a small effect, while an ES of about 0.5 or 0.8 indicate respectively a medium and large effect (Cohen, 1977). Heterogeneity was assessed using the I^2 test.

3. Results

Tables 1 and 2 summarise the main information of the 18 studies included in the quantitative analysis of this systematic review.

3.1. Characteristics of the studies included

Included studies were conducted between 1976 and 2016 with publication years ranging between 2003 and 2018.

Seven studies were performed in the USA, three were from Australia (Poulton and Cowell, 2003; Poulton et al., 2012, 2016), one each from Canada (Charach et al., 2006), Spain (Durá-Travé et al., 2012), Turkey (Bereket et al., 2005), Italy (Germinario et al., 2013), Sweden (Landgren et al., 2017), Denmark (Powell et al., 2015) and Brasil (Granato et al., 2018). Five studies were multicentre (Spencer et al., 2006; Faraone and Giefer, 2007; Swanson et al., 2007; Lisska and Rivkees, 2003; Germinario et al., 2013) with a number of sites ranging between 2 and 87. All multi-site studies were conducted in USA apart from Germinario et al., that was conducted in Italy.

The selected studies include a total of 4868 children and adolescents with ADHD (range = 34-1758; mean = 270.44; SD = 396.60; median = 156); around 80% of included participants were male; 3268 of them received, at least at a certain point, MPH treatment. Adequate data on the impact of MPH on growth and development were available for 2570 subjects (range = 24-410; mean = 142.77; SD = 128.19; median = 88).

Age of subjects at the beginning of treatment was between 3 and 17 years (mean age 8.79, SD = 1.34). Nine studies were limited to pre-adolescent participants (<13 years, mean age = 8.53, DS = 0.80), while the rest of the studies examined both children and adolescents up to 18 years of age.

Only three studies considered pubertal stage (Tanner and Whitehouse, 1976). Bereket et al. (2005) specified that they only included pre-pubertal participants. Zachor et al. (2006), used a simplified method to define the pre-pubertal stage (age range between 4.5 and 8.5 years to

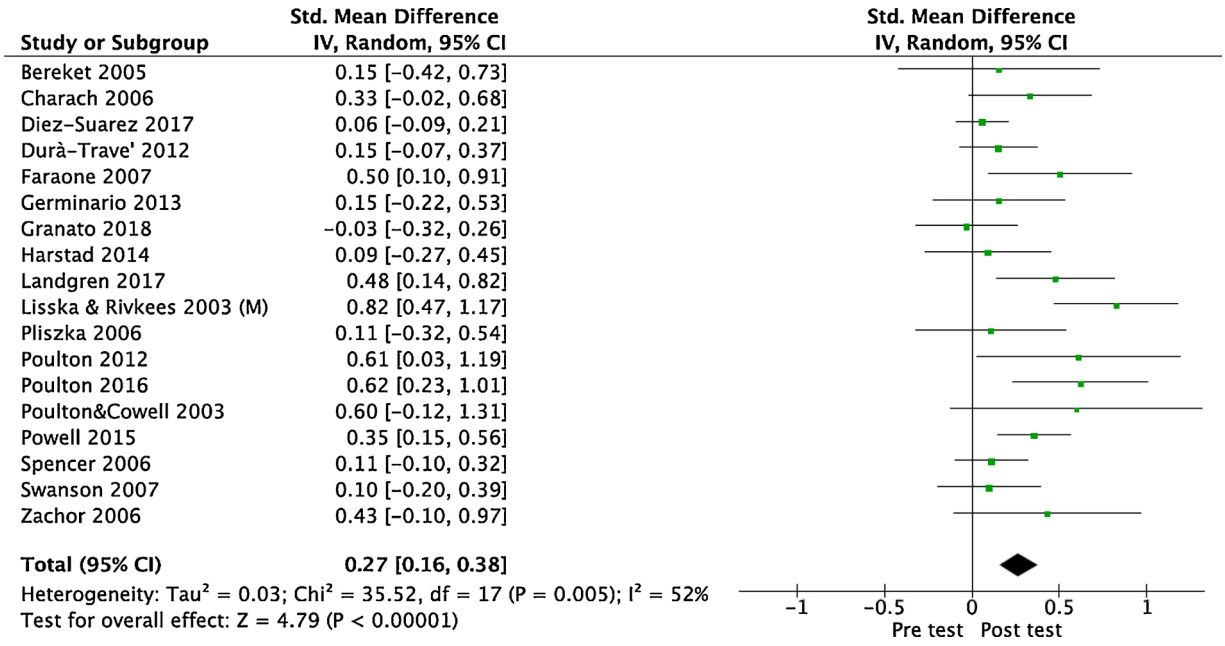

Fig. 1. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of height (MPH and AMP).
Pre–post within-group design analyses for height with stimulant therapy (methylphenidate and amphetamine, when it was not possible to distinguish between the two) at the last follow up assessment.

assure that both genders could be included); Díez-Suárez et al. (2017) as well, used a simplified method by dividing the sample into children (age range between 6 and 12 years) and adolescents (between 13 and 18 years).

3.1.1. *Study Designs and follow up*

All the included studies were observational; 9 were defined as retrospective (based on reviews of clinical records), one was designated as partially retrospective combining data from clinical records and from longitudinal follow up. Eight were prospective.

Duration of follow-up and mean duration of medication treatment ranged between a minimum of 21 months and a maximum of over 72 months (mean: 37.56 months; SD 13.83; median 36).

Eight of the 18 studies included a control sample: in all 1624 subjects (range = 35-394; mean = 232; DS = 133.99; median = 260) including either ADHD subjects (n = 360) or non-ADHD comparisons (n = 1264) or both. Majority of the studies (Harstad et al., 2014; Poulton et al., 2012, 2016; Swanson et al., 2007; Lisska and Rivkees, 2003; Swanson et al., 2017; Granato et al., 2018) included typically neurodevelopmental children as controls, however only three of them reported data for a longitudinal comparison (Swanson et al., 2007; Lisska and Rivkees, 2003; Poulton et al., 2016), while group comparison data where mostly limited only to a single observation at baseline in the other studies. Effects of methylphenidate were, in one case compared to amphetamines (Pliszka et al., 2006b), or, in another case, to atomoxetine (Germinario et al., 2013).

Ten studies selected only initially drug naive patients (Bereket et al., 2005; Charach et al., 2006; Germinario et al., 2013; Lisska and Rivkees, 2003; Poulton et al., 2012; Poulton and Cowell, 2003; Díez-Suárez et al., 2017; Powell et al., 2015; Poulton et al., 2016; Granato et al., 2018), while other 7 included mixed populations that included both drug naive and previously treated patients.

Within the selected 18 studies, the MTA was initially designed as a 14-month randomized clinical trial (RCT) to test hypotheses about four treatment strategies in 579 ADHD children aged 7-9.9 years: medication management (Med), behavior modification (Beh), their combination (Comb), or treatment-as-usual in a community comparison (CC). After the RCT phase, the MTA transitioned into an observational long-term follow-up (LTF) phase, during which medication use was monitored prospectively in terms of patterns of stimulant medication during follow up time as *non-medicated, newly medicated, consistently medicated and inconsistently medicated* (Swanson et al., 2007; Greenfield et al., 2014) or long-term patterns of prospective treatment with medication from childhood through adolescence: *Consistent, Inconsistent,* and *Negligible* (Swanson et al., 2017; The MTA Cooperative Group, 1999).

3.1.2. *Medication and therapeutic dosages*

Eight studies examined methylphenidate (MPH) together with other stimulants (amphetamine). One of them (Pliszka et al., 2006b) compared a sample of subjects continuously treated with MPH for at least one year with a sample treated with amphetamines. The other ten specifically examined the effect of MPH but included different formulations: seven examined immediate and/or modified release formulations, one a trans-dermic patch (Faraone and Giefer, 2007), while the other two studies did not specify the formulation (Granato et al., 2018; Lisska and Rivkees, 2003). Dosages were specified in different ways, but mainly as mean daily dose; two studies did not specify the dose. Average daily doses varied considerably between studies from 0.48 ± 0.22 mg/kg/day (Germinario et al., 2013) to 1.31 ± 0.2 mg/kg/day (Durá-Travé et al., 2012). Daily average dosages of MPH varied from 6 to 85 mg/day, with a mean daily dose of around 29.93 ± 12.14 mg/day. The study examining the effect of trans-dermic MPH delivery reported a time of daily exposures to treatment of between 9 and 12 hours/day (Faraone and Giefer, 2007).

3.1.3. *Primary outcome measures*

The primary outcome measures varied across studies and were somewhat dependent on the period during which the study was conducted. On the basis of our criteria, we were able to include only recent studies that expressed the variations in height, weight and BMI through standardized age and gender normed z-score parameters.

