



NEWSLETTER



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REDUCED EMOTIONAL EMPATHY IN ADULTS WITH SUBCLINICAL ADHD: EVIDENCE FROM THE EMPATHY AND SYSTEMIZING QUOTIENT.

Groen Y, Den Heijer AE, Fuermaier ABM, et al.

Studies in children with ADHD suggest impairments in social cognitive functions, whereas studies in adults with ADHD are scarce and inconclusive. The aim of this study was to investigate the relationship between ADHD traits and self-reported social cognitive style in a sample of adults from the general population. For this purpose, a community sample of 685 adults filled out online self-report questionnaires about ADHD symptoms (ADHD Rating Scale, ARS), social cognitive functioning and friendships. The Empathy Quotient (EQ) with the subscales Cognitive Empathy (CE), Emotional Empathy (EE) and Social Skills (SS), and the Systemizing Quotient (SQ) were included for measuring social cognitive style and the Friendship Questionnaire (FQ) for the quality of friendships. Participants who met the DSM-5 criteria on the ARS ('subclinical ADHD'; n = 56) were compared regarding their social cognitive functioning scores with a control group (n = 56) that was matched for age, sex and student status. With small effect sizes, the subclinical ADHD group showed reduced EE scores on the EQ and a more male social cognitive profile. This result was not influenced by sex or ADHD subtype. This study points to a relationship between traits of ADHD and the emotional aspect of empathy, whereas more complex aspects of empathy were unrelated. These findings should be corroborated in clinical patients with ADHD, employing neuropsychological tests rather than self-report questionnaires

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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.

Alcohol Clin Exp Res. 2018;42:361A.

ADHD SYMPTOMS AND INTRA FAMILIAL RELATIONSHIP QUALITY.

Mendoza MJ, Harrison J, Payne J, et al.

Purpose: Previous literature indicates that adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) may have more strained parent and child relationships throughout the course of adolescence into adulthood. Of the ADHD subtypes, Inattentive-type is suggested to be most related to child-parent stress. Additionally, risk factors such as family history of substance use disorders increase risk of intrafamilial discord. However, no study to date has examined inattentive symptoms and relationship quality in the context of general family functioning, or if ADHD symptoms predict family discord above and beyond a family history of substance use, a common risk factor. We hypothesized that the presence of inattentive symptoms - as opposed to hyperactive symptoms - would be a unique predictor of poor intrafamilial functioning, even after accounting for family history of substance use.

Methods: The current study examined a cohort of children between the ages of 10-12 who either had (FH+; n = 306) or did not have (FH-; n = 81) a family history of substance use disorder. ADHD symptoms of predominantly inattentive-type and predominantly hyperactive/impulsive type were measured using the Conners 3-Parent Report, while intrafamilial dysfunction was assessed by the Parents' FAM-III General Scale score. A hierarchical regression was used to examine the strength of Inattentive and Hyperactive symptoms as predictors of intrafamilial dysfunction while controlling for family substance use history and gender.

Results: Family history positive status was significantly related to decreased intrafamilial functioning. After controlling for family history, Inattentive symptoms were significantly predictive of intrafamilial dysfunction while hyperactive symptoms were not. Post-hoc tests examined which subscales of the FAM-III were most highly related to Inattentive symptoms; results found significant associations for Control, Communication, and Role Performance subscales.

Conclusion: Substance use disorder confers stress and impacts intrafamilial functioning. This environment is exacerbated for children with ADHD. However, our results found that ADHD-Inattentive symptoms are a unique indicator of intrafamilial dysfunction independently of family history of substance use disorders. Adolescents who present inattentive symptoms may not be communicating, performing, or adapting to family demands at the level a family requires, thus resulting in poorer intrafamilial relationships. In therapeutic settings, methods of communication between family members and predominantly-inattentive children may be effective in improving intrafamilial discord

Alcohol Clin Exp Res. 2018;42:45A.

PREDICTING PRENATAL ALCOHOL EXPOSURE HISTORIES USING MEASURES OF ATTENTION AND ACTIVITY.

Inkelis SM, Moore EM, Mattson SN, et al.

Background: Children with fetal alcohol spectrum disorders (FASD) often demonstrate attention deficits and high rates of ADHD. This study examines the use of an objective measure of ADHD symptoms to differentiate FASD from typically developing controls and a heterogeneous clinical contrast group.

Methods: Children with prenatal alcohol exposure (AE; n = 26), typically developing controls (T-CON; n = 38), and non-exposed children with other behavioral conditions/concerns (B-CON; n = 24) age 6-17 years were assessed with the Quotient ADHD System. ADHD was the most common behavioral concern in both the AE group (76.9%) as well as the B-CON group (62.5%). Other concerns in the AE/B-CON groups included internalizing and externalizing disorders. Age-adjusted percentile scores for 11 variables (5 Attention, 6 Motion) were analyzed using multivariate analysis of variance (MANOVA) and discriminant function analysis (DFA) to examine group differences and predictors of group membership, respectively. A follow-up DFA evaluated ability of the Quotient to classify ADHD status.

Results: For the MANOVA, there were significant group differences in Accuracy, Omission Errors, Variability, and Coefficient of Variation (COV; ps < 0.043). T-CON performed significantly better than both AE and B-CON (ps < 0.047); AE did not differ from B-CON. For the DFA, the first function was statistically significant [$\chi^2(22) = 37.808$, $p = 0.019$, $g^2 = 0.377$] and 62.5% of the sample was correctly classified into their diagnosis group, exceeding the value for classification based on chance (34.8%). At the individual group level, 57.7% of AE, 54.2% of B-CON, and 71.1% of T-CON were correctly classified. The practically significant predictors for distinguishing T-CON from AE and BCON were Omission Errors, COV, Variability, Accuracy, Immobility

Duration, Commission Errors, Spatial Complexity, Temporal Scaling, and Area (standardized coefficient > |0.3|). No function reliably discriminated AE and B-CON. The Quotient correctly classified 77% of subjects with ADHD, regardless of exposure history.

Conclusions: AE and B-CON were more inattentive than T-CON, but groups did not differ on Motion variables. Quotient ADHD System is an effective tool for assessment of ADHD symptomatology in children with FASD, and our results extend the validity of this program to detect ADHD in this population. However, this system does not reliably discriminate children with heavy prenatal alcohol exposure from children with other behavioral conditions/concerns without heavy alcohol exposure histories

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An Pediatr. 2018.

HEALTH-RELATED QUALITY OF LIFE IN CASES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH AND WITHOUT PHARMACOLOGICAL TREATMENT.

López-Villalobos JA, Sacristán-Martín AM, Garrido-Redondo M, et al.

Introduction: The health-related quality of life (HRQoL) questionnaire is important in order to assess the effects of therapeutic intervention. The aim of this study is to analyse HRQoL, comparing cases of attention deficit hyperactivity disorder (ADHD) treated with methylphenidate (ADHD-T), untreated cases (ADHD-N), and controls.

Material and methods: The study included a sample of 228 participants between 8 and 14 years old (114 controls, 57 ADHD-T, and 57 ADHD-N). Consecutive sampling was used in ADHD according to DSM-IV criteria (ADHD Rating Scales IV), and random sampling of controls matched by gender and age. The evaluation of HRQoL was made by using KIDSCREEN-52 parent version.

Results: The intensity of ADHD symptoms is significantly lower in ADHD-T than in ADHD-N. There is a moderate significant correlation between greater intensity of ADHD symptoms and worse HRQoL. ADHD cases have significantly worse HRQoL than controls on psychic well-being, mood, relationship with parents and friends, school environment, and social acceptance. The cases of ADHD-T have significantly better HRQoL than ADHD-N in the school dimension, but do not differ significantly in other dimensions of KIDSCREEN-52.

Conclusions: It would be advisable that the treatment of ADHD integrates multi-dimensional therapeutic models that improve the basic symptoms of the disorder, as well as the HRQoL

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Ann Neurol. 2017;82:S328-S329.

PREVALENCE OF NEUROCOGNITIVE AND BEHAVIORAL IMPAIRMENT IN INDIVIDUALS WITH DMD(DUCHENNE MUSCULAR DYSTROPHY), BMD (BECKER MUSCULAR DYSTROPHY) AND DMD CARRIERS.

Golla S, Salunkhe V, Xu L, et al.

Objective: To look at the prevalence of neurocognitive and neurobehavioral impairment including Autism Spectrum Disorders, Mental Retardation, attention deficit disorder, language and developmental disorders, obsessive compulsive disorder, mood disorders, anxiety disorders and other neurocognitive and behavioral impairment in patients with DMD, BMD and DMD carriers. Our data will help generate new hypotheses for disease mechanism and foster early detection and early intervention for patients.

Methods: 303 patients were diagnosed with Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD) or DMD carriers based on chart review. Prevalence of neurocognitive problems and behavioral problems was analysed.

Results: In our study, 41 percent of the cohort suffered from neurocognitive or behavioral problems. More than 15 percent of the population suffered from developmental delay, speech delay and behavior disorder. More than 10 percent suffered from either Attention deficit hyperactivity disorder, sleep disorder and Obstructive sleep apnea and Cognitive Delay while 8 percent of the population suffered from Autism, Anxiety and learning difficulties. While 5 percent and less of the population had language delay, gross motor delay, fine motor delay, Mental retardation, oppositional defiant disorder and pervasive development disorder. (Table Presented) Depression, Bipolar and mood disorders were also seen in this population.

Conclusions: This research study indicates that children and adolescents affected with DMD, BMD and DMD carriers have significant mental and behavioral health comorbidities. Our study indicates that behavior disorder, speech and language delay, cognitive delay, sleep disorder, Attention Deficit Hyperactivity Disorder, Autism, Anxiety, learning difficulties and other delays respectively in this order are very common

Ann Pharmacother. 2018;52:623-31.

IMPACT OF VITAMIN D SUPPLEMENTATION ON ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Elshorbagy HH, Barseem NF, Abdelghani WE, et al.

Background: The role of nutrients and dietary factors in attention-deficit hyperactivity disorder (ADHD) remains unclear. **Objectives:** The primary objective was to evaluate the serum vitamin D level in children with a diagnosis of ADHD. The secondary objective was to detect the effect of vitamin D supplementation on cognitive function in those with vitamin D deficiency.

Methods: A total of 50 children with ADHD and 40 healthy controls were included in the study. We measured the serum level of vitamin D. Patients with vitamin D deficiency were subdivided into 2 groups: one with vitamin D supplementation and the other without vitamin D supplementation. Further assessment and follow-up of children with ADHD was done. The Wisconsin Card Sorting Test, Conners Parent Rating Scale, and Wechsler Intelligence Scale for Children were performed at baseline and follow-up in all cohorts with an ADHD diagnosis.

Results: The diagnosis of vitamin D deficiency was significantly greater in children with ADHD compared with the control group ($P < 0.05$). Children with ADHD had significantly ($P = 0.0009$) lower values of serum vitamin D (17.23 ± 8.98) than the control group (31.47 ± 14.42). The group receiving vitamin D supplementation demonstrated improvement in cognitive function in the conceptual level, inattention, opposition, hyperactivity, and impulsivity domains.

Conclusion: Vitamin D supplementation in children with ADHD may improve cognitive function

Asian J Psychiatry. 2018;35:101-08.

RELATIONSHIP BETWEEN BIPOLAR DISORDER AND ATTENTION DEFICIT HYPERKINETIC DISORDER: AN EXPLORATORY STUDY.

Jhanda S, Malhotra S, Grover S.

Objectives: This study aimed to evaluate the impact of comorbid attention deficit hyperkinetic disorder (ADHD) on Bipolar disorder (BD).

Methods: Patients aged 13-40 years with diagnosis of BD with ADHD ($N = 30$) were compared to those with BD without ADHD ($N = 69$) for clinical course, functional outcome and quality of life.

Results: Those with BD + ADHD had significantly lower age of onset of BD ($p < 0.001$), a significantly higher number of total lifetime episodes ($p = 0.002$), higher number of lifetime manic episodes ($p = 0.008$), higher number of hospitalizations ($p = 0.004$) and higher prevalence of family history of BD as compared to those with BD without ADHD ($p = 0.043$). BD + ADHD group had poor response to conventional mood stabilizers and significantly higher prescriptions of atypical antipsychotics ($p = 0.001$) and higher rates of antidepressant-induced switch. Also, BD + ADHD group had significantly lower level of functioning in personal, occupational and social domains and reduced quality of life. In the BD + ADHD group, 40% patients had persistence of ADHD into adulthood. Comorbid current ADHD had more negative impact on the course and outcome of BD, when compared with those with ADHD in the past.

Conclusions: Comorbid ADHD has negative impact on the course and outcome of BD

Biological Trace Element Research. 2018;1-7.

BLOOD LEVELS OF TRACE ELEMENTS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: RESULTS FROM A CASE-CONTROL STUDY.

Yang R, Zhang Y, Gao W, et al.

Some trace elements may participate in the pathogenesis of attention-deficit hyperactivity disorder (ADHD). This study aimed to investigate the trace element status of zinc (Zn), copper (Cu), iron (Fe), magnesium (Mg), and lead (Pb) in children with ADHD, and to compare them with normal controls. Associations between examined elements and SNAP-IV rating scores of ADHD symptoms were also assessed. Four hundred nineteen children with ADHD (8.8 -1 2.1 years) and 395 matched normal controls (8.9 -1 1.7 years) were recruited in the study. The concentrations of Zn, Fe, Cu, Mg, and Pb in the whole blood were measured by atomic absorption spectrometry. Lower zinc levels ($P < 0.001$) and the number out of normal ranges ($P = 0.015$) were found in children with ADHD when compared with the normal control group. The difference remained when adjusting the factor of BMI z-score. No significant between-group differences were found in levels of other elements. Zinc levels were negatively correlated with parent-rated scores of inattentive subscale of SNAP-IV ($r = -0.40$) as well as with total score of SNAP-IV ($r = -0.24$). Other significant associations were not observed. The present results indicated that there were alterations in blood levels of zinc, which was associated with the symptom scores of ADHD

Birth Defects Research. 2018;110:774.

PREVALENCE AND DETERMINANTS OF ADHD MEDICATION USE IN QUINCEPREGNANCY CHILDREN BETWEEN 1998 AND 2015.

Boukhris T, Lemelin M, Sheehy O, et al.

An increase in attention deficit hyperactivity disorder (ADHD) medication use has been observed over the last two decades. We aimed to: 1) describe the time trends of ADHD medication use among children aged 18 years and under, stratified by sex, age groups, and types of ADHD medication; 2) to determine dosages and switches among ADHD medication users; and 3) to identify and quantify determinants of ADHD medication use in children. Using the Quincepregnancy/Children Cohort, we conducted a longitudinal cohort study to investigate trends in the prevalence of ADHD medication use among singletons liveborn between 1998-2015. We excluded children with autism spectrum disorder. Among treated children with ADHD, we assessed dosages and switches of ADHD medications. Logistic regression models were used to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs) to identify factors associated with ADHD medication use among children. During the study period, we identified 235,132 singletons. We observed a significant increase in the prevalence of overall ADHD medication use ($p < 0.01$). We found that the prevalence rates of ADHD medication use were significantly increased with a higher prevalence for boys vs. girls (67.3% vs 32.1%) and in children 6-11 years old (80.8%). Methylphenidate was the most used (60.5%). We found that 96.7% of ADHD medication prescriptions were at optimal dosage compared to 0.7% and 2.6% at sub-dosage and over-dosage, respectively. We found that 20.4% of children switched to another class of ADHD medications or had concomitant use of ADHD medications. Factors significantly associated with ADHD medication use were male sex, low birthweight, having ADHD diagnosis at age 6-11 years, having asthma and epilepsy, and having depression/ anxiety. Use of antidepressants before the first diagnosis of ADHD was strongly associated with ADHD medication use (aOR=3.06, 95%CI [2.21-4.22]). Younger maternal age, being on welfare, maternal psychiatric disorders, and maternal use of antidepressants during second/third trimesters of pregnancy were also predictors of ADHD medication use in children. Our findings indicate that ADHD medication use increased over time, specifically for children aged 6-11 years. Furthermore, overall ADHD medications are prescribed predominantly according to published recommendations

BMC Neurol. 2018;18.

Computer-assisted rehabilitation of attention in pediatric multiple sclerosis and ADHD patients: A pilot trial.

Simone M, Viterbo RG, Margari L, et al.

Background: The treatment of cognitive deficits is challenging in pediatric onset multiple sclerosis (POMS) and in patients with attention deficit hyperactivity disorder (ADHD). We performed a pilot double-blind RCT to evaluate the efficacy of a home-based computerized-program for retraining attention in two cohorts of POMS and ADHD patients.

Methods: POMS and ADHD patients failing in at least 2/4 attention tests on a neuropsychological battery were randomized to specific or nonspecific computerized training (ST, nST), performed in one-hour sessions, twice/week for 3 months. The primary outcome was the effect of the training on global neuropsychological performances measured by the cognitive impairment index (CII). The efficacy of the intervention was evaluated in each disease group by using repeated measures ANOVA.

Results: Sixteen POMS (9 females, age 15.75 \pm 1.74 years) and 20 ADHD (2 females, age 11.19 \pm 2.49 years) patients were enrolled. In POMS patients the ST exposure was associated to a significantly more pronounced improvement of the CII ($p < 0.0001$) and on cognitive test exploring attention, concentration, planning strategies and visuo-spatial memory performances in comparison to nST exposure. In ADHD patients the difference between the ST and nST on the CII was not statistically significant ($p = 0.06$), but a greater effect of the ST was found only on cognitive test exploring attention and delayed recall of visuo-spatial memory performances.

Conclusions: Our data suggest that a cognitive rehabilitation program that targets attention is a suitable tool for improving global cognitive functioning in POMS patients, whereas it has a less pronounced transfer effect in ADHD patients

Brain Dev. 2018.

MIGRAINE AND ASSOCIATED COMORBIDITIES ARE THREE TIMES MORE FREQUENT IN CHILDREN WITH ADHD AND THEIR MOTHERS.

Kutuk MO, Tufan AE, Guler G, et al.

Objective: Attention deficit and hyperactivity disorder (ADHD) is a neuro-developmental disorder related to internalizing and externalizing disorders as well as somatic complaints and disorders. This study was conducted to evaluate the prevalence of headache subtypes, epilepsy, atopic disorders, motion sickness and recurrent abdominal pain among children and adolescents with ADHD and their parents.

Methods: In a multi-center, cross-sectional, familial association study using case-control design, treatment naïve children and adolescents between 6 and 18 years of age diagnosed with ADHD according to the DSM-5 criteria as well as age- and gender-matched healthy controls and their parents were evaluated by a neurologist and analyzed accordingly.

Results: 117 children and adolescents with ADHD and 111 controls were included. Headache disorder diagnosis was common for both patients and healthy controls (59.0% vs. 37.8%), with a significantly elevated rate in the ADHD group ($p = 0.002$). Migraine was found in 26.0% of ADHD patients and 9.9% of healthy controls. Tension headache was found in 32.4% of ADHD patients and 27.9% of healthy controls. Headache diagnosis was also found to be significantly more common in mothers of children with ADHD than control group mothers (90.5% vs. 36.6%, $p < 0.001$).

Conclusion: Headache diagnoses and specifically migraines were significantly more common among children with ADHD and their mothers, while recurrent abdominal pain was elevated in both parents and ADHD patients. Migraine is an important part of ADHD comorbidity, not only for children but also for mothers. Motion sickness may be reduced among families of ADHD probands

Brain Imaging Behav. 2018;12:882-90.

DIFFERENTIAL BRAIN ACTIVATIONS IN ADULT ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER SUBTYPES: A COUNTING STROOP FUNCTIONAL MRI STUDY.

Shang C-Y, Sheng C, Yang L-K, et al.

Although previous functional neuroimaging studies have found abnormal brain activations in individuals with attention deficit hyperactivity disorder (ADHD), little was known about distinct brain dysfunctions across different ADHD subtypes. The objective of the present study was to investigate the abnormal brain activations associated with two ADHD subtypes, predominantly inattentive (ADHD-PI) and combined (ADHD-C) subtypes. Twenty-five adults with ADHD-PI, 25 with ADHD-C, and 30 healthy controls (HC) participated in this study. The brain function of the participants were assessed by using the counting Stroop task inside the scanner and the Conners' Continuous Performance Test (CCPT) outside the scanner. The HC group showed greater activations in the caudate nucleus and inferior frontal gyrus (IFG) than the ADHD-PI and ADHD-C groups. The ADHD-PI group showed greater activations in the superior parietal lobule (SPL) than the ADHD-C group. In all participants with ADHD, we found negative correlations of activation in the left caudate and the left IFG with the standard deviation of the reaction time of the CCPT, and negative correlations of activation in the left SPL with the reaction time changes across different inter-stimulus intervals. Our results demonstrated altered brain activity in the frontostriatal networks of adults with ADHD-PI and the fronto-striato-parietal networks of adults with ADHD-C. Abnormalities in the parietal areas may represent the main difference between the ADHD-PI and ADHD-C subtypes

Child Abuse Negl. 2018;81:274-85.

ASSOCIATIONS BETWEEN ABUSE/NEGLECT AND ADHD FROM CHILDHOOD TO YOUNG ADULTHOOD: A PROSPECTIVE NATIONALLY-REPRESENTATIVE TWIN STUDY.

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

Child maltreatment has consistently been found to be associated with attention deficit/hyperactivity disorder (ADHD). However, the robustness of this association and the direction of the link between maltreatment and ADHD remain unclear. We used data from the Environmental Risk (E-Risk) Longitudinal Twin Study, a cohort of 2232 British twins, to investigate the associations between exposure to abuse/neglect and ADHD in childhood and in young adulthood, and to test their robustness and specificity. We also aimed to test longitudinal associations between abuse/neglect and ADHD from childhood to young adulthood, controlling for confounders. Results indicated strong associations between abuse/neglect and ADHD in childhood and also in young adulthood. In childhood, the association was concentrated among children with comorbid conduct disorder. Longitudinal analyses showed that childhood ADHD predicted abuse/neglect in later years. This association was again concentrated among individuals with comorbid conduct disorder. Abuse/neglect in childhood was not associated with later ADHD in young adulthood after adjusting for childhood ADHD. Our study does not provide support of a causal link between child abuse/neglect and adult ADHD but highlights the possibility of a long-term effect of disruptive behaviors on the risk for experiencing abuse/neglect. These findings emphasize the need for clinicians treating people with ADHD, especially those with comorbid conduct disorder, to be aware of their increased risk for experiencing abuse/neglect. Interventions aimed at reducing risks of abuse/neglect should also focus on the environment of individuals with disruptive behaviors

Child Adolesc Psychiatry Ment Health. 2018;12.

CHILDHOOD ADHD AND TREATMENT OUTCOME: THE ROLE OF MATERNAL FUNCTIONING.

Rasmussen PD, Storeb+© OJ, Shmueli-Goetz Y, et al.

Background: Relatively little is known about the role of maternal functioning in terms of attention deficit hyperactivity disorder (ADHD) symptoms, attachment style and resilience as predictive factors for treatment outcome when offspring are diagnosed with ADHD.

Objective: To investigate whether maternal functioning is associated with treatment outcome in children with ADHD.

Methods: The study formed part of a larger naturalistic observational study of children with ADHD. A battery of self-report measures was used to assess selected factors in maternal functioning at the point of referral (baseline data); adult ADHD-symptoms, adult attachment style and adult resilience. Associations between these domains and child treatment response were subsequently examined in a 1-year follow up.

Results: Maternal ADHD-symptoms and degree of resilience were significantly correlated to symptom reduction in offspring diagnosed with ADHD. However, the association between maternal attachment style and child treatment response as measured by the ADHD-RS did not reach statistical significance.

Conclusion: To our knowledge, this is the first study to consider potential protective factors along with risk factors in maternal functioning and the impact on child treatment outcome. The study contributes to our knowledge of the potential role of maternal functioning in treatment outcome for children with ADHD

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Clinics in Perinatology. 2018.

BEHAVIORAL AND SOCIOEMOTIONAL DEVELOPMENT IN PRETERM CHILDREN.

Peralta-Carcelen M, Schwartz J, Carcelen AC.

Prematurity is a significant risk factor for impaired neurodevelopmental outcomes. These include motor, cognitive, language, behavioral, and socioemotional competence. Long-term overall function depends on healthy socioemotional functioning. The vulnerability of the preterm brain during critical periods of development contributes to behavioral and socioemotional problems in preterm children. Attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) clinical features are more frequent in preterm children compared with their full-term counterparts; however, true rates of ASD and ADHD vary across studies. Early detection of behavioral and socioemotional problems in preterm children would enable timely early intervention to improve long-term functional outcomes

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CNS Drugs. 2018;32:455-67.

GROWTH AND PUBERTY IN A 2-YEAR OPEN-LABEL STUDY OF LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Banaschewski T, Johnson M, Nagy P, et al.

BACKGROUND: Stimulant medications for the treatment of attention-deficit/hyperactivity disorder have a history of safe and effective use; however, concerns exist that they may adversely affect growth trajectories in children and adolescents.

OBJECTIVE: The objective of this study was to evaluate the longer-term effects of lisdexamfetamine dimesylate on weight, height, body mass index and pubertal development in children and adolescents with attention-deficit/hyperactivity disorder.

METHODS: Children and adolescents aged 6-17 years with attention-deficit/hyperactivity disorder took open-label lisdexamfetamine dimesylate (30, 50 or 70 mg/day) in this open-label 2-year safety and efficacy study. Safety evaluations included treatment-emergent adverse events, measurement of weight, height and body mass index, and self-reported pubertal status using Tanner staging.

RESULTS: The safety analysis population comprised all enrolled participants (N = 314) and 191 (60.8%) completed the study. Weight decrease was reported as a treatment-emergent adverse event in 63 participants (20.1%) and two participants (0.6%) discontinued the study as a result of treatment-emergent adverse events of weight decrease. Growth retardation of moderate intensity was reported as a treatment-emergent adverse event for two participants. From baseline to the last on-treatment assessment, there were increases in mean weight of 2.1 kg (standard deviation 5.83) and height of 6.1 cm (standard deviation 4.90), and a body mass index decrease of 0.5 kg/m² (standard deviation 1.72). Mean weight, height and body mass index z-scores decreased over the first 36 weeks of the study and then stabilised. Changes from baseline to the last on-treatment assessment in mean z-scores for weight, height and body mass index were significantly less than zero (-0.51, -0.24 and -0.59, respectively; nominal p < 0.0001). The proportion of participants with a z-score of < -1 ranged from 5.1% (baseline) to 22.1% (week 84) for weight, 8.2% (baseline) to 12.6% (week 96) for height, and 8.3% (baseline) to 28.8% (week 96) for body mass index. Thirteen participants (4.1%)

shifted to a weight below the fifth percentile at the last on-treatment assessment from a higher weight category at baseline. At the last on-treatment assessment, most participants remained at their baseline Tanner stage or had shifted higher.

CONCLUSIONS: Findings from this comprehensive examination of growth outcomes associated with lisdexamfetamine dimesylate treatment over 2 years were consistent with previous studies of stimulant medications. Whilst mean weight and height increased over the course of the study, there was a small but transient reduction in mean weight, height and body mass index z-scores. A small increase in the proportion of participants in the lowest weight and body mass index categories highlights the importance of the regular monitoring of weight and height. There was no evidence of delayed onset of puberty. CLINICALTRIALS
GOV IDENTIFIER: NCT01328756

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Dev Neuropsychol. 2018;43:256-77.

EMOTIONAL FACE RECOGNITION IN INDIVIDUALS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A REVIEW ARTICLE.

Borhani K, Nejati V.

This review focuses on facial emotion recognition (FER) in individuals with attention-deficit/hyperactivity disorder (ADHD). Behavioral studies of FER in ADHD have resulted in inconsistent findings. Here, we discuss the factors that vary across studies and the way that they influence FER processes in ADHD. Across reviewed studies, fear was the most deficient facial expression to be recognized. Our review suggested that FER deficit in ADHD does not alleviate across development and is partially distinct from ADHD symptoms. In conclusion, assessment of FER in ADHD and targeting that in interventional plans could lead to social skills improvement in ADHD

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Dev Med Child Neurol. 2018;60:51.

NATIONAL SURVEY MAPPING ADULT ATTENTION-DEFICIT-HYPERACTIVITY DISORDER (ADHD) SERVICES.

Eke H, Price A, Ford T, et al.

Introduction: This UK based Mapping Study is a part of the 'Children and Adolescents with ADHD in Transition between Children's Services and Adult Services' project (CATCh-uS). It aims to investigate service provision from the point of view of key stakeholders and create a map of attention-deficit-hyperactivity disorder (ADHD) services for people aged 18 and above. The survey will run twice (2016 and 2018) in order to provide a snapshot of service changes over time.

Patients and method: Service users, clinicians, and commissioners were surveyed using a brief online questionnaire. Survey links were distributed via national organisations such as the National Attention Deficit Disorder Information and Support Service, the Royal College of Psychiatrists, and clinical and academic networks. Methods included direct email, newsletters, and social media.

Results: The 2016 survey received a total of 1448 responses from 684 clinicians, 595 service users, and 169 clinical commissioning groups. Respondents identified 217 unique services, including 27 specialist adult ADHD services, 102 'other' mental health services, 23 voluntary/charity organisations, and 10 private providers. Visual maps show response rates by stakeholder group and UK region. A list of identified services will be published online and disseminated as a resource for service users and clinicians. The survey will be repeated in 2018.

Conclusion: By collecting national level data, informed by stakeholders and presenting it in a format accessible to all, this research aims to inform future service delivery, and improve service users' access to adult ADHD services

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Dev Med Child Neurol. 2018;60:56-57.

ATTENTION, TIME, NUMEROSITY, AND MATH IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT-HYPERACTIVITY DISORDER (ADHD).

Tinelli F, Bartoli M, Anobile G, et al.

Introduction: Time, space, math, and numerosity are ubiquitous dimensions of human lives. An influential theory (ATOM) suggested that all these magnitudes may be encoded by a common neural mechanism, mainly located in the parietal cortex. However, firm evidence for such a generalized mechanism is still lacking. The aim of this study was to test the association of parietal functions in children and adolescents with ADHD.

Patients and method: Fourteen children and adolescents with ADHD and 14 typically developing children and adolescents, matched for age (8-16y) participated in this study. Inclusion criteria were a diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, an IQ more than 70, no neurological or sensory impairment, and no pharmacological treatment. Numerosity and time discrimination thresholds were psychophysically measured. Time was measured in the auditory domain and for both sub and supra second duration intervals. We also measured visuo-spatial sustained attention and symbolic math.

Results: Participants with ADHD performed worse than controls in auditory time perception (both intervals), visual sustained attention, and symbolic math. Visual numerosity estimation was instead relatively spared. Interestingly, numerosity and math skill were positively correlated. Moreover, those children having higher time impairment were not those showing worse attentional skills.

Conclusion: Our results generally confirm ATOM theory, but also show that selective impairments are possible. Moreover, given that time perception deficits do not depend on attention, our results suggest that ADHD may be characterized by a specific time encoding deficit, together with impaired attention skills

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Dev Med Child Neurol. 2018;60:51.

EXPLORING THE ROLE OF INFORMATION IN FACILITATING OR IMPEDING YOUNG PEOPLE'S TRANSITION INTO ADULT ATTENTION-DEFICIT-HYPERACTIVITY DISORDER (ADHD) SERVICES.

Eke H, Price A, Ford T, et al.

Introduction: UK guidelines (National Institute for Health and Clinical Excellence, 2008) emphasise the need for good communication of information between services during transition into adult attention-deficit-hyperactivity disorder (ADHD) services. Emerging findings from a recent systematic review highlight stakeholder needs for information about adult ADHD services and how they vary. This qualitative study explores the role of information in young people's experiences of transition into adult ADHD services and the impact on service engagement and young people's self-agency.

Patients and method: One-hundred and thirty qualitative interviews were conducted; 64 with young people with ADHD aged 14 to 30 years, 38 with clinicians, and 28 with parents/ carers. Participants were recruited from 11 National Health Service Trusts, located across England with varying service configurations. Interim and thematic analysis of data was completed using Framework.

Results: Initial analysis reveals the importance of three kinds of information during the transition process; good communication between child and adult ADHD services; provision of information about what to expect during transition; and information about location, accessibility, and variation of adult ADHD services. Young people, carers, and clinicians describe significant negative impacts related to uncertainty and lack of communication.

Conclusion: This study provides insight into how availability and communication of information between services and stakeholders may support or impede the transition process between child and adult ADHD services. It constitutes a substantial contribution to the evidence base, drawing on interviews from a range of participants across England and from trusts offering different types of services

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Dev Med Child Neurol. 2018;60:34.

EVALUATION OF MANUAL DEXTERITY AND GRIP STRENGTHS IN CHILDREN WITH ATTENTION-DEFICIT-HYPERACTIVITY DISORDER (ADHD).

Durgut E, et al.

Introduction: Attention-deficit-hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder that typically presents with symptoms of inattention, impulsivity, and hyperactivity and may have profound impact on the individual and their family. Many children with ADHD have deficiencies in gross motor skills that could cause problems in both school and social activities. This study was designed to evaluate the dexterity and grip strengths in children with ADHD. **Patients and method:** Ten children with clinical diagnoses of ADHD (1 female, 9 males; mean- \pm SD 8.7- \pm 1.3) and 10 typically developing children (3 females, 7 males; mean- \pm SD 9.3- \pm 1.1) were included in the study. Ages ranged from 7 to 11 years. A dynamometer was used to measure grip strength and a pinch meter to measure lateral, tip, and palmar pinch strengths. Manual dexterity was evaluated with the Nine Hole Peg Test (NHPT). All measurements were done on both sides. Data analyses were performed using SPSS version 20. The Mann-Whitney U test was used to compare variables between the two groups. **Results:** There were statistically significant differences between the grip strengths on both sides ($p=0.001$). Although all of the finish times for NHPT were longer in the ADHD group, only right peg removal time was found to be statistically significant ($p=0.013$). **Conclusion:** The improvement of hand strengths and skills can facilitate child's daily activities and so rehabilitation programs for ADHD can be developed in this direction. But there is a need for more studies in larger populations with ADHD to speak clearly in this regard

Dev Med Child Neurol. 2018;60:56.

APPROPRIATE PARENTAL INVOLVEMENT IN THE TRANSITION OF YOUNG PEOPLE WITH ATTENTION-DEFICIT-HYPERACTIVITY DISORDER (ADHD) FROM CHILDREN'S SERVICES TO ADULT SERVICES IN ENGLAND.

Eke H, Stimson A, Price A, et al.

Introduction: The role that parents have to play in the transition of young people with attention-deficit-hyperactivity disorder (ADHD) from children's services to adult services is acknowledged, but not further defined in the National Institute for Health and Care Excellence (NICE) guidelines for transition. The CATCh-uS project, on the transition of young people with ADHD between child and adult services, studied the parental role in this process and how this is perceived and evaluated by parents, clinicians, and young people.

Patients and method: A 12-month surveillance study identified all young people on medication for ADHD requiring a transition to adult services within six months. Clinicians identified if parents were involved in the process. Sixty-four young people with ADHD at different stages of the transition process, 28 parents of a child with ADHD, 21 child clinicians, and 15 adult clinicians were interviewed about their experiences of transition.

Results: All young people interviewed after a successful transition lived with their parents; their parents had an active role in the process. Analysis will be completed shortly and more detailed findings will be presented at the conference.

Conclusion: Young people, parents, and clinicians acknowledge the involvement of parents in enabling young people's engagement with both children's services and successful transitions to adult services. While NICE guidelines suggest a key worker should oversee this transition and act as a safety net if the process runs off track; in the situations identified by this project this role is taken on by parents in the absence of key workers

Drugs. 2018;1-12.

LISDEXAMFETAMINE DIMESYLATE: A REVIEW IN PAEDIATRIC ADHD.

Frampton JE .

Lisdexamfetamine dimesylate (lisdexamfetamine; Elvanse-«; Tyvense-«), an orally-active dexamfetamine prodrug, is indicated in the EU for the treatment of attention-deficit hyperactivity disorder (ADHD) in children

aged 6 years (including adolescents) when the response to previous methylphenidate (MPH) treatment is clinically inadequate. The original approval of the drug was based on the results of phase III trials in children and adolescents with ADHD who had an inadequate response to previous pharmacotherapy (e.g. MPH) or were treatment naïve. In these studies, short-term treatment with flexibly-dosed lisdexamfetamine demonstrated greater efficacy than atomoxetine, based on a prospective comparison, and osmotic-release oral system (OROS)-MPH, based on a post hoc comparison. Improvements in ADHD symptoms were accompanied by improvements in health-related quality of life and functioning that were maintained as long as treatment with lisdexamfetamine was continued in a long-term extension of one of these trials. In subsequent phase IV head-to-head studies in adolescents with ADHD and an inadequate response to previous pharmacotherapy, lisdexamfetamine demonstrated greater efficacy than OROS-MPH when both medications were force-titrated, but not when they were flexibly-titrated. Lisdexamfetamine was generally well tolerated, with an adverse event profile (e.g. decreased appetite, headache, weight reduction, insomnia and irritability) typical of that reported for other stimulants. Thus, lisdexamfetamine provides an alternative option for the treatment of children and/or adolescents with ADHD who have not responded adequately to previous ADHD pharmacotherapies

Environ Res. 2018;166:205-14.