Two studies also included the height velocity-SDS as a *primary outcome* measure (Lisska and Rivkees, 2003; Poulton and Cowell, 2003). In addition to more standardised measures, one study (Poulton et al., 2012) reported changes in body composition (lean tissue, fat masses, fat distribution, bone mineral density) using the Dual-energy X-ray

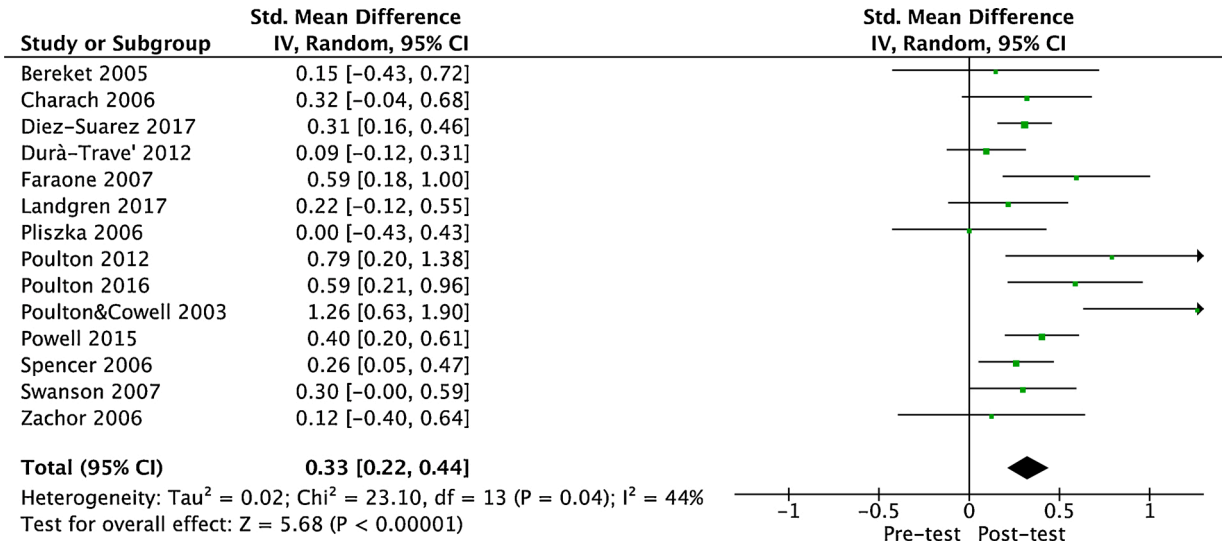

Fig. 2. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of weight (MPH and AMP).
Pre–post within-group design analyses for weight with stimulant therapy (methylphenidate and amphetamine, when it was not possible to distinguish between the two) at the last follow up assessment.

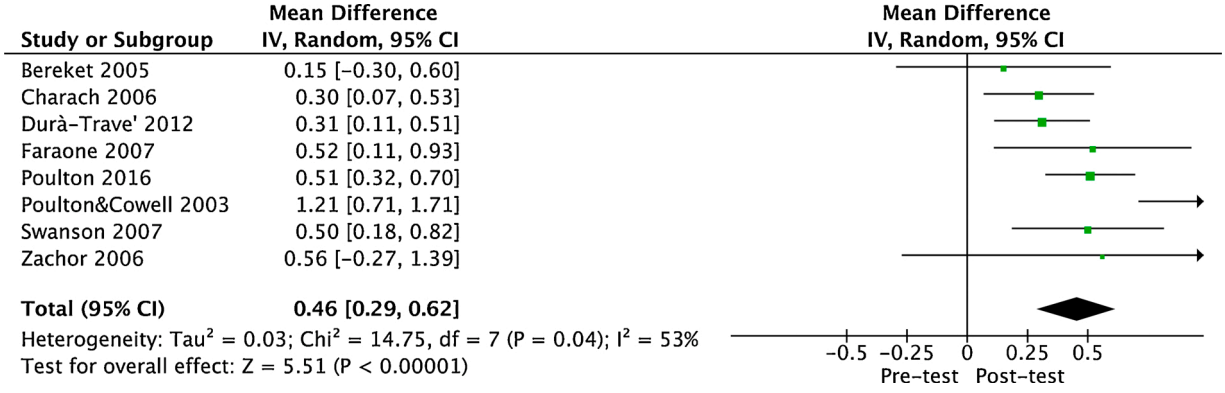

Fig. 3. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of weight (MPH and AMP, 12-18 months of follow up).
Pre–post within-group design analyses for weight with stimulant therapy (methylphenidate and amphetamine) at the 12-18 months follow up assessment.

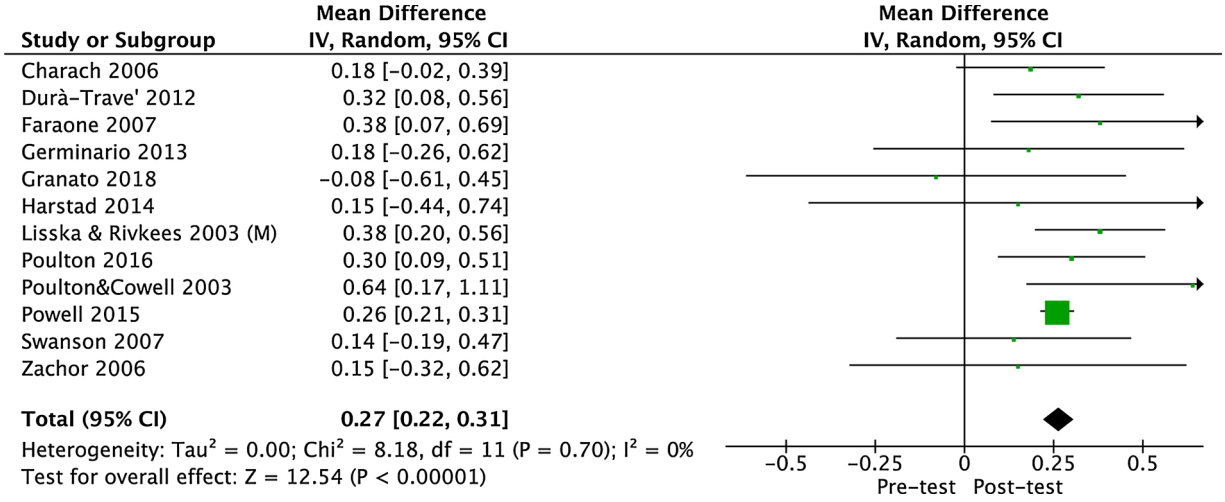

Fig. 4. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of height (MPH and AMP, 24 months of follow up).
Pre–post within-group design analyses for height with stimulant therapy (methylphenidate and amphetamine) at the 24 months follow up assessment.

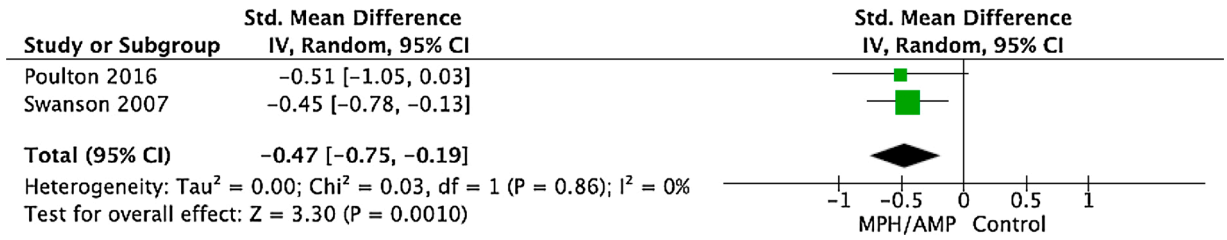

Fig. 5. Forest plot with SMD (=ES) and homogeneity statistics for meta-analysis of weight (control trials).
Meta-analysis of controlled trials for weight with not medicated ADHD subjects and typically developing siblings as control population.

absorptiometry (DEXA) scans.

3.2. Quantitative Analysis

Question 1. Is MPH associated with clinically significant reduction in growth in children with ADHD?

3.2.1. Pre–post within-group design analyses

Eighteen studies for height (Fig. 1) and fourteen studies for weight (Fig. 2) met inclusion criteria for a quantitative meta-analysis. For both height and weight, all but four studies (Díez-Suárez et al., 2017; Harstad et al., 2014; Landgren et al., 2017; Bereket et al., 2005; The MTA Cooperative Group, 2004) reported data on multiple measurements (with a minimum of 2 to a maximum of 6 different measures). For studies including multiple follow-up times, outcome measures were considered at the latest follow up time, varying from a minimum of 21 to a maximum of 72 months. Stimulant therapy (methylphenidate and amphetamine, when it was not possible to distinguish between the two) was associated with a small, however statistically significant pre-post difference both for height (SMD = 0.27, 95% CI 0.16-0.38, $p < 0.0001$; Fig. 1) and weight Z scores, (SMD = 0.33, 95% CI 0.22-0.44, $p < 0.0001$; Fig. 2) with a similar large between trial heterogeneity (respectively $I^2 = 52\%$ and 44%).

We also performed a subset of analyses including the studies reporting data at these two specific follow-up points: 12-18 months and 24-30 months.

A moderately significant pre-post difference for weight Z scores, was found when data were examined at the 12-18 month follow up (SMD = 0.46, 95% CI 0.29-0.62, $p < 0.0001$; Fig. 3). The largest impact of MPH on weight was usually reported at the end of the first 6 months (Poulton et al., 2012, 2016) and in general within the first 18 -24 months of treatment (Poulton and Cowell, 2003; Zachor et al., 2006) with a plateau at subsequent follow-up measures (Powell et al., 2015).

In terms of height, the most significant pre-post difference, was found when examining data at the 24-30 month follow up. These results confirmed the association with a small but highly statistically significant pre-post difference for height Z score comparable to the one found at the last recorded follow up (SMD = 0.27, 95% CI 0.22-0.31, $p < 0.0001$; Fig. 4).

Three studies reported an impact during the first 6-12 months of treatment with a subsequent normalization thereafter (Faraone and Giefer, 2007; Poulton et al., 2012, 2016). Three other studies showed an impact on height later in treatment (Poulton and Cowell, 2003), after 12 (Germinario et al., 2013) or even 24 months (Durá-Travé et al., 2012). Poulton and Cowell (2003) reported a normalization of growth within 30-42 months. In a recent work it was confirmed that the decline in Z-height growth over time plateaued from 12–47 months, though without reaching baseline, but remaining within the expected range for age (Powell et al., 2015). Results at the 3 year follow-up of the MTA study confirmed a suppressive effect on growth during the first two years of treatment, but suggested that this effect on growth is still observable after three years (Swanson et al., 2007).

3.2.2. Analysis of controlled trials

As stated before, only three studies reported data for a longitudinal comparison of height with a control population: not medicated ADHD subjects (Swanson et al., 2007) and typically developing siblings (Lisska and Rivkees, 2003; Poulton et al., 2016); only two studies reported data for weight. In these cases stimulant therapy (methylphenidate and amphetamine) was associated with a moderate, statistically significant difference for weight (SMD = -0.47, 95% CI -0.75, -0.19, $p = 0.0010$; $I^2 = 0\%$, Fig. 5) but not for height Z scores, (SMD = -0.84, 95% CI -1.72, 0.05, $p = 0.06$, $I^2 = 93$, Fig. 6).

3.3. Moderators of the treatment effect

Question 2 and 3. Do patient (baseline auxological parameters, age, gender) and medication characteristics (dose, formulation, length of treatment, drug naïve condition) moderate the effect of MPH on growth?

A set of sensitivity analyses was performed to assess the effect of possible clinical modifiers (MPH as monotherapy, formulation, dose, age, the drug naïve condition) and the effect of the study design (retrospective vs prospective) Fig. A1 and Table A1.

Ten studies for height (Fig. 7) and seven for weight (Fig. 8) examined the effects of MPH as a **monotherapy** confirming the previous results evidencing a small, but statistically significant pre-post difference both for height and weight Z-scores. SMD for height was = 0.23, 95% CI 0.08-0.38, $p = 0.003$; $I^2 = 62$ while SMD for weight was = 0.24, 95% CI 0.14-0.35, $p < 0.0001$; $I^2 = 10$.

The four studies examining the MPH **long-acting formulations** (Durá-Travé et al., 2012; Faraone and Giefer, 2007; Landgren et al., 2017; Spencer et al., 2006) confirmed a similar pre-post difference for

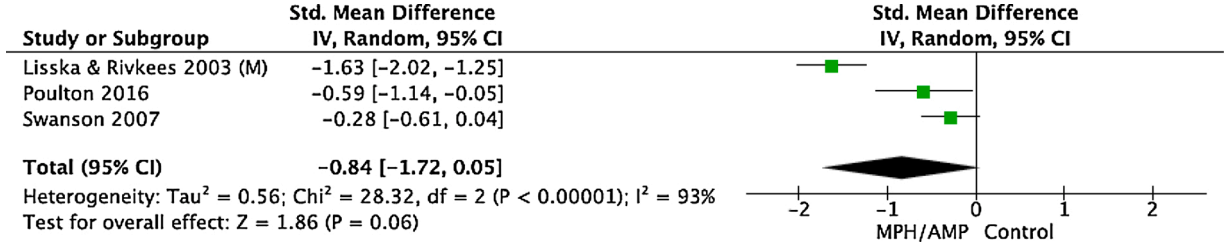

Fig. 6. Forest plot with SMD (=ES) and homogeneity statistics for meta-analysis of height (control trials).
Meta-analysis of controlled trials for height with not medicated ADHD subjects and typically developing siblings as control population

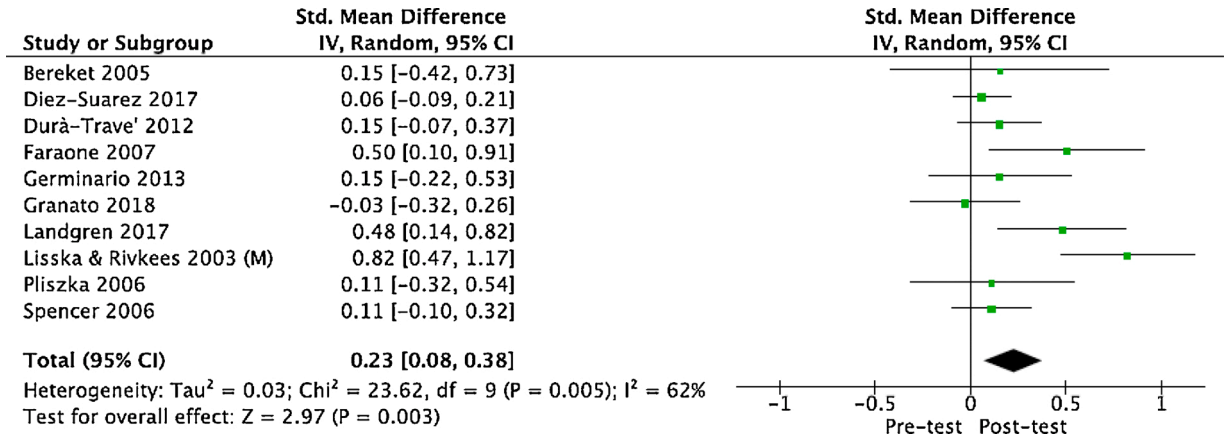

Fig. 7. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of height (MPH).
Pre–post within-group design analyses for height with MPH as mono-therapy.

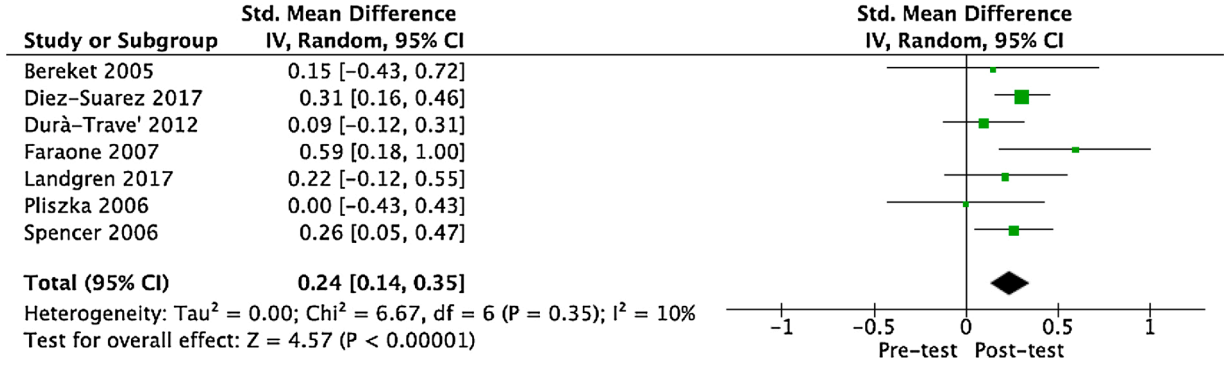

Fig. 8. Forest plot with SMD (=ES) and homogeneity statistics for meta-analysis of weight (MPH).
Pre–post within-group design analyses for weight with MPH as mono-therapy.
Figs. 1–4 and Figs. 7, 8. Forest plots with pre-post standardized mean differences SMDs (ES) and homogeneity statistics for meta-analyses of height and weight Z scores. The forest plots represent each study in the meta-analysis, plotted according to the SMD. The green box on each line shows the SMD for each study. The size of the box stands for the size of the sample size. The black diamond at the bottom of the graph shows the average SMD of all studies of all medications. If a green box or the black diamond stands on the right side of the middle line, this represents a higher Z score on the pre-test in comparison with the post-test, so a decrease. A box/diamond on the left side of the middle line represents a higher Z score on the post-test in comparison with the pre-test, so an increase. If the green box or the black diamond crosses the middle line, then this study reported no significant effect.
Figs. 5, 6. Forest plots with standardized mean differences SMDs (ES) and homogeneity statistics for meta-analyses of height and weight Z scores in controlled trials. If a green box or the black diamond stands on the left side of the middle line, this represents a lower Z score for the medicated subjects compared to the control population at the latest follow up time.

weight Z scores (SMD = 0.32, 95% CI 0.18-0.46, p < 0.0001; I^2 =56), while the effect on standardized values for height resulted slightly smaller with a higher heterogeneity between trials (SMD = 0.09, 95% CI 0.03-0.16, p = 0.006; I^2 =68).

Sensitivity analysis did not reveal a significant effect of **dose** on either height or weight mean Z scores when considering a mean MPH daily dose of < 30 mg/day vs ≥ 30 mg/day. However it is worth noting that some studies evidenced a dose effect by regression models. Charach et al. (2006) reported an effect on height for patients treated with doses out of the usual clinical range (≥2.5/mg/kg/day) at their 48-month follow-up visit. The MTA study confirmed these last results: showing an effect on growth closely related to the dose (Swanson et al., 2007). Powell et al. (2015) reported a stronger dose effect, particularly for weight, in patients treated with doses ≥ 1.5/mg/kg/day even after 72 months. The studies by Poulton et al., showed a dose-related effect to height velocity within the oldest subject group (14-16 years; Poulton et al., 2013) and a larger effect on height and weight for larger doses (Poulton et al., 2016). Interestingly, 2 of the studies reporting a negative impact of stimulants on height did not find any correlation with dose (Zhang et al., 2010; Durá-Travé et al., 2012). Two more trials reported a possible correlation between dose and the impact on weight but not height (Faraone and Giefer, 2007; Landgren et al., 2017).

No significant effects were found for **age** (children <12) or the **drug naïve condition.**

Sensitivity analysis did not reveal a significant effect of **study design** either. A similar pre-post difference for height Z scores was found when including only studies with a prospective design (SMD = 0.25, 95% CI 0.09-0.40, p = 0.002; I^2 =26) or with a retrospective design (SMD = 0.28, 95% CI 0.13-0.44, p = 0.003; I^2 =63), as well as for weight Z scores (SMD = 0.34, 95% CI 0.20-0.48, p < 0.0001; I^2 =0) when including studies with a prospective design compared to the retrospective ones (SMD = 0.32, 95% CI 0.14-0.49, p p = 0.003; I^2 =61).