THE ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL FACTORS AND THE OCCURRENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD). A POPULATION-BASED RETROSPECTIVE COHORT STUDY.

Saez M, et al.

Background: A number of factors contribute to attention deficit hyperactivity disorder (ADHD) and although they are not fully known, the occurrence of ADHD seems to be a consequence of an interaction between multiple genetic and environmental factors. However, apart from pesticides, the evidence is inadequate and inconsistent as it differs not only in the population and time period analysed, but also in the type of study, the control of the confounding variables and the statistical methods used. In the latter case, the studies also differ in the adjustment of spatial and temporal variability. Our objective here, is to provide evidence on an association between environmental factors and ADHD.

Methods: In our study, we used a population-based retrospective cohort in which we matched cases and controls (children free of the disease) by sex and year of birth (n = 5193, 78.9% boys). The cases were children born between 1998 and 2012 and diagnosed with ADHD (n = 116). To evaluate whether there was a geographical pattern in the incidence of ADHD, we first represented the smoothed standardized incidence rates on a map of the region being studied. We then estimated the probability of being a case by using a generalized liner mixed model with a binomial link. As explanatory variables of interest, we included the following environmental variables: distance to agricultural areas, distance to roads (stratified into three categories according to traffic density and intensity), distance to petrol stations, distance to industrial estates, and land use. We control for both observed (individual and family specific variables and deprivation index) and unobserved confounders (in particular, individual and familial heterogeneity). In addition, we adjusted for spatial extra variability.

Results: We found a north-south pattern containing two clusters (one in the centre of the study region and another in the south) in relation to the risk of developing ADHD. The results from the multivariate model suggest that these clusters could be related to some of the environmental variables. Specifically, living within 100 m from an agricultural area or a residential street and/or living fewer than 300 m from a motorway, dual carriageway or one of the industrial estates analysed was associated (statistically significant) with an increased risk of ADHD.

Conclusion: Our results indicate that some environmental factors could be associated with ADHD occurring, particularly those associated with exposure to pesticides, organochlorine compounds and air pollutants because of traffic

Eur Child Adolesc Psychiatry. 2018;1-10.

AGE LEVEL VS GRADE LEVEL FOR THE DIAGNOSIS OF ADHD AND NEURODEVELOPMENTAL DISORDERS.

Bonati M, Cartabia M, Zanetti M, et al.

A number of worldwide studies have demonstrated that children born later in the school year are more likely to receive an ADHD diagnosis than their same school-year peers. There is, however, variation in findings between countries. We aimed to confirm whether relative age is associated with ADHD diagnosis, with or without comorbidities, and to investigate whether relative age is associated with ADHD type and severity, and if this age relationship is in common with other neurodevelopmental disorder. We used the Lombardy Region's ADHD registry. Data on children aged 6 years and older from September 1, 2011 to December 31, 2017 were considered. We calculated incidence ratios to assess the inter-relations between relative age within the school year, using age at diagnosis of ADHD or of other psychiatric disorder, year of diagnosis, and total number of children born in Lombardy during the corresponding timeframe. Data on ADHD type, severity of diagnosed disorder clinical global impressions-severity scale, and repetition of a school-grade were also considered. 4081 children, 2856 of whom with ADHD, were identified. We confirmed that the cumulative incidence of ADHD diagnosis was greatest for younger children, in particular for boys, for whom the prevalence is greater. The relative age effect was not accounted for by ADHD comorbid disorders, ADHD of combined type or severity. The relative age effect was also observed for children with other neurodevelopmental disorders (without ADHD), with a similar profile as ADHD children: the incidence ratio was 1.78 (95% CI 1.07-2.97; $p < 0.0247$) for boys diagnosed before age ten. The findings have a potential implication for diagnostic and therapeutic practice, educational advice, and policies, besides to better plan and organize service systems and appropriately inform parents, children, and citizens

Eur Child Adolesc Psychiatry. 2018;27:821-22.

ARE CHILDHOOD AND ADULT ADHD THE SAME ENTITIES?

Apter A.

Eur Child Adolesc Psychiatry. 2018;1-9.

INCREASED RISK OF DEVELOPING PSYCHIATRIC DISORDERS IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD) RECEIVING SENSORY INTEGRATION THERAPY: A POPULATION-BASED COHORT STUDY.

Tzang R-F, Chang Y-C, Kao K-L, et al.

Parents of children with attention deficit hyperactivity disorder (ADHD) have been found to prefer sensory integration (SI) training rather than guideline-recommended ADHD treatment. This study investigated whether SI intervention for children with ADHD was associated with a reduced risk of subsequent mental disorders. From children < 8-years-old newly diagnosed with ADHD in a nationwide population-based dataset, we established a SI cohort and a non-SI cohort (N = 1945) matched by propensity score. Incidence and hazard ratios of subsequent psychiatric disorders were compared after a maximum follow-up of 9 years. The incidence of psychiatric disorders was 1.4-fold greater in the SI cohort, with an adjusted hazard ratio of 1.41 (95% confidence interval 1.20-1.67), comparing to the non-SI cohort. Risks were elevated for emotional disturbances, conduct disorders, and adjustment disorders independent of age, gender, or comorbidity. Among children with only psychosocial intervention, the incidence of psychiatric disorders was 3.5-fold greater in the SI cohort than in the non-SI cohort. To our knowledge, this is the first study to report an increased risk of developing psychiatric disorders for children with ADHD who received SI compared to those who did not. Potential adverse effects of SI for ADHD children should be carefully examined and discussed before practice

Eur Child Adolesc Psychiatry. 2018;1-12.

MATERNAL BREASTFEEDING AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN: A META-ANALYSIS.

Tseng P-T, Yen C-F, Chen Y-W, et al.

Previous studies have suggested environmental factors may contribute to the risk of attention-deficit/hyperactivity disorder (ADHD). The current meta-analysis examined (1) the difference in the duration of maternal breastfeeding between children with and without ADHD, and (2) the association between maternal breastfeeding and ADHD in children. The data of individual studies were synthesized with a random-effects model. Eleven articles were included in this meta-analysis. Children with ADHD had significantly less breastfeeding duration than controls (Hedges $g = 0.36$, 95% confidence intervals (CIs) = 0.61 to 0.11, $p = 0.005$; difference in means: 2.44 months, 95% CIs = 3.17 to 1.71, $p < 0.001$). In addition, the rates of non-exclusive breastfeeding in children with ADHD is significantly higher in $\Gamma\text{Ç}$ under 3 months $\Gamma\text{Ç}$ (odds ratio (OR) = 1.90, 95% CIs = 1.45 to 2.48, $p < 0.001$) but lower in $\Gamma\text{Ç}$ 6 to 12 months $\Gamma\text{Ç}$ (OR = 0.69, 95% CIs = 0.49 to 0.98, $p = 0.039$) and $\Gamma\text{Ç}$ over 12 months $\Gamma\text{Ç}$ (OR = 0.58, 95% CIs = 0.35 to 0.97, $p = 0.038$) than controls. Children with ADHD received significantly higher rate of exclusive breastfeeding duration under 3 months (OR = 1.51, 95% CIs = 1.20 to 1.89, $p < 0.001$) but lower in over 3 months (OR = 0.52, 95% CIs = 0.29 to 0.95, $p = 0.033$) than controls. Furthermore, an association was found between non-breastfeeding and ADHD children (adjusted OR = 3.71, 95% CI = 1.94 to 7.11, $p < 0.001$). Our results suggest maternal breastfeeding is associated with a lower risk of ADHD in children. Future longitudinal research is required to confirm/refute these findings and to explore possible mechanisms underlying this association

Eur Neuropsychopharmacol. 2018.

ELECTROENCEPHALOGRAPHIC BIOMARKERS AS PREDICTORS OF METHYLPHENIDATE RESPONSE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Arns M, Vollebregt MA, Palmer D, et al.

EEG biomarkers have shown promise in predicting non-response to stimulant medication in ADHD and could serve as translational biomarkers. This study aimed to replicate and extend previous EEG biomarkers. The international Study to Predict Optimized Treatment for ADHD (iSPOT-A), a multi-center, international, prospective open-label trial, enrolled 336 children and adolescents with ADHD (11.9 yrs; 245 males; prescribed methylphenidate) and 158 healthy children. Treatment response was established after six weeks using the clinician rated ADHD-Rating Scale-IV. Theta/Beta ratio (TBR) and alpha peak frequency (APF) were assessed at baseline as predictors for treatment outcome. No differences between ADHD and controls were found for TBR and APF. 62% of the ADHD group was classified as a responder. Responders did not differ from non-responders in age, medication dosage, and baseline severity of ADHD symptoms. Male-adolescent non-responders exhibited a low frontal APF (Fz: R = 9.2 Hz vs. NR = 8.1 Hz; ES = 0.83), whereas no effects were found for TBR. A low APF in male adolescents was associated with non-response to methylphenidate, replicating earlier work. Our data suggest that the typical maturational EEG changes observed in ADHD responders and controls are absent in non-responders to methylphenidate and these typical changes start emerging in adolescence. Clinical trials registration: www.clinicaltrials.gov; NCT00863499 (<https://clinicaltrials.gov/ct2/show/NCT00863499>)

Front Psychiatry. 2018;9.

BLOOD-BOURNE MICRORNA BIOMARKER EVALUATION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER OF HAN CHINESE INDIVIDUALS: AN EXPLORATORY STUDY.

Wang L-J, Li S-C, Lee M-J, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly genetic neurodevelopmental disorder, and its dysregulation of gene expression involves microRNAs (miRNAs). The purpose of this study was to identify potential miRNAs biomarkers and then use these biomarkers to establish a diagnostic panel for ADHD.

Design and methods: RNA samples from white blood cells (WBCs) of five ADHD patients and five healthy controls were combined to create one pooled patient library and one control library. We identified 20 candidate miRNAs with the next-generation sequencing (NGS) technique (Illumina). Blood samples were then collected from a Training Set (68 patients and 54 controls) and a Testing Set (20 patients and 20 controls) to identify the expression profiles of these miRNAs with real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). We used receiver operating characteristic (ROC) curves and the area under the curve (AUC) to evaluate both the specificity and sensitivity of the probability score yielded by the support vector machine (SVM) model.

Results: We identified 13 miRNAs as potential ADHD biomarkers. The ΔCt values of these miRNAs in the Training Set were integrated to create a biomarker model using the SVM algorithm, which demonstrated good validity in differentiating ADHD patients from control subjects (sensitivity: 86.8%, specificity: 88.9%, AUC: 0.94, $p < 0.001$). The results of the blind testing showed that 85% of the subjects in the Testing Set were correctly classified using the SVM model alignment (AUC: 0.91, $p < 0.001$). The discriminative validity is not influenced by patients' age or gender, indicating both the robustness and the reliability of the SVM classification model.

Conclusion: As measured in peripheral blood, miRNA-based biomarkers can aid in the differentiation of ADHD in clinical settings. Additional studies are needed in the future to clarify the ADHD-associated gene functions and biological mechanisms modulated by miRNAs

Fundamental and Clinical Pharmacology. 2018;32:24.

CARDIOVASCULAR SAFETY OF METHYLPHENIDATE IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): THE LILLE EXPERIENCE.

Potey C, Carton L, Marnard O, et al.

Introduction: Methylphenidate (MPH) binds to the dopamine and norepinephrine transporters and inhibits their reuptake, which grants it sympathomimetic properties. This has elicited concerns about the cardiovascular safety of MPH. The available data seems rather reassuring, studies mostly reporting small increases in blood pressure and heart rate without clinical significance [1]. There is only little data in adults, and some authors point at a risk for rare but potentially serious cardiovascular events [2].

Material and methods: MPH is only authorized in France for child ADHD, but is also prescribed in adults. To frame these off-label practices, the CAMTEA-MPH system was set up in Lille in November 2016, similar to the system for off-label baclofen. Enrolled patients benefit from multidisciplinary consultations with psychiatrists and pharmacologists. This allows for a thorough screening and careful assessment before initiating treatment with MPH. Patients receive a cardiovascular evaluation, and, if MPH is initiated, regular cardiovascular assessments when the posology is modified and then every three months.

Results: As of December 2017, 85 naïve patients had been screened and 11 enrolled. 10 other patients were included in the follow-up after starting MPH elsewhere. 2 patients were excluded because of a history of myocardial infarction. A Wolf-Parkinson-White syndrome was suspected in 3 screened patients: 2 were included and prescribed MPH after validation by a cardiologist, and 1 is awaiting further cardiac testing. Since November 2016, only 2 notifications of cardiovascular adverse events were notified to our pharmacovigilance center, collected thanks to the regular monitoring of the included patients: one, non-serious, of intermittent tachycardia in a naïve patient, and one, serious, of paroxysmic hypertension in a patient already treated by an immediate release formulation of MPH switched for a sustained release formulation when included in CAMTEA-MPH.

Discussion/Conclusion: Even if these preliminary data seem reassuring in terms of cardiovascular safety, further studies are required to improve our knowledge of the MPH safety profile in adults

Future Science OA. 2018;4.

QUANTITATIVE EEG FEATURES SELECTION IN THE CLASSIFICATION OF ATTENTION AND RESPONSE CONTROL IN THE CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER .

Bashiri A, Shahmoradi L, Beigy H, et al.

Aim: Quantitative EEG gives valuable information in the clinical evaluation of psychological disorders. The purpose of the present study is to identify the most prominent features of quantitative electroencephalography (QEEG) that affect attention and response control parameters in children with attention deficit hyperactivity disorder.

Methods: The QEEG features and the Integrated Visual and Auditory-Continuous Performance Test (IVA-CPT) of 95 attention deficit hyperactivity disorder subjects were preprocessed by Independent Evaluation Criterion for Binary Classification. Then, the importance of selected features in the classification of desired outputs was evaluated using the artificial neural network.

Results: Findings uncovered the highest rank of QEEG features in each IVA-CPT parameters related to attention and response control.

Conclusion: Using the designed model could help therapists to determine the existence or absence of defects in attention and response control relying on QEEG

Int Clin Psychopharmacol. 2018;33:229-32.

EFFECTIVENESS OF PARENTAL TRAINING, METHYLPHENIDATE TREATMENT, AND THEIR COMBINATION ON ACADEMIC ACHIEVEMENTS AND BEHAVIOR AT SCHOOL OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Golubchik P, Hamerman H, Manor I, et al.

This study aimed to compare the effectiveness of parental training (PT), methylphenidate treatment (MPH), and the combination of PT and MPH treatment (PT/MPH) on school achievements in children with attention-deficit hyperactivity disorder (ADHD). Twenty eight ADHD patients (age: 10.1-11.11 years) were divided into three groups: (a) PT (N=10), (b) PT/MPH (N=8), and (c) MPH alone (N=10). Their grades in academics and conduct, from their school reports before and after treatment (6 months), were coded as achievement scores. No significant differences in baseline academic and conduct scores were found between the groups ($F=0.033$, $d.f.=2$, $P=0.97$ and $F=0.024$, $d.f.=2$, $P=0.98$, respectively). No significant changes before versus after treatment were detected in academic (3.83 ± 0.93 vs. 3.85 ± 0.88 , paired $t=0.086$, $d.f.=9$, $P=0.93$, NS) or conduct (3.90 ± 1.10 vs. 4.10 ± 1.00 , paired $t=1.50$, $d.f.=9$, $P=0.17$, NS) scores in the PT group. The same was true for the PT/ MPH group (academic scores: 3.75 ± 0.98 vs. 4.05 ± 0.83 , $d.f.=7$, $t=0.927$, $P=0.38$; conduct scores: 3.85 ± 0.83 vs. 4.12 ± 0.83 , $d.f.=7$, $t=0.79$, $P=0.45$). Only the MPH group showed significant improvements in those scores (academic scores: $3/73 \pm 0.85$ vs. $4/44 \pm 0.48$, $d.f.=9$, $t=3.33$, $P=0.0088$; conduct scores: 3.80 ± 0.70 vs. 4.60 ± 0.70 , $d.f.=9$, $t=3.2$, $P=0.011$). Methylphenidate alone is superior to either parental training or parental training/ methylphenidate in improving academics and conduct at school

Int J Environ Res Public Health. 2018;15.

HEAVY METALS EFFECT ON SUSCEPTIBILITY TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: IMPLICATION OF LEAD, CADMIUM, AND ANTIMONY.

Lee M-J, Chou M-C, Chou W-J, et al.

Background: Heavy metals are known to be harmful for neurodevelopment and they may correlate to attention deficit/hyperactivity disorder (ADHD). In this study, we aim to explore the relationships between multiple heavy metals (manganese, lead, cadmium, mercury, antimony, and bismuth), neurocognitive function, and ADHD symptoms.

Methods: We recruited 29 patients with ADHD inattentive type (ADHD-I), 47 patients with ADHD hyperactivity/impulsivity type (ADHD-H/I), and 46 healthy control children. Urine samples were obtained to measure the levels of the aforementioned heavy metals in each child. Participants cognitive function and clinical symptoms were assessed, respectively.

Results: We found ADHD-H/I patients demonstrated the highest antimony levels ($p = 0.028$), and ADHD-I patients demonstrated the highest cadmium levels ($p = 0.034$). Antimony levels were positively correlated with the severity of ADHD symptoms that were rated by teachers, and cadmium levels were negatively correlated with the Full Scale Intelligence Quotient. Lead levels were negatively correlated with most indices of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV), but positively correlated with inattention and hyperactivity/impulsivity symptoms ($p < 0.05$).

Conclusion: Lead, cadmium and antimony were associated with susceptibility to ADHD and symptom severity in school-age children. Eliminating exposure to heavy metals may help to prevent neurodevelopmental disorders in children

Int J Psychophysiol. 2018;130:9-20.

JUNIOR TEMPERAMENT CHARACTER INVENTORY TOGETHER WITH QUANTITATIVE EEG DISCRIMINATE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER COMBINED SUBTYPE FROM CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER COMBINED SUBTYPE PLUS OPPOSITIONAL DEFIANT DISORDER.

Chiarenza GA, Villa S, Galan L, et al.

Oppositional defiant disorder (ODD) is frequently associated with Attention Deficit Hyperactivity Disorder (ADHD) but no clear neurophysiological evidence exists that distinguishes the two groups. Our aim was to identify biomarkers that distinguish children with Attention Deficit Hyperactivity Disorder combined subtype (ADHD_C) from children with ADHD_C + ODD, by combining the results of quantitative EEG (qEEG) and the Junior Temperament Character Inventory (JTCl). 28 ADHD_C and 22 ADHD_C + ODD children who met the DSMV criteria participated in the study. JTCl and EEG were analyzed. Stability based Biomarkers identification methodology was applied to the JTCl and the qEEG separately and combined. The qEEG was tested at the scalp and the sources levels. The classification power of the selected biomarkers was tested with a robust ROC technique. The best discriminant power was obtained when TCl and qEEG were analyzed together. Novelty seeking, self-directedness and cooperativeness were selected as biomarkers together with F4 and Cz in Delta; Fz and F4 in Theta and F7 and F8 in Beta, with a robust AUC of 0.95 for the ROC. At sources level: the regions were the right lateral and medial orbito-frontal cortex, cingular region, angular gyrus, right inferior occipital gyrus, occipital pole and the left insula in Theta, Alpha and Beta. The robust estimate of the total AUC was 0.91. These structures are part of extensive networks of novelty seeking, self-directedness and cooperativeness systems that seem dysregulated in these children. These methods represent an original approach to associate differences of personality and behavior to specific neuronal systems and subsystems

Iran J Pediatr. 2018;28.

BMI CHANGES IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER BEFORE AND AFTER TREATMENT WITH METHYLPHENIDATE.

Kousha M, Dalili S, Kiani SA, et al.

Objectives: We aimed to assess BMI changes in children and adolescents with Attention deficit hyperactivity disorder before and after treatment with methylphenidate.

Methods: This was a prospective cohort study on 90 adolescents with a diagnosis of ADHD. Clinicians measured height by a tape meter, weight by the Seca scale and BMI, was calculated. Spearman's correlation test was used to determine the correlation between age and BMI. The level of statistical significance was established with at least 0.05 in SPSS v21.

Results: Results showed that 65 patients (72.2%) were boys. Most of the participants (41) were aged between 7 - 11 years. Most of them (58 patients) had combined type of disorder. A total of 22 (24.4%) attention deficit and 10 (11.1%) hyperactive type of disorder were noted. Mean of height, weight, and BMI in participants were significantly higher after 1 year of treatment with methylphenidate.

Conclusions: ADHD could be indicated as a risk factor for overweight and obesity in Iranian adolescents; thus, clinicians should consider it from the beginning of the diagnosis of ADHD

Iranian Red Crescent Medical Journal. 2015;17.

NO EVIDENCE FOR ASSOCIATION BETWEEN NOREPINEPHRINE TRANSPORTER-3081 (A/T) POLYMORPHISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN IRANIAN POPULATION.

Eslami Amirabadi MR, Davari-Ashtiani R, Khademi M, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) can lead to drastic problems for the patient and its worldwide prevalence is 5%-12%. It also has many comorbidities with other disorders, and the genetic contribution seems the most significant cause.

Objectives: The current study was conducted to investigate the association between norepinephrine transporter-3081 (A/T) polymorphisms and ADHD in Iranian population.

Patients and Methods: Participants were chosen from children and adolescents diagnosed with ADHD referred to Imam Hoseyn Hospital. A child and adolescent psychiatrist confirmed the diagnosis using the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL) semi-structural interview. The control group was from pupils of schools in Tehran (capital city of Iran) who had no history or presence of psychiatric and medical complications. Also, a child and adolescent psychiatrist confirmed their health using the K-SADS-PL semi-structural interview. Genetic examinations were DNA distraction, Polymerase Chain Reaction (PCR), and Restricted Fragment Length Polymorphism (RFLP), which were conducted according to standard protocols. The statistical analysis was performed using chi-square and Fisher's exact test in SPSS version 21.

Results: The percentages of ADHD subtypes for combined, inattentive, and hyperactive/impulsive were 72.2%, 17.2%, and 11.9%, respectively. There was no significant association between norepinephrine transporter polymorphism and ADHD ($P = 0.81$). Moreover, no significant relationship was found between gender [male ($P = 0.92$) and female ($P = 0.63$)] and polymorphism. No significant association was found between subtypes of ADHD [combined ($P = 0.46$), inattentive ($P = 0.41$), hyperactive/impulsive ($P = 0.32$)] and polymorphism SCL6A2. This lack of association can also be seen in gender in every subtype.

Conclusions: The results of the study show no significant association between norepinephrine transporter polymorphism SCL6A2 and ADHD

Ir J Psychol Med. 2018;1-10.

THE POWERLESS OR THE EMPOWERED? STAKEHOLDERS' EXPERIENCES OF DIAGNOSIS AND TREATMENT FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN IRELAND.

Carr-Fanning K, Mc GC.

Introduction: In Ireland, attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed condition in Child and Adolescent Mental Health Services (CAMHS). However, little is known about the experiences of stakeholders affected by ADHD in their pathways through care, especially in Ireland. **Objectives:** The aim of this stakeholder voice study was to explore stress and coping among parents and Children and Young People (C/YP) affected by ADHD in an Irish context, in order to contribute to knowledge about what works and what needs to change in practice from a service user perspective.

Methods: In total, 15 C/YP (7-18 years) with ADHD and their parents participated in semi-structured interviews, which were triangulated using other sources (e.g. visual methods), to contribute to a highly contextualised understanding of lived experiences. Transcribed interviews were analysed using a deductive approach to Thematic Analysis informed by a theoretical framework of stress and coping theory and Bronfenbrenner's bio-ecological model.

Results: Some degree of difficulty in their pathway through care was identified by participants in all case studies. Findings identified barriers to diagnosis, including delays in diagnosis, such as scepticism, stigma, and label avoidance from gatekeepers; poor multiagency working; and misdiagnosis. Once received, diagnosis may serve as an access to empowerment, providing knowledge, understanding, and support.

However, C/YP and their parents also reported distressing experiences and a sense of powerlessness within CAMHS and with treatment; such as tensions around medical management, stigma, and a lack of child- and family-centred practice.

Conclusions: Despite the professionals and the systematic supports available, stakeholders did not feel that they were fully understood, listened to, or participants in accessing diagnosis and care planning

J Fam Health. 2016 Sep;26:29-33.

FAMILY APPROACHES TO DEALING WITH A CHILD'S ADHD.

AlAzzam M, ALBashtawy M.

J Policy Anal Manage. 2018;37:384-402.

SPECIAL EDUCATION FINANCING AND ADHD MEDICATIONS: A BITTER PILL TO SWALLOW.

Morrill MS.

Accurate diagnosis of attention deficit/hyperactivity disorder (ADHD) in children is difficult because the major symptoms, inattentiveness and hyperactivity, can be exhibited by any child. This study finds evidence of systematic differences in diagnosis and treatment of ADHD due to third party financial incentives. In some states, due to the financing mechanism for special education, schools face a financial incentive to facilitate the identification of children with ADHD. Using variation in special education funding policies across states, we find that children living in states with financial incentives are about 15 percent more likely to report having ADHD and are about 22 percent more likely to be taking medication for ADHD. We provide support that these findings are causal by leveraging variation from two states that implemented policy changes during the time period studied

JAMA. 2018 May;319:2009-20.

TRENDS IN PRESCRIPTION MEDICATION USE AMONG CHILDREN AND ADOLESCENTS-UNITED STATES, 1999-2014.

Hales CM, Kit BK, Gu Q, et al.

Importance: Access to appropriate prescription medications, use of inappropriate or ineffective treatments, and adverse drug events are public health concerns among US children and adolescents.

Objective: To evaluate trends in use of prescription medications among US children and adolescents.

Design, Setting, and Participants: US children and adolescents aged 0 to 19 years in the 1999-2014 National Health and Nutrition Examination Survey (NHANES)-serial cross-sectional, nationally representative surveys of the civilian noninstitutionalized population.

Exposures: Sex, age, race and Hispanic origin, household income and education, insurance status, current health status.

Main Outcomes and Measures: Use of any prescription medications or 2 or more prescription medications taken in the past 30 days; use of medications by therapeutic class; trends in medication use across 4-year periods from 1999-2002 to 2011-2014. Data were collected through in-home interview and direct observation of the prescription container.

Results: Data on prescription medication use were available for 38277 children and adolescents (mean age, 10 years; 49% girls). Overall, use of any prescription medication in the past 30 days decreased from 24.6% (95% CI, 22.6% to 26.6%) in 1999-2002 to 21.9% (95% CI, 20.3% to 23.6%) in 2011-2014 (beta = -0.41 percentage points every 2 years [95% CI, -0.79 to -0.03]; P = .04), but there was no linear trend in the use of 2 or more prescription medications (8.5% [95% CI, 7.6% to 9.4%] in 2011-2014). In 2011-2014, the most commonly used medication classes were asthma medications (6.1% [95% CI, 5.4% to 6.8%]), antibiotics (4.5% [95% CI, 3.7% to 5.5%]), attention-deficit/hyperactivity disorder (ADHD) medications (3.5% [95% CI, 2.9% to 4.2%]), topical agents (eg, dermatologic agents, nasal steroids) (3.5% [95% CI, 3.0% to 4.1%]), and antihistamines (2.0% [95% CI, 1.7% to 2.5%]). There were significant linear trends in 14 of 39 therapeutic

classes or subclasses, or in individual medications, with 8 showing increases, including asthma and ADHD medications and contraceptives, and 6 showing decreases, including antibiotics, antihistamines, and upper respiratory combination medications.

Conclusions and Relevance: In this study of US children and adolescents based on a nationally representative survey, estimates of prescription medication use showed an overall decrease in use of any medication from 1999-2014. The prevalence of asthma medication, ADHD medication, and contraceptive use increased among certain age groups, whereas use of antibiotics, antihistamines, and upper respiratory combination medications decreased

J Abnorm Child Psychol. 2018 Apr;46:491-504.

APPLIED PROBLEM SOLVING IN CHILDREN WITH ADHD: THE MEDIATING ROLES OF WORKING MEMORY AND MATHEMATICAL CALCULATION.

Friedman LM, Rapport MD, Orban SA, et al.

The difficulties children with ADHD experience solving applied math problems are well documented; however, the independent and/or interactive contributions of cognitive processes underlying these difficulties are not fully understood and warrant scrutiny. The current study examines two primary cognitive processes integral to children's ability to solve applied math problems: working memory (WM) and math calculation skills (i.e., the ability to utilize specific facts, skills, or processes related to basic math operations stored in long-term memory). Thirty-six boys with ADHD-combined presentation and 33 typically developing (TD) boys aged 8–12 years old were administered multiple counterbalanced tasks to assess upper (central executive [CE]) and lower level (phonological [PH STM] and visuospatial [VS STM] short-term memory) WM processes, and standardized measures of mathematical abilities. Bias-corrected, bootstrapped mediation analyses revealed that CE ability fully mediated between-group differences in applied problem solving whereas math calculation ability partially mediated the relation. Neither PH STM nor VS STM was a significant mediator. When modeled together via serial mediation analysis, CE in tandem with math calculation ability fully mediated the relation, explained 79% of the variance, and provided a more parsimonious explication of applied mathematical problem solving differences among children with ADHD. Results suggest that interventions designed to address applied math difficulties in children with ADHD will likely benefit from targeting basic knowledge of math facts and skills while simultaneously promoting the active interplay of these skills with CE processes

J Appl Dev Psychol. 2018 May;56:42-51.

IS THERE A DEVELOPMENTAL GAP IN VISUAL SEARCH FOR CHILDREN WITH REPORTED ATTENTION PROBLEMS?

Quiroga MA, Santacreu J.

We report an analysis of developmental patterns in visual search for 6 to 12-year-old children. A typically developing sample of 1442 children is compared with two samples (N = 1160 and N = 947) of children with teacher-reported attentional problems. Inclusion criteria for these two groups are low academic achievement and probable attention problems as the reason for the low achievement. The three groups completed DiViSA, a computerized visual search test. Obtained data show two patterns of visual search development. Children with teacher-reported attentional problems show hastiness, inaccuracy and slowness. Children with attention problems perform as if they were younger, in terms of visual search. Data show a performance lag in visual search of about two to three years at every tested grade for the children with attentional difficulties. However the development patterns of children with and without attention problems are parallel, showing improvement with age in both groups

J Child Adolesc Psychopharmacol. 2018;28:306-13.

EFFICACY AND SAFETY OF AMPHETAMINE EXTENDED-RELEASE ORAL SUSPENSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Childress AC, Wigal SB, Brams MN, et al.

Objectives: To determine the efficacy and safety of amphetamine extended-release oral suspension (AMPH EROS) in the treatment of attention-deficit/hyperactivity disorder (ADHD) in a dose-optimized, randomized, double-blind, parallel-group study.

Methods: Boys and girls aged 6 to 12 years diagnosed with ADHD were enrolled. During a 5-week, open-label, dose-optimization phase, patients began treatment with 2.5 or 5 mg/day of AMPH EROS; doses were titrated until an optimal dose (maximum 20 mg/day) was reached. During the double-blind phase, patients were randomized to receive treatment with either their optimized dose (10-20 mg/day) of AMPH EROS or placebo for 1 week. Efficacy was assessed in a laboratory classroom setting on the final day of double-blind treatment using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale and Permanent Product Measure of Performance (PERMP) test. Safety was assessed measuring adverse events (AEs) and vital signs.

Results: The study was completed by 99 patients. The primary efficacy endpoint (change from predose SKAMP-Combined score at 4 hours postdose) and secondary endpoints (change from predose SKAMP-Combined scores at 1, 2, 6, 8, 10, 12, and 13 hours postdose) were statistically significantly improved with AMPH EROS treatment versus placebo at all time points. Onset of treatment effect was present by 1 hour postdosing, the first time point measured, and duration of efficacy lasted 13 hours postdosing. PERMP data mirrored the SKAMP-Combined score data. AEs (>5%) reported during dose optimization were decreased appetite, insomnia, affect lability, upper abdominal pain, mood swings, and headache.

Conclusion: AMPH EROS was effective in reducing symptoms of ADHD and had a rapid onset and extended duration of effect. Reported AEs were consistent with those of other extended-release amphetamine products

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J Child Adolesc Psychopharmacol. 2018;28:350-53.

COMPARISON OF DEPRESSION AND BURNOUT LEVELS OF MOTHERS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BEFORE AND AFTER TREATMENT.

Gokcen C, Coskun S, Kutuk MO.

Objective: This study aimed to compare the depression and burnout levels of mothers of children having attention-deficit/hyperactivity disorder (ADHD) between the child's pre- and posttreatment periods.

Method: The study sample consisted of 40 children aged between 4 and 10 years and their mothers. Initially, 40 cases participated, but during the follow-up, 19 cases dropped out. The Beck Depression Inventory (BDI), the Maslach Burnout Inventory (MBI), and the Turgay DSM-IV Based Child and Adolescent Behaviour Disorders Screening and Rating Scale (T-DSM-IV-S) were used.

Results: Among the mothers, posttreatment BDI scores, MBI-emotional exhaustion, and personal accomplishment were significantly lower than the pretreatment scores. In the treatment's second month, all T-DSM-IV-S subscale scores showed a statistically significant decrease.

Conclusions: It was concluded that treatment of children with ADHD would have a favorable impact on their mothers' depressive symptoms, which would consequently decrease negative parental attitudes, hence reducing the risk of behavioral disorder in children with ADHD and exerting a positive effect on their treatment

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J Child Adolesc Psychopharmacol. 2018;28:331-38.

L-CARNOSINE AS ADJUNCTIVE THERAPY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL.

Ghajar A, Aghajan-Nashtaei F, Afarideh M, et al.

Objectives: This study aimed to investigate the efficacy and tolerability of l-carnosine as an add-on to methylphenidate in management of children with attention-deficit/hyperactivity disorder (ADHD).

Methods: This was an 8-week, randomized, double-blind placebo-controlled study. Fifty-six drug-free children and adolescents aged 6-17 years old with a diagnosis of ADHD entered the study. The patients were randomly assigned to l-carnosine (800 mg/d in two divided doses) or placebo plus methylphenidate (0.5-1.5 mg/kg/d) for 8 weeks. Children were assessed using the Teacher and Parent ADHD Rating Scale-IV (ADHD-RS-IV) at baseline and at weeks 4 and 8 postbaseline.

Results: Fifty patients completed the study, and all had two postbaseline measurements. Using the general linear model repeated measures, significant effect was observed for time treatment interaction on total and inattention subscales of the Parent ADHD-RS (Greenhouse-Geisser corrected: $F = 3.783$, $df = 1.444$, $p = 0.041$ and $F = 4.032$, $df = 1.600$, $p = 0.030$). Improvements in the Teacher ADHD-RS were not significantly different between the two groups in total (Greenhouse-Geisser corrected: $F = 0.200$, $df = 1.218$, $p = 0.705$), as well as inattention and hyperactivity subscale scores ($p = 0.956$ and 0.281 , respectively). The frequency of side effects was not significantly different between the two treatment arms.

Conclusions: l-carnosine, as a supplementary medication, might be beneficial in treatment of children with ADHD. However, further investigations and different doses of l-carnosine are required to replicate these findings in children with ADHD

J Child Adolesc Psychopharmacol. 2018;28:298-305.

IMPROVEMENTS IN IRRITABILITY WITH OPEN-LABEL METHYLPHENIDATE TREATMENT IN YOUTH WITH COMORBID ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND DISRUPTIVE MOOD DYSREGULATION DISORDER.

Winters DE, Fukui S, Leibenluft E, et al.

Objective: The purpose of this open-label study was to examine the effects of long-acting methylphenidate (MPH) treatment on irritability and related emotional symptoms associated with disruptive mood dysregulation disorder (DMDD) in youth with comorbid attention-deficit/hyperactivity disorder (ADHD).

Methods: The sample included 22 medication-free male and female subjects (ages 9-15) who met criteria for both DMDD and ADHD. Participants underwent a 4-week trial of long-acting MPH treatment (Concerta- α), with weekly dosing increases until a therapeutic dose was reached. Repeated measures t-tests were used to compare pre- and posttreatment ratings of primary and secondary measures. The primary outcome was self-report irritability. Secondary outcomes included parent and child ratings of emotional frequency, emotional lability, and negative affect (NA). Multiple regression was used to examine the impact baseline hyperactivity, age, gender, race, socioeconomic status, or comorbid diagnosis had on treatment outcomes.

Results: Significant improvements (medium to large effect sizes) in child-rated irritability as well as parent and child ratings of emotional lability, NA, and anger were found. As anticipated, ADHD symptoms also improved. While a majority of the sample saw improvement in child-rated irritability (71%), symptoms worsened a small proportion (19%), and an even smaller portion experienced no change (10%). No demographics, psychiatric comorbidities, or severity of ADHD symptoms influenced treatment outcomes.

Conclusions: Study findings suggest that MPH treatment significantly improved mood and emotional symptoms associated with DMDD comorbid with ADHD. These findings, coupled with good tolerability in this open-label pilot study supports further research into the use of MPH as a first-line treatment for DMDD. Future work examining MPH treatment of youth with DMDD with and without comorbid ADHD is needed

J Child Adolesc Psychopharmacol. 2018;28:314-21.