3.4. Growth adverse effects on individual level

Considering the importance of possible clinical effects at individual level in clinical practice, we also evaluated the available single patient data in terms of appetite suppression, weight loss, deviation or decreasing from expected Z scores values and medication cessation.

Only a minority of studies (5/18; 27.7%) reported individual level data about stimulants adverse effects on appetite and growth (either effects on height or weight). The most prevalent adverse effect was

appetite suppression. Zachor et al., 2006 (n = 81) reported that 54 subjects (about 60%) presented with this effect, but only 10 subjects changed medication due to this adverse effect.

Landgren et al. (2017) evidenced that 28 out of 69 (41%) individuals deviated and decreased from their expected height Z score values at least 0.5 SD during the treatment period. The treatment effect on height development on a group level was minimal, about -0.2 SD (subjects with the greater decrease between baseline and follow up were on average taller at baseline), but the group of children with height <1.5 SD increased from 5% (5 subjects) to 10% (8 subjects). In the study by Granato et al. (2018) 3 individuals overall (3.2%) became thin, with a minimum weight Z score of −2.81.

In two patients there were sufficient concerns about growth rates to recommend cessation of medication (Poulton and Cowell, 2003) while another subject ceased medication for appetite suppression associated to insomnia, tics and headache (Poulton et al., 2016).

3.5. Effect of MPH on puberty

Question 4. Does MPH affect the timing of puberty?

Data is currently limited on the impact of either ADHD or MPH on the timing of puberty. Using a questionnaire for self-staging of pubertal maturation, Spencer et al. (1996) did not detect any obvious influence of methylphenidate in 124 boys with ADHD, the most of them treated with stimulant medication. A comparable study of 124 girls with ADHD and a matched control group also found no evidence for an influence of MPH on pubertal development in girls with ADHD (Biederman et al., 2003). Unfortunately, no information on duration of treatment with stimulant medication was reported for this sample, leaving open the possibility that the girls had not been treated long enough for either their growth or pubertal development to be affected.

A recent publication from the MTA found no evidence to suggest that stimulant medications significantly impacted the timing of puberty. Within this study a subset of participants with ADHD (n = 342) and a control group without ADHD (n = 159) completed self-report Tanner staging at the 36-month follow-up assessment. Further comparisons were made for the participants in the ADHD group who were *always* (n = 61), *never* (n = 56), *newly* (n = 74) and *inconsistently* (n = 116) medicated with stimulants. No statistically significant differences in Tanner stages of pubertal development were found between the ADHD and non-ADHD groups at the age of assessment (between 10 and 14 years of age) or among the ADHD medication subgroups (Greenfield et al., 2014).

Poulton et al. (2013) did report a delay in pubertal maturation for 14 to 16-year-old adolescents after three years of continuous treatment with stimulant medication. Of the 65 boys (age range 12.0-15.9) recruited for the study, the 22 aged 14.0-15.9 years reported significantly less advancement in their pubertal development compared to controls with no significant correlation with the dose of medication. No significant difference in the stage of puberty was found at 12.0-13.9 years of age. These findings suggest that stimulant medication may delay the rate of maturation during puberty but not the onset of puberty. However, the very small sample sizes limit the generalizability and replication in larger groups is required.

3.6. Effect of MPH on body composition and metabolism

Question 5. Does MPH affect body composition and/or bone metabolism?

Only two trials investigated bone mineral density and bone turnover as an index of changes in body composition related to stimulant medication. These reported contrasting results.

The pilot study conducted by Lahat et al. (2000) compared 10 ADHD subjects treated with MPH for 12 to 24 months (mean 13 ± 4) with 10 controls. Laboratory data and bone mineral density did not differ between the two groups and no child deviated from his height percentile during the treatment period.

The prospective study of Poulton et al. (2012) examined 34 children aged 4.7-9.1 years, newly diagnosed with ADHD and treated with dexamphetamine or methylphenidate. This group found significant reductions over 3 years in sex and height corrected Z scores for bone mineral content and bone mineral density compared to data gathered from 241 healthy children.

In a later publication Poulton et al. (2016) examined bone age over the first 3 years of treatment (dexamphetamine or methylphenidate) in ADHD children compared with their healthy siblings (controls). There were no significant growth differences between the two groups at baseline. The ADHD patients (n = 40) showed no significant maturational delay compared to the 22 children belonging to the control group (RUS score: 49 U/year, 95% CI: 44–55, vs. 55 U/year, 95% CI: 47–63, P = 0.27). A subgroup of patients underwent serial biochemistry and dual-energy X-ray absorptiometry, recording a significant reduction in fat (5.61 ± 3.56–4.22 ± 3.09 kg, P < 0.001) and leptin (3.88 ± 2.87–2.57 ± 1.94 ng/ml, P = 0.017). No medication effect was found on the rate of maturation, which was mostly predicted by baseline leptin levels.

4. Discussion

ADHD is a chronic condition frequently persisting during late adolescence and adulthood (Kooij et al., 2005). As current recommendations are to continue treatment for as long as it is needed and helpful (NICE National Institute for Clinical Excellence, 2018), patients can, in theory, receive a pharmacological treatment for many years with consequent concerns related to potential long-term risks.

The findings of this review suggest that long term MPH use is associated, at the group level, with relatively minor impacts on height and weight in ADHD children and adolescents (pre-post difference for height Z score: SMD = 0.27 and weight Z score: SMD = 0.35). These estimates suggest that stimulants, at a therapeutically daily dose varying between studies from 0.48 ± 0.22 mg/kg/day (Germinario et al., 2013) to 1.31 ± 0.2 mg/kg/day (Durá-Travé et al., 2012) and a mean daily dose of around 29.93 ± 12.14 mg/day, could slow height gain by approximately 1.39 cm and weight gain by approximately 1.96 kg for a 10-year-old boy over a 2-year period. When considering MPH as a monotherapy (pre--post difference for height Z score: SMD = 0.23 and weight Z score: SMD = 0.24) the growth gain decrease can be estimated around 1.25 cm less for height and 1.43 kg less for weight for the same 10-year-old boy. Over a 2-year-period, MPH could diminish gains in height by 1.65 cm and by 2.6 kg in weight for a 14-year-old boy. These effects however seem to be limited in time with a subsequent normalization (Poulton & Cowell, 2003; Faraone and Giefer, 2007; Zhang et al., 2010; Poulton et al., 2012; Kim et al., 2014; Poulton et al., 2016) and for most individuals are likely to have minimal clinical or personal significance. Whether these changes are of concern would depend substantially on the individual child stature, as gaining 1,5 cm less could have a clinically significant impact only for subject with a height Z score < 2 DS at baseline. According to the studies reporting individual data, losses in expected growth were not considered clinically significant enough to stop treatment apart from two subjects (Poulton and Cowell, 2003). Physicians generally did not advice to discontinue medication, underscoring the suggestion that stimulant associated deficits in growth did not pass a threshold that would be considered clinically significant. Subjects with the larger impact between baseline and follow up were on average taller at baseline, while the percentage of subjects who were considered very short or very light, tended to increase in a minimal part (<10%) from baseline to the last observation (Landgren et al., 2017).

The extremely heterogeneous nature of the included studies, and the many methodological limitations of the currently published papers on this topic, do however limit our ability to draw firm conclusions. One of the main methodological limitations in analysing MPH effects on growth relates to the definition of outcomes; for this reason we included only recent studies preferably expressing the variations in height, weight and

BMI through standardized age and gender normed Z-score parameters. Methods of outcome measures were in fact an issue for earlier studies, particularly those published before the mid-90 s. Most of these studies considered means of absolute weight and height as the primary outcome with only a few using the more standardised measures of percentiles calculated from standardized growth charts. Percentiles are still associated with significant imprecision since the averaging of percentiles tends to overemphasize the small differences near the mean and underestimate similar differences at the extremes (Spencer et al., 1996). More recent publications have generally considered Z scores for height, weight and height velocity as primary outcomes. These measures are clearly superior to the previous ones: they allow for more valid comparisons as they correct for age and sex, avoid mathematical distortions, and show similar sensitivity to change at all levels of the curve.

When used with country specific norms, Z scores can also account for geographic and ethnic variability. They are however dependent on accurate population norms. This can be an issue for many countries, including some of those used in the US, where much of the research has been conducted, using norms that can be out of date and do not account for the secular changes in growth measured in the general population over time (www.cdc.gov/growcharts). Despite the use of more appropriate outcome measures in recent studies and considering the controversial results of the studies of the seventies and the eighties, it is somewhat surprising that relatively few long-term studies have been carried out in the last years and that many of those that have been conducted are affected by significant methodological limitations, precluding an accurate quantitative comparison.

A further important methodological limitation relates to the statistical management of the age of the participants. Since height does not vary linearly with age, the wider the age range of the sample being studied, the more vulnerable are direct comparisons of averaged height measurements to produce spurious results (Chinchilli et al., 1990). It is also important to notice that growth, and height in particular, can be described as a wave motion with a six-month periodicity. As a consequence it is generally agreed that at least 4 measurements of height, taken six months apart are required to reduce the potential for error when assessing growth status.

A more narrow definition of age of participants within the studies is however not enough to get more reliable results. In the majority of the studies included, the mean age at enrolment is about 10 years suggesting that many of those included will have been in puberty: during this time of development the height velocity increases most and is also the most variable, as the timing of puberty varies considerably between otherwise similar individuals. It would therefore be most appropriate to stratify the population according to specific stage of pubertal status as well as age. Alternatively, the analysis could be performed after excluding those subjects who were within puberty. This would however result in the loss of a considerable amount of data and leave a considerable hole in our understanding. Since most studies included all patients regardless of their pubertal status in their analyses, and none of the study actually assessed pubertal status independently of age, this may have diminished the power to detect an impact of MPH on growth. It is also important to notice that most studies included a male population (about 80% of the sample in the meta-analysis) preventing a clear comparison with the opposite gender and partially confounding the accuracy of data when the male and female populations were analysed together, considering the different pubertal maturation onset of the two genders.