OPTIMIZATION OF METHYLPHENIDATE EXTENDED-RELEASE CHEWABLE TABLET DOSE IN CHILDREN WITH ADHD: OPEN-LABEL DOSE OPTIMIZATION IN A LABORATORY CLASSROOM STUDY.

Wigal SB, Childress A, Berry SA, et al.

Objective: To examine methylphenidate extended-release chewable tablets (MPH ERCT) dose patterns, attention-deficit/hyperactivity disorder (ADHD) symptom scores, and safety during the 6-week, open-label (OL) dose-optimization period of a phase 3, laboratory classroom study.

Methods: Boys and girls (6-12 years) diagnosed with ADHD were enrolled. MPH ERCT was initiated at 20 mg/day; participants were titrated in 10-20 mg/day increments weekly based on efficacy and tolerability

(maximum dose, 60 mg/day). Dose-optimization period efficacy assessments included the ADHD Rating Scale (ADHD-RS-IV), analyzed by week in a post hoc analysis using a mixed-effects model for repeated measures with final optimized dose (20, 30/40, or 50/60 mg), visit, final optimized dose and visit interaction, and baseline score as terms. Adverse events (AEs) and concomitant medications were collected throughout the study.

Results: Mean MPH ERCT daily dose increased weekly from 29.4 mg/day after the first dose adjustment at week 1 (n = 90) to 42.8 mg/day after the final adjustment at week 5 (n = 86). Final optimized MPH ERCT dose ranged from 20 to 60 mg/day. Mean final optimized MPH ERCT dose ranged from 40.0 mg/day in 6-8 year-old participants to 44.8 mg/day for 11-12 year-old participants. There was a progressive decrease in mean (standard deviation) ADHD-RS-IV total score from 40.1 (8.72) at baseline to 12.4 (7.88) at OL week 5, with similar improvement patterns for hyperactivity/impulsivity and inattentiveness subscale scores. Participants optimized to MPH ERCT 50/60 mg/day had a significantly higher mean (standard error) ADHD-RS-IV score at baseline compared with participants optimized to MPH ERCT 20 mg/day (42.4 [1.34] vs. 35.1 [2.55]; $p = 0.013$). Treatment-emergent AEs were reported by 65/90 (72.2%) participants in the dose-optimization period.

Conclusions: Dose-optimization period results describing relationships between change in ADHD symptom scores and final optimized MPH ERCT dose will be valuable for clinicians optimizing MPH ERCT dose

J Child Adolesc Psychopharmacol. 2018;28:322-30.

A 1.5-YEAR FOLLOW-UP OF PARENT TRAINING AND ATOMOXETINE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND NONCOMPLIANT/DISRUPTIVE BEHAVIOR IN AUTISM.

Arnold LE, Ober N, Aman MG, et al.

Objective: To examine status of children with autism spectrum disorder (ASD) 10 months after a 34-week clinical trial of atomoxetine (ATX) and parent training (PT).

Methods: In a 2 +ù 2 design, 128 children with ASD and attention-deficit/hyperactivity disorder (ADHD) were randomly assigned ATX, PT+placebo, PT+ATX, or placebo alone. PT was weekly for 10 weeks, and then monthly. ATX/placebo was titrated over 6 weeks [1.8 mg/kg/d], and then maintained until week 10. Responders continued to week 34 or nonresponse. Placebo nonresponders had a 10-week ATX open trial; ATX nonresponders were treated clinically. All continued to week 34. With no further treatment from the study, all were invited to follow-up (FU) at 1.5 years postbaseline; 94 (73%) participated. Changes from Week 34 to FU and from baseline to FU were tested by one-way analysis of variance or chi-squared test. PT versus no PT was tested by chi-squared test, Fisher's exact test, Welch's t-test, Student's t-test, and Mann-Whitney's U test.

Results: For the whole sample, the primary outcomes (parent-rated ADHD on the Swanson, Nolan, and Pelham [SNAP] scale and noncompliance on the Home Situations Questionnaire [HSQ]) deteriorated mildly from week 34 to FU, but were still substantially better than baseline (SNAP: $t = 12.177$, $df = 93$, $p < 0.001$; HSQ: $t = 8.999$, $df = 93$, $p < 0.001$). On the SNAP, 61% improved 30% from baseline (67% did at week 34); on noncompliance, 56% improved 30% from baseline (77% did at week 34). Outcomes with PT were not significantly better than without PT (SNAP $p = 0.30$; HSQ $p = 0.27$). Originally assigned treatment groups did not differ significantly. Only 34% still took ATX; 27% were taking stimulants; and 25% took no medication.

Conclusions: The majority retained their 34-week end-of-study improvement 10 months later, even though most participants stopped ATX. For some children, ATX continuation may not be necessary for continued benefit or other drugs may be necessary. Cautious individual clinical experimentation may be justified. Twelve sessions of PT made little long-term difference. ClinicalTrials.gov Identifier: Atomoxetine, Placebo and Parent Management Training in Autism (Strattera) (NCT00844753)

Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences. 2018;1092:313-19.

RAPID QUANTITATIVE ANALYSIS OF METHYLPHENIDATE AND RITALINIC ACID IN ORAL FLUID BY LIQUID CHROMATOGRAPHY TRIPLE QUADRUPOLE MASS SPECTROMETRY (LC-QQQ-MS).

Mulet CT, Arroyo-Mora LE, Leon LA, et al.

Methylphenidate (MPH), which is metabolized into ritalinic acid (RA), is an amphetamine derivative largely used in the treatment of attention-deficit hyperactivity disorder, a neurological condition commonly diagnosed in early childhood. Ensuring that patients comply with clinical treatment is crucial and compliance is generally monitored in blood or urine specimens which, especially in the case of children, can be challenging to obtain on a repetitive basis. Here we report validation of a specific, non-invasive, and rapid dilute-and-shoot analytical method for the detection and quantitation of MPH and RA in oral fluid (OF). The method is based on liquid chromatography coupled to triple quadrupole MS with electrospray ionization utilizing dynamic MRM mode. Subject OF specimens were collected using a Quantisal™ device, processed, and diluted for analysis with seven-point quadratic calibration curves (weighting of 1/x) using MPH-d9 and (-)-threo-RA-d10 as internal standards. QC samples and diluted specimens showed intra- and inter-day bias and imprecision values no greater than -12%. The LOD and LOQ for MPH were 0.1 and 0.5 ng/mL, respectively, and 0.2 ng/mL and 0.5 ng/mL for RA, respectively, indicating the validity of the method for identification and confirmation at low concentrations. Selectivity was specific for the analytes of interest and matrix effects were minimized through the use of internal standard based quantitation

Journal of Cyber Therapy and Rehabilitation. 2017;10:43-44.

ASSESSMENT OF THE ATTENTION PERFORMANCE TEST BASED ON VIRTUAL REALITY: A COMPARISON WITH THE TRADITIONAL CONTINUOUS PERFORMANCE TEST.

Eom H, Lee S, Hong Y-J, et al.

The Virtual Reality-Continuous Performance Task was developed to add ecological validity in assessing attention in school-aged children. This study aims to investigate the attention-measuring capacity of VR-CPT in a classroom setting compared to the traditional computerbased tool to measure attention. A total of 38 participants (M=11.97, SD= 2.52), 18 typically developing children and 20 with ADHD according to the DSM-V, were recruited to receive CPT in virtual reality. VR-CPT consisted of two conditions: without a virtual teacher and with a virtual teacher's visual and auditory cues in a classroom setting. Participants' attentional performance was measured on five different domains: accuracy, commission error, omission error, reaction time, and reaction time variability. The results suggested that there were positive associations between ADHD-Rating Scale scores and reaction time ($p=0.017$), reaction time variability, commission error, and omission error, and a negative association with the total accuracy in VR-CPT (All p 's<0.01). A multiple regression analysis suggested that predictabilities of traditional CPT ($p=0.002$, $R^2=0.414$) and VR-CPT ($p<0.01$, $R^2=0.391$) on ADHD symptoms were comparable. The results also suggested that reaction time variability was smaller when teacher and social cues were present than when absent ($\chi^2=5.158$, $p=0.023$). The study demonstrated that VR-CPT program in a classroom setting showed association and comparable predictability with traditional attention test. Also, the presence of social cues from the virtual teacher seemed to affect attention levels, specifically reaction time variability

Journal of Head Trauma Rehabilitation. 2018;33:E94.

BODY-ORIENTED THERAPY CAN IMPACT EXECUTIVE ABILITIES IN 6-7 YEARS OLD CHILDREN WITH ADHD.

Kiselev S, Parshakova A.

Background It is known that children with ADHD have deficit in executive abilities. The goal of this study was to reveal the effect of body-oriented therapy on executive abilities in 6-7 years age children with ADHD. We compared the efficacy of two methods of treatment (body-oriented therapy for children vs. conventional

motor exercises) in a randomized controlled pilot study. The research was supported by Russian Foundation for Basic Research, grant No 15-06-06491A.

Methods and Participants 18 children with ADHD between 6 to 7 years of age were included and randomly assigned to treatment conditions according to a 2 x 2 cross-over design. The body-oriented therapy included yogas' exercises and breathing techniques. To assess the executive functions and attention in children we used 5 subtests from NEPSY (Tower, Auditory Attention and Response Set, Visual Attention, Statue, Design Fluency). Effects of treatment were analyzed by means of an ANOVA for repeated measurements.

Results The ANOVA has revealed ($p < .05$) that for all 5 subtests on executive functions and attention the body-oriented therapy was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.47-0.93).

Conclusions The findings from this pilot study suggest that bodyoriented therapy can effectively influence the executive abilities in children with ADHD. However, it is necessary to further research the impact of body-oriented therapies on the prevention and treatment of ADHD in children

Journal of Head Trauma Rehabilitation. 2018;33:E90.

DEFICIT OF VISUAL MEMORY IN DELAYED RECALL CONDITION IN ADHD CHILDREN.

Kiselev S.

It is known that children with ADHD have deficit in prefrontal cortex function including deficit in working memory (Martinussen et al., 2012). In our previous research we have revealed that ADHD children have deficit in memory for faces and for names in delayed recall condition (Kiselev & Lvova, 2014; Kiselev & Lvova, 2016). The goal of this research was to examine the hypothesis that children with ADHD have deficit in visual memory in delayed recall condition. The research was supported by Russian Foundation for Basic Research, grant No 15-06-06491A. The experimental group included 17 children with ADHD at age 8-9-years. The control group included 17 typically developing children. The children from experimental and control group were matched for IQ, gender and age. Children from both groups were assessed with visual memory subtest from Luria's neuropsychological assessment battery. This subtest is designed to assess the ability to perform visual memory for objects in immediate and delayed conditions. Two-way ANOVA was used to reveal group differences in reproducing the objects in two conditions. We have not revealed significant differences between children from experimental and control group in the reproducing the objects in immediate condition. However, the interaction of condition type and group was significant ($p = 0.05$). ADHD children were less successful in reproducing the objects in delayed condition. In view of the obtained results, it can be assumed that children with ADHD have specific (not global) deficit in memory in delayed recall condition

J Intellect Disabil Res. 2017;61:830-31.

DISEASE BURDEN AND SYMPTOM STRUCTURE OF AUTISM IN NEUROFIBROMATOSIS TYPE 1: A STUDY OF THE INTERNATIONAL NF1-ASD CONSORTIUM TEAM (INFACt).

Morris SM, Acosta MT, Garg S, et al.

Background: Recent reports have demonstrated a higher incidence of autism spectrum disorder (ASD) and substantially elevated autistic trait burden in individuals with neurofibromatosis type 1 (NF1). However, important discrepancies regarding the distribution of autistic traits, sex predominance and association between ASD symptoms and attentional problems have emerged, and critical features of the ASD phenotype within NF1 have never been adequately explored.

Methods: Using anonymised, individual-level primary data from six tertiary referral centres in the USA, Belgium, UK, and Australia, the distribution of ASD and attention-deficit/hyperactivity disorder (ADHD) traits, ASD symptom structure, latent structure, base rate derived from mixture modelling and familiarity were determined.

Results: Of the 531 patients included in the analysis, 247 were male patients (46.5%); median age was 11 years (range, 2.5-83.9 years). QAT scores were continuously distributed and pathologically shifted; 13.2% (95% CI, 10.3-16.1%) of individuals scored within the most severe range (i.e. above the first percentile of the

general population distribution) in which the male to female ratio was markedly attenuated (1.6:1) relative to idiopathic ASD. Autistic symptoms in this NF1 cohort demonstrated a robust unitary factor structure, with the first principal component explaining 30.9% of the variance in SRS-2 scores, and a strong association with ADHD symptoms ($r = 0.61$). Within-family correlation for QAT burden (intraclass correlation coefficient, 0.73 in NF1-affected first-degree relatives) exceeded that observed in the general population and ASD family samples.

Conclusion: This study provides confirmation that the diversity of mutations that give rise to NF1 function as quantitative trait loci for ASD, and the within-family correlation implicates a high degree of mutational specificity for this ASD-associated disorder

J Psychopathol Behav Assess. 2018;1-13.

PARENT EMOTION EXPRESSION AND AUTONOMIC-LINKED EMOTION DYSREGULATION IN CHILDHOOD ADHD.

Musser ED, Lugo Y, Ward AR, et al.

Despite evidence that ADHD is associated with disruptions in emotion regulation, few studies have examined the biological correlates of emotion dysregulation among children with this disorder. Prior work has pointed to roles of the parasympathetic and sympathetic nervous system, as indexed via respiratory sinus arrhythmia (RSA) and cardiac pre-ejection period (PEP), respectively. Work in typically developing populations suggests that parenting behavior and parental emotion expression may shape the development of these systems. To date, a single study has examined the independent and interactive roles of autonomic nervous system functioning and parent emotion expression in youth with ADHD. This study seeks to extend that work. 86 children (42 with ADHD), aged 8-12 years, and a parent completed a parent-child interaction task, while electrocardiography and impedance cardiography data were recorded to derive RSA and PEP. Parent and child emotion word use (positive and negative valence) were coded from recordings of the task. Parents of youth with ADHD used fewer positive emotion words throughout the task. Additionally, throughout the task, children with ADHD engaged in excessive RSA withdrawal from baseline. Further, the association between RSA reactivity and ADHD diagnosis was moderated by parent positive emotion word use. Specifically, those with RSA augmentation and parents displaying high positive affect across the task conditions were least likely to have an ADHD diagnosis. If replicated and extended, these results support the use of interventions specifically designed to increase parental modeling of positive emotions, while simultaneously focusing on building emotion regulation skills in youth with ADHD

J Psychopathol Behav Assess. 2018;40:194-205.

TEST-RETEST MEASUREMENT INVARIANCE OF CLINIC REFERRED CHILDREN'S ADHD SYMPTOMS.

Gomez R, Vance A, Stavropoulos V.

This study examined the test-retest measurement invariance of ratings of the ADHD symptoms. Mothers of a group of 217 clinic-referred children (boys = 169, girls = 49; age range = 7 to 17-years) completed ratings of the ADHD symptoms presented in a modified version of the Strengths and Weaknesses of ADHD-Symptoms and Normal Behavior Scale (SWAN-M) twice, 12-months apart. Confirmatory factor analysis (CFA) of their ratings at both time points provided more support for the bifactor model of ADHD [orthogonal general and specific factors for inattention (IA) and hyperactivity/impulsivity (HI) symptoms] over the 2-factor oblique model (factors for inattention IA and HI symptoms). For the bifactor model, measurement invariance testing using multiple-group CFA indicated support for configural and full scalar test-retest invariance when the chi-square difference test was applied. For metric invariance, all but one symptom showed invariance. When the differences in approximate fit indices were applied, there was support for full measurement invariance (configural, metric and scalar). The findings indicate that observed scores (based on maternal ratings of the SWAN-M), twelve months apart, are comparable as they have the same measurement properties. Several practical, theoretical, research and clinical implications of the findings are discussed

J Am Acad Child Adolesc Psychiatry. 2018 Jun;57:428-35.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PRESCHOOLERS: THE ACCURACY OF A SHORT SCREENER.

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

Objective: Although early and accurate screening is required for the remediation of attention-deficit/hyperactivity disorder (ADHD), possible gender differences have not been extensively studied. We examined the classification accuracy of the parent and preschool teacher version of the Strengths and Difficulties Questionnaire (SDQ) hyperactivity-inattention (HI) subscale in girls and boys.

Method: The study was part of the Norwegian Mother and Child Cohort Study (MoBa). Parents and preschool teachers rated a total of 238 girls and 276 boys (mean age 3.5 years) with the SDQ HI subscale. Blinded to the parent and teacher ratings, interviewers classified the children by ADHD diagnoses with the Preschool Age Psychiatric Assessment Interview.

Results: Areas under the curves for the parent HI subscale scores were good for both girls and boys (0.87 and 0.80, respectively). Preschool teacher classifications were fair (0.76) for girls and poor (0.62) for boys, a significant difference ($p = .017$). The subscale accurately identified children without ADHD at low parent scores ($=4$), and fairly accurately identified ADHD at high scores ($=9$), with maximum probabilities of finding true cases of 0.75 in girls and 0.55 in boys. Intermediate scores gave the best balance between sensitivity and specificity with low probabilities of correctly identifying children with ADHD.

Conclusion: The parental SDQ HI subscale was useful for screening for ADHD in preschool girls and boys. For preschool teachers, the subscale was useful for screening girls

Journal of the American Pharmacists Association. 2018;58:e140-e241.

MISSISSIPPI PHARMACISTS' PERCEPTIONS AND KNOWLEDGE OF ADHD IN CHILDREN.

Crider A, Holmes E.

Objective: Pharmacists have the potential to play a significant and positive role in the treatment of children with attentiondeficit/ hyperactivity disorder (ADHD). However, there is lack of comprehensive data available to describe pharmacists' understanding of, experiences with, and perceptions of, the condition. The objectives of this study are to measure community pharmacists' knowledge of, familiarity with, confidence in, counseling for, and perceptions of, ADHD and its associated treatments for children.

Methods: The study employed a descriptive, cross-sectional design by use of a self-administered survey distributed electronically to 6,872 email addresses on record at the Mississippi State Board of Pharmacy on October 7th, 2016. A reminder was distributed seven days later. IRB exemption was granted before the study commenced. Eighteen questions on the survey were used to measure demographic characteristics as well as knowledge, familiarity, confidence, and perceptions, and qualitative responses. Descriptive statistics were used to meet objectives.

Results: 676 surveys were received for a 9.8% response rate. 368 met study criteria (practicing community pharmacist), and of those, 48 surveys were incomplete. 320 responses were used in final data analysis. Most respondents were female, white/Caucasian, and had a PharmD. Respondents were more familiar with and knowledgeable about pharmacologic ADHD treatments than diagnostic criteria. Pharmacists were confident in their ability to work with children with ADHD but felt some patients were inappropriately diagnosed and treated.

Conclusion: Pharmacists were familiar, knowledgeable, and confident in the pharmacological treatment of ADHD in children, but less so when it came to diagnosis of these patients. Pharmacists may benefit from additional training in diagnosis, but future research is needed to evaluate the need and acceptability of such training, particularly in community pharmacists. The results of this study are limited in generalizability due to the regional nature of this study and the small response rate

Medicine (Baltimore). 2018 Jun;97:e10923.

ARE ADHD MEDICATIONS UNDER OR OVER PRESCRIBED WORLDWIDE?: PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS.

Moreira-Maia CR, Massuti R, Tessari L, et al.

INTRODUCTION: Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder, characterized by age inappropriate and impairing levels of inattention and/or hyperactivity/impulsivity. Pharmacotherapy is an important part of the ADHD multimodal treatment. The extent to which ADHD is pharmacologically over or under treated worldwide is controversial. We aimed to estimate the pooled worldwide rate of ADHD pharmacological treatment in individuals with and without the disorder.

METHOD AND ANALYSIS: We will include published or unpublished studies reporting the rates of ADHD pharmacological treatment in participants with and without ADHD of any age group. Population-based, cohort, or follow-up studies, as well as data from insurance health system and third-party reimbursements will be eligible. Searches will be performed in a large number of electronic databases, including Medline, Embase, CINAHL, Cochrane, PsycINFO, Web of Science, and Scopus. The primary outcome will be the prevalence of ADHD pharmacological treatment in individuals with ADHD and without ADHD. Two independent reviewers will perform the screening, and data extraction process. Study quality/bias will be assessed with the Newcastle-Ottawa scale by 2 independent reviewers. To test the robustness of the findings, we will perform a series of sensitivity and meta-regression analysis. Analyses will be performed with R and STATA software.

ETHICS AND DISSEMINATION: No IRB approval will be necessary. The results of this systematic review and meta-analysis will be presented at international conferences and published in peer-reviewed journals.

REGISTRATION AND STATUS: PROSPERO 2018 CRD42018085233

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Mol Psychiatry. 2018;1-13.

THE CONTRIBUTION OF COMMON GENETIC RISK VARIANTS FOR ADHD TO A GENERAL FACTOR OF CHILDHOOD PSYCHOPATHOLOGY.

Brikell I, Larsson H, Lu Y, et al.

Common genetic risk variants have been implicated in the etiology of clinical attention-deficit/hyperactivity disorder (ADHD) diagnoses and symptoms in the general population. However, given the extensive comorbidity across ADHD and other psychiatric conditions, the extent to which genetic variants associated with ADHD also influence broader psychopathology dimensions remains unclear. The aim of this study was to evaluate the associations between ADHD polygenic risk scores (PRS) and a broad range of childhood psychiatric symptoms, and to quantify the extent to which such associations can be attributed to a general factor of childhood psychopathology. We derived ADHD PRS for 13,457 children aged 9 or 12 from the Child and Adolescent Twin Study in Sweden, using results from an independent meta-analysis of genome-wide association studies of ADHD diagnosis and symptoms. We estimated associations between ADHD PRS, a general psychopathology factor, and several dimensions of neurodevelopmental, externalizing, and internalizing symptoms, using structural equation modeling. Higher ADHD PRS were statistically significantly associated with elevated neurodevelopmental, externalizing, and depressive symptoms ($R^2 = 0.26$ – 0.69%), but not with anxiety. After accounting for a general psychopathology factor, on which all symptoms loaded positively (mean loading = 0.50, range = 0.09–0.91), an association with specific hyperactivity/impulsivity remained significant. ADHD PRS explained ~ 1% (p value < 0.0001) of the variance in the general psychopathology factor and ~ 0.50% (p value < 0.0001) in specific hyperactivity/impulsivity. Our results suggest that common genetic risk variants associated with ADHD, and captured by PRS, also influence a general genetic liability towards broad childhood psychopathology in the general population, in addition to a specific association with hyperactivity/impulsivity symptoms

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NeuroImmunoModulation. 2018;1-6.

A REVIEW ON THE ROLE OF INFLAMMATION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Leffa DT, Torres ILS, Rohde LA.

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition that impairs quality of life in social, academic, and occupational contexts for both children and adults. Although a strong neurobiological basis has been demonstrated, the pathophysiology of ADHD is still poorly understood. Among the proposed mechanisms are glial activation, neuronal damage and degeneration, increased oxidative stress, reduced neurotrophic support, altered neurotransmitter metabolism, and blood-brain barrier disruption. In this way, a potential role of inflammation has been increasingly researched. However, evidence for the involvement of inflammation in ADHD is still scarce and comes mainly from (1) observational studies showing a strong comorbidity of ADHD with inflammatory and autoimmune disorders; (2) studies evaluating serum inflammatory markers; and (3) genetic studies. A co-occurrence of ADHD with inflammatory disorders has been demonstrated in a large number of subjects, suggesting a range of underlying mechanisms such as an altered immune response, common genetics, and environmental links. The evaluation of serum inflammatory markers has provided mixed results, likely due to the small sample sizes and high heterogeneity between biomarkers. However, there is evidence that increased inflammation during the early development may be a risk factor for ADHD symptoms. Although genetic studies have demonstrated a potential role for inflammation in this disorder, there is no clear evidence. To sum up, inflammation may be an important mechanism in ADHD pathophysiology, but more studies are still needed for a more precise conclusion

Neuropsychiatr Dis Treat. 2018;14:1329-37.

SIX MONTHS METHYLPHENIDATE TREATMENT IMPROVES EMOTION DYSREGULATION IN ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A PROSPECTIVE STUDY.

Gamli IS, Tahiroglu AY.

Purpose: Individuals with attention deficit/hyperactivity disorder (ADHD) may suffer from emotional dysregulation (ED), although this symptom is not listed among the diagnostic criteria. Methylphenidate (MPH) is useful in reducing emotional symptoms in ADHD. The aim of the present study was to determine both psychosocial risk factors and presence of ED in adolescents with ADHD before and after MPH treatment.

Participants and methods: Eighty-two patients aged 12-18 years with ADHD were included as participants. The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime, the Difficulties in Emotion Regulation Scale (DERS), sociodemographic form, and the Inventory of Statements About Self-Injury were administered. Results were compared before and after 6 months MPH treatment.

Results: A significant improvement was detected on DERS for impulsivity (15.9-16.8 initial vs 14.2-16.5 final test, $p < 0.01$) and total score (88.4-123.3 initial vs 82.4-12.7 final test, $p < 0.05$) across all patients taking MPH regardless of subtype and sex. Despite treatment, a significant difference remained for impulsivity, strategies, and total score in patients with comorbid oppositional defiant disorder (ODD) compared with those without ODD, but no difference was detected for conduct disorder comorbidity. In patients who self-harm, scores for goals, impulsivity, strategies, clarity, and total score were higher before treatment; furthermore, impulsivity and total score remained high after treatment. In maltreated patients, goals, impulsivity, strategies, and total scores were significantly higher before treatment; however, their symptoms were ameliorated after treatment with MPH.

Conclusion: Individuals with severe ED may self-medicate by smoking and/or self-harming. MPH led to significant improvements in ED possibly owing, in part, to a decrease in impulsivity, so that individuals felt more able to supervise their emotions and engage in goal-directed behaviors. ED should be considered particularly in patients with additional psychosocial factors and ODD comorbidity, and included in the treatment plan

NeuroRegulation. 2016;3:170.

BE CALM & PAY ATTENTION! AN OVERVIEW OF ASSESSMENT FINDINGS AND INTERVENTION STRATEGIES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Thompson L, Thompson M.

Participants will learn about diagnosis and intervention. Diagnosis will cover both a brief overview of DSM-5 criteria for both Inattentive and Combined presentations of Attention- Deficit/Hyperactivity Disorder (ADHD) and also mention of comorbidities. An explication of how adding additional measures from single-channel EEG data collection and administration of continuous performance tests supports the diagnosis. The salient areas to be covered during the clinical interview will also be covered; namely, the person's strengths, family matters (with mention of Judith Lubar's use of genograms), social functioning, school and/or work performance, medical factors (allergies, sleep apnea, head injuries, etc.), and extracurricular interests. Data from questionnaires and, for more objective test data, continuous performance tests (Test of Variables of Attention [T.O.V.A.] and Integrated Auditory and Visual Continuous Performance Test [IVA]) will be shown. The various patterns found on single-channel (Cz) EEG assessment will be discussed in the light of the published norms for theta/beta power ratios. EEG patterns (excess theta, excess alpha, spindling beta, all seen with single channel assessment) will be shown. Recent updates on the utility of theta/beta as a marker for ADHD will be shared. Patients who have a diagnosis of ADHD symptoms can vary from children with a relatively simple difficulty with attention span to patients who have a complex array of other difficulties and comorbidities that involve other networks, such as learning disabilities, Asperger's syndrome, autism spectrum disorders, affect disorders, and movement disorders, including Tourette syndrome. This will be acknowledged but not expanded upon in this presentation. Finally, intervention will be discussed with mention of diet, sleep, and exercise but with the main focus being on how to do effective neurofeedback intervention combined with biofeedback with this population. Finally, there will be mention of research that addresses the question of whether neurofeedback can be considered an efficacious treatment for ADHD

NeuroRegulation. 2016;3:180-81.

WHAT THE SHAM IS GOING ON? REDEFINING ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND THE INHERENT PROBLEMS WITH NEUROFEEDBACK SHAM (PLACEBO-CONTROLLED) PROTOCOLS IN AN OPERANT CONDITIONING MODEL.

Cannon R, Carroll S.

There have been scarce advances in the uncovering of the etiology of Attention-Deficit/Hyperactivity Disorder (ADHD) over the past 30 years, despite advances in neuroimaging and neurophysiological methodologies. However, the amount of data accrued is extensive, yet an integrative model has yet to be constructed with clarity and standardization. In any type of problem in which a solution is evasive the primary lack of clarity and integration may be attributed to the operational operant definition given to the topic under investigation, as opposed to the methods used to investigate and treat the particular issue. ADHD is the most commonly diagnosed disorder in children and is projected to affect 5% to 7% of children worldwide and often continue on into adolescence and adulthood causing moderate difficulties for individuals across numerous adaptive contexts (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Importantly, recent data indicate there has been no increase in the prevalence rate of ADHD worldwide when tightly controlled analytics are used. This does not account for analytic methods or diagnostic criteria and variability (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Additional problems exist in the accurate diagnosis of a "pure" ADHD sample since the comorbidity rate has been estimated to be as high as 80% (Pritchard, Nigro, Jacobson, & Mahone, 2012) and variable cases of ADHD may also classify with up to five comorbid psychiatric diagnoses. Additionally, ADHD as a single diagnostic indicator occurs in less than 20% of the cases, or even less (Barkley & Brown, 2008; Yaryura-Tobias, Rabinowitz, & Neziroglu, 2003). There has been an increasing discourse over neurofeedback techniques and outcomes using sham/placebo-controlled methods yet the aforementioned difficulties remain everpresent (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Gevensleben et al., 2014; Guez et al., 2015; Hale et al., 2014; Lenartowicz & Loo, 2014; Loo, Lenartowicz, & Makeig, 2015; Micoulaud-Franchi et al., 2014; Polanczyk et al., 2007; Pritchard et al., 2012; Steiner, Frenette, Rene, Brennan, & Perrin, 2014; van Dongen-Boomsma, Vollebregt, Slaats- Willemse, & Buitelaar, 2013; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2013). Current problems, diagnostic

issues, and recommendations for a concise, standard set of metrics and interventions will be presented and discussed

Obes Facts. 2018;11:217-18.

FUSSY EATING IN A SAMPLE OF OBESE CHILDREN WITH AND WITHOUT ANXIETY, DEPRESSION, AUTISM OR ADHD.

Olafsdottir AS, Thorsteinsdottir S, Brynjolfsdottir B, et al.

Introduction: Fussy eating has been identified as a possible factor for contributing to and maintaining obesity in children. Furthermore, research has indicated that fussy eating is possibly related to emotional- and/or behavioral disorders. Limited variety in the diet and low consumption of fruit and vegetables has been associated with Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). Especially, rejecting bitter tastes and food types such as vegetables is common in children with autism. However, no studies have been published to date on the association of fussy eating in obese children with and without these disorders, and mental disorders such as anxiety and depression.

Methods: Participants were obese children (n = 105) who were referred for family-based obesity treatment at the Children's Medical Centre in Iceland between 2011 and 2016. The children were aged 4 to 18 years (mean 12.0; SD 3.0). Mean BMI-SDS (Body Mass Index Standard Deviation Score) was 3.53 (SD 0.86). The primary outcome measure was fussy eating i.e. being a fussy eater or not as measured by a questionnaire based on Kauer et al (2015). Logistic regression was used to estimate the relationship between fussy eating and number of disorders (mental and/or neurodevelopmental disorders), adjusting for gender and age.

Results: Fussy eating was common in the group; 30.8% according to behavioral definition and 39.8% as experienced by parents. The number of mental and/or neurodevelopmental disorders with obesity was directly related to children's fussy eating. Having three or more disorders was associated with increased odds of fussy eating in obese children [odds ratio (OR), 5.50; 95% confidence interval (CI), 2.00;16.70]. After adjusting for gender and age, the odds of fussy eating when having three or more disorders remained significant but slightly lower (OR, 4.06; 95% CI, 1.33- 13.08). Having two disorders still raised the odds of fussy eating in the unadjusted model (OR, 4.81; 95% CI, 1.53;16.50) but not in the adjusted model. When analysing the difference between those who rejected bitter taste, based on disorders, it was evident that 80.0% of children with autism rejected bitter taste as described by parents, compared with 37.8% of those who did not have autism (p = 0.029). This difference was not seen for other disorders. Only 2% of participants rejected sweet taste irrespective of type of disorders.

Conclusion: Fussy eating was common in this sample of children attending obesity treatment and increased with number of disorders. Future research and clinical care models should explore ways to work with tastes in pediatric obesity treatment since fussy eating may result in lower adherence to dietary advice

Oman Medical Journal. 2018;33:193-99.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND PARENTAL FACTORS IN SCHOOL CHILDREN AGED NINE TO TEN YEARS IN MUSCAT, OMAN.

Al-Ghannami SS, Al-Adawi S, Ghebremeskel K, et al.

Objectives: The objectives of this study were to determine the prevalence of attention deficit hyperactivity disorder (ADHD) and specific parental risk factors that may contribute to the development of ADHD in children.

Methods: The study was conducted in Oman among fourth-grade students (aged nine to 10 years). A standardized Arabic version of the National Initiative for Children's Health Quality Vanderbilt Assessment Scale (Teachers questionnaire) was used to determine the presence of ADHD. Parental factors such as socioeconomic status, education, and occupation were documented.

Results: The prevalence rate of ADHD was 8.8%. Poor maternal education status, low familial socioeconomic status, and paternal occupation were significantly associated with an increased risk of ADHD.

Conclusions: This was the first study that examined familial and parental characteristics of children with ADHD as potential risk factors for the condition. Such psychosocial factors could be employed to further the development of more proficient preventative measures and remedial services

Pediatr Int. 2017 Nov;59:1217-18.

RESOLUTION OF METHYLPHENIDATE OSMOTIC RELEASE ORAL SYSTEM-INDUCED HAIR LOSS IN TWO SIBLINGS AFTER DOSE ESCALATION.

Ardic UA, Ercan ES .

This report describes the cases of two siblings who experienced hair loss after treatment with methylphenidate (MPH) osmotic release oral system (OROS). Hair loss was resolved after discontinuation of the drug, but the children re-initiated treatment, after which hair loss again occurred, but they continued the treatment. After dose escalation, the hair loss resolved. This is the first report to describe resolution of OROS-MPH-induced hair loss after dose escalation

Pediatrics. 2018;141.

PEDIATRIC ADHD MEDICATION EXPOSURES REPORTED TO US POISON CONTROL CENTERS.

King SA, Casavant MJ, Spiller HA, et al.

OBJECTIVES: To describe the characteristics and trends of exposures to attention-deficit/hyperactivity disorder (ADHD) medications among individuals 0 to 19 years old reported to US poison control centers.

METHODS: National Poison Data System data from 2000 through 2014 were retrospectively analyzed to examine pediatric ADHD medication exposures.

RESULTS: From 2000 through 2014, there were 156365 exposures reported to US poison control centers related to ADHD medications. The overall rate of reported exposures increased 71.2% from 2000 to 2011, followed by a 6.2% decrease from 2011 to 2014. Three-fourths (76.0%) of exposures involved children \geq 12 years old. Methylphenidate and amphetamine medications accounted for 46.2% and 44.5% of exposures, respectively. The most common reason for exposure was therapeutic error (41.6%). Intentional medication exposures (including suspected suicide and medication abuse and/or misuse) were reported most often among adolescents (13–19 years old), accounting for 50.2% of exposures in this age group. Overall, the majority of exposed individuals (60.4%) did not receive health care facility treatment; however, 6.2% were admitted to a hospital for medical treatment, and there were 3 deaths. The increasing number and rate of reported ADHD medication exposures during the study period is consistent with increasing trends in ADHD diagnosis and medication prescribing. Exposures associated with suspected suicide or medication abuse and/or misuse among adolescents are of particular concern.

CONCLUSIONS: Unintentional and intentional pediatric exposures to ADHD medications are an increasing problem in the United States, affecting children of all ages

Pediatrics. 2018;141.

PREDICTORS OF MEDICATION CONTINUITY IN CHILDREN WITH ADHD.

Brinkman WB, Sucharew H, Majcher JH, et al.

OBJECTIVES: To identify predictors of attention-deficit/hyperactivity disorder (ADHD) medication continuity, hypothesizing greater continuity among children with (1) greater child acceptance of treatment, (2) parent belief in longer time course for ADHD, (3) positive differential between parent-perceived need for and concerns about medication, and (4) greater parent-perceived alliance with their child's doctor.

METHODS: We conducted a prospective longitudinal cohort of 89 children aged 6 to 10 years old newly treated for ADHD by 1 of 44 pediatricians in 11 practices. Parents completed validated surveys on their beliefs about ADHD and medicine. We audited charts and obtained pharmacy dispensing records. In our analyses, we examined the relationship between predictor variables (eg, sociodemographic and clinical

characteristics, quality of care, and belief measures) and short-term (first 90 days after starting medication) and long-term (91-450 days) medication continuity as defined by the number of days covered with medication.

RESULTS: Children had a median of 81% of days covered over 0 to 90 days and 54% of days covered over 91 to 450 days after starting medicine. In the first 90 days, medication coverage related to child age, satisfaction with information about medicine, medication titration, symptom reduction, parent beliefs about control over symptoms, uncertainty about treating with medicine, and working alliance. Long-term medication continuity related to child acceptance of treatment and differential between parent-perceived need for and concerns about medication at 3 months, not baseline factors.