The conclusions from our review should be therefore examined by considering the above mentioned limitations in the field and the methodological limitations of our approach. The poor quality of the studies limited the possibility to make direct between-study comparisons. Most studies did not have a control group and failed to report important information on individual data, including the effects of dropouts and previous treatment, or the rating of clinical significance of growth effects by physicians, parents, or patients. Other possible mediators as prenatal factors, such as toxic exposures, hereditary influences or ethnic and socio-demographic composition of their samples were generally not described. Our statistical analyses have therefore limited power due to the number of studies available for analysis.

The mechanisms by which stimulants may affect growth are not completely understood. Growth suppression in ADHD children can be a consequence of decreased appetite and reduction in caloric intake (Cortese et al., 2013; Ptacek et al., 2014; Vitiello, 2008), endocrinological or dietary factors (Ptacek et al., 2009) or could be caused by the dopaminergic effect of stimulants with the acute inhibition of growth hormone (De Zegher et al., 1993). Another possible mechanism is the effect of stimulants on slowing the growth of cartilaginous tissue and consequently the bone growth (Kilgore et al., 1979), with possible osteopenic effects for stimulants users (Howard et al., 2017).

When discussing the long-term effects, it is important to consider that changes, although with a generally minimal clinical impact, can vary on an individual basis. Higher baseline weight and height are often associated with a greater impact by stimulant medication, with the strongest correlation for weight (Safer and Allen, 1973; Mattes and Gittelman, 1983; Spencer et al., 1992; Zeiner, 1995; Schertz et al., 1996; Sund and Zeiner, 2002; Zachor et al., 2006; Faraone and Giefer, 2007) indicating that basal auxological characteristics may represent an important clinical correlate. Spencer et al. (2006) divided the sample by using Z scores quartiles for weight and height and confirmed a stronger effect for tallest and heavier children. Despite data suggesting that overweight and taller children may be more sensible to medication effects, a finding that could be seen as reassuring to patients of smaller stature, from a clinical point of view it remains important to remember that effects need to be measured at an individual level for individual patients.

Time of follow-up represents another important variable, when evaluating the possible impact of stimulants on growth: medication effects tend to attenuate over time both for weight and height. According to the results of previous reviews (Poulton, 2005; Vitiello, 2008), effects on height would manifest later in time with respect to weight (Faraone and Giefer, 2007; Spencer et al., 2006; Lisska and Rivkees, 2003), with a similar trend of generally remitting in time (Poulton and Cowell, 2003; Klein and Mannuzza, 1988; Safer and Allen, 1973), and time of follow up appears to be influenced by the condition of drug-naïvity at the beginning of the study. Drug naïve subjects have been shown to present a greater weight and BMI loss with MPH transdermal delivery system (Faraone and Giefer, 2007). This characteristic pattern and the possible normalization of the auxological parameters over time may explain the negative results deriving from the studies including subjects already on stimulants and not drug naïve patients (Pliszka et al., 2006b). The recent study by Powell et al. (2015) confirms this trend, with a temporary lag halt in growth and a Z height growth plateau after 12-47 months of follow up in a population of 410 drug-naïve ADHD subjects.

Although our sensitivity analysis did not reveal an effect for dose when setting the limit of a MPH dosage $<$ vs $\geq$ 30 mg/day, it is important to evidence that several studies have shown that, in a minority of patients treated with doses higher than usual, these dosages could be more predictive of height deficits (Charach et al., 2006; Lisska and Rivkees, 2003; Pliszka et al., 2006b; Faraone and Giefer, 2007; Poulton et al., 2013; Powell et al., 2015; Díez-Suárez et al., 2017; Poulton et al., 2016). In the Preschool ADHD Treatment Study (PATS study; Swanson et al., 2006), preschool children receiving prolonged treatment (n = 95), showed a yearly height deficit of about 20% (-1.38 cm / year) and a weight deficit of about 55% (-1.32 Kg / year) than expected, regardless of the administered dose (mean dose 14 mg/day). This finding could be explained by the young age of the sample evidencing a possible higher sensitivity to MPH according to the age range of patients, with particular attention to the younger children.

Safety findings on growth parameters from a recent open-label 2-year lisdexamfetamine dimesylate trial in ADHD subjects aged 6–17 years (N = 314) appear consistent with previous studies of stimulant medications (Banaschewski et al., 2018). Mean weight, height and body

mass index Z-scores transiently decreased over the first 36 weeks of the study and then stabilised, with no evidence of delayed onset of puberty.

In order to minimize growth adverse events, one of the recommended strategies by clinical guidelines (NICE, 2018; Taylor et al., 2004), is to plan a break from medication, referred as a "drug holiday" (Van de Loo-Neus et al., 2011; Ibrahim and Donyai, 2015).

A recent comprehensive search of the literature identified 22 studies published from 1972 to 2013 with the aim to map the experience of drug holidays from ADHD medication. The authors found evidence for a positive impact on child growth with longer breaks from medication, and shorter breaks could reduce insomnia and improve appetite (Ibrahim and Donyai, 2015). While older studies suggested that withdrawal or interruption of treatment may attenuate the suppressive effect of stimulants on growth due to a rebound phenomenon (Safer et al., 1972), with significant effects both on height (Klein et al., 1988) and weight (Satterfield et al., 1979), more recent studies, on the other hand, do not support the hypothesis of a rebound effect of growth after suspension of treatment or did not confirm a positive correlation with "drug holiday" (Pliszka et al., 2006b; Spencer et al., 2006; Lisska and Rivkees, 2003; Poulton and Cowell, 2003; Vitiello, 2008).

The discrepancy between these results can potentially be reconciled when one takes into account that those studies that reported correlations often examined together both drug naïve and subjects on treatment from a long time. On the other hand, the studies that did not find a correlation often did not control the drug holiday in detail, leaving it to the parents to decide when and how to have drug holidays, without a distinction in terms of length of therapeutic suspension (weeks vs. months).

The ultimate index of growth is whether or not an individual reaches their target height (expected height as an adult); however none of the selected longitudinal studies included the reaching of target height (estimated as a genetic variable taking into account parental height) at the end of development as the main outcome. The majority of studies in adult patients treated with psychostimulants as children suggest that final height may not be significantly impaired, although, in the light of more recent publications (Swanson et al., 2017), this hypothesis still remains uncertain and requires further investigation. Biederman et al. (2010) in their case-control study with a ten-year follow up, did not find any evidence that stimulant treatment could affect final adult height in a sample with a mean age about 21 years. A recent search from the National Epidemiologic survey on Alcohol and Related Conditions (NESARC) data collected in 2004-2005, confirmed the absence of any significant difference in the final adult height in ADHD subjects treated with stimulants during the developmental age ($n = 216$), compared to ADHD never treated with stimulants ($n = 591$) and a control sample ($n = 34652$; Peyre et al., 2013). This finding was further confirmed in a recent longitudinal study comparing 243 ADHD to 394 controls. No statistically significant differences in adult height were found between the two groups (Harstad et al., 2014).

The recent publication of MTA outcomes in early adulthood (25 years of age; Swanson et al., 2017) however contradicts the previous findings, with the ADHD group reported to be 1.29 ± 0.55 cm shorter than the control group and showing a higher impact on height for subjects constantly treated compared to the ADHD sample discontinuing medication. This discrepancy of findings of MTA with the other studies appears to be related to changes in the clinical use of medication and differences in the cumulative dose, to the adequate separation of treated and untreated ADHD subjects and to the average age of treatment initiation.

All this information should be however read in the context of different potential confounding factors including epigenetics (i.e. low birth weight of the child and of their parents and grandparents), the positive secular trend of growth, the progression age of menarche and a possible genetic condition known as constitutional delay of growth and puberty (CDGP, Howard, 2018). This is a relatively frequent condition (2-3% of children), generally self limited and representing the extreme end of normal pubertal timing, and the commonest cause of delayed puberty in both boys and girls associated with adverse health outcomes including short stature, reduced bone mineral density and compromised psychosocial health (Zhu and Chan, 2017). At the moment it would be very costly to genetically examine all methylphenidate-treated patients to exclude such possible confounding variables. However, future progress in gene discovery and technical developments may facilitate the availability of genetic diagnosis as part of clinical care for patients on a pharmacological treatment and a possible condition of self-limiting delay puberty. At the moment, studies using a self-controlled case series design could be useful in giving more information about data at an individual level, in order to obtain more precise indication for clinical practice for the management of possibly more vulnerable subjects.

5. Conclusions

Results from the present review reveal that long-term treatment with methylphenidate might be associated with a slight growth deficit, in particular with respect to height, with a minimal clinical impact and which generally remits in adulthood. It is however possible that a clinically significant and meaningful impact may be observed on a small minority of individuals. The clinical meaning of a height deficit must be examined in the context of the advantages deriving from medication and the magnitude of the deficit: some caveat about groups of individuals who may be more severely affected is important and caution should be used in more vulnerable subjects (i.e.: the younger ones or the shortest ones with low baseline height or familiar low height as well as subjects showing a decreasing curve in height development). As specifically stated in the last NICE guidelines (2018) a planned break in treatment over school holidays should be offered if subjects' height is significantly affected by medication over time.

The impact of methylphenidate on weight is significantly less worrying, as it may change during the whole life. The limited data on pubertal maturation available at the moment seem to favour the exclusion of a possible drug effect on sexual maturation in treated ADHD subjects.