CONCLUSIONS: Adherence is a process that can change over time in response to experiences with treatment. Interventions are needed to promote productive interactions between pediatricians and families in support of continuity

Pediatr Int. 2018;60:523-28.

PATTERN OF VIDEO GAME USE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TYPICAL DEVELOPMENT.

Kietglaiwansiri T, Chonchaiya W.

Background: Video game playing is a favorite leisure activity among children worldwide. Individuals with attention-deficit/hyperactivity disorder (ADHD) often lack self-control, making them at risk for substance abuse and game addiction. There are conflicting results, however, between studies on the pattern of video gaming and game addiction between those with ADHD and healthy controls. We therefore compared the pattern of video game use and game addiction between Thai children with ADHD and healthy controls.

Methods: A total of 80 participants with ADHD (median age, 9.5-áyears) and 102 controls (median age, 10-áyears) were recruited in this study. ADHD was diagnosed by a developmental pediatrician. Each control subject's teacher completed the ADHD questionnaire to ensure that they did not have the diagnosis of ADHD. Pattern of video game use and Game Addiction Screening Test (GAST) were completed by participants'ÖÖ parents.

Results: More than half of the children with and without ADHD spent >2-áh/day playing video games rather than engaging in other age-appropriate leisure activities, particularly on weekends. Participants with ADHD, however, had a higher rate of compulsive video game use than controls (37.5% vs 11.8%, $P < 0.001$).

Conclusions: Although video game playing was relatively prevalent in children regardless of ADHD status, those with ADHD had a higher rate of problematic video game use than controls. The pattern of leisure activities including video game use should be assessed during health supervision visits. As such, those at risk for game addiction could be identified early, resulting in appropriate intervention

Pediatr Int. 2018;60:529-34.

INTERNET ADDICTION AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EFFECTS OF ANXIETY, DEPRESSION AND SELF-ESTEEM.

Kahraman, Demirci E.

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. Behavioral disinhibition, poor neurocognitive skills and immediate reward preference in children with ADHD have been suggested as risk factors for Internet addiction (IA). The aim of the present study was therefore to investigate the relationship between IA and depression, anxiety, and self-esteem in adolescents with ADHD, and to identify the features of Internet use that predict IA.

Methods: We studied 111 patients with ADHD aged 12-18-áyears, and 108 healthy controls. The ADHD patients and controls were asked to complete a sociodemographic data form, the Internet Addiction Scale (IAS), Children's Depression Inventory, Childhood Screening Scale for Anxiety in Children, and the Rosenberg Self-Esteem Scale.

Results: IAS total score in the adolescents with ADHD was significantly higher than in the control group. Compared with the control group, the ADHD group depression scale score was significantly higher, and self-esteem score significantly lower ($P < 0.05$ for both). There was no difference between the groups in anxiety score. IAS score had a positive correlation with depression and anxiety scores, and a negative correlation with self-esteem score.

Conclusion: The relationship between IA scale score and depression, anxiety and self-esteem scale scores were similar in the ADHD and the control group. In addition, IAS subscale and total scores were significantly higher in the ADHD group than the control group, even after controlling for the effects of self-esteem, depression and anxiety scores. Thus, ADHD is thought to be an independent risk factor for depression, anxiety and self-esteem, and, hence, for IA

PeerJ. 2018;2018.

IDENTIFYING POTENTIALLY MARKER SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Arias VB, Esnaola I, Rodríguez-Medina J.

Background. For the diagnosis of attention-deficit/hyperactivity disorder (ADHD), the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) proposes that adherence to six symptoms in either group (inattention and hyperactivity/impulsivity) will lead to the diagnosis of one of three presentations of the disorder. Underlying this diagnostic algorithm is the assumption that the 18 symptoms have equal relevance for the diagnosis of ADHD, all are equally severe, and all have the same power to detect the presence of the disorder in all its degrees of severity, without considering the possibility of using marker symptoms. However, several studies have suggested that ADHD symptoms differ in both their power to discriminate the presence of the disorder and the degree of severity they represent. The aim of the present study was to replicate the results of previous research by evaluating the discriminative capacity and relative severity of ADHD symptoms, as well as to extend the investigation of this topic to Spanish-speaking Latin American samples.

Methods. The properties of ADHD symptoms rated by the parents of 474 Chilean children were analyzed. Symptom parameters were estimated using the graded response model.

Results. The results suggest that symptoms of ADHD differ substantially in both the accuracy with which they reflect the presence of the disorder, and their relative severity. Symptoms "easily distracted by extraneous stimuli" and "have difficulty sustaining attention in tasks" (inattention) and "is on the go, acting as if driven by motor" (hyperactivity/impulsivity) were the most informative, and those with relatively lower severity thresholds.

Discussion. The fact that symptoms differ substantially in the probability of being observed conditionally to the trait level suggests the need to refine the diagnostic process by weighting the severity of the symptom, and even to assess the possibility of defining ADHD marker symptoms, as has been done in other disorders

Psychiatry and Clinical Psychopharmacology. 2018 Jun;28:177-84.

ALLELE FREQUENCIES OF DOPAMINE D4 RECEPTOR GENE (DRD4) AND CATECHOL-O-METHYLTRANSFERASE (COMT) VAL158MET POLYMORPHISM ARE ASSOCIATED WITH METHYLPHENIDATE RESPONSE IN ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A CASE CONTROL PRELIMINARY STUDY.

Akay AP, Yazicioglu ÇE, Güney SA, et al.

Objectives: In this study, it was aimed to analyse the relationship between clinical improvement in adolescents with attention deficit/hyperactivity disorder (ADHD) and the presence of allele frequencies of dopamine D4 receptor (DRD4), and Val158Met polymorphism of catechol-O-methyltransferase (COMT) genes.

Methods: Thirty-four adolescents (age range, 13–18 years) with ADHD participated in this study. Thirty-two patients were males and two were females. Du Paul ADHD Rating Scale-Clinician version (ARS) and Clinical Global Impression-severity of impairment (CGI-S) were used for the evaluation of symptom severity. Fifty healthy age-matched adolescents were recruited as controls.

Results: When the groups with (n = 9) and without (n = 25) 7-repeat alleles for DRD4 were considered, there was a statistically significant decrease of DuPaul ARS total and hyperactivity scores in those treated with OROS-methylphenidate. When the Val/Met allele-positive group for COMT gene (n = 17) was compared with the Val/Val allele-positive group (n = 13) and Met/Met allele-positive group (n = 4), there was a statistically significant decrease of ARS total scores, ARS attention scores, and CGI scores in adolescents with ADHD treated with OROS-MPH.

Conclusions: Specific data from further studies with a larger sample sizes would provide more insights to replicate the current findings

Psychiatry Res. 2018;267:256-65.

DISTRIBUTION OF ADHD SYMPTOMS, AND ASSOCIATED COMORBIDITY, EXPOSURE TO RISK FACTORS AND DISABILITY: RESULTS FROM A GENERAL POPULATION STUDY.

Vogel SWN, Ten HM, Bijlenga D, et al.

The aim of this study was to examine whether ADHD is a dimensional trait in the adult general population. We studied whether an increased number of ADHD symptoms was associated with higher comorbidity, exposure to risk factors (childhood abuse and parental psychopathology), and disability. We ascertained whether even low numbers of ADHD symptoms were associated with an increased burden of disease. Data were used from the second wave of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2, N = 5303). NEMESIS-2 is a nationally representative face-to-face survey on mental health of the Dutch general population. ADHD symptoms, mental comorbidity, and disability were assessed using the Adult ADHD Self-Report Scale Screener, the Composite International Diagnostic Interview version 3.0, and the Medical Outcomes Study Short Form Health Survey, respectively. Dose-response relationships were found between the number of ADHD symptoms and Axis I and II mental disorders; exposure to risk factors; and mental and physical disability. Our study supports the notion that ADHD is a dimensional trait in the adult general population. Even low numbers of symptoms were associated with an increased burden of disease, and therefore these should be identified and treated

Psycho-Oncology. 2018;27:1597-607.

BEHAVIORAL SYMPTOMS AND PSYCHIATRIC DISORDERS IN CHILD AND ADOLESCENT LONG-TERM SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH CHEMOTHERAPY ONLY.

Liu W, Cheung YT, Brinkman TM, et al.

Background: Prevalence of emotional, behavioral, and psychiatric outcomes in child and adolescent survivors of childhood acute lymphoblastic leukemia treated on a chemotherapy-only protocol were not well defined.

Methods: Self- and parent-reported emotional and behavioral symptoms were assessed for 161 survivors of childhood acute lymphoblastic leukemia (51.0% female; mean [SD] age 12.1[2.6] years; 7.5[1.6] years post-diagnosis). Age- and sex-adjusted scores were calculated for standardized measures and compared with 90th percentile of norms. Frequencies of survivor psychiatric disorders from structured diagnostic interviews with parents were compared with the general population. Parent emotional distress and post-traumatic stress symptoms were assessed. Associations between child symptoms/disorders and parent distress were examined with log-binomial models, adjusting for highest parent education.

Results: Compared with population expectations (10%), more survivors self-reported symptoms of inattention (27.9; 95% CI, 21.0%-35.7%), hyperactivity/impulsivity (26.0%; CI, 19.2%-33.6%), and oppositional-defiant behavior (20.1%; CI, 14.1%-27.3%). Parents reported survivors with more symptoms of inattention (23.6%; CI, 17.2%-31.0%), higher frequencies of obsessive-compulsive disorder (10.3% vs 2%) and oppositional defiant disorder (16.0% vs 9.5%), but not attention-deficit/hyperactivity disorder (7.1% vs 7.8%) or generalized anxiety disorder (3.2% vs 4.1%), compared with national norms. Parent-report of child anxiety disorders was associated with parent self-reported emotional distress but not survivor self-report of anxiety.

Conclusion: A significant minority of survivors have long-term psychiatric morbidity, multi-informant assessment is important to understand these symptom profiles and to inform selection of appropriate interventions. Interventions targeting inattention and oppositional behavior in children and emotional distress in parents are warranted in families with survivors who display behavioral problems

Psychol Assess. 2018 Jun.

IMPACT OF CHILD AND INFORMANT GENDER ON PARENT AND TEACHER RATINGS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Anastopoulos AD, Beal KK, Reid RJ, et al.

Attention-deficit/hyperactivity disorder (ADHD) rating scales typically provide normative tables arranged according to child age, child gender, and type of informant, which facilitates addressing the fifth edition of the Diagnostic and Statistical Manual of Mental Health Disorders developmental deviance requirement for diagnosing ADHD. Missing, however, is any consideration of the gender of the informant. The purpose of this paper was to conduct an exploratory examination of informant gender via secondary analyses of a large data set used to standardize the ADHD Rating Scale-5. Two (informant gender) by two (child gender) ANOVAs were conducted separately for parents and teachers using inattention (IN) symptoms, hyperactive-impulsive (HI) symptoms, the total impairment score related to IN, and the total impairment score for HI as dependent variables. Results showed that female parents rated male children significantly higher on both IN symptoms and impairment related to IN than did male parents. Female teacher ratings were also significantly higher than male teacher ratings for male children in terms of HI symptoms and with respect to impairment ratings related to both HI and IN. A significantly higher percentage of female parents (7.7%) identified male children as being at risk for ADHD relative to male parents (4.1%). This same pattern emerged for female teachers (11.9%) versus male teachers (5.3%). Such results suggest that informant gender may play a clinically meaningful role in assessing ADHD in children and adolescents, which is consistent with the developmental literature addressing gender stereotypes in children. Future research is needed to determine whether similar informant gender differences exist in other rating scale measures of ADHD.

Public Significance Statement—Our study found that when parents and teachers rate attention-deficit/hyperactivity disorder (ADHD) behaviors in children, boys are nearly twice as likely to be identified as at risk for ADHD when rated by females versus males. Although preliminary, this finding suggests that it may be important for researchers and clinicians to take informant gender into account when assessing ADHD in children.

Psychol Neurosci. 2018;11:132-45.

BEHAVIORAL AND ELECTROPHYSIOLOGICAL STUDY OF ATTENTION PROCESS IN PRETERM INFANTS WITH CEREBRAL WHITE MATTER INJURY.

Gutiérrez-Hernández CC, Harmony T, Carlier MEM.

This study explored the effect of an early attention-stimulation program (EASP) on preterm infants with cerebral white matter injury and attention delay (AD). Monthly behavioral measures (from 3 to 8 months of age) and EEG recordings using a 2-tone oddball paradigm were collected at the beginning and at the end of the treatment. Ten full-term and 21 preterm infants with periventricular leukomalacia (PVL) and AD were examined. Eleven preterm infants were randomly assigned to the EASP (treatment preterm group) and 10 to a nontreatment preterm group. The behavioral results showed a significant improvement of attention in the treatment preterm group at 7 months of age. The electrophysiological data showed that deviant tones elicited greater P3a than standard tones in all 3 groups at 3 months of age; while at 8 months, only the healthy group showed this positive peak. In the treatment preterm group, deviant tones elicited a greater Nc than standard tones. In the nontreatment preterm group, the deviant tones did not elicit greater P3a or Nc than the standard tones at 8 months of age. These results demonstrate that when preterm infants with brain damage were treated with EASP, electrophysiological markers associated with the involuntarily capture of

attention were observed, but these markers differed from those in healthy infants. Therefore, we propose that treatment with EASP may decrease the attention deficits associated with PVL in preterm infants

Razavi International Journal of Medicine. 2017;5.

THE COMPARISON OF DIVIDED, SUSTAINED AND SELECTIVE ATTENTION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, CHILDREN WITH SPECIFIC LEARNING DISORDER AND NORMAL CHILDREN.

Maghsoodloonejad F, Razini HH.

Background: High incidence of learning disorders has caught the psychologists' attention in recent years. Objectives: The objective of this study was to compare divided, sustained and selective attention in children with attention deficit hyperactivity disorder, children with a specific learning disorder and normal children.

Methods: The study was a descriptive, causal-comparative and fundamental research. The population consisted of all children with attention deficit hyperactivity disorder (ADHD) and children with specific learning psychology (SLD), aged 7 to 12 years old, who referred to counseling and psychiatric clinics in Tehran in 2016, as well as normal primary school children. 36 children with attention deficit hyperactivity disorder and 47 children with specific learning difficulties were selected through convenience sampling, and 43 ordinary primary school children with cluster-randomly sampling method. Continuous performance test, word color Stroop test and the Wechsler scales were used as the instruments of the study. Descriptive and inferential statistics along with multivariate analysis of variance in Spss-21 were used to analyze data.

Results: The results of this study showed that weakness in divided, selective and sustained attention in children with attention deficit hyperactivity disorder and children with specific learning disorder is more than normal children ($P < 0.05$). However, there was no significant difference between these variables in children with attention deficit hyperactivity disorder and children with specific learning disorder ($P < 0.01$).

Conclusions: The results showed that the rate of comorbidity was very high in children with attention deficit-hyperactivity disorder and children with specific learning disorder

Res Dev Disabil. 2018;78:125-35.

THE ADHD RATING SCALE-IV PRESCHOOL VERSION: FACTOR STRUCTURE, RELIABILITY, VALIDITY, AND STANDARDISATION IN A DANISH COMMUNITY SAMPLE.

Alexandre JL, Lange A-M, Bilenberg N, et al.

Background: ADHD is a debilitating disorder with symptoms often appearing in early childhood. To facilitate early identification, developmentally appropriate and validated assessment tools for the preschool-age are needed.

Aims: The current study aims to examine the psychometric properties of the ADHD Rating Scale (RS)-IV Preschool Version (-P) in a Danish community sample and provide national standardisation data.

Methods and procedures: Parents ($n = 916$) and kindergarten teachers ($n = 275$) of preschool children, aged 3-5 years, completed the ADHD RS-IV-P.

Outcomes and results: Confirmatory factor analysis indicated that a three-factor model (inattention, hyperactivity, and impulsivity) best fit the data regardless of rater. Scales generally showed acceptable internal consistency, test-retest reliability, inter-rater reliability, and criterion validity. Boys received higher ratings on the ADHD RS-IV-P than girls and younger preschool children were rated as more inattentive than older preschool children.

Conclusions and implications: Our findings support the reliability and validity of the ADHD RS-IV-P and a three-factor model of ADHD. However, high factor correlations and similarity in model fit suggest that more research is needed to clarify the organisation of ADHD symptoms in preschool children. Furthermore, the external validity of separate ADHD dimensions at this age should be examined

Revista de Psicopatología y Psicología Clínica. 2018 Apr;23:59-74.

FACTORES PROTECTORES Y DE RIESGO DEL TRASTORNO DE CONDUCTA Y DEL TRASTORNO DE DÉFICIT DE ATENCIÓN E HIPERACTIVIDAD. UNA REVISIÓN SISTEMÁTICA. = PROTECTIVE AND RISK FACTORS FOR CONDUCT DISORDER AND ATTENTION DEFICIT-HYPERACTIVITY DISORDER. A SYSTEMATIC REVIEW.

Villanueva-Bonilla C, Ríos-Gallardo ÁM.

Conduct disorder (CD) and attention deficit-hyperactivity disorder (ADHD) are the most frequent clinical disorders in children and adolescents. The aim of the review was to identify the protective and risk factors of CD and ADHD to guide the design of intervention programs that allow to modify the risks and strengthen the characteristics that contribute to the non-manifestation of the symptomatology. The existing literature was analyzed from January 2012 to June 2017 through a search conducted in Scopus, Pubmed, Sciencedirect and PsycINFO. In conclusion, individual and family factors are predominant in both types of disorder, where variables of both protection and risk were found, with the emotional and cognitive variables being the most frequent in the individual factors and in family factors the quality of the relationship between parents and son.

Sao Paulo Med J. 2018 Mar;136:157-64.

TRANSLATION AND VALIDATION OF THE BROWN ATTENTION-DEFICIT DISORDER SCALE FOR USE IN BRAZIL: IDENTIFYING CASES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG SAMPLES OF SUBSTANCE USERS AND NON-USERS. CROSS-CULTURAL VALIDATION STUDY.

Kakubo SM, Mendez M, Silveira JD, et al.

BACKGROUND: The Brown Attention-Deficit Disorder Scale (BADDs) was developed as a self-report assessment that was designed to screen for presence of symptoms of attention deficit hyperactivity disorder (ADHD). The objective here was to translate and validate the adult self-report BADDs for use in Brazil.

DESIGN AND SETTING: Cross-cultural validation study conducted in an addiction unit at a public university hospital.

METHODS: This study included a control group (n = 100) and a drug-user group (n = 100). Both groups included subjects aged 18 to 60 years old. The control group had no prior diagnosis of drug addiction and the drug-user group included participants with a diagnosis of addiction. Each participant answered Brazilian Portuguese translations of both the BADDs and the Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) questionnaires, in paper-and-pencil format.

RESULTS: The drug-user group scored higher than the control group on both scales. The mean scores on ASRS were 27.26 (standard deviation, SD: 11.99) and 25.85 (SD: 8.65) respectively (P > 0.05). The mean scores on BADDs were 79.56 (SD: 29.61) and 79.31 (SD: 18.09), respectively (P > 0.05). Cronbach's alpha for BADDs was 0.95. BADDs presented fair sensitivity (72% accuracy) and fair specificity (88% accuracy).

CONCLUSION: This study provides discriminative validity evidence for use of BADDs among Brazilian adults with substance-use disorders

Schizophr Bull. 2018;44:824-33.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND PSYCHOSIS IN 22Q11.2 DELETION SYNDROME.

Niarchou M, Calkins ME, Moore TM, et al.

Objective: 22q11.2 Deletion Syndrome (22q11.2DS) is associated with increased risk for schizophrenia in adulthood while Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent diagnosis in childhood. Inattention symptoms are pronounced in 22q11.2DS and given that attentional impairment is a core feature of schizophrenia, inattention symptoms may reflect underlying ADHD, psychosis, or both. We investigate whether inattention is associated with psychosis in 22q11.2DS and in other groups at risk for psychosis but without the deletion (ND) (idiopathic clinical risk and first degree family members of individuals with schizophrenia).

Methods: One hundred thirty-seven individuals with 22q11.2DS (mean age: 14.0), 84 ND individuals with subthreshold psychosis (mean age: 16.9) and 31 ND individuals with family history of psychosis (mean age: 17.0) were included in the study. Psychopathology was assessed using research diagnostic assessments.

Results: ADHD total symptoms were associated with overall levels of subthreshold psychosis symptoms in 22q11.2DS (+1 =.8, $P = .04$). Inattention symptoms were specifically associated with positive (+1 =.5, $P = .004$), negative (+1 =.5, $P = .03$), and disorganized (+1 =.5, $P < .001$) symptoms, while hyperactivity-impulsivity symptoms were associated with disorganized symptoms (+1 =.5, $P = .01$). The prevalence of ADHD inattention symptoms was higher in 22q11.2DS with subthreshold psychosis compared to ND individuals with subthreshold psychosis ($P < .001$), even when adjusting for cognitive impairment and overall psychopathology. The pattern was similar when comparing individuals with 22q11.2DS and ND individuals with family history of psychosis.

Conclusions: This is the first study to examine the associations between ADHD symptoms and psychosis in 22q11.2DS. Our findings support a potentially important role of ADHD inattention symptoms in psychosis in 22q11.2DS

Sci Total Environ. 2018;642:1362-68.

OUTDOOR AIR POLLUTION, GREENSPACE, AND INCIDENCE OF ADHD: A SEMI-INDIVIDUAL STUDY.

Markevych I, Tesch F, Datzmann T, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a frequently occurring neurodevelopmental disorder, symptoms of which first appear in early childhood. Etiology of ADHD is not well understood. We investigated whether outdoor air pollution and greenspace affect ADHD incidence in children residing in Saxony.

Methods: 66,823 children, all beneficiaries of the statutory health insurance company AOK PLUS and born between 2000 and 2004, were followed until 2014. We considered any child with at least one ICD-10-GM F90 diagnosis by a child/adolescent psychiatrist, neuropaediatrician, or psychotherapist an ADHD case. Children's home addresses were known up to their four-digit postal code area. Population-weighted mean values of particulate matter with diameter of $< 10 \mu\text{m}$ (PM10), nitrogen dioxide (NO₂), and MODIS Normalized Difference Vegetation Index (NDVI) were calculated for 186 postal code areas. Associations with each exposure were assessed by two-level adjusted Poisson regression models.

Results: 2044 children (3.06%) were diagnosed with ADHD within the observation period. An increase of PM10 and NO₂ by $10 \mu\text{g}/\text{m}^3$ raised the relative risk of ADHD by a factor of 1.97 [95% CI: 1.35-2.86] and 1.32 [1.10-1.58], respectively. A 0.1-unit increase in NDVI decreased the relative risk of ADHD by a factor of 0.82 [0.68-0.98]. Better access to child/adolescent psychiatrists was the most important confounder that increased ADHD risk across all models.

Conclusion: Our results provide some evidence that air pollution might affect ADHD. Future studies with more detailed address information and better control for confounders, in particular socioeconomic status and parental psychopathology, should replicate the observed associations

Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2016 Apr;33:232-38.

CLASSIFICATION OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TYPICALLY DEVELOPING CHILDREN BASED ON ELECTROENCEPHALOGRAM PRINCIPAL COMPONENT ANALYSIS AND K-NEAREST NEIGHBOR.

Yang J, Guo Q, Li W, et al.

This paper aims to assist the individual clinical diagnosis of children with attention-deficit/hyperactivity disorder using electroencephalogram signal detection method. Firstly, in our experiments, we obtained and studied the electroencephalogram signals from fourteen attention-deficit/hyperactivity disorder children and sixteen typically developing children during the classic interference control task of Simon-spatial Stroop, and we completed electroencephalogram data preprocessing including filtering, segmentation, removal of artifacts and so on. Secondly, we selected the subset electroencephalogram electrodes using principal component analysis(PCA)method, and we collected the common channels of the optimal electrodes which occurrence rates were more than 90%in each kind of stimulation. We then extracted the latency(200~450ms) mean amplitude features of the common electrodes. Finally, we used the k-nearest neighbor(KNN)classifier based on Euclidean distance and the support vector machine(SVM)classifier based on radial basis kernel

function to classify. From the experiment, at the same kind of interference control task, the attention-deficit/hyperactivity disorder children showed lower correct response rates and longer reaction time. The N2 emerged in prefrontal cortex while P2 presented in the inferior parietal area when all kinds of stimuli demonstrated. Meanwhile, the children with attention-deficit/hyperactivity disorder exhibited markedly reduced N2 and P2 amplitude compared to typically developing children. KNN resulted in better classification accuracy than SVM classifier, and the best classification rate was 89.29% in Stl task. The results showed that the electroencephalogram signals were different in the brain regions of prefrontal cortex and inferior parietal cortex between attention-deficit/hyperactivity disorder and typically developing children during the interference control task, which provided a scientific basis for the clinical diagnosis of attention-deficit/hyperactivity disorder individuals

Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2016 Jun;33:526-32.

VOXEL-BASED MORPHOMETRY IN MEDICATED-NAIVE BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER(ADHD).

Liu Q, Chen L, Li F, et al.

Attention-deficit/hyperactivity disorder(ADHD) is one of the most common neuro-developmental disorders occurring in childhood, characterized by symptoms of age-inappropriate inattention, hyperactivity/impulsivity, and the prevalence is higher in boys. Although gray matter volume deficits have been frequently reported for ADHD children via structural magnetic resonance imaging, few of them had specifically focused on male patients. The present study aimed to explore the alterations of gray matter volumes in medicated-naive boys with ADHD via a relatively new voxel-based morphometry technique. According to the criteria of DSM-IV-TR, 43 medicated-naive ADHD boys and 44 age-matched healthy boys were recruited. The magnetic resonance image(MRI) scan was performed via a 3T MRI system with three-dimensional(3D) spoiled gradient recalled echo(SGPR) sequence. Voxel-based morphometry with diffeomorphic anatomical registration through exponentiated lie algebra in SPM8 was used to preprocess the 3DT1-weighted images. To identify gray matter volume differences between the ADHD and the controls, voxel-based analysis of whole brain gray matter volumes between two groups were done via two sample t-test in SPM8 with age as covariate, threshold at $P < 0.001$. Finally, compared to the controls, significantly reduced gray matter volumes were identified in the right orbitofrontal cortex (peak coordinates $[-2, 52, -25]$, $t = 4.01$), and bilateral hippocampus (Left: peak coordinates $[14, 0, -18]$, $t = 3.61$; Right: peak coordinates $[-14, 15, -28]$, $t = 3.64$) of ADHD boys. Our results demonstrated obvious reduction of whole brain gray matter volumes in right orbitofrontal cortex and bilateral hippocampus in boys with ADHD. This suggests that the abnormalities of prefrontal-hippocampus circuit may be the underlying cause of the cognitive dysfunction and abnormal behavioral inhibition in medicated-naive boys with ADHD

Sleep. 2018;41:A101.

CHARACTERIZING THE EFFECTS OF SLEEP EXTENSION ON OVERNIGHT EEG DYNAMICS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Fitzroy AB, Cremone A, Spencer RM.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is associated with impaired sleep in children, and short sleep duration is associated with increased inattention and hyperactivity/impulsivity. These findings suggest that unmet sleep need underlies some portion of the sleep disturbances often observed in ADHD. Thus, we hypothesized that extending sleep duration in children with ADHD would reduce sleep atypicality.

Methods: Overnight EEG data were collected from 11 children (6 - 9 y.o.) previously diagnosed with ADHD and 10 typically developing (TD) children (6 - 9 y.o.) on a typical sleeping night, and on the last day of a 5-night sleep extension protocol. Dynamic changes in spectral power over the course of the night were assessed using power envelopes generated by Hilbert-transforming the overnight EEG after filtering into subdelta (0.1 - 0.5 Hz), delta (0.5 - 4 Hz), theta (4 - 8 Hz), and sigma (12 - 16 Hz) frequency bands, and by performing wavelet based time-frequency decomposition of the EEG data.

Results: On the typical sleeping night, children with ADHD had increased delta activity during the first two hours of the night ($p = 0.047$) and increased subdelta activity during the second two hours of the night ($p = 0.047$) relative to TD children. These differences were not evident after following the sleep extension protocol (p 's > 0.4).

Conclusion: Our results suggest that children with ADHD have unmet sleep need that is dissipated by a sleep extension protocol, as indicated by the increased subdelta and delta power early in the night for ADHD children on the typical night but not the extended sleep night

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Sleep. 2018;41:A288.

DO MARKERS OF OBSTRUCTIVE SLEEP APNEA SEVERITY PREDICT ATTENTION PROBLEMS IN CHILDREN?

Dhaliwal S, Lewin D, Huntley E.

Introduction: Sleep disordered breathing in children has been linked to attention concerns. Left untreated, OSA may give rise to the clinical diagnosis of Attentional Deficit Hyperactivity Disorder and contribute to other behavior problems. The aims of the current project were to test whether (a) severity of OSA predicted greater ADHD symptom scores and clinical diagnosis, and (b) markers of OSA severity were differentially related to clinically significant externalizing behavioral disorders.

Methods: In a prospective study, the parents of 71 children with OSA and 35 without (53% female, mean age = 7.9 years; SD = 1.4 years) completed the Child Behavioral Checklist (CBCL), yielding scaled scores in domains of attention and behavior problems. Children also underwent a one-night polysomnography study. OSA severity was determined by obstructive apnea hypopnea index ($1 < \text{AHI} \leq 5$ mild, $5 < \text{AHI} \leq 10$ moderate, $\text{AHI} > 10/\text{hr}$ severe). Linear regressions adjusted for age, body mass index (BMI), race, and parental education.

Results: OSA severity was related to lower parental education, African American race, and body mass index ($p < .05$). OSA severity exhibited a dose-response positive association with attention problems, at each severity level above mild ($+1 = 4.36$, $p = .02$ for moderate; $+1 = 9.93$, $p < .001$ for severe). OSA severity also predicted ADHD diagnostic thresholds ($+1 = 3.53$, $p < .05$ for moderate; $+1 = 5.99$, $p < .01$ for severe OSA). Between-group analyses indicated that children with OSA also experienced greater general externalizing behaviors, as well as greater conduct problems ($p < .05$), and trended toward greater oppositional defiance ($p = .076$).

Conclusion: OSA severity is linked to both attention difficulties and clinical thresholds of ADHD. Children with OSA exhibited increased symptoms of externalizing, conduct and oppositional behavioral problems. Future work shared neural mechanisms and improved diagnosis of co-morbid OSA, behavior and attention problems

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Sleep. 2018;41:A303-A304.

SLEEP AND ADHD IN CHILDREN: ARE PEDIATRIC RESIDENTS CONSIDERING SLEEP PROBLEMS WHEN DIAGNOSING ADHD?

Reinecke K, Vaughn B, Fan Z, et al.

Introduction: The purpose of this study is to determine whether pediatric residents consider sleep problems when assessing patients with hyperactivity and inattention. The symptoms of Attention Deficit/ Hyperactivity Disorder (ADHD) are also often seen in sleep disorders such as obstructive sleep apnea (OSA) and restless leg syndrome (RLS). The commonly used NICHQ Vanderbilt Assessment Scale does not screen for sleep problems; therefore, the sleep evaluation must be in the interview, exam, and diagnostic testing. The hypothesis is that residents may not adequately assess sleep prior to diagnosing ADHD, which may be due to limited education about sleep.

Methods: Pediatric residents at two large academic institutions were surveyed using the online Qualtrics platform. The survey asked about the diagnostic approach to ADHD, including typical screening questionnaires, differential diagnosis, physical exam components, and testing. Questions were also included

about the diagnostic approach to sleep problems, as well as barriers that interfere with evaluation of sleep. Results were compared using standard descriptive statistics.

Results: Thirty questionnaires were returned, with 28 completed. All residents used the Vanderbilt scale; residents were aware that sleep problems were not included in this questionnaire. Although 52% considered sleep problems in the top 5 differential diagnoses, only 28% routinely screened for OSA, and only 7% routinely screened for RLS. The pharynx, which may reveal tonsillar enlargement concerning for OSA, was ranked in the top 3 most important physical exam components by only 25%. The 3 most frequently endorsed barriers to screening for sleep problems were lack of training (86%), lack of time (71%), and lack of access to questionnaires (54%); lack of time was most frequently chosen as the most significant.

Conclusion: Although about half of pediatric residents consider sleep an important component of the differential diagnosis for ADHD, only a minority screened for the treatable sleep disorders of RLS and OSA. Assessment for sleep disorders in patients with hyperactivity and inattention might be improved with more resident education as well as increased access to tools that expedite screening for sleep disorders

Sleep. 2018;41:A390.

ARE REFERRALS TO SLEEP CLINIC NECESSARY PRIOR TO POLYSOMNOGRAPHY IN CHILDREN WITH ADHD?

Hammond R, Paasch V, Ewen J, et al.

Introduction: Children with ADHD may be difficult to study in the lab due to lack of compliance with the equipment or difficulty adjusting to equipment. Because sleep clinic is an opportunity to provide screening and education regarding PSGs, we hypothesized that patients referred to sleep clinic prior to PSG would have better sleep.

Methods: A retrospective chart review was performed on all children with ADHD who completed polysomnography during a one-year period. Data were obtained on referral source, sleep efficiency, sleep latency, wake after sleep onset (WASO), and technician-rated set-up compliance. Analyses included regression modeling and scaled JZS Bayes factor analyses.

Results: A total of 69 children were included in this study (22 were female). 34 children were referred to the lab from sleep clinic and 35 children were referred from other clinics. Bayes factor analyses demonstrated that it is more likely than not that referral source (sleep clinic vs. other) has no effect on quality of sleep in the lab, as recorded by sleep latency, sleep efficiency and WASO. The data suggest that it is 3.5 times more likely that there is no effect of referral source on sleep efficiency than an actual effect exists. Bayes factors for a null association between referral source and WASO is 2.2; for referral source and sleep latency, 3.5. Regression analysis yields no significant effect for referral source on technologist-rated set-up difficulty. Regression analysis also failed to show an effect on any parameter, even after controlling for sex and/or age.

Conclusion: Our results indicate that referrals from sleep clinic do not impact sleep quality variables compared to referral from other sources. This may indicate that there is no benefit to PSG compliance gained by referral first to the sleep clinic. Thus, a reduction in the wait time and unnecessary medical costs can be avoided by direct referral to the lab. Future studies which compare other populations of children with neurodevelopmental disabilities would provide insight into which patients benefit from the additional education/preparation provided by sleep clinic

Sleep. 2018;41:A284.

THE IMPACT OF MEDICATIONS ON SLEEP IN THE LAB FOR CHILDREN WITH ADHD.

Hoosier T, Gregory L, Paasch V, et al.

Introduction: Children with ADHD have a higher prevalence of sleep problems: prolonged sleep latency, increased night wakings, and restlessness. Stimulant medications are known to increase sleep difficulty while non-stimulant medications (alpha-agonists) are known to improve sleep. Some published studies indicate that parents overestimate sleep difficulty based on actigraphy results. Very few studies have evaluated sleep in children with ADHD using polysomnography. We hypothesize that patients on stimulant medication will

have more difficulty with sleep and patients on an alpha agonist would have less difficulty with sleep compared to patients not taking medication based on results from polysomnography.

Methods: A retrospective chart review was performed on all children under 18 years of age with ADHD referred to our sleep lab in a one-year period, by child neurologists, child psychiatrists and developmental pediatricians. We obtained information on the patient's age, sex, sleep efficiency, sleep latency, and wakefulness after sleep onset (WASO). Analyses included regression modeling and scaled JZS Bayes factor analyses. Bayes factor analyses allow for greater certainty than traditional frequentist tests when establishing a lack of effect (i.e., accepting the null hypothesis).

Results: Of the 69 children studied, 28 children were taking a stimulant, 8 were taking an alpha agonist, 9 were on both medications, and 24 were not on either. Bayes factor analyses report on the likelihood that the null hypothesis is correct (no difference in sleep parameters caused by medication), as compared to the likelihood of the alternative hypothesis (medications are associated with a difference in sleep parameters). Our data suggest no relationship between either medication and any sleep parameter. For stimulants, sleep efficiency Bayes factor was 2.9, WASO was 3.9, and sleep latency was 2.4. Regression modeling established no association between either medication and any sleep parameter, even when controlling for age and/or sex.

Conclusion: Our data suggests that medication likely has no impact on sleep for children with ADHD in the lab. These findings are limited by the retrospective nature of the study

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Sleep. 2018;41:A304.

A FULL SLEEP ASSESSMENT IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDERS (ADHD).

Miano S, Ninfa A, Casadei A, et al.

Introduction: One of the most extensively researched areas concerns sleep disorders associated with ADHD. Based on sleep information, the main aim of our study was to classify children with ADHD in one of the following 5 phenotypes: 1) narcolepsy-like; 2) sleep onset insomnia; 3) obstructive sleep apnea syndrome; 4) sleep hyperkinesia, and/or periodic limb movements; and 5) sleep epilepsy and/or EEG interictal epileptiform discharges. Secondary aim was to explore differences ADHD patients and controls in the slow wave activity (SWA) scalp distribution and source by using high density EEG (HD-EEG).