Considering the identified gaps in the current literature and the concerns form the European Medicine Agency, in 2012 the European Commission granted funding for a large research projects on long term safety of methylphenidate: the "*Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects* "(ADDUCE; http://adhd-adduce.org). The project includes a Work Package aimed to conduct a 2-year prospective cohort study with appropriate control groups (ADHD youngsters NOT taking medications and normally developing children and adolescents) to directly address scientific questions about prevalence, clinical significance, development and moderating and/or mediating factors of four specific classes of potential long-term adverse effects of MPH (growth, neurological, psychiatric and cardiovascular health), with height velocity, as a primary outcome (Inglis et al., 2016). This large long-term study, including different control groups, should provide more suitable evidence compared to the ones currently available. It has now been completed and the results are currently being analysed for publication.

In conclusion and taking into account continuing uncertainties we do not feel that there is at the current time any evidence to suggest a need to change current clinical practice guidelines for monitoring of growth and pubertal parameters in children on stimulant medication. These all support the careful assessment of the growth parameters before starting stimulant treatment and the periodic monitoring through repeated measurement of weight and height and subsequent plotting of these on standardised growth charts. Particular caution should be taken in preschool children where adverse effects are more likely and the final dose of methylphenidate should be achieved progressively, on the basis of the minimum effective dose for optimal treatment (Swanson et al., 2006; Graham et al., 2011; Banaschewski et al., 2006).

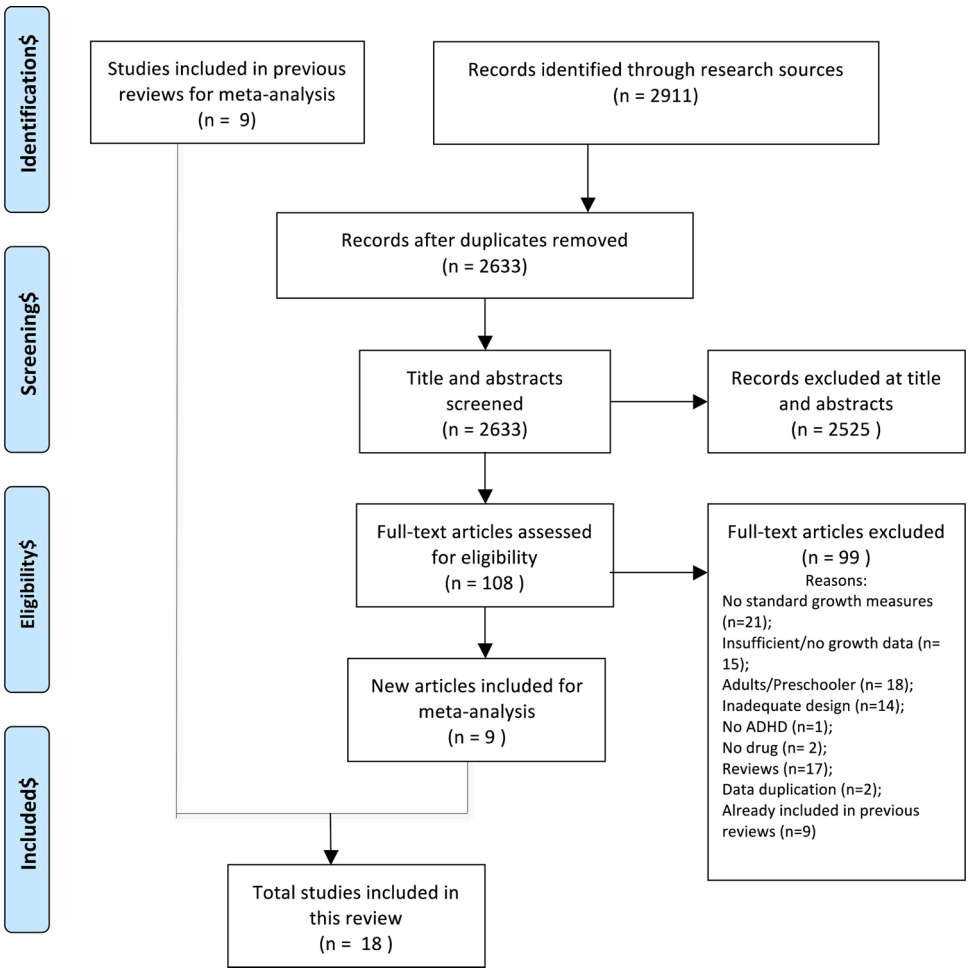

Fig. A1. Harvest plot.
Graphical representation of possible clinical correlation within the studies. Numbers are the number of studies examining the variable expressed in the row. Width and height of the columns represent respectively the number of the studies and the total the sample size. Grey columns represents height, black stay for weight.

Disclosures

Dr. Balia had collaborations within projects from the European Union (7th Framework Program) and as sub-investigator in sponsored clinical trials by Lundbeck, Otsuka, Janssen Cilag and Angelini.

Prof. Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships.

Prof. Buitelaar has served as a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Vifor and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

Dr. Carucci had collaborations within projects from the European Union (7th Framework Program) and as sub- investigator in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen Cilag and Angelini. Travel support from Fidia Farmaceutici.

Prof. Coghill served in an advisory or consultancy role for Medice, Shire/Takeda. He received conference support or speaker's fee by Servier, Medice, and Shire. He has been involved in clinical trials conducted by Shire and Tova. He received royalties from Oxford University Press. The present work is unrelated to the above grants and relationships.

Prof. Danckaerts received speaker's fees by Shire and Medice. She is involved in clinical trials conducted by Shire and received royalties form Oxford University Press. The present work is unrelated to the above grants and relationships

Prof. Dittmann has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the organizations or companies indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda and Theravance. He owns Eli Lilly stock.

Prof. Gagliano was in the advisory boards for Eli Lilly and Shire. She is/has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen and Otsuka. She has been speaker for Novartis, Eli Lilly and Shire.

Dr. Garas has no competing interests to report

Prof. Chris Hollis reports grants from European Union FP7 programme, H2020, National Institute of Health Research (NIHR) and Medical Research Council (MRC) during the conduct of the study; He is a member of the European ADHD Guideline Group (EAGG) and NICE ADHD Guideline Committee.

Dr Inglis has no competing interests to report

Dr. Kovshoff has no competing interests to report

Table A1
Summary of sensitivity analyses.

Moderators of treatment effect	Height	Weight
MPH as monotherapy	YES	YES
MPH formulation	YES	YES
MPH dose	NO	NO
Subjects age	NO	NO
Drug naive condition	NO	NO
Study design (prospective vs retrospective)	NO	NO

Dr. Lampis served in an advisory or consultancy role for Kyowa Kirin. He received conference support or speaker's fee by Ipsen, He has been involved in clinical trials conducted by Ipsen. The present work is unrelated to the above grants and relationships.

Dr. Elizabeth Liddle has had grant support from the Wellcome Trust.

Prof. Konrad got funding for an IIT from Vifor and received royalities from Springer, Kohlhammer and Oxford University.

Dr. Panei is a consultant to the Local Health Units Rome 1 and Rome 2 of the Health Service of the Lazio region. The present work is unrelated to the above appointments.

Dr. Nagy has no competing interests to report

Dr. Romaniello had a collaboration as sub-investigator in sponsored clinical trial by Lundbeck.

Dr Suzanne McCarthy has received speaker's fee, travel support and research support from Shire.

Prof. Sonuga-Barke's financial declarations are: Speaker fees, and conference support from Shire Pharma. Consultancy from Neurotech solutions, Copenhagen University and Berhanderling, Skolerne, KU Leuven. Book royalties from OUP and Jessica Kingsley. Financial support received from Arrhus Univeristy and Ghent University for visiting Professorships. Grants awarded from MRC, ESRC, Wellcome Trust, European Union, NIHR, Nuffield Foundation, Fonds Wetenschappelijk Onderzoek-Vlaanderen (FWO), MQ – Transforming Mental health, The Waterloo Foundation. Editor-in-Chief JCPP – supported by a buy-out of time to Kings College London and personal Honorarium. Non-financial declarations are: Member of the European ADHD Guidelines Group

Dr. Usala has no competing interests to report

Prof. Ian Wong reports grants from European Union FP7 programme and Hong Kong Research Gran Council during the conduct of the study; grants from Shire, grants from Janssen-Cilag, grants from Eli-Lily, grants from Pfizer, outside the submitted work; and Prof Wong was a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group and the British Association for Psychopharmacology ADHD guideline group and acted as an advisor to Shire.

Dr. Zuddas served in an advisory or consultancy role for Angelini, EduPharma, Servier. He received conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier and Shire. He received royalties from Giunti OS, Oxford University Press. The present work is unrelated to the above grants and relationships.

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Appendix A

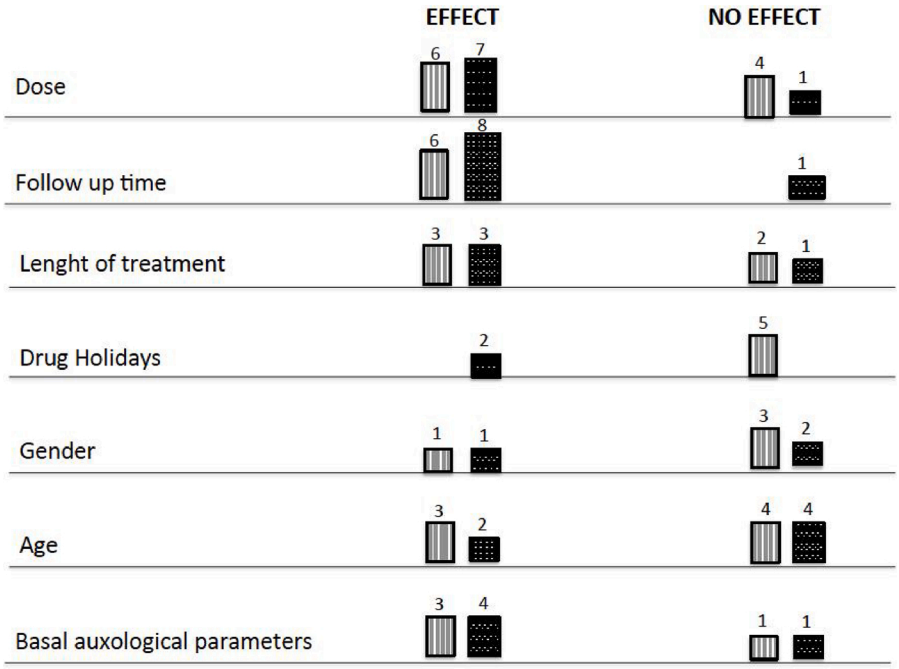
Appendix B

Medical subject headings [MeSH] and terms as free text word used for the search

"MPH": Methylphenidate OR methylphenidate hydrochloride OR methylphenidate hcl OR metadata OR Medikinet OR methylin OR Ritalin OR equasym OR daytrana OR concerta.

"Side effects": adverse effects OR adverse reaction OR adverse reactions OR side effect OR side effects OR untoward effect OR untoward effects OR adverse drug experience OR adverse drug experiences OR adverse drug reaction OR adverse drug reactions OR drug experience report OR drug experience reports OR toxic reaction OR toxic reactions OR toxic effect OR toxic effects OR complication OR complications OR undesired effect OR undesired effects OR unwanted drug effect OR unwanted drug effects OR "drug toxicity" OR "adverse drug reaction" OR "unwanted drug effects".

"ADHD": hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR adhd OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome OR syndromes hyperkinetic OR hyperkinetic syndrome childhood.



"Growth": "growth velocity" OR "growth spurt: AND "height" or "stature": AND "adult height" OR "adult stature" OR definitive stature".

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMAa) flow diagram on growth effects. aPRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org).

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of mental Disorders, 5th ed (DSM-5).

Banaschewski, T., Johnson, M., Nagy, P., et al., 2018. Growth and Puberty in a 2-Year Open-Label Study of Lisdexamfetamine Dimesylate in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. CNS Drugs. 32, 455-4.

Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., et al., 2006. Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. Eur Child Adolesc Psychiatry 15 (8), 476–479.

Bereket, A., Turan, S., Karaman, M.G., Haklar, G., Ozbay, F., Yazgan, M.Y., 2005. Height, weight, IFGSI, IGFBPS3 and thyroid functions in prepubertal children with attention deficit hyperactivity disorder: effect of methylphenidate treatment. Horm Res 63, 159–164.

Biederman, J., Faraone, S.V., Monuteaux, M.C., Plunkett, E.A., Gifford, J., Spencer, T., 2003. Growth deficits and attention-deficit/hyperactivity disorder revisited: impact of gender, development, and treatment. Pediatrics 111 (5 Pt 1), 1010–1016.

Biederman, J., Spencer, T.J., Monuteaux, M.C., Faraone, S.V., 2010. A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects. J. Pediatr. 157 (4), 635–640.

Charach, A., Figueroa, M., Chen, S., Ickowicz, A., Schachar, R., 2006. Stimulant treatment over 5 years: effects on growth. J Am Acad Child Adolesc Psychiatry 45 (4), 415–421.

Chinchilli, V.M., McEnery, P.T., Chan, J.C., 1990. Statistical methods and determination of sample size in the Growth Failure in Children with Renal Diseases Study. J Pediatr 116, 32–36.

Coghill, D.R., Banaschewski, T., Soutullo, C., et al., 2017. Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry. 26 (11), 1283–1307.

Cohen, J., 1977. Statistical Power Analysis for the Behavioural Science. Academic Press, New York.

Cortese, S., Holtmann, M., Banaschewski, T., Buitelaar, J., Coghill, D., et al., 2013. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. J Child Psychol Psychiatry 54 (3), 227–246.

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A.J., et al., 2018. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 5, 727–738.

De Zegher, F., Van Den Berghe, G., Devlieger, H., et al., 1993. Dopamine inhibits growth hormone and prolactin secretion in the human newborn. Pediatr Res 34 (5), 642–645.

Díez-Suárez, A., Vallejo-Valdivielso, M., Marín-Méndez, J.J., de Castro-Manglano, P., Soutullo, C.A., 2017. Weight, Height, and Body Mass Index in Patients with Attention-Deficit/Hyperactivity Disorder Treated with Methylphenidate. J Child Adolesc Psychopharmacol 27 (8), 723–730.

Durá-Travé, T., Yoldi-Petri, M.E., Gallinas-Victoriano, F., Zardoya-Santos, P., 2012. Effects of osmotic-release methylphenidate on height and weight in children with attention-deficit hyperactivity disorder (ADHD) following up to four years of treatment. J Child Neurol 27 (5), 604–609.

European Union, 2009. Referrals document. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Methylphenidate_31/WC500011125.pdf.

Faraone, S.V., Giefer, E.E., 2007. Long-term effects of methylphenidate transdermal delivery system treatment of ADHD on growth. J Am Acad Child Adolesc Psychiatry 46, 1138–1147.

Faraone, S.V., Biederman, J., Morley, C.P., Spencer, T.J., 2008. Effect of stimulants on height and weight: a review of the literature. J Am Acad Child Adolesc Psychiatry 47, 994–1009.

Faraone, S.V., Buitelaar, J., 2010. Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 19 (4), 353–364.

Findling, R.L., Wigal, S.B., Bukstein, O.G., Boellner, S.W., Abikoff, H.B., et al., 2009. Long-term tolerability of the methylphenidate transdermal system in pediatric attention-deficit/hyperactivity disorder: a multicenter, prospective, 12-month, open-label, uncontrolled, phase III extension of four clinical trials. Clin Ther 31 (8), 1844–1855.

Germinario, E.A., Arcieri, R., Bonati, M., Zuddas, A., Masi, G., et al., 2013. Attention-deficit/hyperactivity disorder drugs and growth: an Italian prospective observational study. J Child Adolesc Psychopharmacology 23 (7), 440–447.

Graham, J., Coghill, D., 2008. Adverse effects of pharmacotherapies for attention-deficit hyperactivity disorder: epidemiology, prevention and management. CNS Drugs 22 (3), 213–237.

Graham, J., Banaschewski, T., Buitelaar, J., Coghill, D., Danckaerts, M., et al., 2011. European Guidelines Group. European guidelines on managing adverse effects of medication for ADHD. Eur Child Adolesc Psychiatry 20 (1), 17–37.

Granato, Mf, Ferraro, Aa, Lellis, Dm, Casella, Eb, 2018. Associations between Attention-Deficit Hyperactivity Disorder (ADHD) Treatment and Patient Nutritional Status and Height. Behav Neurol. 2, 7341529.

Greenfield, B., Hechtman, L., Stehli, A., Wigal, T., 2014. Sexual maturation among youth with ADHD and the impact of stimulant medication. Eur Child Adolesc Psychiatry 23 (9), 835–839.

Hanc, T., Cieslik, J., 2008. Growth in stimulant-naive children with attention-deficit/hyperactivity disorder using cross-sectional and longitudinal approaches. Pediatrics 121 (4), e967–74.

Harstad, E.B., Weaver, A.L., Katusic, S.K., Colligan, R.C., Kumar, S., et al., 2014. ADHD, stimulant treatment, and growth: a longitudinal study. Pediatrics 134 (4), e935–44.

The ADDUCE Consortium, Hennissen, L., Bakker, M.J., Banaschewski, T., et al., 2017. Cardiovascular Effects of Stimulant and Non-Stimulant Medication for Children and Adolescents with ADHD: A Systematic Review and Meta-Analysis of Trials of Methylphenidate, Amphetamines and Atomoxetine. CNS Drugs 31, 199–215. https://doi.org/10.1007/s40263-017-0410-7.

Howard, J.T., Walick, K.S., Rivera, J.C., 2017. Preliminary Evidence of an Association Between ADHD Medications and Diminished Bone Health in Children and Adolescents. J Pediatr Orthop 37, 348–354.

Howard, S.R., 2018. Genes underlying delayed puberty. Molecular and Cellular Endocrinology 476, 119–128.

Ibrahim, K., Donyai, P., 2015. Drug Holidays From ADHD Medication: International Experience Over the Past Four Decades. J Atten Disord 19 (7), 551–568.

Inglis, S.K., Carucci, S., Garas, P., et al., 2016. Prospective observational study protocol to investigate long-term adverse effects of methylphenidate in children and adolescents with ADHD: the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study. BMJ Open 6 e010433.

Jensen, P.S., Arnold, L.E., Severe, J.B., et al., 2004. National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: Changes in Effectiveness and Growth After the End of Treatment. Pediatrics 113 (4), 762–769.

Kilgore, B.S., Dickinson, M.A., Burnett, C.R., Lee, J., Schedewie, H.K., et al., 1979. Alterations in cartilage metabolism by neurostimulant drugs. J Pediatr 94, 542–545.

Kim, H.W., Kim, S.O., Shon, S., et al., 2014. Effect of methylphenidate on height and weight in Korean children and adolescents with attention-deficit/hyperactivity disorder: a retrospective chart review. J Child Adolesc Psychopharmacology 24 (8), 448–453.

Klein, R.G., Landa, B., Mattes, J.A., Klein, D.F., 1988. Methylphenidate and growth in hyperactive children, in a controlled withdrawal study. Arch Gen Psychiatry 45 (12), 1127–1130.