Methods: A case-control sleep study in children with ADHD was carried out. Children with ADHD (mean age 10.1 \pm 2.1 years), underwent a battery of sleep questionnaires, a video-PSG-HD-EEG (256 channels), MSLT, and 1-week actigraphy. SWA topography and source during the first cycle of NREM sleep were analysed in both groups.

Results: 30 patients and 30 controls were recruited. The narcoleptic-like phenotype was found in 4 children, a sleep onset insomnia in 5 children, an obstructive sleep apnea in 7 children, a sleep hyperkinesia and/or periodic limb movements in 8 children, while an EEG interictal epileptiform discharges and/or nocturnal epilepsy in 5 subjects. All patients had a mean total sleep time < 9 hours at actigraphy. ADHD patients slept less and had a higher AHI than controls measured by PSG. At scalp topography, both groups showed a similar distribution of SWA, but with a group specific activity pattern. In ADHD subjects, the focus of slow wave activity was observed over centro-parietal regions, whereas in controls it was prominent over frontal regions. The statistical non parametric comparison of localized sources showed a significantly greater delta power over the posterior cingulates in ADHD group compared to controls.

Conclusion: The study confirms the relevant association between ADHD and defined sleep disorders, inducing a chronic sleep deprivation. The HD-EEG mapping and source analysis confirms a maturation delay of SWA, which may also reflect a state of sleep deprivation

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Sleep. 2018;41:A283-A284.

SLEEPING AT HOME: FEASIBILITY AND TOLERABILITY OF AMBULATORY POLYSOMNOGRAPHY FOR USE WITH ADOLESCENTS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Lunsford-Avery JR, Kollins SH, Krystal AD.

Introduction: Polysomnography (PSG) is the gold-standard objective sleep assessment. However, particularly in pediatric samples, PSG is associated with sleep disturbances resulting from discomfort in the lab environment, a difficulty further amplified in youth with behavioral disorders such as ADHD. Ambulatory PSG records sleep at home, reduces lab-related sleep disturbances, and is acceptable to typically-developing children, and thus, may be a useful tool for sleep studies with ADHD youth. This study is the first to examine the feasibility and tolerability of ambulatory PSG with an ADHD sample. Initial data loss observed during the study (pulled wires) led to a solution (taping wires to the recorder). A crossover study examining data collected prior and subsequent to tape use investigated the effectiveness of this solution for increasing feasibility of ambulatory PSG with ADHD adolescents.

Methods: Twenty-two adolescents (aged 13-17; 13 ADHD, 9 Healthy Controls) participated in three nights of ambulatory PSG (Philips Alice PDx Portable Sleep System). Monitors were attached by a trained technician and participants subsequently slept at home and removed monitors each morning. Scored sleep studies assessed completeness of PSG data. The clinician-administered At-Home PSG Tolerability Rating Scale [Lunsford-Avery & Krystal] assessed the comfort of the system, system-related sleep disturbances, and overall study satisfaction.

Results: Data collection improved following use of tape (n = 11; 94% nights successfully collected) compared to use without tape (n = 11; 70%) at the trend level (p = .08). On average, adolescents indicated mild discomfort, minimal sleep disruptions, and overall satisfaction with the system. Groups did not differ in their ratings of the acceptability/ tolerability of ambulatory PSG (p's > .10).

Conclusion: Ambulatory PSG is a feasible and acceptable method for collecting sleep data in adolescents with ADHD. However, ADHD symptoms (e.g., fidgeting) resulted in a risk for data loss (e.g., pulled wires). Taping wires to the recording box eliminated data loss. This modification should be implemented when using ambulatory PSG with this population

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PROFILING DATABASES TO FACILITATE COMPARISON OF CHILD HEALTH SYSTEMS ACROSS EUROPE USING STANDARDISED QUALITY MARKERS.

Liyanage H, Shinneman S, Hoang U, et al.

Models of child primary health care vary across Europe. There are three categories, primary care paediatricians, general practitioner based, or mixed. This paper describes the metadata schema used in the profiling process of candidate data sources for appraisal for the Models of Child Health Appraised (MOCHA) project using the MOCHA International Research Opportunity Instrument (MIROI). The ten clinical indicators included: asthma, antibiotic stewardship, immunisation, rickets, diarrhea, epilepsy, depression, ADHD, enuresis and care of women during pregnancy. Our metadata allows us to identify data within included data sources concerning any of the 10 clinical indicators identified for comparative analysis within the MOCHA project. From the 30 countries we found a minimum of 5 and a maximum of 36 different databases for each indicator

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THE COGNITIVE REMEDIATION THERAPY PROGRAM AMONG CHILDREN WITH ADHD: TUNISIAN EXPERIENCE.

Hamza M, Abbes Z, Yahyia HB, et al.

Background: Attention-Deficit Hyperactivity Disorder (ADHD) is associated with neuropsychological deficits including executive and attentional impairments. The cognitive remediation therapy is a new promising technique designed to improve the neurocognitive abilities damaged in ADHD.

Aim: Adapt and apply the cognitive remediation program CRT (Cognitive Remediation Therapy) for children and adolescents with ADHD and to evaluate its effectiveness on attentional and executive abilities.

Methods: Children and adolescents with ADHD, diagnosed using the K-SADS-PL questionnaire was involved in the study. The CRT program was administered for an average period of fourteen weeks with a rate of one session per week of 40 minutes each. The Attentional Network Test was administered prior to the intervention and one week after.

Results: Of the 30 patients included, 14 had reached the end of the program. Among them, nine patients passed the attentional test post CRT, thus constituting our final sample. Their average age was 9 years. The mean number of sessions performed was 14.5. Post CRT, the mean of patient's response time was found to be shorter ($p=0,004$) and the frequency of omissions errors was also lesser than that found at the initial assessment. Patients also committed fewer errors in incongruent situations in post program, with a significant improvement of the conflict effect ($p= 0.009$) signing a better executive control.

Conclusions: Cognitive remediation is a promising new modality in the treatment of ADHD. Further research is needed to better document its effects and the optimal conditions required for setting it up

Zhonghua Liu Xing Bing Xue Za Zhi. 2018 Apr;39:464-68.

POTENTIAL INTERACTION EFFECT ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BETWEEN MOTHER'S EDUCATIONAL LEVEL AND PRESCHOOLERS' DIETARY PATTERN.

Yan SQ, Cao H, Gu CL, et al.

Objective: To explore the interaction effect between mother's educational level and preschoolers' dietary pattern on attention-deficit/hyperactivity disorder (ADHD).

Methods: In 2014, there were 16 439 children aged 3-6 years old from 91 kindergartens in Ma'anshan municipality of China. A semi-quantitative food frequency questionnaire and the 10-item Chinese version of the Conners' Abbreviated Symptom Questionnaire (C-ASQ) were administered to assess the usual dietary intake and symptoms on ADHD. Social-demographic information was collected through questionnaires. Unconditional logistic regression was used to analyze the multiplication interaction effect between mother's educational level and preschoolers' dietary pattern on ADHD. Excel software was used to analyze the additive interaction effect of mother's educational level and preschoolers' dietary pattern on ADHD.

Results: Results showed that factors as: mother's low educational level [$aOR=1.31$ (1.13-1.52)], scores related to preschoolers in the top quintile of "food processing" [$aOR=1.31$ (1.16-1.48)] and "snack" [$aOR=1.45$ (1.29-1.63)] patterns showed greater odds while preschoolers in the top quintile of "vegetarian" [$aOR=0.80$ (0.71-0.90)] showed less odds for having ADHD symptoms. Both multiplication and additive interactions were observed between mothers with less education. The processed dietary patterns ($OR=1.17$, 95%CI: 1.11-1.25), relative excess risk of interaction (RERI), attributable proportion (AP) and the interaction index (SI) appeared as 0.21, 0.13 and 1.47, respectively. Multiplication interaction was observed between levels of mother's low education and the snack dietary pattern ($OR=1.21$, 95%CI: 1.14-1.29), with RERI, AP and SI as 0.49, 0.26 and 2.36, respectively. However, neither multiplication interaction or additive interaction was noticed between levels of mother's low education and the vegetarian dietary pattern ($OR=0.97$, 95%CI: 0.92-1.03), with RERI, AP and SI as 0.09, 0.05 and 1.15, respectively.


Conclusions: Levels of mother's low education presented a risk factor for ADHD symptoms in preschool children. Both multiplication interaction and additive interaction were observed between mother's low education levels and the processed dietary pattern. Multiplication interaction was noticed between mother's education levels and the snack dietary pattern but not with the vegetarian dietary pattern

RESEARCH ARTICLE

Open Access



Computer-assisted rehabilitation of attention in pediatric multiple sclerosis and ADHD patients: a pilot trial

Marta Simone^{1†}, Rosa Gemma Viterbo^{2†}, Lucia Margari¹ and Pietro Iaffaldano^{2*} 

Abstract

Background: The treatment of cognitive deficits is challenging in pediatric onset multiple sclerosis (POMS) and in patients with attention deficit hyperactivity disorder (ADHD). We performed a pilot double-blind RCT to evaluate the efficacy of a home-based computerized-program for retraining attention in two cohorts of POMS and ADHD patients.

Methods: POMS and ADHD patients failing in at least 2/4 attention tests on a neuropsychological battery were randomized to specific or nonspecific computerized training (ST, nST), performed in one-hour sessions, twice/week for 3 months. The primary outcome was the effect of the training on global neuropsychological performances measured by the cognitive impairment index (CII).

The efficacy of the intervention was evaluated in each disease group by using repeated measures ANOVA.

Results: Sixteen POMS (9 females, age 15.75 ± 1.74 years) and 20 ADHD (2 females, age 11.19 ± 2.49 years) patients were enrolled. In POMS patients the ST exposure was associated to a significantly more pronounced improvement of the CII ($p < 0.0001$) and on cognitive test exploring attention, concentration, planning strategies and visuo-spatial memory performances in comparison to nST exposure. In ADHD patients the difference between the ST and nST on the CII was not statistical significant ($p = 0.06$), but a greater effect of the ST was found only on cognitive test exploring attention and delayed recall of visuo-spatial memory performances.

Conclusions: Our data suggest that a cognitive rehabilitation program that targets attention is a suitable tool for improving global cognitive functioning in POMS patients, whereas it has a less pronounced transfer effect in ADHD patients.

Trial Registration: ClinicalTrials.gov; [NCT03190902](https://clinicaltrials.gov/ct2/show/study/NCT03190902); registration date: June 15, 2017; retrospectively registered.

Keywords: Multiple sclerosis, Attention deficit, Rehabilitation, ADHD

Background

The presence of cognitive deficits of varied intensity is a characteristic of psychiatric disorders of childhood and adolescence such as Attention Deficit Hyperactivity Disorder (ADHD), but also of neurological pathologies such as pediatric onset multiple sclerosis (POMS).

ADHD is one of the most common neurodevelopmental disorders characterized by pervasive patterns of inattention

and/or impulsivity/hyperactivity and a range of cognitive dysfunctions that often persist into adulthood [1, 2].

POMS represent 5–10% of total MS population [3]. Cognitive dysfunction is one of the most remarkable features of MS and particularly in POMS. The percentage of patients with POMS with at least a mild cognitive deficit ranges from 30 to 50% [4–9]. The most affected cognitive domains in POMS are complex attention, information processing speed, executive functions, verbal and visual memory, reasoning and problem solving [4, 9]. Longitudinal studies from US and Canada groups showed a cognitive stability in POMS patients over time [10, 11]. The US study reported an overall percent of patients with

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cognitive impairment, defined as having one-third or more test scores in the impaired range, of 37.3% at baseline and 32.3% after a mean follow-up of 1.64 year [10]. A Canadian study, examining patients and controls over a 1-year period found that controls generally showed greater improvement than patients, and 25% of patients showed clinically significant decline [11].

In contrast, an Italian longitudinal study demonstrated that cognitive impairment in POMS tend to worsen after a mean period of 2 years since baseline evaluation [12]. At follow-up 75% of the cases were classified as having a deteriorating cognitive performance. Changes were prominent in tests of verbal memory, complex attention, verbal fluency, and receptive language. However the same group reversed their initial negative findings showing that after 5 years from baseline there was more stability than decline [13].

Interestingly, a variety of psychiatric symptoms can occur in POMS. Approximately one-third of children suffer from depressive symptoms and one-fourth of POMS report fatigue [12, 14]. Moreover, one study has reported ADHD as one of the most frequent comorbid psychiatric disorder in POMS [15]. The functional consequences of cognitive impairment can be particularly striking in children and adolescents, since they occur during their formative years, therefore it may affect their academic and social activities. Cognitive training during the developmental age when brain plasticity is at the highest expression can induce a strengthening of the key brain networks implicated in POMS and ADHD.

In adult onset MS patients several studies examined the efficacy of cognitive rehabilitation programs related to attention and additional cognitive domains [16, 17]. Some of them provided class I evidence of beneficial effects of these training programs through randomized clinical trials (RCTs) [18–20].

To date the efficacy of specific cognitive rehabilitation interventions has never been evaluated by a RCT in POMS. Whereas, the fMRI effect of a working memory training has been reported in a small case series of 5 juvenile MS patients [21]. Conversely, in the last years, several RCTs [22–25] assessed the efficacy of cognitive training as a potential non-drug alternative treatment for ADHD disorder [26]. Most of the cognitive trainings focused on the working memory or attention dysfunctions. Preliminary evidence suggests that cognitive remediation might be at least partially effective in the ADHD treatment [27–32]. It is argued that cognitive training can potentially reduce ADHD symptoms and might improve functioning by targeting neuropsychological deficits thought to mediate ADHD pathophysiology [33–37].

In this exploratory pilot study, we assessed by a double-blind RCT the efficacy of a home-based computerized program for retraining attention dysfunction in

two cohorts of POMS and ADHD patients. The results in POMS were compared to those obtained in ADHD patients.

Methods

Standard protocol approval, patient consent and recruitment

The study was conducted with approval of the institutional review board (Comitato Etico Indipendente Azienda Ospedaliero-Universitaria Consorziale Policlinico - Approval Number: 0070059/CE). Parents of the participants signed an informed consent.

Recruitment (September–December 2015, predetermined) and assessments were performed at the MS Centers and at the Child Neuropsychiatry Unit both of the University of Bari. Due to the monocentric nature of the study and due to the absence of external funding resources the recruitment has been limited only to referrals to the these two centers. Clinical trial registration information: ClinicalTrials.gov number NCT03190902. Clinical trial registration date: June 15, 2017.

Study population

POMS

We recruited POMS outpatients consecutively referred to the MS Centers at the University of Bari who met the inclusion/exclusion criteria during the study period. Inclusion criteria were: POMS diagnosed according to the most recent diagnostic criteria [38], aged < 18 years, with an Expanded Disability Status Scale (EDSS) score ≤ 5.5 , impairment on at least 2/4 attention tests (see below) defined as scores < 1.5 standard deviation (SD) of normative values [9, 12, 13]. To facilitate recruitment we excluded only patients with important impairments on other cognitive tasks, defined as performance ≤ 2.0 SD of normative values, still including subjects with milder degrees of impairment (e.g. cognitive scores between 1.51 and 1.99 SD below the normative values). Exclusion criteria were: severe visual loss (unable to read Times New Roman font 16 with the best correction), major psychiatric illness (any severe disabling psychiatric disorders [i.e. major depression, obsessive-compulsive disorder, psychotic disorder] which could interfere with: the understanding of the protocol and of the informed consent; the overall engagement in the study and in particular with the adherence with the treatment regimen and the compliance with the study visits and procedures), alcohol or substance abuse, education < 5 years, previous cognitive rehabilitation training, ongoing relapse or steroid treatment during the 30 days preceding enrollment. Disease-modifying treatments (DMTs) and symptomatic treatments were maintained unchanged during the study.

ADHD

We enrolled ADHD outpatients consecutively referred to the Child Neuropsychiatry Unit at the University of Bari. We included only ADHD patients with the subtype inattention, not previously exposed or not treated with any psychotropic drug. ADHD diagnosis was performed according the DSM-5 criteria and the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention- Deficit/Hyperactivity Disorder (MTA) - Swanson, Nolan, and Pelham IV Rating Scale (MTA-SNA-P-IV), Conner's Parent Rating Scale Revised (CPRS-R), Conner's Teacher Rating Scale Revised (CTRS-R), Child Behavior Checklist (CBCL), Kiddie Schedule for Affective Disorder and Schizophrenia (K-SADS). The same inclusion/exclusion criteria referring the cognitive performances were applied to the ADHD patients.

Study procedures

We applied the same study procedures already reported in a previous study which evaluate the effect of the cognitive rehabilitation program in adult-onset MS patients [18]. Patients were randomized to receive a specific computer training (ST) or to receive a nonspecific computer training (n-ST) with a 1:1 ratio. Randomization was performed by an independent researcher on the basis of a computerized list of random numbers. A psychologist, blind to the study, was responsible for administering and evaluating the neuropsychological tests, whereas an independent researcher, who was not blind to the study, was responsible for setting up the ST and n-ST programs, explaining the training procedure and supervising the training program.

As defined by the study protocol, during the study period, in case of a suspected MS relapse, the patient underwent a neurological examination within 48 h and a standard steroid treatment was prescribed if needed. A confirmed MS relapse was a reason for study discontinuation.

Study design

This is a single-centre, parallel group double blind-RCT.

Assessment and outcome measures

At the baseline visit, a neurologist and a child/adolescent neuropsychiatrist collected demographic and clinical information of POMS and ADHD (familiar background, any past medical history) patients.

The handedness was evaluated in both groups by the Edinburgh Inventory [39].

The neuropsychological assessment was performed by a psychologist. Two alternate versions of the tests were used at different assessment points.

The primary outcome was to evaluate the effect of the cognitive training on neuropsychological performances.

The neuropsychological test battery assessed the following cognitive areas:

- Verbal learning and delayed recall: Selective Reminding Test (SRT) and Selective Reminding Test–Delayed (SRT-D) from the Rao Brief Repeatable Battery (BRB) [40];
- Visuo-spatial learning and delayed recall: Spatial Recall Test (SPART) and Spatial Recall Test–Delayed (SPART-D) from the BRB [40];
- Concentration, attention, processing speed, working memory and cognitive flexibility: Symbol Digit Modalities Test (SDMT) from the BRB and the Trail Making Tests (TMT) A and B [41];
- Expressive language: Semantic Verbal Fluency Test (SVFT), in which the subject is asked to produce as many words as possible belonging to a semantic category (colors, animals, fruits, cities) within 120 s. The score is the average of correct words [42].
- Planning: Tower of London Test (TOL). The initial and target configuration of the TOL were presented under the form of 2 identical kits made of a wooden base (22 16 1 2 cm) with 3 rods of 12, 8, and 4.5 cm, and 3 balls (yellow, red, and blue) of 3 cm in diameter. The subject was required to obtain the target configuration in a minimum number of moves, according to the following rules: move only 1 ball at a time; place at most 1 ball on the shortest peg and 2 balls on the middle one; move each ball only from one peg to another. There were no time limits. The execution time and the number of moves were recorded by the examiner. The results (target configuration attained or not, abandoned) and any rule violations were noted [43].
- Depression: self-assessed by patients through the Children's Depression Inventory (CDI) with the assistance of the psychologist [44].
- Kiddie Schedule for Affective Disorder and Schizophrenia (K-SADS).

The psychologist administered the above battery, using alternative versions of the tests, at baseline, and within 1 week following the end of the training program. At the same time intervals, self-assessed measures were also repeated.

Intervention

The ST was based on the Attention Processing Training program (APT) [45]. This program targets focused, sustained, selective, alternating and divided attention and consists of a group of hierarchically organized tasks that exercise different components of attention, proceeding from sustained to selective, alternating and finally divided attention exercises. The sequence of the exercises places increasing demands on complex attention control and working memory systems (e.g. identification

of target numbers or letters in the presence of distracter images and noises).

The n-ST consisted of a series of nonspecific exercises including the following: text reading and comprehension: e.g. reading brief text extracted from novels, journals, newspaper (without requesting a feedback nor verbal nor written); give feedback on proverbs comprehension; description of pictures: e.g. try to provide a brief verbal description of simple pictures; enumerating words classified in different categories; trying to provide at least 3 synonyms for a given list of words; etc.

Before starting the training at home, a psychologist who was not blind to the patient assignment group conducted a training session for each patient at the MS Clinic, in the presence of the caregiver/parent, in which instructions and procedures for the use of the ST and n-ST were provided (Patients and their parents were not aware about the treatment arm assigned). Each patient was treated at home twice a week for three consecutive months. Each training session lasted 1 h. Each patient applied the training on his/her own under the supervision of the caregiver/parent, who also collected and stored forms reporting patient performance during each training session. During the study period, the psychologist called patients every week and met patients and their caregiver/parent every month to check patient compliance and possible difficulties in the use of the training program.

Statistical analysis

Given the exploratory nature of this pilot trial, no sample size analysis was performed. Continuous variables were described as mean and standard deviation (SD), categorical variables as frequency and percentage. Group comparison has been performed using the Student's *t* test, the Mann-Whitney *U* test and the Fisher's exact test when appropriate.

A global score, defined Cognitive Impairment Index (CII), allowing the evaluation of changes in cognitive performances independently by the number of cognitive tests failed at the neuropsychological evaluation, was obtained using the mean and SD from the normative values for each test [13, 46–48].

For each patient, a grading system was applied to individual cognitive tests, based on the number of SDs below the control mean (i.e. grade 0 was given if the patient scored at or above the control mean, 1 if he/she scored below the control mean, but at or above 1 SD below the control mean, and so on until all patient scores were accommodated) [13, 46–48]. Finally, all the patient's scores were summed to give one overall measure of cognitive function.

The efficacy of ST on the global cognitive functioning, measured by the CII, and on performance of each cognitive test was evaluated in each disease group by using a 2

(Group–ST and n-ST) \times 2 (Time–baseline, 3 months) mixed factorial design, with repeated measures on the second factor.

Finally, the comparative efficacy of the ST on the global neuropsychological performances between the 2 disease groups was assessed by using a generalized linear model. In this model the estimated mean difference between performances recorded after training and those recorded before training on the CII for each disease group was compared. Age, sex and school education were included as covariates in this model.

Statistical analysis was performed by using SPSS software (SPSS, version 22.0; SPSS, Chicago, Ill).

Results

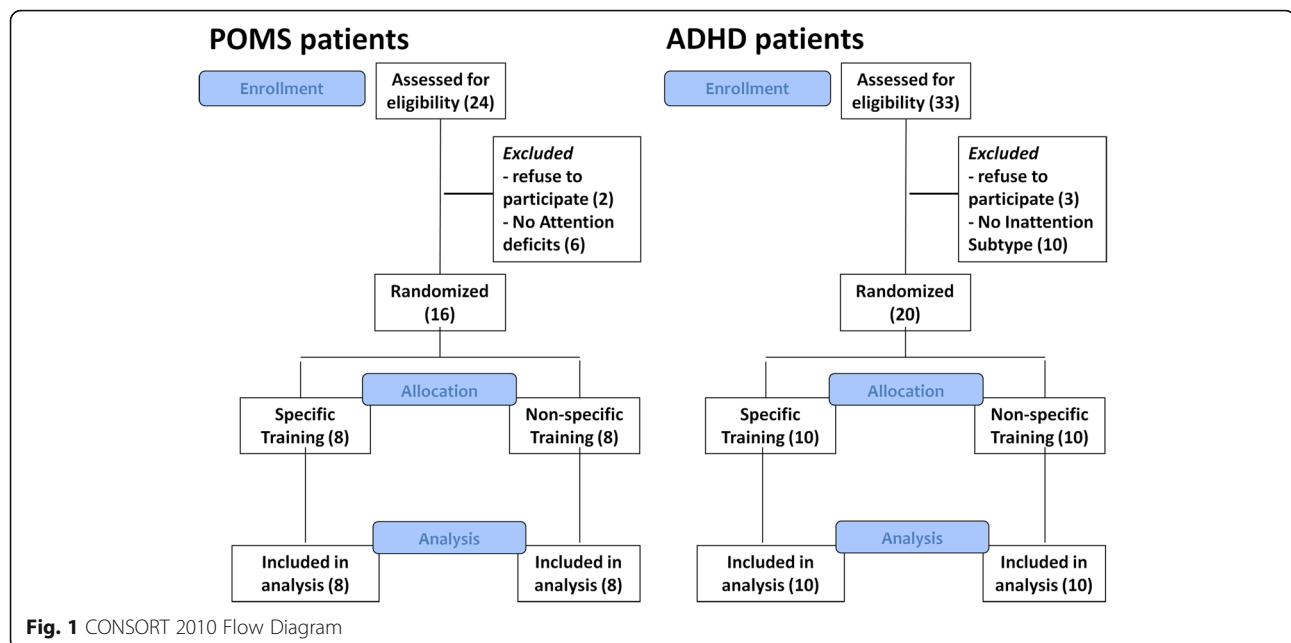
Twenty-four POMS and 33 ADHD patients were assessed for eligibility during the recruitment period. In the POMS group, 2 patients refused to participate, 6 patients did not meet the inclusion criteria regarding the presence of deficits on at least 2/4 attention performance tests. In the ADHD group, 3 patients refused to participate, 10 patients were excluded because they were affected by a combined ADHD. Finally, 16 POMS and 20 ADHD patients were enrolled. All the patients enrolled completed the study procedures and assessments. No patients with POMS reported relapses during the study period. There were no drop-out (Fig. 1).

The comparison of the baseline cognitive performances between the 2 disease conditions is reported in Table 1. ADHD patients showed significantly worse attention, concentration, processing speed, working memory and cognitive flexibility performances at baseline as measured by the SDMT, TMT-A and TMT-B ($p < 0.05$) in comparison to POMS patients.

Comparisons of baseline demographic, clinical characteristics, neuropsychological performances (NP) of POMS, and ADHD subgroups underwent ST and n-ST are reported in Tables 2 and 3, respectively. At baseline, no differences were found between the 2 treatment arms regarding sex, age, and in terms of NP performances. The mean \pm SD, median (min-max) age, disease duration and EDSS score of the entire POMS cohort were: 15.8 ± 1.7 years, 16.4 (12.4–17.9); 3.4 ± 3.0 years, 2.4 (0.1–10.5); 2.3 ± 0.9 EDSS score, 2.25 (1–3.5), respectively. All POMS patients were under stable (at least 6 months) first line DMTs. The mean \pm SD, median (min-max) age of the entire ADHD cohort were: 11.2 ± 2.5 years, 11.7 (7.4–17.6). No ADHD patients received psychoactive medications during the study period.

Cognitive performances in POMS

The NP before and after the cognitive training are reported in Table 4.



After the 3-month cognitive training, the ST exposure was associated to a significantly more pronounced reduction of the CII in comparison to the nST exposure ($p < 0.0001$) (Table 4 and Fig. 2a). POMS patients treated with ST had a significant higher improvement in their performances on SDMT ($p < 0.0001$), TOL ($p < 0.0001$), TMT-A ($p = 0.01$), SPART ($p = 0.004$) and SPART-D ($p = 0.004$) in comparison to those treated with nST (Table 4 and Fig. 3).

Cognitive performances in ADHD

Unlike in POMS, the difference between the ST and nST subgroups in ADHD patients on the global

neuropsychological performances measured by the CII did not reach statistical significance ($p = 0.06$) (Table 4 and Fig. 2b). A greater effect of the ST in comparison to the nST in ADHD patients was found only for performances on SDMT ($p = 0.004$), and SPART-D ($p = 0.04$) (Table 4 and Fig. 4). No differences were found between the two treatment arms in other cognitive domains.

The generalized linear model performed to evaluate the magnitude of the effect of the ST in both the disease groups demonstrated a significant greater reduction of the CII in POMS than that observed in ADHD patients ($p = 0.042$).

Table 1 Comparison of baseline neuropsychological performances in POMS and ADHD

Cognitive test	POMS	ADHD	P value
SRT- LTS	27.3 (10.1); 24 (9–52)	30.9 (6.8); 28.5 (20–44)	0.1
SRT – CLTR	21.3 (9.1); 21.5 (2–40)	21.9 (8.6); 21 (7–44)	1.0
SPART	21.0 (3.8); 22 (15–25)	19.8 (4.6); 20 (13–30)	0.2
SDMT	22.5 (4.5); 23 (16–29)	17.3 (8.5); 14.5 (8–43)	0.002
Trail Making Test A ^a	37.0 (10.6); 37.5 (21–58)	54.0 (23.1); 57 (8–100)	0.02
Trail Making Test B ^a	108.1 (68.6); 97.5 (0–233)	182.7 (64.9); 188 (96–333)	0.004
SRT-D	6.0 (2.2); 6 (0–9)	6.7 (2.0); 7 (3–11)	0.5
SPART-D	6.9 (1.2); 7 (5–10)	6.5 (2.3); 5.5 (4–10)	0.2
Tower of London ^a	15.7 (5.8); 14 (10–31)	14.7 (10.1); 14 (0–33)	0.7
Cognitive Impairment Index	22.4 (3.1); 22 (19–29)	23.6 (4.2); 24 (16–30)	0.3
CDI	12.9 (6.9); 15 (0–25)	13.4 (7.0); 14.5 (2–25)	1.0

Data are reported as mean (SD), Median (min – max)

Abbreviations: POMS pediatric onset multiple sclerosis, ADHD Attention Deficit Hyperactivity Disorder, ST specific training, nST non specific training, SRT-LTS Selective Reminding Test Long Term Storage, SRT-CLTR Selective Reminding Test – Consistent Long-Term Retrieval, SRT-D Selective Reminding Test–Delayed, SPART Spatial Recall Test, SPART-D Spatial Recall Test–Delayed, SDMT Symbol Digit Modalities Test, CDI Children's Depression Inventory

^aUnit of measure: time in seconds

Table 2 Baseline demographic and clinical characteristics of POMS and ADHD subgroups underwent specific and non specific training

POMS			
Variable	Specific training (n = 8)	Non specific training (n = 8)	p - value (t, U, or Fisher's exact test)
Sex (F/M)	5/3	4/4	1.0
Age, years	15.8 (2.0)	15.7 (1.5)	1.0
Disease Duration, years	3.5 (3.5)	3.3 (2.6)	0.96
Handedness, n. right-handed (%)	7 (87.5)	8 (100)	0.97
Disease modifying therapy, n			
Nothing	2	2	0.67
Interferon beta	6	4	
Glatiramer Acetate	0	1	
Natalizumab	0	1	
Annualized Relapse Rate	0.4 (0.5)	0.3 (0.5)	0.72
EDSS, median (min - max)	2.0 (1.0–3.5)	3.0 (1.0–3.5)	0.28
ADHD			
Variable	Specific training (n = 10)	Non specific training (n = 10)	
Sex (F/M)	0/10	2/8	0.47
Age, years	11.5 (3.0)	11.3 (2.0)	0.58
Handedness, n. right-handed (%)	9 (90)	9 (90)	1.0

Abbreviations: POMS pediatric onset multiple sclerosis, EDSS Expanded Disability Status Scale, ADHD Attention Deficit Hyperactivity Disorder

Discussion

This pilot study confirms the presence of a cognitive impairment in children affected by ADHD and POMS, with a more severe deficit of attention, concentration, processing speed, working memory and cognitive flexibility performances in ADHD than POMS.

Most importantly, the results of this controlled, double-blind, randomized study, demonstrate that a home-based computerized training of specific aspects of attention, the APT, has a different effect on cognitive functions in POMS and ADHD patients.

In POMS, APT improves in the short-term the global cognitive functions and individual performances in several cognitive domains. POMS patients improved in SDMT and TMT-A performances, which evaluate concentration, attention, processing speed, working memory and cognitive flexibility.

Furthermore, we observed an improvement also in cognitive domains not specifically trained by the program. Patients with POMS improve their executive functioning, planning strategies, visuo-spatial memory and delayed recall performances, as assessed by TOL, SPART and SPART-D test scores.

These findings indicate that APT induces both a near transfer effect in the domain of the planning strategies and a far transfer effect in the domain of visuo-spatial memory.

Interestingly a previous RCT [18], which assessed the efficacy of APT in adult MS, found a significant improvement exclusively on tasks of sustained attention such as

the PASAT and, marginally, the SDMT. No effect was detected on tests tapping other aspects of attention or other cognitive domains. The different effect of APT in POMS and adult MS provides support for the idea that restorative exercises started during the developmental age can induce a greater strengthening of the key brain networks implicated in attention processing. This can be explained by a greater brain plasticity in younger patients. Indeed, recent RCTs focused on attention rehabilitation and assessing fMRI outcomes demonstrated that intensive ST improved some aspects of cognitive functioning and also affected neural plasticity and increased fMRI brain activity in the cerebellum of adult MS patients with impaired attention and/or memory [19, 49].

Therefore, early detection and management of cognitive dysfunction is momentous in POMS.

Longitudinal studies in patients with POMS have provided conflicting results about the evolution of the cognitive deficits. Most of them [10, 11] have shown a stability in cognitive performance in POMS over time suggesting a lack of the expected age-related cognitive development. An Italian study lasting over 5 years demonstrated that cognitive deficits, mainly in visual-spatial learning and expressive language, tend to worsen over time, affecting the patient's academic and professional achievements [13, 50].

Different studies have provided some information about the predictive factors associated to the longitudinal evolution of the cognitive performances in patients with POMS. Till C and colleagues reported that a longer

Table 3 Baseline neuropsychological performances in POMS and ADHD subgroups underwent specific (ST) and non specific (nST) trainings

POMS			
Cognitive test	ST	nST	P value
SRT- LTS	29.9 (12.6)	24.6 (6.5)	0.2
SRT - CLTR	22.1 (11.0)	20.4 (7.5)	0.6
SPART	19.3 (4.4)	22.8 (2.0)	0.1
SDMT	24.5 (4.6)	20.5 (3.6)	0.1
Trail Making Test A	39.4 (11.5)	34.6 (9.8)	0.5
Trail Making Test B	108.4 (61.4)	107.9 (79.4)	1.0
SRT-D	6.3 (2.8)	5.8 (1.5)	0.2
SPART-D	6.8 (1.0)	7.0 (1.4)	1.0
Tower of London	15.8 (5.4)	15.6 (6.6)	0.8
Cognitive Impairment Index	22.5 (3.9)	22.3 (2.4)	0.9
CDI	14.5 (7.6)	11.4 (6.3)	0.4
ADHD			
Cognitive test	ST	nST	P
SRT- LTS	32.2 (6.9)	29.6 (6.7)	0.4
SRT - CLTR	25.5 (8.2)	18.3 (7.8)	0.1
SPART	18.3 (4.9)	21.2 (4.2)	0.1
SDMT	17.1 (5.5)	17.4 (11.1)	0.4
Trail Making Test A	61.9 (17.3)	46.1 (26.2)	0.1
Trail Making Test B	160.8 (45.4)	204.6 (75.9)	0.3
SRT-D	7.1 (2.1)	6.2 (1.8)	0.6
SPART-D	6.0 (2.2)	6.9 (2.3)	0.2
Tower of London	15.9 (9.1)	13.5 (11.3)	0.5
Cognitive Impairment Index	23.8 (4.7)	23.4 (4.0)	0.8
CDI	13.5 (7.6)	13.2 (6.7)	0.9

Abbreviations: POMS pediatric onset multiple sclerosis, ADHD Attention Deficit Hyperactivity Disorder, ST specific training, nST non specific training, SRT-LTS Selective Reminding Test Long Term Storage, SRT-CLTR Selective Reminding Test – Consistent Long-Term Retrieval, SRT-D Selective Reminding Test–Delayed, SPART Spatial Recall Test, SPART-D Spatial Recall Test–Delayed, SDMT Symbol Digit Modalities Test, CDI Children's Depression Inventory

disease duration was associated with greater deterioration in visuomotor integration and an increased lesion volume was associated with slower psychomotor speed over a 1 year follow-up [11]. Recently, Pastò and colleagues reported that the major predictor of cognitive stability or improvement over a follow-up longer than 4 years in patients with POMS was a higher cognitive reserve [51].

The availability of an easy to use and home-based cognitive training is of paramount importance in this pediatric population. In this light, another recent study investigated the feasibility of a home-based computerized program for working memory training in patients with POMS [52] supporting the use of this kind of approach to treat cognitive dysfunction in this specific population. Moreover,

given all these premises, a computerized cognitive training would be recommended for all the patients with POMS as a tool to maintain level of cognitive functioning (i.e. before impairment becomes apparent) and to increase the cognitive reserve.

Referring to the ADHD population, our results show that APT is effective in improving the targeted cognitive domains which has been specifically trained by the program. In this population, APT determines only a slight improvement of the global cognitive functions, as measured by the reduction of the CII. These findings indicate that there is a less pronounced transfer effect in ADHD patients in comparison to POMS patients after the exposure to a cognitive training with a focus on attention. Although the different effect of the cognitive training in the two disease groups may be due to the more severe baseline cognitive impairment in ADHD patients, these results seem to be consistent with the majority of previous studies on cognitive rehabilitation which trains attention in ADHD patients [22, 28, 30, 53]. In these studies it has been shown an improvement of the targeted ability with only a limited transfer to other cognitive performances. As a matter of fact, by considering attention as the key impairment in ADHD, the main selection criteria in such studies were based on the central-deficit assumption [29]. Moreover, the theoretical premise of these studies was that the remediation of attention deficits could reduce ADHD associated cognitive and behavioral difficulties [28, 30, 33, 53]. There is no a specific profile of executive functions impairment in ADHD [54].