Klein, R.G., Mannuzza, S., 1988. Hyperactive boys almost grown up. III. Methylphenidate effects on ultimate height. Arch Gen Psychiatry 45 (12), 1131–1134.

Kooij, J.J., Buitelaar, J.K., van den Oord, E.J., Furer, J.W., Rijnders, C.A., Hodiamont, P. P., 2005. Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. Psychol Med. 35 (6), 817–827.

Kramer, J.R., Loney, J., Ponto, L.B., Roberts, M.A., Grossman, S., 2000. Predictors of adult height and weight in boys treated with methylphenidate for childhood behavior problems. J Am Acad Child Adolesc Psychiatry 39 (4), 517–524.

Lahat, E., Weiss, M., Ben-Shlomo, A., Evans, S., Bistritzer, T., 2000. Bone mineral density and turnover in children with attention-deficit hyperactivity disorder receiving methylphenidate. J Child Neurol. 15 (7), 436–439.

Landgren, M., Nasic, S., Johnson, M., et al., 2017. Blood pressure and anthropometry in children treated with stimulants: a longitudinal cohort study with an individual approach. Neuropsychiatr Dis Treat. 16 (13), 499–506.

Lisska, M.C., Rivkees, S.A., 2003. Daily methylphenidate use slows the growth of children: a community based study. J Pediatr Endocrinol Metab. 16 (5), 711–718.

Mattes, J.A., Gittelman, R., 1983. Growth of hyperactive children on maintenance regimen of methylphenidate. Arch Gen Psychiatry 40 (3), 317–321.

NICE National Institute for Clinical Excellence, 2018. Attention Deficit Hyperactivity Disorder: Diagnosis and Management. Nice Guideline NG87.

Peyre, H., Hoertel, N., Cortese, S., Acquaviva, E., Delorme, R., et al., 2013. Long-term effects of ADHD medication on adult height: results from the NESARC. The Journal of clinical psychiatry 1123–1124.

TEXAS CONSENSUS CONFERENCE PANEL ON PHARMACOTHERAPY OF CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER, Pliszka, S.R., Crismon, M.L., Hughes, C.W., 2006a. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 45 (6), 642–657. https://doi.org/10.1097/01.chi.0000215326.51175.eb.

Pliszka, S.R., Matthews, T.L., Braslow, K.J., Watson, M.A., 2006b. Comparative effects of methylphenidate and mixed salts amphetamine on height and weight in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 45 (5), 520–526.

Polanczyk, G.V., Willcutt, E.G., Salum, G.A., et al., 2014. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int J Epidemiol 43 (2), 434–442.

Poulton, A., Cowell, C.T., 2003. Slowing of growth in height and weight on stimulants: a characteristic pattern. J Paediatr Child Health 39 (3), 180–185.

Poulton, A., 2005. Growth on stimulant medication; clarifying the confusion: a review. Arch. Dis. Child 90, 801–806.

Poulton, A., Briody, J., McCorquodale, T., Melzer, E., Herrmann, M., et al., 2012. Weight loss on stimulant medication: how does it affect body composition and bone metabolism? A prospective longitudinal study. Int J Pediatr Endocrinol (1), 30.

Poulton, A.S., Melzer, E., Tait, P.R., Garnett, S.P., Cowell, C.T., et al., 2013. Growth and pubertal development of adolescent boys on stimulant medication for attention deficit hyperactivity disorder. Med J Aust 198 (1), 29–32.

Poulton, A.S., Bui, Q., Melzer, E., Evans, R., 2016. Stimulant medication effects on growth and bone age in children with attention-deficit/hyperactivity disorder: a prospective cohort study. Int Clin Psychopharmacol 31 (2), 93–99.

Powell, S.G., Frydenberg, M., Thomsen, P.H., 2015. The effects of long-term medication on growth in children and adolescents with ADHD: an observational study of a large cohort of real-life patients. Child Adolesc Psychiatry Ment Health 28 (9), 50.

Ptacek, R., Kuzelova, H., Paclt, I., Zukov, I., Fischer, S., 2009. ADHD and growth: anthropometric changes in medicated and non-medicated ADHD boys. Med Sci Monit 15 (12). CR595-9.

Ptacek, R., Kuzelova, H., Stefano, G.B., Raboch, J., Kream, R.M., Goetz, M., 2014. ADHD and growth: questions still unanswered. Neuro Endocrinol Lett. 35 (1), 1–6.

Rapport, M.D., Moffitt, C., 2002. Attention deficit/hyperactivity disorder and methylphenidate. A review of height/weight, cardiovascular, and somatic complaint side effects. Clin Psychol Rev. 22 (8), 1107–1131.

Safer, D., Allen, R., Barr, E., 1972. Depression of growth in hyperactive children on stimulant drugs. N Engl J Med 287 (5), 217–220.

Safer, D.J., Allen, R.P., 1973. Factors influencing the suppressant effects of two stimulant drugs on the growth of hyperactive children. Pediatrics 51 (4), 660–667.

Satterfield, J.H., Cantwell, D.P., Schell, A., Blaschke, T., 1979. Growth of hyperactive children treated with methylphenidate. Arch Gen Psychiatry 36 (2), 212–217.

Schertz, M., Adesman, A.R., Alfieri, N.E., Bienkowski, R.S., 1996. Predictors of weight loss in children with attention deficit hyperactivity disorder treated with stimulant medication. Pediatrics 98 (4 pt1), 763–769.

Spencer, T., Biederman, J., Wright, V., Danon, M., 1992. Growth deficits in children treated with desipramine: a controlled study. J Am Acad Child Adolesc Psychiatry 31 (2), 235–242.

Spencer, T.J., Biederman, J., Harding, M., O'Donnell, D., Faraone, S.V., et al., 1996. Growth deficits in ADHD children revisited: evidence for disorder-associated growth delays? J Am Acad Child Adolesc Psychiatry 35, 1460–1469.

Spencer, T.J., Faraone, S.V., Biederman, J., Lerner, M., Cooper, K.M., et al., 2006. Concerta Study Group. Does prolonged therapy with a long-acting stimulant suppress growth in children with ADHD? J Am Acad Child Adolesc Psychiatry 45 (5), 527–537.

Storebø, O.J., Ramstad, E., Krogh, H.B., Nilausen, T.D., Skoog, M., et al., 2015. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Database Syst Rev.

Storebø, O.J., Pedersen, N., Ramstad, E., Kielsholm, M.L., Nielsen, S.S., et al., 2018. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies. Cochrane Database Syst Rev.

Sund, A.M., Zeiner, P., 2002. Does extended medication with amphetamine or methylphenidate reduce growth in hyperactive children? Nord J Psychiatry 56 (1), 53–57.

Swanson, J., Greenhill, L., Wigal, T., Kollins, S., Stehli, A., et al., 2006. Stimulant-related reductions of growth rates in the PATS. J Am Acad Child Adolesc Psychiatry 45, 1304–1313.

Swanson, J.M., Elliott, G.R., Greenhill, L.L., Wigal, T., Arnold, L.E., et al., 2007. Effects of stimulant medication on growth rates across 3 years in the MTA follow-up. J Am Acad Child Adolesc Psychiatry 46 (8), 1015–1027.

Swanson, J.M., Arnold, L.E., Molina, B.S.G., et al., 2017. Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression. J Child Psychol Psychiatry 58 (6), 663–678.

Swanson, J.M., Arnold, L.E., Jensen, P.S., et al., 2018. Long-term outcomes in the Multimodal Treatment study of Children with ADHD (the MTA). From beginning to end. In: Banaschewski, T., Coghill, D., Zuddas, A. (Eds.), Oxford Textbook: Attention Deficit Hyperactivity Disorder. Oxford University Press, Oxford, UK, pp. 218–232.

Tanner, J.M., Whitehouse, R.H., 1976. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 51 (3), 170–179.

Taylor, E., Döpfner, M., Sergeant, J., Asherson, P., Banaschewski, T., et al., 2004. European clinical guidelines for hyperkinetic disorder - first upgrade. Eur Child Adolesc Psychiatry 13 (Suppl 1), 17–30.

The MTA Cooperative Group, 1999. Multimodal Treatment Study of Children with ADHD): a 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 56, 1073–1086.

The MTA Cooperative Group, 2004. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. Pediatrics 113 (4), 762–769.

Van de Loo-Neus, G.H., Rommelse, N., Buitelaar, J.K., 2011. To stop or not to stop? How long should medication treatment of attention-deficit hyperactivity disorder be extended? Eur Neuropsychopharmacology 21 (8), 584–599.

Vitiello, B., 2008. Understanding the risk of using medications for attention deficit hyperactivity disorder with respect to physical growth and cardiovascular function. Child Adolesc Psychiatr Clin N Am 17 (2), 459–474.

Zachor, D.A., Roberts, A.W., Hodgens, J.B., Isaacs, J.S., Merrick, J., 2006. Effects of long-term psychostimulant medication on growth of children with ADHD. Res Dev Disabil 27 (2), 162–174.

Zeiner, P., 1995. Body Growth and Cardiovascular Function after Extended Treatment (1.75 Years) with Methylphenidate in Boys with Attention-Deficit Hyperactivity Disorder. Journal of Child and Adolescent Psychopharmacology 5 (2), 129–138.

Zhang, H., Du, M., Zhuang, S., 2010. Impact of long-term treatment of methylphenidate on height and weight of school age children with ADHD. Neuropediatrics 41 (2), 55–59.

Zhu, J., Chan, Y.M., 2017. Adult consequences of self-limited delayed puberty. Pediatrics. https://doi.org/10.1542/peds.2016-3177(2017).

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http://adhd.marionegri.it/index.php/newsletter/cancellazione-newsletter

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

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