Therefore, it is necessary to find out other approaches focusing on multiple neuropsychological processes to optimize the transfer of effect from cognitive deficit to clinical symptoms in ADHD.

It is noteworthy that in our study design we have also included a comparative training based on a nonspecific reinforce of text reading, comprehension and verbal performances that could have had an impact on the global cognitive functions [55, 56]. This could explain why in the nST group we have observed an improvement of the CII, although not statistically significant. These results are in line with previous findings in adult onset MS treated with the same cognitive training [18].

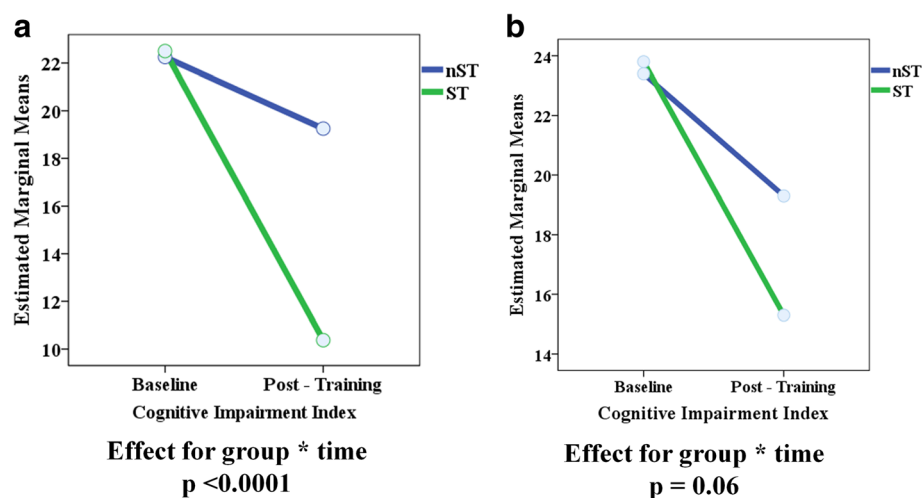
Several limitations of this study deserve discussion. First, the inclusion of two very diverse patient populations (POMS and ADHD), with small sample sizes in each group, may limit the generalizability of our findings. Secondly, the mean EDSS score level of our POMS cohort is slightly higher than that previously reported in other cohorts. This was due to the inclusion criteria which required only the enrollment of patients with a discrete cognitive deficit (with impairment in at least 2/4 attention) and thus with a slightly more severe course. Thirdly, we did not measure effort assessment (e.g.,

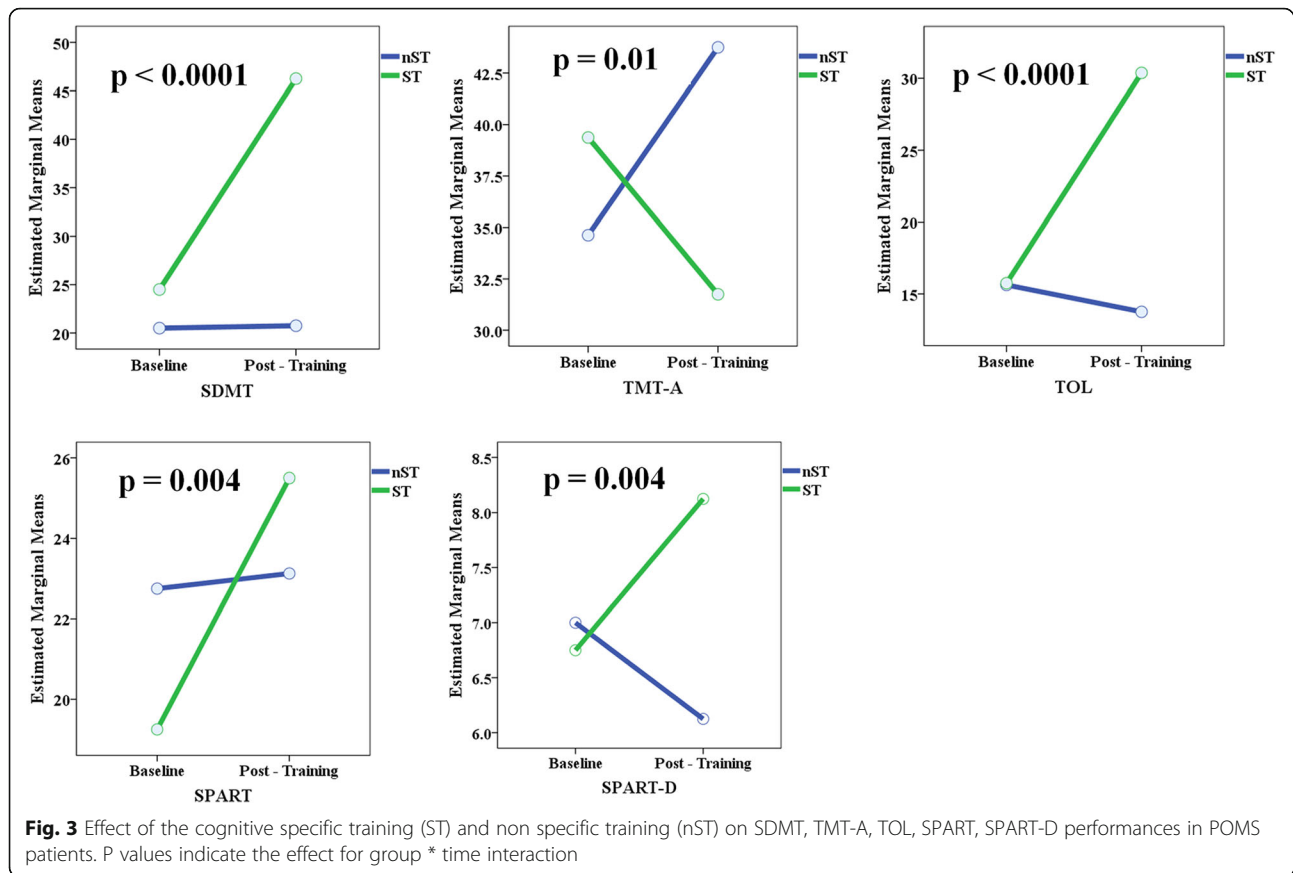
Table 4 Impact of 3-month ST and nST training on cognitive performances in POMS and ADHD groups

Cognitive Test	ST		nST		<i>p</i> -value
	Baseline	Post - Treatment	Baseline	Post - Treatment	Effect for group × time
POMS					
SRT- LTS	29.9 (12.6)	35.4 (5.0)	24.6 (6.5)	28.9 (4.2)	0.72
SRT - CLTR	22.1 (11.0)	27.3 (5.2)	20.4 (7.5)	22.6 (6.1)*	0.30
SPART	19.3 (4.4)	25.5 (1.7)*	22.8 (2.0)	23.1 (1.9)	0.004
SDMT	24.5 (4.6)	46.3 (6.7)*	20.5 (3.6)	20.8 (4.1)	< 0.0001
Trail Making Test A	39.4 (11.5)	31.8 (6.6)	34.6 (9.8)	43.8 (10.2)	0.01
Trail Making Test B	108.4 (61.4)	70.5 (32.1)	107.9 (79.4)	64.0 (61.3)	0.87
SRT-D	6.3 (2.8)	8.1 (0.8)	5.8 (1.5)	6.4 (0.7)	0.28
SPART-D	6.8 (1.0)	8.1 (0.8)*	7.0 (1.4)	6.1 (0.8)	0.004
Tower of London	15.8 (5.4)	30.4 (2.5)*	15.6 (6.6)	13.8 (2.0)	< 0.0001
Cognitive Impairment Index	22.5 (3.9)	10.4 (3.3)*	22.3 (2.4)	19.3 (2.2)*	< 0.0001
ADHD					
SRT- LTS	32.2 (6.9)	34.9 (7.3)	29.6 (6.7)	30.5 (6.8)	0.50
SRT - CLTR	25.5 (8.2)	27.3 (5.0)	18.3 (7.8)	22.6 (4.4)	0.51
SPART	18.3 (4.9)	22.0 (4.2)*	21.2 (4.2)	21.2 (3.7)	0.06
SDMT	17.1 (5.5)	35.8 (7.2)*	17.4 (11.1)	22.1 (11.4)	0.004
Trail Making Test A	61.9 (17.3)	38.4 (22.2)*	46.1 (26.2)	31.5 (16.9)	0.51
Trail Making Test B	160.8 (45.4)	108.7 (61.0)*	204.6 (75.9)	178.0 (131.11)	0.51
SRT-D	7.1 (2.1)	6.8 (2.0)	6.2 (1.8)	6.6 (1.0)	0.41
SPART-D	6.0 (2.2)	7.7 (2.0)*	6.9 (2.3)	6.6 (1.2)	0.04
Tower of London	15.9 (9.1)	30.5 (11.0)*	13.5 (11.3)	17.9 (12.6)	0.27
Cognitive Impairment Index	23.8 (4.7)	15.3 (5.6)*	23.4 (4.0)	19.3 (3.6)*	0.06

Abbreviations: POMS pediatric onset multiple sclerosis, ADHD Attention Deficit Hyperactivity Disorder, ST specific training, nST non specific training, SRT-LTS Selective Reminding Test Long Term Storage, SRT-CLTR Selective Reminding Test Consistent Long-Term Retrieval, SRT-D Selective Reminding Test-Delayed, SPART Spatial Recall Test, SPART-D Spatial Recall Test-Delayed, SDMT Symbol Digit Modalities Test, CDI Children's Depression Inventory

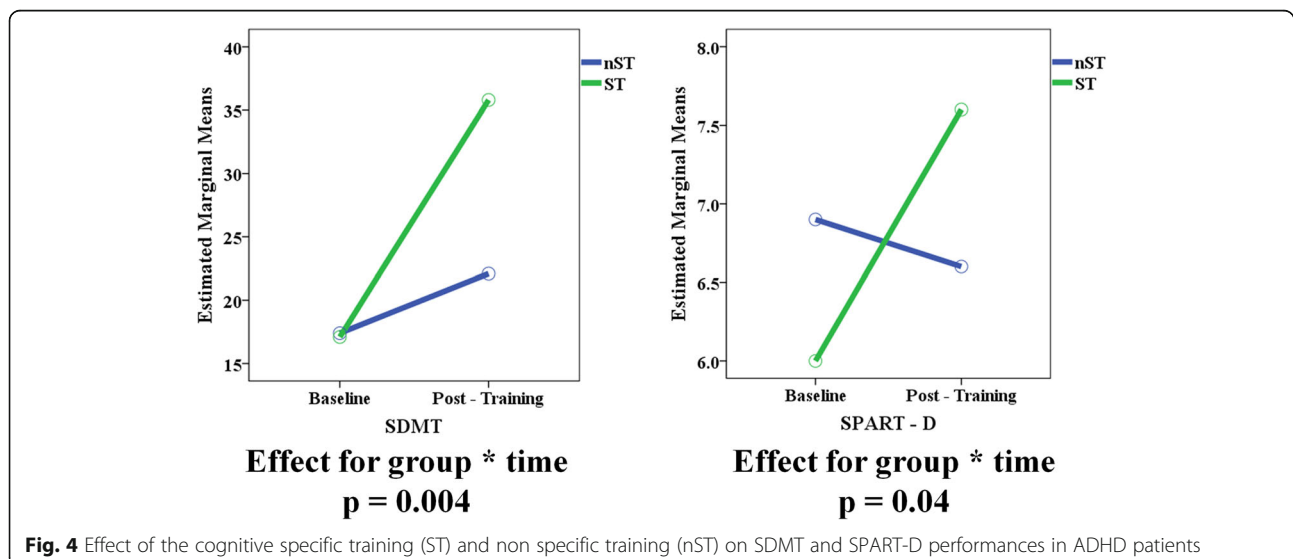
*Indicate significant Effect for time (Baseline vs Post - Treatment comparison); $p < 0.05$

**Fig. 2** Cognitive Impairment Index before and after the cognitive specific training (ST) and non specific training (nST) in POMS (a) and ADHD (b)



symptom validity measures), and most importantly we did not include measures of “clinically meaningful change” such as (e.g., school performance or parent reported behaviors) in the study protocol. Fourthly, we have applied the same cognitive battery to two different disease groups: POMS and ADHD. It is possible that the

outcome assessments performed during the RCT were not sensitive to deficits in ADHD, but we choose the outcomes more recommended in POMS (at least in Italy and Europe) [9, 12, 13] and for a better comparison between the two groups, we used the same outcome assessments also in ADHD patients.



Referring to the statistical analysis, we should mention that we did not perform a multiple comparisons correction, therefore there is a potential risk of false positive results. We did so because we don't think that the statistical approach of adjusting for multiple testing is necessary or even adequate. Reducing the type I error for null associations increases the type II error for those associations that are not null.

Finally, another limitation of this study should be discussed. The possibility that the positive effect of the ST we have observed is at least in part due to an expectancy effects among participants assigned to the ST.

However, this pilot study was designed for a fast evaluation of the efficacy of a cognitive training (in treated vs untreated patients) in the two different groups of pediatric patients (POMS or ADHD) with attention impairment. The internal validity and the consistency of the results are assured by a randomized controlled design and robust statistical analysis, which in part might mitigate all these limitations.

Conclusions

Our results indicate that a cognitive rehabilitation program that targets attention may be a suitable tool for improving global cognitive functioning in POMS patients, whereas it has a less pronounced transfer effect in ADHD patients. Future RCTs on larger populations of both POMS and ADHD patients, including a healthy subjects control group, clinical and fMRI outcomes, are needed to confirm the efficacy of cognitive rehabilitation programs. Furthermore, future studies aimed to evaluate the efficacy of computerized cognitive rehabilitation program on remediating attention deficits should include a more specific sustained attention task as efficacy measure. Studies aimed at identifying factors that influence transfer effects, as well the mechanism underlying these effects, especially in ADHD patients and in subpopulations of POMS with and without ADHD symptoms are desirable.

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; CDI: Children's Depression Inventory; nST: Non specific training; POMS: Pediatric onset multiple sclerosis; SDMT: Symbol Digit Modalities Test; SPART: Spatial Recall Test; SPART-D: Spatial Recall Test-Delayed; SRT-CTLR: Selective Reminding Test – Consistent Long-Term Retrieval; SRT-D: Selective Reminding Test-Delayed; SRT-LTS: Selective Reminding Test Long Term Storage; ST: Specific training

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MS recruited patients and collected, analysed and interpreted the data. RGV performed the neuropsychological evaluations and collected, analysed and interpreted the data. LM performed the study supervision and a critical revision of the manuscript for intellectual content. PI defined the study concept and design and collected, analysed and interpreted the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted with approval of the institutional review board (Comitato Etico Indipendente Azienda Ospedaliero-Universitaria Consorziata Policlinico - Approval Number: 0070059/CE). Parents of the participants signed an informed consent.

Competing interests

Marta Simone reports no disclosures.

Rosa Gemma Viterbo has received speaker honoraria from Biogen Idec and Teva.

Lucia Margari reports no disclosures.

Pietro Iaffaldano has served on scientific advisory boards for Biogen Idec and Bayer-Shering, and has received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Merck-Serono, Teva and Novartis.

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Poster presentation 80

Attention, time, numerosity, and math in children and adolescents with attention-deficit-hyperactivity disorder (ADHD)

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Introduction: Time, space, math, and numerosity are ubiquitous dimensions of human lives. An influential theory (ATOM) suggested that all these magnitudes may be encoded by a common neural mechanism, mainly located in the parietal cortex. However, firm evidence for such a generalized mechanism is still lacking. The aim of this study was to test the association of parietal functions in children and adolescents with ADHD.

Patients and method: Fourteen children and adolescents with ADHD and 14 typically developing children and adolescents, matched for age (8–16y) participated in this study. Inclusion criteria were a diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, an IQ more than 70, no neurological or sensory impairment, and no pharmacological treatment. Numerosity and time discrimination thresholds were psychophysically measured. Time was measured in the auditory domain and for both sub and supra second duration intervals. We also measured visuo-spatial sustained attention and symbolic math.

Results: Participants with ADHD performed worse than controls in auditory time perception (both intervals), visual sustained attention, and symbolic math. Visual numerosity estimation was instead relatively spared. Interestingly, numerosity and math skill were positively correlated. Moreover, those children having higher time impairment were not those showing worse attentional skills.

Conclusion: Our results generally confirm ATOM theory, but also show that selective impairments are possible. Moreover, given that time perception deficits do not depend on attention, our results suggest that ADHD may be characterized by

a specific time encoding deficit, together with impaired attention skills.



Age level vs grade level for the diagnosis of ADHD and neurodevelopmental disorders

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Abstract

A number of worldwide studies have demonstrated that children born later in the school year are more likely to receive an ADHD diagnosis than their same school-year peers. There is, however, variation in findings between countries. We aimed to confirm whether relative age is associated with ADHD diagnosis, with or without comorbidities, and to investigate whether relative age is associated with ADHD type and severity, and if this age relationship is in common with other neurodevelopmental disorder. We used the Lombardy Region's ADHD registry. Data on children aged 6 years and older from September 1, 2011 to December 31, 2017 were considered. We calculated incidence ratios to assess the inter-relations between relative age within the school year, using age at diagnosis of ADHD or of other psychiatric disorder, year of diagnosis, and total number of children born in Lombardy during the corresponding timeframe. Data on ADHD type, severity of diagnosed disorder clinical global impressions–severity scale, and repetition of a school-grade were also considered. 4081 children, 2856 of whom with ADHD, were identified. We confirmed that the cumulative incidence of ADHD diagnosis was greatest for younger children, in particular for boys, for whom the prevalence is greater. The relative age effect was not accounted for by ADHD comorbid disorders, ADHD of combined type or severity. The relative age effect was also observed for children with other neurodevelopmental disorders (without ADHD), with a similar profile as ADHD children: the incidence ratio was 1.78 (95% CI 1.07–2.97; $p < 0.0247$) for boys diagnosed before age ten. The findings have a potential implication for diagnostic and therapeutic practice, educational advice, and policies, besides to better plan and organize service systems and appropriately inform parents, children, and citizens.

Keywords Attention-deficit hyperactivity disorder · Age factors · Children · School · Italy · Epidemiology

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurobiological condition characterized by developmentally inappropriate and impairing patterns of inattention,

hyperactivity, and impulsivity [1]. ADHD symptoms usually become more evident in school-aged children, are more frequent in boys than girls, and tend to persist into adulthood [2]. The reported range in prevalence is very wide (from 0.2 to 34.5%), and heterogeneity in the methodological approaches used contributes to these differences [3]. ADHD diagnosis in children is a multiple-step process based on clinical evaluation, teacher ratings of behavior and performance in school, and parental rating [4]. Evidence of clinically significant impairment in social and school functioning is required for an appropriate diagnosis.¹

As for other psychiatric disorders occurring during the developmental age, the categorical and relatively simple symptomatological core of ADHD often does not appear alone. Frequently, a wide variety of concurrent psychiatric disorders contribute to the psychopathological status of children and adolescents with ADHD, with a well-established

The list of participants, in addition to the authors, is part of the Lombardy ADHD Group and is reported in the acknowledgements.

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consensus among authors that the presence of overlapping psychiatric disorders is more likely to be the rule than the exception [4–6]. The overall prevalence of psychiatric disorders associated with ADHD in children and adolescents ranges from about 40–80% depending on the sample [7–9], with higher rates in clinically referred ADHD children (67–87%) [5].

Youth with ADHD experience greater academic impairment, including lower grades, grade repetition, and school dropout than their peers, and medication efficacy in improving academic outcomes needs further evidence [10–16]. Furthermore, the association between relative age and ADHD has been reported, with the youngest children in the school year having 1.2–2.0 times increased risk of receiving an ADHD diagnosis or prescription [17, 18]. Relative age effects have been reported strong for learning disabilities but not for other disabilities [19], although attention and learning problems are on a continuum (and not simply present or absent) and usually coexist [20]. This relative age effect was shown consistently in countries with high prescribing rates for ADHD, resulting in concerns that ADHD might be overdiagnosed or misdiagnosed [16, 21]. This association and the risk of academic impairment may thus have an impact on maturity differences in the classroom and how they are evaluated and handled, and on the long-lasting negative effects on personal achievements and health outcomes [22, 23]. A large Finnish study spanning a 14-year period showed the association between relative age and age at ADHD diagnosis, in particular in children diagnosed with ADHD before the age of ten, and showed for the first time that the association was not accounted for by comorbid disorders such as conduct disorder, oppositional defiant disorder (ODD), or learning disorder (LD) [24].

Younger children in a school year are at a slightly greater psychiatric risk than older children, not only of ADHD, but of different disorders [22], but interest has been growing in the influence of young relative age within the school year towards the diagnosis of ADHD [25]. Different countries use different cut-off dates for school entry, comparisons so between countries are illuminating. The matter is important because of the potential implications for diagnostic practice and educational advice and policies.

We, therefore, aimed to confirm the association between relative age (defined as the child's age within their school year) and ADHD in a different additional national context: if it is stronger at the younger end of the school-age range, if comorbid disorders have a role, and if such an association is specific to ADHD with and without comorbidities or if it is present also with other mental disorders without ADHD.

Methods

This study was designed as a review of patient medical records identified from the regional ADHD Registry database. Written informed consent was obtained for all patients before collection data in the Registry. Data were anonymised prior to use for research purposes. Formal ethical review board approval was not required for the present analysis of the data. The present research was approved by the Institutional Review Board of the IRCCS Istituto di Ricerche Farmacologiche “Mario Negri” in Milan, Italy.

Data collection and participants

In June 2011, the official regional ADHD Registry was activated in Lombardy and was designed as a disease-oriented registry collecting information not only on ADHD patients treated with pharmacological therapy, but also on all patients who access ADHD centers for a diagnosis of suspected ADHD. Italian legislation [26] requires data on all ADHD patients receiving methylphenidate or atomoxetine treatment (the only two drugs licensed for ADHD in Italy) to be reported in the Registry. The regional Registry is part of a more general project aimed to ensure appropriate ADHD management for every child and adolescent once the disorder is suspected and reported, and includes commonly acknowledged diagnostic and therapeutic procedures as well as educational initiatives for health care workers (child neuropsychiatrists and psychologists) of the Lombardy Region's health care system who provide assistance to ADHD patients and their families [27–29].

The regional ADHD Registry represents a distinctive tool, internationally, aimed to ensure the appropriate care of, and the safety of drug use in, ADHD children [27–29]. All collected data, i.e., those concerning the diagnostic evaluation and the systematic monitoring assessments described, were analyzed monthly, and the findings were reported and periodically discussed with all 18 ADHD centers belonging to the Lombardy ADHD Group. This is a clinical multicenter study, in which all patients received a rigorous diagnostic assessment (according to national and international guidelines) [30, 31], approved by all involved clinicians and monitored by a registry-based data collection method.

In Italy, primary school enrolment begins during the calendar year in which a child turns 6 years old, with the school year starting in mid-September. The eldest children in a school year are, therefore, born in January (aged 6 years and 8 months) and the youngest children are born in December (aged 5 years and 8 months). Because the aim of our study was to investigate the effect of relative

age after starting school, we included children diagnosed with ADHD from age 6 years onwards. Seven mandatory steps were applied at the time of diagnostic evaluation: (1) the clinical anamnestic and psychiatric interview; (2) the neurological examination; (3) the evaluation of cognitive level by Wechsler Scales; (4) the Schedule for affective disorders and schizophrenia for school-age children (K-SADS) for a complete psychopathology overview and comorbidity assessment; (5) the child behavior checklist (CBCL) and/or the conners' parent rating scale-revised (CPRS-R) rated by parents; (6) the conners' teacher rating scale-revised (CTRS-R) rated by teachers; and (7) the clinical global impressions–severity scale (CGI-S) to quantify symptom severity. This diagnostic pathway was agreed on, approved, and shared by all participating ADHD centers [5].

We identified the number of children born in each month during the study period from the regional database that contains the demographic information of the population and which is routinely updated.

Type of ADHD (according to the items of the *DSM-IV-TR*) and CGI-Severity scale score (for all diagnosed children) were considered for the present investigation, as well as the cases of school rejection.

Procedures

We compared all children diagnosed with ADHD to children with other diagnosed disorders except ADHD (“without ADHD” group) for the association with relative age. ADHD subtype was also evaluated. To assess the possible contribution of comorbid disorders to the association between relative age and diagnosed disorder, we then stratified cases according to the presence of ADHD.

Statistical analyses

We estimated the cumulative incidence of ADHD (and corresponding 95% CIs) with a Poisson-regression model, assuming a Poisson error distribution. We initially calculated the cumulative incidence of ADHD and of other mental disorders without ADHD per 1000 births, in the total sample and, separately, for boys and girls, for each month of birth and by blocks of 4 months (i.e., January–April, May–August, and September–December). The numerator was the number of children with ADHD and without ADHD born in a specific period and the denominator was the total number of children born in Lombardy during the corresponding timeframe. Next, to assess whether a possible relative age effect was a function of the presence of a comorbid disorder, we estimated the cumulative incidence for children with and without comorbidity. We estimated incidence ratios of ADHD or other mental disorders separately for boys and

girls, for each birth month, and we compared every month with births in January. To improve the precision of these estimates and better reflect the way in which adults might think of children within a school year (i.e., as one of the eldest or one of the youngest in the class), we estimated incidence ratios for children born within 4-month periods (January–April, May–August, and September–December), and compared the two younger periods with the eldest group of children (i.e., those born in January–April). Furthermore, to assess whether any relative age effect was affected by actual age at diagnosis (with a greater effect at the younger end of the school-age range), we stratified the sample on median age at diagnosis (age 9 years) as either age 7–9 years or age 10 years or older. We estimated incidence ratios of ADHD and disorders without ADHD by comparing the youngest and middle groups, by relative age, with those born during January–April. Children diagnosed between 1998 and 2003 who were aged 7–9 years at diagnosis were born between 1991 and 1996, whereas those aged 10 years or older were born between 1991 and 1993. Cross tabulations with Chi square, when appropriate, were made to explore the univariate associations. We performed statistical analyses with SAS version 9.4.

Results

Between September 1, 2011, and December 31, 2017, 4081 children from the 18 ADHD regional centers were evaluated for ADHD. 11 children with severe or profound intellectual disability (eight with ADHD) were excluded, resulting in a sample of 4070 children (M: 3439, 85%; F: 631, 15%).

2856 of 4070 subjects evaluated (70%) met the diagnostic criteria for ADHD (M: 2458, 86%; F: 398, 14%). The mean age at ADHD diagnosis in the sample was 9.3 years (SD 2.5, range 6–17). 1669 of 2856 ADHD patients (58%) had ADHD of combined type (ADHD-C), 934 (33%) of inattentive type (ADHD-I), and 253 (9%) of hyperactive/impulsive type (ADHD-H).

Incidence ratios for ADHD diagnosis among children born later in the year were generally higher than those for children born earlier in the year (Table 1). Compared with boys born in January, incidence ratios increased from 1.11 (95% CI 0.57–2.16) for those born in February to 2.25 (1.21–4.19; $p < 0.009$) for births in December. Among girls, similar increased incidence ratios were noted although not statistically significant. Figure 1 provides a visual presentation of the cumulative trend of ADHD incidence among boys and girls, by birth month.

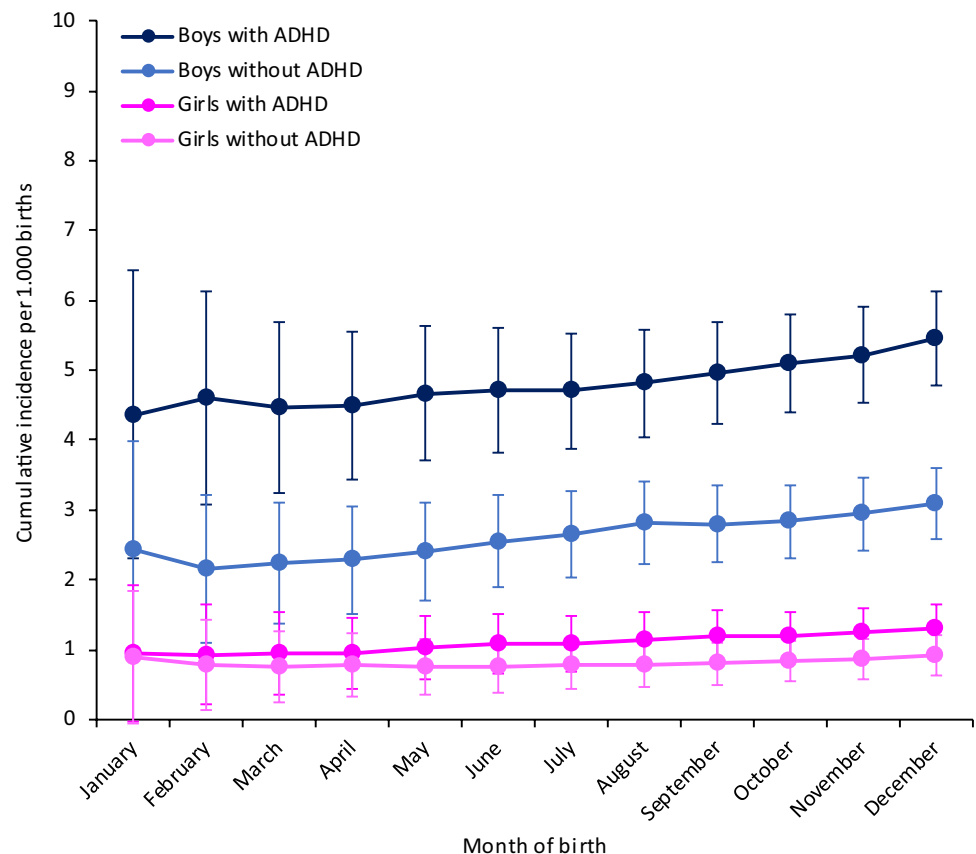
Similar features were observed for the 1214 children (M: 981, 80%; F: 233, 20%; mean age at diagnosis in the sample was 9.7 years, SD 2.4, range 6–17) without ADHD or with subthreshold ADHD (Table 2; Fig. 1), in particular for boys.

Table 1 Incidence ratios of ADHD per 1000 births by month of birth, in girls and boys

	Boys (N=2458)			Girls (N=398)		
	Cases (%)	Incidence ratio (95% CI)	p	Cases (%)	Incidence ratio (95% CI)	p
January	170 (7)	Reference		25 (6)	Reference	
February	159 (6)	1.11 (0.57–2.16)	0.7594	21 (5)	1.06 (0.24–4.62)	0.9367
March	163 (7)	0.6 (0.49–1.90)	0.9162	22 (6)	1.06 (0.25–4.53)	> 0.9999
April	169 (7)	1.07 (0.54–2.08)	0.8547	29 (7)	0.99 (0.22–4.47)	> 0.9999
May	194 (8)	1.24 (0.66–2.34)	0.5008	33 (8)	1.26 (0.32–4.98)	0.8580
June	203 (8)	1.16 (0.60–2.23)	0.6663	28 (7)	1.43 (0.36–5.67)	0.6926
July	211 (9)	1.06 (0.55–2.04)	0.8544	31 (8)	1.19 (0.30–4.80)	> 0.9999
August	231 (9)	1.30 (0.70–2.43)	0.4099	45 (11)	1.77 (0.49–6.44)	0.7768
September	225 (9)	1.39 (0.75–2.57)	0.2911	38 (10)	1.54 (0.41–5.87)	0.9816
October	228 (9)	1.44 (0.78–2.65)	0.2455	41 (10)	1.24 (0.31–4.94)	0.7982
November	246 (10)	1.55 (0.84–2.87)	0.1619	49 (12)	2.12 (0.59–7.57)	0.2375
December	259 (11)	2.25 (1.21–4.19)	0.0087	36 (9)	2.01 (0.50–8.06)	0.3138

ADHD attention-deficit hyperactivity disorder

Fig. 1 Cumulative incidence of ADHD and other psychiatric disorders, by month of birth and sex. Data points depict the cumulative incidence per 1000 births, and error bars represent the 95% CI. ADHD attention-deficit hyperactivity disorder



The small numbers, although respect a monthly increasing trend during the year, limit the statistical significance. Overall, LD (57%), anxiety disorders (17%), sleep disorders (14%), and ODD (10%) were the most frequent disorders in subjects without ADHD. The small numbers limit further stratified analyses.

Table 3 shows incidence ratios of ADHD among boys and girls by 4-month periods (January–April, May–August, and September–December). Compared with the oldest boys in each school year (i.e., those born January–April), the incidence ratio of ADHD diagnosis for the youngest boys in the school year (i.e., those born

Table 2 Incidence ratios of without ADHD per 1000 births by month of birth, in girls and boys

	Boys (<i>N</i> =981)			Girls (<i>N</i> =233)		
	Cases (%)	Incidence ratio (95% CI)	<i>p</i>	Cases (%)	Incidence ratio (95% CI)	<i>p</i>
January	67 (7)	Reference		20 (9)	Reference	
February	49 (5)	0.78 (0.29–2.07)	0.6173	12 (5)	0.78 (0.15–4.09)	0.8377
March	67 (7)	1.01 (0.41–2.46)	0.9902	18 (8)	0.79 (0.16–4.03)	> 0.9999
April	65 (7)	1.04 (0.42–2.56)	0.9325	12 (5)	0.99 (0.21–4.71)	> 0.9999
May	79 (8)	1.16 (0.49–2.73)	0.7407	18 (8)	0.74 (0.14–3.75)	> 0.9999
June	86 (9)	1.37 (0.59–3.18)	0.4656	16 (7)	0.88 (0.18–4.39)	> 0.9999
July	95 (10)	1.34 (0.58–3.05)	0.4906	22 (9)	1.06 (0.24–4.66)	> 0.9999
August	110 (11)	1.57 (0.70–3.50)	0.2676	18 (8)	0.88 (0.19–4.21)	> 0.9999
September	78 (8)	1.10 (0.46–2.61)	0.8259	21 (9)	1.07 (0.24–4.78)	0.9328
October	86 (9)	1.24 (0.53–2.88)	0.6200	22 (9)	1.28 (0.31–5.31)	> 0.9999
November	108 (11)	1.72 (0.77–3.86)	0.1797	28 (12)	1.30 (0.30–5.55)	> 0.9999
December	91 (9)	2.21 (0.96–5.07)	0.0564	26 (11)	2.08 (0.50–8.65)	0.6680

Table 3 Incidence ratios of ADHD and without ADHD per 1000 births by month of birth, in girls and boys

ADHD						
	Boys (<i>N</i> =2458)			Girls (<i>N</i> =398)		
	Cases (%)	Incidence ratio (95% CI)	<i>p</i>	Cases (%)	Incidence ratio (95% CI)	<i>p</i>
January–April	661 (27)	Reference		97 (24)	Reference	
May–August	839 (34)	1.15 (0.84–1.59)	0.3858	137 (34)	1.37 (0.69–2.72)	0.3593
September–December	958 (39)	1.54 (1.13–2.09)	0.0058	164 (41)	1.64 (0.84–3.22)	0.1441
Without ADHD						
	Boys (<i>N</i> =981)			Girls (<i>N</i> =233)		
	Cases (%)	Incidence ratio (95% CI)	<i>p</i>	Cases (%)	Incidence ratio (95% CI)	<i>p</i>
January–April	248 (25)	Reference		62 (27)	Reference	
May–August	370 (38)	1.42 (0.93–2.17)	0.1056	74 (32)	1.00 (0.44–2.25)	0.9971
September–December	363 (37)	1.55 (1.01–2.38)	0.0418	97 (42)	1.53 (0.72–3.28)	0.2670

Month of birth was categorized into three groups of relative age

ADHD attention-deficit hyperactivity disorder

September–December) was 1.54 (95% CI 1.13–2.09; $p < 0.0058$). The corresponding incidence ratio for girls was 1.64 (0.84–3.22). A similar picture was observed for non-ADHD diagnosed children. Concerning the type of ADHD, the incidence ratio of ADHD diagnosis for the youngest boys in the school year (i.e., those born September–December) compared with the oldest children was 1.58 (95% CI 1.10–2.29; $p < 0.0139$) for children with a disorder of combined type (ADHD-C). No statistical significance was observed for the other two types of ADHD, as well as no relative age effect in ADHD risk according to CGI-S score (less or ≥ 5) was noted.

A relative age effect was noted among children who received a diagnosis of ADHD at age 6–9 years (Table 4). No increase in the incidence ratio for ADHD diagnosis was recorded, however, among children diagnosed at a later age

(10 years or older). A similar trend was also observed for the group of children with other diagnosed disorders.

Of 2856 ADHD children, 834 (29%) received a diagnosis of ADHD only, while 2022 (71%) had at least one comorbid psychiatric disorder (OR 1.67, IC 1.46–1.93). Comorbid psychiatric disorders were more frequent in patients with ADHD-C subtype (OR 1.36, IC 1.16–1.60), and in ADHD patients with a CGI-S score equal to or greater than 5 than patients with only ADHD or non-ADHD ($\chi^2 222$, $p < 0.0001$).

Of the 3574 patients with at least one psychiatric disorder, 834 (23%) were diagnosed only with ADHD and 523 (15%) only with one other psychiatric disorder, while 2217 (62%) had two or more mental disorders (of whom 2022 also had ADHD). The rate of ODD (16 vs 10%; $p < 0.0001$) was significantly higher in ADHD patients, while an inverse data

Table 4 Incidence ratios of ADHD and without ADHD by year of diagnosis, age at first diagnosis, and month of birth

ADHD						
	Age 6–9 years (<i>N</i> = 1715)			Age 10–17 years (<i>N</i> = 1141)		
	Cases (%)	Incidence ratio (95% CI)	<i>p</i>	Cases (%)	Incidence ratio (95% CI)	<i>p</i>
January–April	442 (26)	Reference		316 (28)	Reference	
May–August	549 (32)	1.20 (0.82–1.75)	0.3404	427 (37)	1.17 (0.77–1.76)	0.4668
September–December	724 (42)	1.69 (1.18–2.43)	0.0038	398 (35)	1.28 (0.85–1.94)	0.2354
without ADHD						
	Age 6–9 years (<i>N</i> = 650)			Age 10–17 years (<i>N</i> = 564)		
	Cases (%)	Incidence ratio (95% CI)	<i>p</i>	Cases (%)	Incidence ratio (95% CI)	<i>p</i>
January–April	157 (24)	Reference		153 (27)	Reference	
May–August	218 (34)	1.26 (0.74–2.15)	0.3974	226 (40)	1.34 (0.78–2.28)	0.2872
September–December	275 (42)	1.78 (1.07–2.97)	0.0247	185 (33)	1.27 (0.73–2.22)	0.3914

Age at diagnosis splits into age 6–9 and age ≥ 10 years. Month of birth was categorized into three groups of relative age

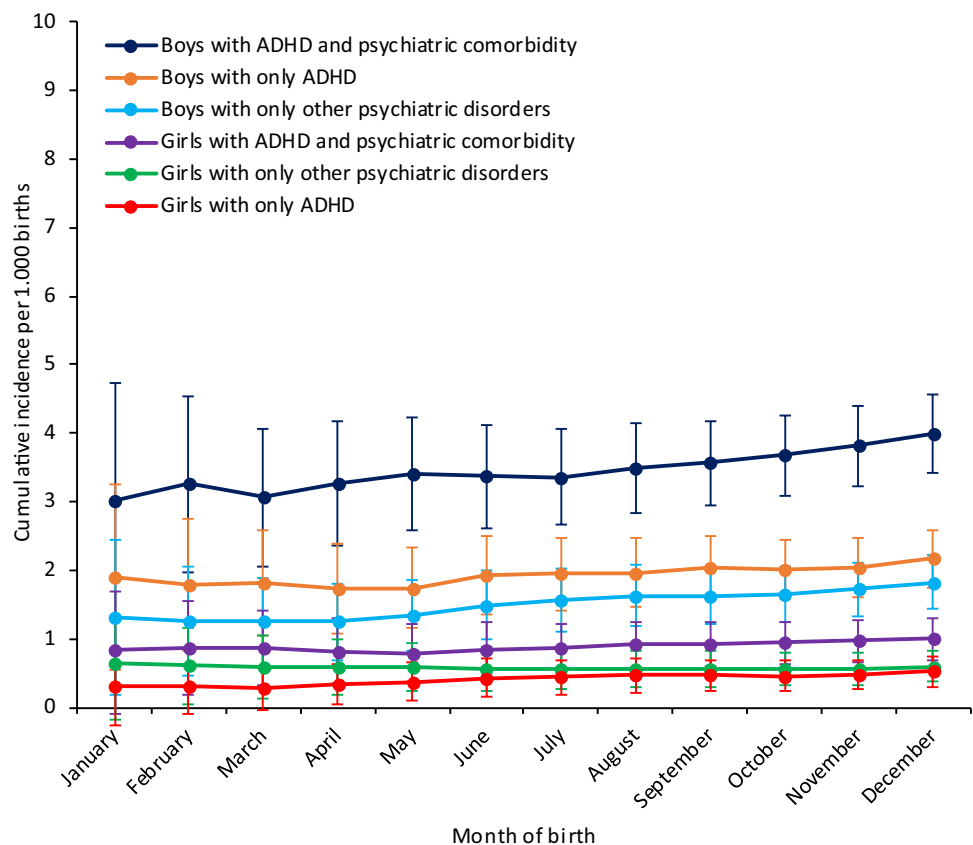
ADHD attention-deficit hyperactivity disorder

proportion was observed for LD (40 vs 57%; $p < 0.0001$), and anxiety disorders (7 vs 17%; $p < 0.0001$). Similar rates (14%) between the two groups were observed for sleep disorders.

Figure 2 shows the cumulative incidence of ADHD among children with and without comorbid or other

psychiatric disorders by birth month. For all six groups of children, the cumulative incidence of diagnosis increased for those born later in the year, with the highest proportion noted among those born in December. Compared with the oldest boys in each school year (i.e., those born January–April), the incidence ratio of ADHD diagnosis for the

Fig. 2 Cumulative incidence of ADHD in children with and without comorbid or other psychiatric disorders, by month of birth and sex. Data points depict the cumulative incidence per 1000 births, and error bars represent the 95% CI. *ADHD* attention-deficit hyperactivity disorder



youngest boys in the school year (i.e., those born September–December) was 1.55 (95% CI 1.08–2.23; $p < 0.0163$) for boys with ADHD and psychiatric comorbidity, and 1.80 (95% CI 1.02–3.18; $p < 0.0399$) for boys with only other psychiatric disorders. For both boys with only ADHD and for all girls, the noted relative age effect was not statistically significant. Similar results were seen among the youngest boys with ADHD and a LD (the most frequent disorder in the studied population) with an incidence ratio of 1.71 (95% CI 1.06–2.75; $p < 0.0254$).

More ADHD-C patients received drug prescription treatments (methylphenidate) at the time of the diagnosis than ADHD-I or ADHD-H patients (29% vs 12%; incidence ratio of 2.98, 95% CI 2.43–3.66; $p < 0.0001$), but no association with younger relative age in the school year was found (Chi-square test, $p = 0.9645$). Similarly, the incidence ratio of ADHD patients with a CGI-S score equal to or greater than five than patients with a lower score receiving drug prescriptions was 6.61 (95% CI 5.42–8.07; $p < 0.0001$), but no association was observed with patient's relative age at school (Chi-square test, $p = 0.9019$).

3747 of the 4070 subjects considered had completed at least their first year of school at the time of evaluation, and 5.7% had repeated a grade. The rate was double for patients diagnosed with other psychiatric disorders alone (7.2%) or with ADHD (6.5%) compared to children who received a diagnosis of ADHD only (3.4%) or no psychiatric diagnosis (3.6%). The incidence of grade repetition for the youngest children (i.e., those born September–December) was slightly higher than those born in January–April for both children with (0.34 vs 0.25) and without (0.28 vs 0.21) ADHD, although the small numbers limit statistical significance.

Discussion

In both boys and girls, the cumulative incidence of clinically diagnosed ADHD or other developmental disorders is greater among children within the school year, and the strength of the association is greater for children born during September–December. The association is independent of type of ADHD, presence of comorbidities, ADHD severity, and pharmacological prescription at the end of the diagnostic assessment. Furthermore, a risk that needs additional confirmation was observed for repeating a grade for the younger children.

Thus, our study findings confirm an association between younger relative age in the school year and diagnosis of ADHD, and that the findings are not affected by the presence of comorbidities in agreement with what was reported in other countries, in particular by the most recent and large study [24]. Furthermore, our study findings show that the association is not exclusive to ADHD, but can be observed

for other developmental disorders in children without ADHD. Thus, recent findings from a country with low diagnosis and prescribing rates for ADHD [27], and with 1-year early primary school enrolment than in other countries [24], not only add weight to the cumulative evidence in favour of a relative age effect for ADHD diagnosis, but add that such an effect is common for developmental disorders that appear at school, with the affected children directed for evaluation at the child psychiatric services.

The present study has several strengths. First, use of the same approach as a recent and well performed study [24] that also made the point about available evidence, i.e., to confirm the results and go further. Second, use of a specific ADHD register collecting information on an evidence-based and shared strategy for diagnostic evaluation and monitoring of the disorder among the 18 participating ADHD centers [27]. The use of an *ad hoc* clinical registry allows us to use more appropriate data without having to resort to proxies or face to many limitations as in the previous studies using administrative databases [27–29]. Third, since the data were collected as part of the monitoring of ADHD patients' care, information on educational characteristics and academic achievement was available. It was, therefore, possible to consider grade repetition as one of the potential adverse outcomes related to early access to school of these patients. In other studies, this was not adequately taken into account [24]. Furthermore, the potential misclassification of the previous studies [24] due to the fact that it was not known that young children had been held back a year at school has been overcome.

Our study also has some limitations. Since we have analyzed the cases from the regional ADHD registry database, there was no general population comparison in the present study. Although the registry on ADHD care collects information on children referred to all the 18 public, free regional ADHD centers, it misses those who were diagnosed, treated, and followed only in private practice. However, these cases should be a rarity, at least for ADHD diagnosis in Lombardy. Even if a third [32] or a fourth [33, 34] of referrals to child and adolescent mental health services are turn away, the regional ADHD project (and registry) is long lasting and represents a specific challenge, but also an opportunity, for the Healthcare Directorate of the Lombardy Region, involving all the child and adolescent mental health units of the health system. However, registry collects information only on patients who access ADHD centers for a diagnosis or treated with pharmacological therapy (in a country, where prescribing rates for ADHD are very low), this affects the absolute cumulative incidence rates that were low than those in other countries [24]. Second, even if the size of the population is one of the larger published studies, as is the large amount of information available, the evaluation of potential outcomes related to the association between

neurodevelopmental disorders and younger relative age in the school year needs further data collection, as well as different research approaches.

Our findings confirm [24] that the relative age effect was affected by a child's actual age, particular among the youngest children (aged 6–9 years), suggesting that relative age has a greater effect on clinical diagnosis in younger children attending school. Moreover, the effect also seemed to decline with age supporting the immaturity hypothesis of ADHD [18], known as the “maturational lag” [35] and supported by a series of neuroanatomical and functional studies [36, 37]. Younger children are less mature in terms of self-regulation, and teachers are, therefore, more likely to raise concerns about these children to their parents, which could lead parents to seek an assessment [38]. The developmental immaturity hypothesis could also be extended to explain the relative age effect here reported associated also to other mental disorders (in children without ADHD, and other mental disorders). However, further studies are needed as done in regard for ADHD, and caution is necessary as long as findings of further investigations show that relative age hypothesis may be applied in other mental disorders in children.

Children with ADHD show significant academic underachievement, poor academic performance, and educational problems [39]. Children with ADHD are more likely to be expelled, suspended, or repeat a grade compared to controls [12, 13]. Teachers and parents should thus be aware of a child's relative age to prevent or reduce these adverse outcomes.

Findings indicate that developmental immaturity is mislabelled as a mental disorder and this is risk of unnecessary medication, since overdiagnosis induces overmedication [17–19].

Teachers' and parents' formal evaluations (conners' teacher and parent rating scale-revised) and not their impressions are essential for the clinical diagnosis of ADHD [5], as guaranteed by the Lombardy registry's procedures. Since the study took into account only children who arrived at a service (ADHD center), however, we do not know if there is a lower referral by both teachers and parents for older children with suspected ADHD. A systematic underdiagnosis due to teachers' and parents' perceptions, concerns, or attitudes may, therefore, exist. Because it is not only a specific, potential limitation for ADHD care detection, but also for other neurodevelopmental disorders, as shown in the present study more efforts and initiatives are needed such as formal teacher training to help recognize and properly refer children with suspected neurodevelopmental disorders.

Younger children may be at a greater educational disadvantage than their older school-year peers due to ADHD or other psychiatric disorders. There is evidence that ADHD symptoms, necessary for diagnosis, can appear before

school-entry age [30, 31]. In this case, the association between school-year relative age and ADHD diagnosis is, therefore, an expression of delayed diagnosis in children with neurodevelopmental immaturity with access school early. Relatively young children would struggle more than their older peers to meet the behavioral expectations of the classroom, but it could be that early access to school makes a latent disorder, even though it would have appeared anyway a year later [40]. In such a context, the need to diagnose mental disorders early, to refer, and to treat appropriately is well known, regardless of patient age [38]. In our study, we do not have information on children from disadvantaged backgrounds at preschool and early school. These children start school with a higher prevalence of mental health difficulties, compared with their more advantaged peers [41]. These children need extra support in the preschool and early years to help narrow these inequalities. The relation between disadvantaged backgrounds and relative age is unknown, as its potential implications for health and education of children, and should be explored in the future research.

The child's relative age and individual needs should be kept in mind by teachers in their educational activities within the classroom, and they should be kept in mind by the clinicians diagnosing and managing the care of children with neurodevelopmental disorders.

A number of studies examined the relative age effect on brief-run or long-run educational outcomes, lifelong earning, success, self-esteem, well-being, and school sports, with divergent findings due also to the fact that the national school systems are different, including educational programs, evaluations, and expectations [39]. However, children who are younger within their school year are more likely to have special educational needs, and for children with complex difficulties, being relatively young for their school year may be an additional stressor that may undermine mental health [40].

Future research should assess both teachers' and parents' perceptions of problematic behavior and thresholds for concern in children who are young for year level.

In practice, clinicians need to ensure they assess attentional capacity and impulse control relative to the child's chronological age and overall developmental status, rather than age for year level for children with suspected ADHD [38]. The same assessment must be done, however, for any developmental disorder that affects performance and school attendance. Finally, also policymakers, in their planning and programming of services, should be aware that early access to school is a critical decision that can affect long-term outcomes, and not only educational ones. The decision should be personalized, involving parents and future teachers, also taking into account the socioeconomic and the health related quality of life settings. All this is valid not only for a more

appropriate management of ADHD, but of all child psychiatric disorders, and for all children.

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Author contributions MB had the idea for the study, designed it, and drafted the initial report. MC and MZ managed and analyzed the data. LR, AD, and MAC drafted sections of the initial report. All authors participated in study design, contributed to interpretation of data, critical review and revision of the report, and approved the final report as submitted. MB is guarantor for the study.

Compliance with ethical standards

Conflict of interests We declare no competing interests.

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Junior temperament character inventory together with quantitative EEG discriminate children with attention deficit hyperactivity disorder combined subtype from children with attention deficit hyperactivity disorder combined subtype plus oppositional defiant disorder



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ABSTRACT

Oppositional defiant disorder (ODD) is frequently associated with Attention Deficit Hyperactivity Disorder (ADHD) but no clear neurophysiological evidence exists that distinguishes the two groups. Our aim was to identify biomarkers that distinguish children with Attention Deficit Hyperactivity Disorder combined subtype (ADHD_C) from children with ADHD_C + ODD, by combining the results of quantitative EEG (qEEG) and the Junior Temperament Character Inventory (JTIC).

28 ADHD_C and 22 ADHD_C + ODD children who met the DSMV criteria participated in the study. JTIC and EEG were analyzed. Stability based Biomarkers identification methodology was applied to the JTIC and the qEEG separately and combined. The qEEG was tested at the scalp and the sources levels. The classification power of the selected biomarkers was tested with a robust ROC technique. The best discriminant power was obtained when TCI and qEEG were analyzed together. Novelty seeking, self-directedness and cooperativeness were selected as biomarkers together with F4 and Cz in Delta; Fz and F4 in Theta and F7 and F8 in Beta, with a robust AUC of 0.95 for the ROC. At sources level: the regions were the right lateral and medial orbito-frontal cortex, cingulate region, angular gyrus, right inferior occipital gyrus, occipital pole and the left insula in Theta, Alpha and Beta. The robust estimate of the total AUC was 0.91. These structures are part of extensive networks of novelty seeking, self-directedness and cooperativeness systems that seem dysregulated in these children. These methods represent an original approach to associate differences of personality and behavior to specific neuronal systems and subsystems.

1. Introduction

Oppositional defiant disorder (ODD) and Attention Deficit Hyperactivity Disorder combined subtype (ADHD_C) are developmental disorders that are among the most commonly diagnosed mental health conditions in childhood (Hamilton and Armando, 2008; Loeber et al., 2009). Community samples show a prevalence rate for ODD ranging between 2 and 14% (Boylan et al., 2007; Loeber et al., 2000). ODD is more prevalent in boys than in girls with ratio's ranging from 3:1 to 9:1 prior to adolescence (Loeber et al., 2000). ODD is a condition involving

problems in self-control of emotions and behaviors. The essential features are frequent and persistent pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness (American Psychiatric Association, 2013). The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context or it impacts negatively on social, educational, or other important areas of functioning. Neurocognitive impairments associated with ODD include lower IQ, deficiencies in inhibitory control, abnormalities in emotional processing and social cognition, and abnormalities in reinforcement processing. These impairments are thought to be related to

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abnormalities in underlying brain mechanisms. Noordermeer et al. (2016) in a systematic review and meta-analysis of neuroimaging studies in children with ODD/CD, reported evidence of smaller brain structures and lower brain activity in the following areas: bilateral amygdala, bilateral insula, right striatum, left medial/superior frontal gyrus, and left precuneus. Similar evidence was found by Calzada-Reyes et al. (2016) in adolescents with ODD and in young adults with conduct disorder using quantified electroencephalogram (qEEG). The authors reported a pattern of beta activity excess with a peak at 17.1 Hz on bilateral fronto-temporo-striatal regions and alpha band power decrease on left central-temporal and right fronto-central-temporal regions.

One of the most frequent comorbidity associated to ODD is ADHD. The MTA study reports a frequency of 39.9% superior to anxiety disorder (34%) and conduct disorder (14%) (MTA, 1999). The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity that interferes with functioning or development and causes impairment in multiple settings: home, school and work. Population surveys suggest that in most cultures ADHD occurs in about 5% of children (Szatmari, 1992). One of the most cited model of ADHD_C is the one proposed by Barkley (1997a, 1997b, 1997c, 2006) which describes ADHD_C as a deficit in behavioral inhibition of four executive neuropsychological functions: working memory, self-regulation of affect–motivation–arousal, internalization of speech and reconstruction. Extensive neuroimaging studies (ERPs, PET, fMRI) have demonstrated that during the execution of cognitive tasks, children with ADHD show a pattern of hypoactivation of the prefrontal lobes and of the striatal regions. (Cortese et al., 2012; di Michele et al., 2005; Castellanos et al., 1994, 1996; Lou et al., 1984, 1989; Rubia et al., 1999, 2001, 2011; Hastings and Barkley, 1978; Klorman, 1992; Taylor, 1986). Neurophysiological studies have shown that different EEG patterns exist in ADHD children. The most frequent EEG patterns consist of elevated high amplitude theta with deficit or excess of beta activity and reduced alpha activity. This profile has been found primarily in children with the combined type of ADHD (Chabot et al., 1996, 2001; Clarke et al., 2001). Several studies have been conducted to associate these neurophysiological patterns with the diverse and multiform comorbidities present in ADHD subjects (Barry et al., 2003; Chabot et al., 2015). Although ADHD_C and ODD seem to share some similarities at neuro-functional level, Barry and Clarke (2009) and Clarke et al. (2002) found little EEG difference between groups of children with ADHD, with and without ODD. Their comment on this finding was: “considering the widespread occurrence of such comorbid disorders in school-age children, it is surprising how little reliable data are available on their EEG correlates. Further work is required to establish unique EEG signatures for such disorders and to resolve how they interact with the EEG deviations associated with ADHD itself.” On the other hand, Jaworska et al. (2013) examining qEEG relationships between anger and non-angry adults with ADHD noted increased beta1 associated with anger and it was interpreted as modest resting cortical hyperarousal.

To clinically assess the temperament and character of the children we used the Italian version (Andriola et al., 2012) of the Junior Temperament Character Inventory (JTCI) of Cloninger (Cloninger et al., 1993). The reason for this choice was that this is the only scale that has been translated into Italian and validated on a population of 459 subjects ranging in age from 6 to 15.9 years. The JTCI scale implements a psychobiological model in which personality is composed of temperament and character traits. In this model, temperament is defined as those aspects of personality that are emotion-based, moderately heritable, developmentally stable regardless of social and cultural influences (Cloninger et al., 1994; Cloninger and Svrakic, 2000). Four dimensions of temperament have been identified: 1) harm avoidance (HA, anxiety prone vs risk taking), 2) novelty seeking (NS, impulsive vs rigid), 3) reward dependence (RD, sociable vs aloof), 4) persistence (PS, persevering vs easily discouraged). Neuroimaging studies with SPECT and fMRI have identified the neural systems that underlie these

dimensions. Novelty-seeking dimension is hypothesized to be regulated by the amygdaloid subdivision of the limbic system which receives sensory input through the orbital prefrontal network (MacLean, 1958, 1990; Kelly et al., 1973; Kelly, 1980) while persistence is associated with specific areas of the lateral orbital and medial prefrontal cortex and ventral striatum (Gusnard et al., 2003). These basic emotional drives of temperament are regulated by 3 dimensions of character considered in terms of higher cognitive functions that regulate an individual's goal, values and mental self-government: 1) Self-Directedness (SD) expresses the individual's competence toward autonomy, reliability, and maturity 2) Cooperativeness (CO) is the ability to get along with other people by being tolerant, empathic, helpful, and forgiving, 3) Self-Transcendence (ST) is a person's ability to identify with nature and the world as a whole as a person seeks to understand what is beyond their individual human existence and is able to sublimate and act altruistically.

These seven TCI personality factors seem to be biologically distinct because each dimension has a unique genetic cause (Gillespie et al., 2003), a unique role in information processing (Cloninger, 2004) and a specific brain circuitry (Cloninger, 2002). Neuroimaging studies with SPECT and fMRI have identified the neural systems that underlie these dimensions. Cloninger has described the functional neuroanatomy of the four dimensions of temperament and how they are related to specific subdivisions of the limbic system (Cloninger, 2002). Therefore, harm avoidance is hypothesized to be a behavioral manifestation of individual differences in the septal subdivision of the limbic system regulating the tonic opposition of sexual drive necessary for reproduction versus the preservation of personal safety (MacLean, 1958, 1962, 1990). Individuals with high scores on HA show reduced white matter structural integrity in distributed brain areas, including cortico-limbic pathways involved in emotional processing and reappraisal (Westlye et al., 2011). Furthermore, a significant negative correlation between scores on HA and gray matter volume was found in the right cuneus and inferior parietal lobule, in the left precuneus, middle occipital gyrus and middle frontal gyrus and bilaterally in the inferior frontal gyrus of normal subjects (Gardini et al., 2009). The novelty-seeking dimension is hypothesized to be regulated by the amygdaloid subdivision of the limbic system which receives sensory input through the orbital prefrontal network (MacLean, 1958, 1990; Kelly et al., 1973; Kelly, 1980). Significant positive correlations were observed between scores on novelty seeking and cerebral blood flow in the left anterior cingulate and in the right anterior and posterior insula (Sugiura et al., 2000). Recently, a significant positive correlation between scores on NS and gray matter volume in normal subjects was found in the right superior and middle frontal gyri and in the posterior cingulate gyrus (Gardini et al., 2009). The reward dependence dimension has been associated with the thalamo-cingulate subdivision of the limbic system also called the circuit of Papez, “the mechanism of emotion” (Papez, 1937). It is hypothesized to regulate the tonic opposition of social attachment and aloofness by its role in selective attention to salient emotional events (Cloninger and Svrakic, 2000). Persistence is hypothesized to be associated with the ventral striato-thalamic-prefrontal circuit. It seems to regulate reward-guided choice behavior (Schultz et al., 1998). Individual differences in persistence in humans are strongly correlated with responses measured by fMRI in a circuit involving the ventral striatum, orbitofrontal cortex/rostral insula, and prefrontal/cingulate cortex (Gusnard et al., 2001, 2003). In addition, a significant negative correlation between scores on persistence and gray matter volume in normal subjects was found in the right caudate and rectal frontal gyrus (Gardini et al., 2009).

Character is often described as the ability of the human being to act intentionally and purposefully (Self-Directedness); it involves our concepts of self and our relations with other people (Cooperativeness) and the world as a whole (Self-Transcendence). Therefore, character is expression of higher cognitive functions depending on the integrity of the thalamo-neocortical system and centrally integrated in the prefrontal cortex, the principal network in modulating goal-directed behavior

(Nauta, 1971; Fuster, 1997). P300 amplitude in parietal areas is positively correlated with Self-Directedness and Contingent Negative Variation (CNV) amplitude is negatively correlated with Cooperativeness and Self-Transcendence (Cloninger, 1998; Vedeniapin et al., 2001). Furthermore, a recent study showed that the young adult females showed greater Cooperativeness as well as larger relative global and regional gray matter volumes (GMVs) than the matched males, particularly in the social-brain regions including bilateral posterior inferior frontal and left anterior medial prefrontal cortices (Yamasue et al., 2008).

There is a convergent evidence in the literature that both adults and children with ADHD have high level of NS, and low levels of SD and CO. (Donfrancesco et al., 2015; Park et al., 2016; Kim et al., 2017). The same pattern has been found in children with only ODD. Children and adolescents with both ODD and ADHD showed decreased levels of Persistence and Self-directedness (Kim et al., 2010).

From a methodological point of view the subdivision of temperament into four dimensions and character in 3 dimensions (particularly cooperativeness and self-directedness) seemed appropriate to describe the symptomatology of our two groups of patients where some symptoms seem to overlap. While these temperamental and character dimensions are subtended by distributed neural systems, we highlight that a correlation between personality factors and neural networks is necessary to develop methods that study “specific” aspects of the personality. Also, we do not stand only with the results of the clinical scale, but we also pay attention to the neurophysiological findings that distinguish the two groups, which implicitly takes into account the neural systems involved in that differentiation. It is our believe that the combination of both sources of information is what provides the best chance for obtaining a more clear understanding about their differences.

Having said that, the purpose of this study was to identify biomarkers that could distinguish children with ADHD_C from children with ADHD_C + ODD, by combining the results of qEEG and JTIC. It is expected that the combined use of clinical indices together with the EEG spectra at the sources can effectively discriminate the two groups.

2. Methods

2.1. Material

This study was conducted by recruiting consecutive patients from the ADHD Centre of the Child and Adolescent Neuropsychiatry Department of Rho hospital. The following protocol was approved by the Ethical Committee of the hospital.

2.2. Subjects

2.2.1. Inclusion criteria

Fifty Patients between 6 and 15 years of age (28 subjects, 25 males and 3 females, with ADHD_C mean age:10.1, SD:3.1 and 22 subjects with ADHD_C + ODD, 21 males and 1 female, mean age:10.3, SD:2.2) were included in the study if they met all of the following criteria: patients met DSM-V diagnostic criteria for ADHD_C and ADHD_C + ODD, scored at least 1.5 standard deviations above the age norm for their diagnostic subtype using published norms for the Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) (Swanson, 1992) subscale scores, and scored above one of the given cut-offs ($T\text{-score} > 55$) of the Conners subscales based on age and gender (Conners, 1997). Patients scored > 15 points on the narrow band ADHD questionnaires for parents (SDAG) and teachers (SDAI) (Cornoldi et al., 1996). ODD behavior was also evident during clinical examination and during testing. The attitude was provocative and challenging not performing properly the test's instructions, surely not because of lack of understanding or inattention. This oppositional attitude persisted even after the subjects were reprimanded. The response was to

continue clearly verbalizing their challenge to authority, claiming that they did not want to change their attitude.

2.2.2. Exclusion criteria

Patients were excluded from the study if they met any of the following criteria: presence of documented psychiatric disorders of the parents, weight < 20 kg at assessment visit, a documented history of Bipolar type I or II disorder, history of psychosis or pervasive developmental disorder, seizure disorder, head injury with loss of consciousness or concussion, migraine, neurological/systemic medical disease (e.g.: lupus, diabetes) or with history of stroke or arterio-venous malformation or brain surgery. Functional comorbidities such as visual or auditory processing problems were not an exclusion criterion but were documented with IQ testing. Additional exclusion criteria were: serious suicidal risk as assessed by the investigator, history of alcohol or drug abuse within the past 3 months or currently using alcohol or drugs.

2.3. Clinical protocol

The clinical assessment was conducted according to the following protocol. Family history was obtained by clinical interviewing one or both parents. At the first visit, after explaining to the patient and the parent/caretaker the purpose and the procedures of the study, informed consent was obtained from both parents, adolescents and children. Adequate time to consider the information was provided. In the assessment phase the following information was obtained: demographics, medical and psychiatric history, previous and concomitant medications, physical and neurological examination, laboratory samples, Electrocardiogram (ECG), qEEG, Amsterdam Neuropsychological Test (ANT, de Sonneville, 2014) a battery to test executive functions and attention, SNAP-IV ADHD scale revised (SNAP IV – Swanson, 1992; Gaub and Carlson, 1997), Conners' rating scale-R for teachers and parents (CTRS-S-Conners, 1997), narrow band ADHD questionnaires for parents (SDAG) and for teachers (SDAI), Cornoldi et al., 1996). Children Depression Rating Scale, derived from the Hamilton Rating Scale for Depression (HAM-D), Pediatric Anxiety Rating Scale (PARS) were used to exclude mood and anxiety disorders. None of the children had a history of neither pharmacological nor behavioral treatment for their symptoms. Italian version of JTIC of Cloninger (Cloninger et al., 1993) was administered to the parents (Andriola et al., 2012).

The mean IQ (WISC-III) of the subjects with ADHD_C and ADHD_C + ODD was 109,6 SD:12.0, and 102,7 SD:15.8 respectively.

2.3.1. Junior temperament and character inventory (JTIC)

We used the Italian version of JTIC-parent version. It consists of 108 statements to which the parents must answer “true” or “false”. The parent had to report, without time constraint, how his or her child usually acted and felt. The 108 items measure the 7 dimensions of the Cloninger psychobiological model of personality (Cloninger et al., 1993). In the Italian version, (Andriola et al., 2012) also showed that the Parent reports of each of the JTIC dimensions had good internal consistency and test-retest reliability over 3 months.

2.4. Neurophysiologic assessment

2.4.1. EEG data acquisition

Twenty minutes of eyes closed resting EEG were recorded from 19 electrodes, using Electro-caps which place the sensors in accordance with the International 10/20 Electrode Placement System, referenced to linked earlobes. A differential eye channel (diagonally placed above and below the eye orbit) was used for detection of eye movements. All electrode impedances were below 5000 Ω . The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points). All EEG data were collected on the same digital system compatible with the demands of the protocol in order to achieve amplifier equivalence. A standard calibration system

was provided with the digital EEG machine. Data were sampled at a rate of 256 Hz with 12-bit resolution. To avoid drowsiness during EEG recordings and to guarantee similar conditions throughout the different sessions, all the patients were recorded in the morning, instructed to keep their eyes closed and stay awake. Patients were monitored with a closed-circuit television system, throughout EEG recording. During the recording, the technician was aware of the subject's state to avoid drowsiness.

2.4.2. qEEG at the scalp

The raw EEG data were visually edited by trained EEG technologists, to identify and eliminate biological (e.g., muscle movement, EMG) and non-biological (e.g., electrical noise in the room) artifacts. This was augmented by a computerized artifact detection algorithm. Two minute artifact-free data, collected from the beginning of the EEG recording were then submitted to frequency analysis. The EEG spectra were calculated using the High Resolution Spectral (HRS) model (Pascual-Marqui et al., 1998; Valdes-Sosa et al., 1990; Szava et al., 1993) for all the channels by means of the Fast Fourier Transform (FFT), in a frequency range from 0.39 Hz to 19.11 Hz, with a frequency resolution of 0.39 Hz. The spectra were Log transform, to approach to Gaussianity (John et al., 1980; Gasser et al., 1982) and the Z-transform was calculated against the Cuban Normative Database (Szava et al., 1993). Significant test re-test reliability for these measures has been demonstrated (John et al., 1983, 1988; Kondacs and Szabo, 1999).

2.4.3. qEEG source analysis (qEEGT)

2.4.3.1. Source density localization. The source density localization analysis was performed for frequencies between 0.39 and 20 Hz and for all the sources in the cerebral cortex for a grid of 3244 sources. The Variable Resolution Electrical Tomography (VARETA) method (Bosch-Bayard et al., 2001) was used in the source localization analysis. VARETA is a technique for estimating the distribution of the primary current in the source generators of EEG data. Like LORETA (Pascual-Marqui et al., 1998), VARETA is a Discrete Spline Distributed Solution. Spline estimates are the spatially-smoothest solutions compatible with the observed data. VARETA applies different amounts of spatial smoothing for different types of generators, with the actual degree of smoothness in each voxel being determined by the data itself; hence the use of the term variable resolution. VARETA allows spatially-adaptive nonlinear estimates of current sources and eliminates the “ghost solutions” (artifactual interference patterns) often present in linearly-distributed inverse solutions. In this way, VARETA produces focal solutions for point sources, as well as distributed solutions for diffuse sources. In addition, anatomical constraints are placed upon the allowable solutions by introducing a “gray matter weight” for each voxel. The effect of these weights on the inverse solution is to prohibit sources in which the mask is zero (for example, CSF or white matter). A three-concentric spheres Lead Field (Riera and Fuentes, 1998), defined over a grid of 3244 points located in the gray matter of the Montreal Neurological Institute (MNI) template (Evans et al., 1993, 1994) was used to solve the forward EEG problem and generating the voltage at the 19 electrodes of the 10–20 System.

The EEG activity was re-referenced to the average reference at each time point for this analysis, as required by VARETA and other inverse solution methods. To render the inverse solution in different subjects comparable for statistics at the sources, VARETA uses the same regularization parameter for all subjects. The value for this parameter is obtained from the subjects in the normative database, and it was also used for the norms calculations. After transformation to the average reference, the geometric power is applied to standardize by a global scale factor to control for individual differences in power values due to skull thickness, hair volume, electrode impedance, and other factors of variance that can affect EEG amplitudes but are not related to electrophysiological variability. This procedure is described in detail elsewhere (Bosch-Bayard et al., 2001). The anatomical accuracy of the

functional qEEG source localization obtained by VARETA and other methods has been repeatedly confirmed by co-registration with other brain imaging modalities e.g. functional magnetic resonance, fMRI (Mulert et al., 2004), positron emission tomography, PET (Zumsteg et al., 2005; Bolwig et al., 2007), and computerized tomography (Prichep et al., 2001). It has also been used satisfactorily for source localization in psychiatric patients with insomnia (Corsi-Cabrera et al., 2012).

Two minutes of artifact-free EEG were also submitted for the computation of the spectra at the EEG sources using Variable Resolution Electrical Tomography (VARETA) (Bosch-Bayard et al., 2001). The EEG sources were located using a grid defined over the gray matter of the probabilistic MRI Brain Atlas (Evans et al., 1993). The standard positions of the International 1020 electrodes positioning system were used for the Lead Field calculation (Riera and Fuentes, 1998). With this Lead Field, VARETA was applied to the cross-spectral matrices calculated for all frequencies and leads at the scalp, to calculate the spectra at the sources space with the same frequency resolution (from 0.39 to 20 Hz with a frequency resolution of 0.39 Hz: high spectral resolution, HSR). Obtaining the value of the spectra for every source of the gray matter at each frequency constitutes a new type of Neuroimaging technique that has been termed Quantitative EEG Tomographic Analysis (qEEGT) (Bosch-Bayard et al., 2001).

To account for age differences, the Z-spectra were computed relative to the normative values of the Cuban Normative Database. The sources were then superimposed upon MRI slices of the MNI Atlas (Evans et al., 1993), and the values computed for each frequency in every voxel were encoded using a color palette with hues proportional to the standard- or Z-scores of deviations from expected normative values. The significance levels of the images are corrected for the large number of comparisons by using the random fields theory, introduced by Worsley et al. (1995). This approach proposes a unified statistical theory for assessing the significance of apparent signal observed in noisy difference images, giving an estimate of the corrected *p*-value for local maxima of Gaussian fields over search regions of any shape or size in any number of dimensions.

2.5. Statistical analyses

As a first step, to assess whether there were statistical differences of the scores of the JTIC between the two groups, a MANCOVA test was performed: the group was included as a categorical factor and the IQ and Age were included as two continuous factors. They were tested against the dependent vector conformed by 7 dimensions of TCI. The only significant effect was the Group effect. Neither the Age or IQ were significant.

To further validate this result, an additional ANCOVA test was performed, using a univariate model for each variable. This analysis revealed that there were significant differences only for the variables NS and SD between the groups. The results are summarized in Table 1. These results were also validated by an additional univariate *t*-test for the JTIC variables, which also showed significant effects only for NS and SD.

A more detailed discussion of these results is given in Section 3.1.

2.5.1. Stability based biomarkers identification methodology

The methodology used in this paper has been described in detail in Bosch-Bayard et al., 2018. In summary, to achieve stability and robustness, the method is divided in two steps, based on subsampling both for the parameter estimation as well as for the validation procedure. In the first step, a random subsample of the original sample is generated using the 30% of the variables and the 70% of the subjects. A classification procedure is applied to this subsample. In our case we use the General Linear Model via elastic net (GLMNet, Friedman et al., 2008) which is a logistic penalized regression method. This method extracts a sparse subset of classifiers from the whole set of variables,

Table 1
ANCOVA results for the univariate model of all JTCl variables.

	DF	NS		HA		RD		PS		SD		CO		ST	
		F	p	F	p	F	p	F	p	F	p	F	p	F	p
Intercept	1	1,06	0,31	5,46	0,024	0,44	0,51	0,84	0,37	1,86	0,18	2,76	0,10	0,80	0,38
Age	1	0,14	0,71	3,65	0,06	0,31	0,58	0,02	0,9	0,17	0,69	0,05	0,82	0,02	0,89
IQ	1	0,09	0,76	2,75	0,10	0,57	0,46	0,03	0,87	0,25	0,62	3,89	0,055	1,13	0,29
Group	1	12,15	0,001	2,52	0,12	0,91	0,35	0,46	0,50	14,57	0,0004	0,91	0,35	1,74	0,20
Total	48														

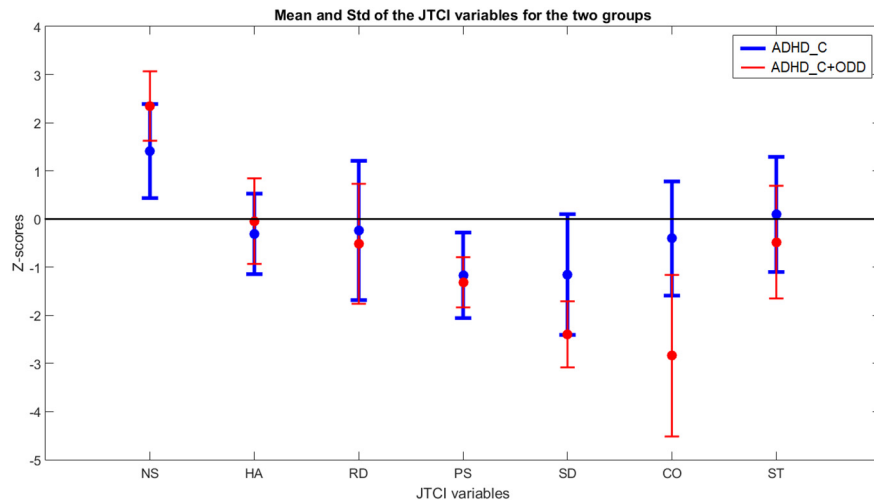


Fig. 1. Z-scores and SD of the variables of the JTCl scale for the two groups. NS = novelty seeking, HA = harm avoidance, RD = reward dependence, P = persistence, SD = self-directedness, CO = cooperativeness, ST = self-transcendence.

while discarding the rest. The random procedure is repeated a sufficiently number of times (500 times in our case). In each realization, the classifiers are kept. Those variables which were selected as classifiers in at least 50% of the times participated in the classification procedure and stored as the more stable biomarkers. With these variables, the final classification equation is built. The ROC technique is used to measure the classification power of the selected set of biomarkers. To ensure a more stable estimation of the area under the curve, again the sub-sampling technique is used. In this case, all biomarkers are kept while generating a subsample with about the 70% of the subjects. The ROC area is calculated for the 10, 20 and 100% of False Positive (FP) and these numbers are stored. The procedure is randomly repeated a sufficiently high number of times (500 in our case). With these values, empirical distributions of the ROC values are obtained at the three levels of FP. The values of these distributions at the 50% of the curve are given as the stable estimate of area under the ROC, which characterizes the predictive classification power of the selected set of biomarkers.

2.5.2. Biomarkers identification at the source level

As second step, instead of staying at scalp level, we also applied the technique to the source spectra obtained with the qEEG procedure. Both approaches have their intrinsic value and serve for different purposes: obtaining the best set of classifiers at the scalp level, if successful, would allow us, for example, to design specific purpose EEG recording devices with the smallest number of electrodes, able to identify clinical subgroups. This may be useful in epidemiologic studies in which it is necessary to identify persons at risk in big populations. On the second hand, applying the procedure at the source level, would allow us to identify the brain regions more directly related to the distinction between subgroups, which is our final goal from the research point of view. From the methodological point of view, while the procedure at the scalp give less information about the brain areas, the number of

variables participating in the selection procedure is smaller, which allows for a better performing of the selection methodology because the number of random repetitions may cover more combinations of the original space.

To clarify the previous sentence, in our study, when applying the GLMNet method for the Biomarkers identification at the source level, the number of variables is extremely high (3623 sources \times 49 frequencies = 159,887 variables). One strategy is to use the Brain Atlas Segmentation (67 regions) where voxels activity in an area is averaged. This method has advantages like: 1) statistically more robust (diminishes the effect of outliers) and 2) increases the chances of regions to become biomarkers because of a smaller number of variables. But, on the other hand, if the region is big and few voxels are significant, the average can mask those significant voxels activity. Furthermore, the problem size still exists after Atlasing: 67 regions \times 49 freqs = 3283 variables. In order to reduce the number of variables we decided to apply the preprocessing step proposed in Bosch-Bayard et al. (2018) named “indfeat” (Weiss and Indurkha, 1998). It consists in performing univariate *t*-tests for each variable between the two groups and eliminating those variables which indfeat indices lower to 1. In this way we reduced the number of variables to 604. The 7 TCI measurements were also included in the analysis.

3. Results

3.1. Behavioral results

Fig. 1 shows the mean and SD for the Z-score of the variables of the JTCl scale for the two groups. The temperament of children with ADHD_C and ADHD_C + ODD showed differences when compared to norms. Both groups exhibited higher values of novelty seeking and lower values of self-directedness and cooperativeness. However,

subjects with ADHD_C + ODDs had even significantly higher levels of novelty seeking and lower level of Self-Directedness and Cooperativeness than subjects with ADHD_C.

A MANCOVA analysis of the scores of the JTCI Temperament scale between the two groups, with the group as a categorical factor and two continuous factors (IQ and Age), showed that the only significant effect was the Group ($F = 3.52$; $df = [7,39]$; $p < 0.01$). Neither the Age nor IQ were significant (age: $F = 0.51$; $df = [7,39]$; $p > 0.8$; IQ: $F = 1.06$; $df = [7,39]$; $p > 0.4$). For this model, we didn't find significant differences between the slopes of the two groups. An additional ANCOVA test, using a univariate model for each variable of the JTCI, revealed that there were significant differences between the groups only for the variables Novelty Seeking and Self-directedness. The ADHD_C + ODD had in the temperament domain higher z score values of novelty seeking than the ADHD_C children and in the character, domain had lower Z score value of self-directedness compared with children with ADHD_C (Table 1). Since no significant effects were found in the independent variables, the *t*-test was also used. The univariate *t*-test of each variable, showed significant results between the groups only for NS ($t = -3.46$; $df = 46$; $p < 0.001$); SD ($t = 4.52$; $df = 46$; $p < 0.0001$) and CO ($t = 5.83$; $df = 46$; $p < 0.0001$).

3.2. Biomarkers results

We applied the biomarkers selection methodology to the Z-scores of the JTCI scale as well as to the Z-spectra at the electrodes and at the sources separately. Then we applied the same methodology to the Z-spectra at the electrodes combined with the JTCI Z-scores (Z-spectra + Z-JTCI) and to the Z-spectra at the sources combined with the JTCI Z-scores (Z-sources + Z-JTCI). The discrimination power of each classification equation was measured by the robust area under the ROC (rAUC) at the 10%, 20% and the total area. The results are summarized in Table 2.

As it can be observed in Table 2, the best discrimination power was obtained when the JTCI Z-scores were combined with the qEEG or the qEEGT parameters. This was especially evident at a low rate of False Positives (10% and 20%) which is a very desirable characteristic in a classifier, since a high number of True Positive are identified at a cost of a low number of False Positive.

The procedure was also carried out with the Log of the raw values of the spectra both at the electrodes (qEEG parameters) and at the sources (qEEGT parameters). In both cases, the discrimination power of the classification equations was higher with the Z-values than with the log of the raw values. Therefore, in what follows, we will report the results obtained using the Z-values of the qEEG and the qEEGT parameters, combined with Z-scores of the JTCI scale.

The procedure was also applied to the Absolute Power of the traditional Broad Band model (Delta: 1.5–3.5 Hz; Theta 3.9–7.2 Hz; Alpha: 7.5–12.5 Hz and Beta: 12.8–19.11 Hz), again separately and combined with the Z-scores of the JTCI scale. The discrimination power obtained with these datasets was significantly worse than the ones obtained with the HRS model. Our conclusion regarding these results is that summarizing by frequencies is not a good choice for the classification purpose, since averaging among frequencies may mask or cancel out the

Table 2

Robust AUC values (rAUC) at the 10% and 20% of false positives as well as the total AUC obtained by the biomarkers identification methodology, applied to each set of variables separately and combined.

Dataset	# of variables	rAUC (10%)	rAUC (20%)	rAUC (Total)
Z-JTCI	7	0.59	0.70	0.88
Z-spectra	912	0.48	0.66	0.80
Z-sources	3283	0.61	0.72	0.81
Z-JTCI + Z-spectra	919	0.89	0.95	0.95
Z-JTCI + Z-sources	3290	0.78	0.86	0.91

Table 3

Best set of classifiers obtained for the Z-scores of JTCI scale combined with the Z-values of the qEEG parameters (scalp).

Variable	Origin	Frequency	Frequency band	ϕ coefficients
Novelty seeking	JTCI			0.0255
Self-directedness	JTCI			−0.0912
Cooperativeness	JTCI			−0.0985
F4	EEG	1.17 Hz	DELTA	−0.0593
F4	EEG	1.56 Hz		−0.2581
Cz	EEG	1.56 Hz		−0.1768
Fz	EEG	4.30 Hz	THETA	0.3155
F4	EEG	5.47 Hz		0.1129
F7	EEG	15.62 Hz	BETA	−0.1284
F8	EEG	17.58 Hz		−0.0589

Table 4

Best set of classifiers obtained for the Z-scores of JTCI scale combined with the Z-values of the qEEGT parameters (sources).

Variable	Origin	Frequency	Frequency band	ϕ coefficients
Novelty seeking	JTCI			0.0334
Self-directedness	JTCI			−0.0644
Cooperativeness	JTCI			−0.0957
Insula left	EEG	4.68 Hz	THETA	0.1057
Lat. orbito-frontal gyrus right	EEG	6.63 Hz		−0.1037
Lat. orbito-frontal gyrus right	EEG	8.97 Hz	ALPHA	0.0692
Lat. orbito-frontal gyrus right	EEG	9.36 Hz		0.0300
Cingular region right	EEG	9.36 Hz		0.0182
Lat. orbito-frontal gyrus right	EEG	9.75 Hz		0.0153
Lat. orbito-frontal gyrus right	EEG	11.31 Hz		−0.0835
Angular gyrus right	EEG	11.7 Hz		0.1284
Inf. occipital gyrus right	EEG	17.55 Hz	BETA	−0.0849
Occipital pole left	EEG	17.55 Hz		−0.0093
Lat. orbito-frontal gyrus right	EEG	19.11 Hz		−0.0460
Medial orbitofrontal gyrus right	EEG	19.11 Hz		−0.0506

differences between groups present in specific frequencies.

Tables 3 and 4 show the classification equations obtained by the biomarkers selection methodology for the data sets composed by the combinations of the Z-scores of the JTCI scale with the Z-spectra at the electrodes (qEEG) and the Z-spectra at the sources (qEEGT) respectively. In both, the first three variables participating in the equation belong to the JTCI scale and the rest to the qEEG/qEEGT parameters. In each table, it is specified the name of the electrode (qEEG) or the brain region (qEEGT) selected as well as the frequency in which they were selected as biomarkers. The last column of each table (ϕ Coefficients) shows the coefficient that accompanies each variable in the classification equation.

In both cases, Self-directedness (SD) and Cooperativeness (CO) of the JTCI scale were selected in > 90% of the times, Novelty Seeking (NS) was selected about 70% of the times. SD, CO and NS participated in the classification procedure.

Fig. 2 shows the topographical distribution of the biomarkers selected from the qEEG parameters, summarized by frequency bands. In Delta band, F4 and Cz, in Theta band Fz and F4 electrodes, in Beta band F7 and F8 were selected.

Fig. 3 shows the brain regions selected as biomarkers from the qEEGT parameters at the sources level. In Theta band the left insula and the right lateral fronto-orbital gyrus were selected. In Alpha band the most significant regions were the right lateral fronto-orbital gyrus, the right angular gyrus, and the right cingular region. In Beta band, the

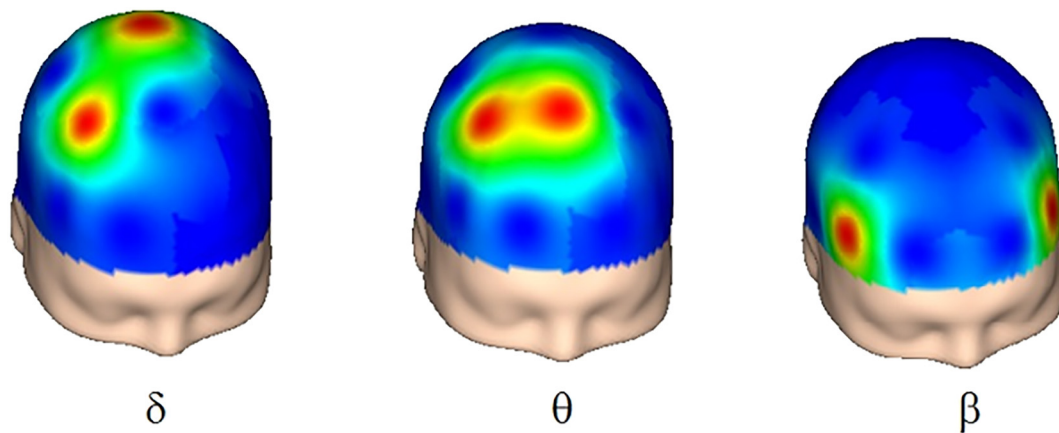


Fig. 2. Topographical distribution of the biomarkers in the different traditional Broad Band Models. In Delta band, only F4 and Cz; in Theta band only Fz and F4; in Beta band F7 and F8 were selected.

most significant sources were the right lateral fronto-orbital gyrus, the right medial fronto-orbital gyrus, the right inferior occipital gyrus and the left occipital pole. The orbito-frontal cortex (OFC), therefore, is the area most present in all frequency bands except delta band where no regions of interest were present (see also Table 4).

The classification power of the two equations (at the scalp and at the sources) is shown in Fig. 4. The left side of the figure shows the results obtained by the biomarkers at the scalp and the right side shows the results of the obtained by the biomarkers at the sources. The upper part contains boxplots which show the mean, standard deviation and quantiles for the two groups for both equations. The scatterplots inside the boxplots show the score of each subject in each group for the two classification equations, at the scalp and at the sources respectively. The lower part of the figure shows the two robust ROC curves estimated by the stability procedure.

As an additional step, to understand how the variables selected as

biomarkers behaved in each group, we calculated linear regression equations for each variable using the Group as the independent variable. In this way, the sign of the slope (m) of the linear equation indicates which of the groups had bigger values for the variable. Since ADHD_C was before ADHD_C + ODD, a positive sign of m indicates that ADHD_C had lower values than ADHD_C + ODD and vice versa. Table 5 shows the values and the significance (p) of the slope of the Z-scores of the JTCI scale selected as biomarkers; Table 6 shows the values and the significance (p) of the slope of the biomarkers selected from the qEEG parameters at the scalp and Table 7 shows the values and the significance (p) of the slope of the biomarkers selected from the qEEGT parameters at the sources. Note that NS, SD and CO showed a highly significant slope between the groups. However, from the qEEG and qEEGT parameters, only in the right hemisphere there were the most significant differences: F4 at 1.7 Hz, F4 at 5.4 Hz and F8 at 17.5 Hz had significant regression values, while the rest of the variables considered

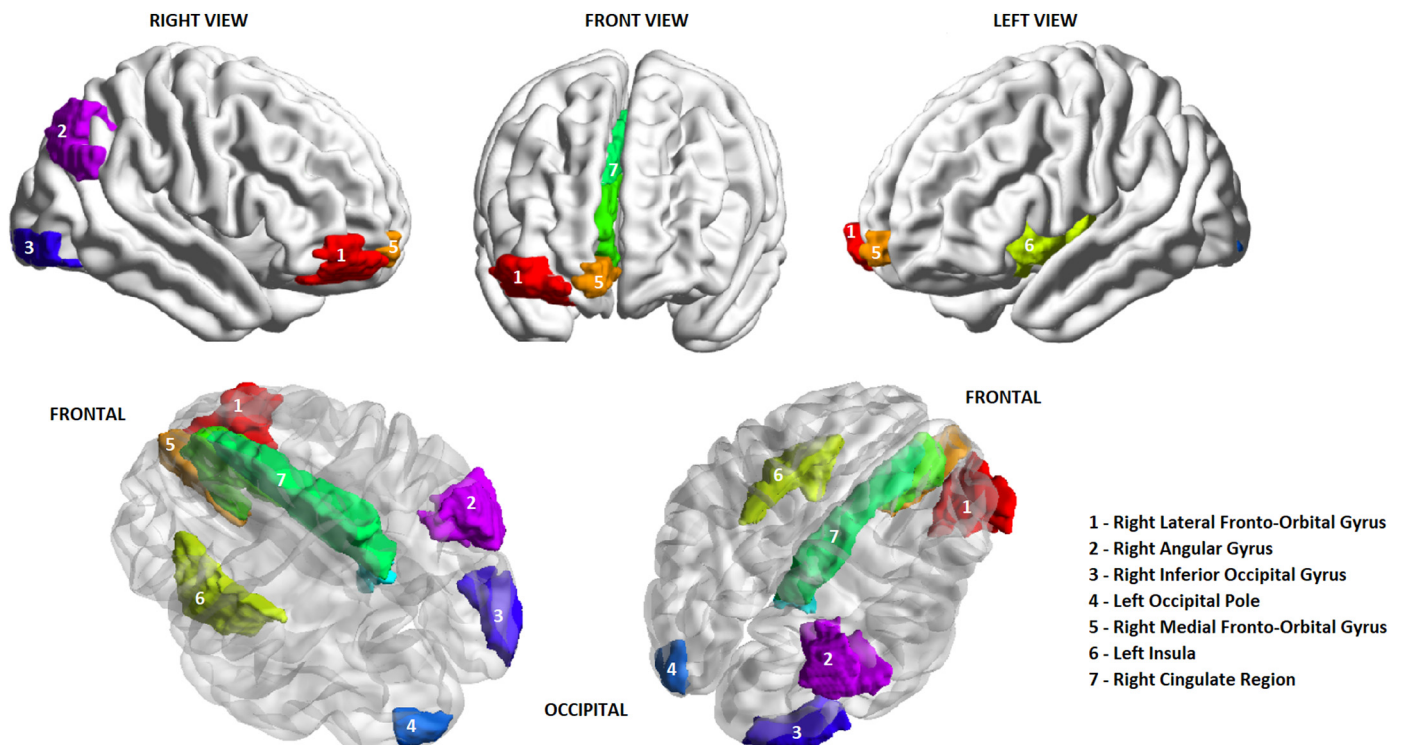


Fig. 3. Tomographical distribution of the biomarkers at the sources, showing the brain regions selected as biomarkers: Left Insula, Right lat. Orbito-frontal gyrus right, right Cingulate region, Right Angular gyrus, Right Inf. Occipital gyrus, Left Occipital pole, Right medial Orbito-frontal gyrus.

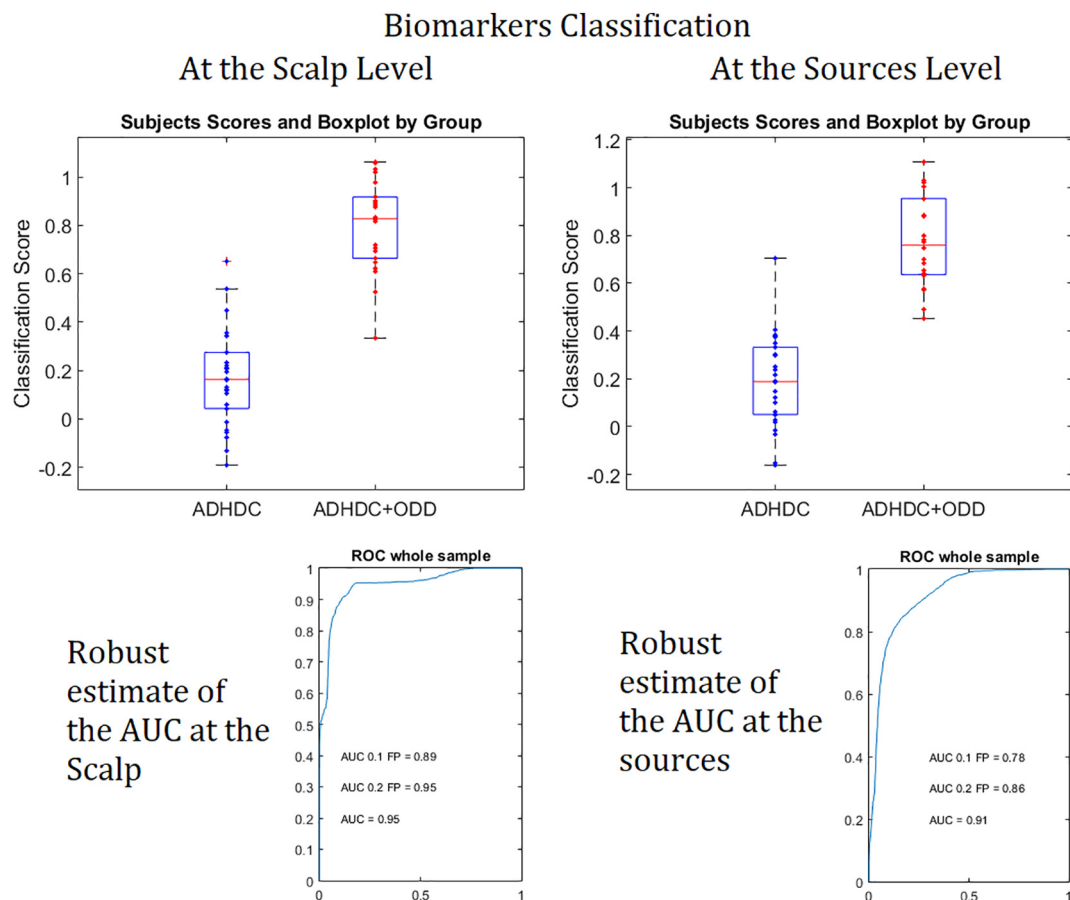


Fig. 4. Classification power of the two equations at the scalp level (left side) and at the sources (right side). The upper part contains boxplots which show the mean, standard deviation and quantiles for the two groups for both equations. The scatterplots inside the boxplots show the score of each subject in each group for the two classification equations, at the scalp and at the sources respectively. The lower part of the figure shows the two robust ROC curves estimated by the stability procedure.

Table 5

Slope value (m) and Significance (p) of the linear regression between the two groups for the biomarkers selected from the JTCI scale.

Variable	m(slope)	p
Novelty seeking	0.86	0.0015
Self-directedness	−1.3	9.2e-6
Cooperativeness	−2.4	2.3e-6

Table 6

Slope value (m) and Significance (p) of the linear regression between the two groups for the biomarkers selected from the qEEG parameters (scalp).

Variable	Frequency	Frequency band	m(slope)	p
F4	1.17 Hz	DELTA	−0.24	0.05
F4	1.56 Hz		−0.19	0.08
Cz	1.56 Hz		−0.06	0.6
Fz	4.30 Hz	THETA	−0.14	0.19
F4	5.47 Hz		−0.21	0.03
F7	15.62 Hz	BETA	0.03	0.74
F8	17.58 Hz		−0.21	0.004

separately didn't show a significant regression between groups. The children with ADHD_C had significantly greater activity in those frequency bands than the ADHD_C + ODD.

Table 7

Slope values (m) and Significance (p) of the linear regression between the two groups for the biomarkers selected from the qEEG parameters (sources).

Variable	Frequency	Frequency Band	t-Values	p
Insula left	4.68 Hz	THETA	0.25	0.16
Lat. orbito-frontal gyrus right	6.63 Hz		−0.041	0.84
Lat. orbito-frontal gyrus right	8.97 Hz	ALPHA	0.028	0.88
Lat. orbito-frontal gyrus right	9.36 Hz		0.0014	0.99
Cingular region right	9.36 Hz		0.022	0.92
Lat. orbito-frontal gyrus right	9.75 Hz		0.19	0.23
Lat. orbito-frontal gyrus right	11.31 Hz		0.052	0.72
Angular gyrus right	11.7 Hz		0.14	0.43
Inf. occipital gyrus right	17.55 Hz	BETA	−0.3	0.22
Occipital pole left	17.55 Hz		−0.32	0.17
Lat. orbito-frontal gyrus right	19.11 Hz		−0.122	0.58
Medial Orbitofrontal gyrus right	19.11 Hz		−0.11	0.66

4. Discussion

Bosch-Bayard et al. (2018) have given strong evidence of the validity and robustness of the biomarkers selection procedure based on the GLMNet method. GLMNet itself has also been successfully applied in different clinical situations (Casanova et al., 2011; Hernandez-Gonzales et al., 2011). The fact that, to our knowledge, this method of combining behavioral and neurophysiological data in the same classification procedure has been applied for the first time is of particular relevance in this context since we were able to obtain the best classifiers that discriminated the two groups.

The best results were obtained when the methodology was applied by combining JTCI values (behavioral level) and the z values (instead of raw spectra scores) of the qEEG (scalp) or qEEGT (sources) parameters (neurophysiological level). In both procedures (at the scalp and at the sources level), the JTCI measurements of NS, SD and CO were selected as biomarkers. At the scalp level, the best classifiers from the qEEG parameters were F4 and Cz in the delta band; F4 and Fz in theta band and F7 and F8 in beta band (15.6 and 17.5 Hz respectively) (see Table 3). The discrimination power of the classification equation obtained with this data, validated by the robust ROC estimation (Bosch-Bayard et al., 2018), was of 0.95 for the Total AUC, 0.89 at a 10% of FP and 0.95 at a 20% of FP. The left upper panel of Fig. 4 shows a boxplot with the discrimination between the two groups obtained by this procedure. It can be noted that there is an almost perfect separation between the groups, which explains the high value obtained for the robust area under the ROC. The scatterplot inside the boxplot shows the score of each subject. The lower left panel of the figure shows the stable ROC curve estimation obtained by the stability procedure.

At the sources level, the selected biomarkers were the left insula and the right lateral fronto-orbital gyrus in Theta band; the right lateral fronto-orbital gyrus, the right angular gyrus, and the right Cingular region in Alpha band; and the right lateral fronto-orbital gyrus, the right medial fronto-orbital gyrus, the right inferior occipital gyrus and the left occipital pole in Beta band. The orbito-frontal cortex (OFC), therefore, is the area most present in all frequency bands except delta band where no biomarkers were selected (see Table 4). The robust estimation of the AUC for this classification equation was of 0.91 for the Total area, 0.78 at a 10% of FP and 0.86 at a 20% of FP. The right upper panel of Fig. 4 shows a boxplot of the discrimination between the two groups at the sources. The scatterplot inside the boxplot show the score of each subject. Compared to the scalp, the classification at the sources is even better than at the scalp: the groups are more compact and separated. The lowest values of the AUC, especially at the 10% and 20% rate of False positives are explained for the existence of an outlier in the ADHD_C groups, who is mixing the distributions. The lower left panel of the figure shows the stable ROC curve estimation obtained by the stability procedure at the sources.

Although the results at the sources level showed a high classification power of the equation, they may be influenced by the approaches used in this work, especially the summarization by brain regions. The number of variables to be considered at the source level is extremely high. In this work we used a summarization by brain regions. However, in Fig. 3 it can be noted that some of the selected areas are rather big. Moreover, some of the not selected areas are even bigger. One brain region may be related to different functions. If the area that is responding to a specific function is only a small part of a large region, then when summarizing the whole area, the function of this small part may not be well represented in the whole average of the region. This may cause that the specific area does not appear as biomarker. To solve this problem, some procedures still should be tested: a) using a finer brain segmentation, which produces small areas; b) using a priori knowledge to restrict the number of sources (or areas) to be included in the analysis; c) applying some a priori statistical test to eliminate sources/areas which do not contain information to differentiate the groups (for example where there are not significant differences between the groups); or d) performing a priori algorithms, like principal components analysis, to select the areas to be considered in a data driven procedure. These alternatives should be considered in the future to improve the performance of the classification equation.

From a visual inspection of Tables 6 and 7 it can be noted that, when analyzed separately, the majority of the variables that were selected as biomarkers, do not have high classification power to differentiate the groups: only the three JTCI variables (NS, SD and CO), F4 at 1.1 and 5.4 Hz and F8 at 17.5 Hz reached a significant regression between the groups (p value of the slope regression). However, the classification equation has a high classification power. Therefore, it is not each

variable by itself but the combination of all of them (the behavioral as well as the neurophysiological ones) that produced the equation with the high classification power. This is one of the strengths of the used method.

Another strength of this method is that, by construction, the obtained results should not be attributed to overfitting, as it has been demonstrated in Bosch-Bayard et al. (2018). In this way, the method guarantees the extraction of a classification equation, with a small number of biomarkers and a stable statistical behavior, i.e., the obtained equation has a high statistical power and is not very sensible to small perturbations in the data.

4.1. Results at the behavioral level

The temperament of children with ADHD_C and ADHD_C + ODD showed higher values of novelty seeking compared to norms. Also, in the character domain, both groups exhibited lower values of self-directedness and cooperativeness compared to norms. However, when the two groups were compared to each other, subjects with ADHD_C + ODDs had significantly higher level of novelty seeking and lower level of Self-Directedness and Cooperativeness than subjects with ADHD_C. These results are compatible with Barkley's (1997a, 1997b, 1997c, 2006) model that interprets these behavioral disorders as a problem of regulation of inhibitory control at all levels: affective, emotional, motivational and linguistic. Children with high values of novelty seeking are children who have the tendency to react to new stimuli or signals of approval or potential punishments. It implies that they need elevated levels of stimulation, and they have the tendency of exploration and enthusiasm, but they are impulsive and ease to get bored. They are messy, fickle, excitable, irritable, and unstable in personal relationships and have sudden bursts of anger. The temperamental dimension of NS, is more pronounced in subjects with ADHD_C + ODD than ADHD_C. The clinical symptomatology reported by the parents and teachers together with the clinical observations fully confirms these results. Melegari et al. (2015) reported that the ADHD children showed a temperamental profile characterized by high Novelty Seeking, low Reward Dependence and low Persistence. Meanwhile, the ODD children shared the high Novelty Seeking with the ADHD children, but they showed higher Persistence than the ADHD children.

Although in our sample we didn't find significant differences in persistence between the two groups, probably because they had in common the ADHD_C, both groups were less persistent compared to norms. Children with low persistence values appear unable to maintain consistent behavior in front of intermittent reinforcements. Low values of persistence reflect lack of perseverance, determination and consistency; therefore, in front of frustration and fatigue these children are inclined to abandon the tasks. These features appear to be one of the clinical characteristic of ADHD.

As the character is concerned, subjects with ADHD_C + ODD showed a significant lower capacity of Self-Directedness (SD) and Cooperativeness (CO) compared to the subjects with ADHD_C. Children with low SD appear aimless, inept, just unproductive and easily blaming others. Low SD stands for immaturity, childishness, lack of self-sufficiency, responsibility and reliability. They are not responsible for their own actions and have low self-esteem and self-confidence. Children with low CO are prejudiced, insensitive, hostile, revengeful, opportunistic and disloyal. All these characteristics are more pronounced in ADHD_C + ODD children.

4.2. Biomarkers results

Significant differences between the groups were found in the absolute power spectra z-score in the right hemisphere (F4 at 1.7 Hz and at 5.4 Hz and F8 at 17.5 Hz) The group of children with ADHD_C had significant higher values in the delta, theta and beta bands than e group of children with ADHD_C + ODD. It has been frequently reported that

children with ADHD have EEG patterns consisting of elevated delta and theta absolute power with deficit or excess of beta activity. This profile has been found primarily in children with the combined type of ADHD (Chabot et al., 1999; Clarke et al., 2001). F4 and F8 cover part of the prefrontal cortex and middle frontal gyrus and in particular the dorso-lateral prefrontal cortex. These areas play a fundamental role in several executive functions, executive control of behavior” (Kübler et al., 2006), inferential reasoning (Goel et al., 1997; Knauff et al., 2002), decision making (Rogers et al., 1999). These functions are impaired in children with ADHD_C (Barkley, 1997a, 1997b; Barkley et al., 1992; Goodyear and Hynd, 1992). These two groups of children that have in common ADHD_C seem to lack in the executive control of behavior. It is also known that these areas of the right hemisphere are involved in modulating emotions, reacting properly to stressful situations, understanding other intentions for deciding appropriate behavior. Children with ADHD_C + ODD appear more dysregulated in modulating social behavior and in the control of mood and motivational drive, function(s) that are important components of the personality of an individual.

The biomarkers at the sources identification level confirmed the above results at the electrode sites and showed the regions that best classified the 2 groups.

Many researches support that the main disorders associated with dysregulated OFC connectivity/circuitry are related with decision-making, emotion regulation, and reward expectation (Paulus et al., 2002; Toplak et al., 2005; Verdejo-Garcia et al., 2006). More specifically, a large meta-analysis of the existing neuroimaging studies demonstrated that activity in medial parts of the OFC is related to the monitoring, learning, and memory of the reward value of reinforcers, whereas activity in lateral OFC is related to the evaluation of punishers, which may lead to a change in ongoing behavior (Ernst et al., 2004; Kringelbach, 2005; Kringelbach and Rolls, 2004). OFC seems to be important in signaling the expected rewards/punishments of an action given the details of a situation. In doing this, the brain can compare the expected reward/punishment with the actual delivery of reward/punishment, thus making the OFC critical for adaptive learning (Schoenbaum et al., 2011). Significant positive correlations were observed between scores of novelty seeking and cerebral blood flow in the orbital prefrontal network, particularly the anterior cingulate, the right anterior and posterior insula (Sugiura et al., 2000). It has been reported that children with ADHD showed a decrease in total cerebral volume and total cortical volume reduction throughout the cortex. The ADHD group also showed a significant decrease in cortical folding in all four lobes bilaterally. After correction for multiple comparisons, this effect was only observed in the right frontal lobe (Wolosin et al., 2009). These recent findings add evidence to the notion of dysfunction of this neural circuitry controlling motivation, reward, and impulsivity, including the OFC.

Self-directedness significantly correlates with changes in the medial prefrontal network (Brodman areas 8/9, BA8/9), suggesting deficit of executive functions as lack of initiative, inability to organize or prioritize activities (Damasio, 1985; Joseph, 1999). Self-directedness was strongly correlated with fMRI response magnitudes in BA9/10 when subjects were carrying out simple executive tasks (Gusnard et al., 2001). Self-directedness was also negatively correlated with reaction times of the same task. Likewise, Bechara et al. (1994, 1996, 1997, 1998) have found that patients with bilateral medial prefrontal lesions cannot anticipate future positive or negative consequences of their actions. It has been also reported that self-directedness in individuals with either borderline or antisocial personality disorder is associated with low activity in the medial prefrontal network) and low cooperativeness with low activity in the orbital prefrontal network. (London et al., 2000; Soloff et al., 2000). Yamasue et al. (2008) have identified for the first time the areas of the brain strongly correlated with cooperativeness: the bilateral posterior inferior frontal gyrus and the antero medial prefrontal cortices. The sources localization method has shown that these areas are dysregulated, and the TCI confirmed this evidence showing

that the children with ADHD_C + ODD have less human altruistic cooperation than children with ADHD_C.

The cingulate cortex is an integral part of the limbic system, which is involved with emotion formation and processing, learning, and memory (Lane et al., 1998). Neuroimaging studies show that separate areas of anterior cingulate cortex are involved in cognition and emotion and therefore it can be proposed as an interface that integrates the traits of temperament with those of character (Cloninger, 2002). Bush et al. (1999) have reported that subjects with ADHD failed to activate the anterior cingulate cortex (ACC) during a counting Stroop test and activated the fronto-striatal-insular network, indicating ACC hypo-activity of this region.

The insula together with the anterior cingulate cortex are considered the critical areas of the “salience network,” believed to be involved in consciousness. It regulates diverse functions linked to emotion or the regulation of the body's homeostasis. Young patients with ADHD were found to have a bilateral reduction in anterior insular cortex (AIC) gray matter volumes compared to healthy controls. Furthermore, the left AIC was found to positively correlate with oppositional symptoms, while the right AIC was found to associate with both attention problems and inhibition (Lopez-Larson et al., 2012).

The angular gyrus is part of the Default Mode Network (DMN). The DMN function assists in processing and understanding a person's internal, reflective world and the world of self and others. Russell-Chapin et al. (2013) have reported that children with ADHD have difficulty activating the DMN in a resting or quiet state.

In conclusion, the correlation between temperament, character and cerebral function are weak or inconsistent, unless it doesn't pay attention to a specific temperament or a specific cerebral region with its connections. This is the case when TCI dimensions are analyzed together with qEEG data with source level analysis. These methods open the way for a new and original approach to associate differences of personality and behavior to specific neuronal systems and subsystems and could provide a powerful tool for understanding pathophysiology of behavioral disorders.

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(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 e N. 1077 del 02/02/2017) Capofila Progetto: UONPIA Azienda
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