NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD OTTOBRE 2020

Alcohol Clin Exp Res. 2020.

BEERS WITH PEERS: CHILDHOOD ADHD AND RISK FOR CORRELATED CHANGE IN PERCEIVED PEER AND PERSONAL ALCOHOL USE ACROSS YOUNG ADULTHOOD.

Kennedy TM, Walther CAP, Pedersen SL, et al.

Background: ADHD poses risk for problematic alcohol use through adulthood. Perceived peer alcohol use, one of the strongest correlates of individuals own alcohol use, is especially salient for adolescents with ADHD. The extent to which this risk extends into young adulthood is unknown, as well as how change in these constructs is associated throughout young adulthood.

Methods: In the Pittsburgh ADHD Longitudinal Study, 358 individuals with childhood-diagnosed ADHD and 239 without were prospectively followed from ages 18 to 29. Piecewise, bivariate longitudinal growth modeling was used to examine the change in both peer alcohol use and individuals heavy drinking (binge-drinking frequency), their between-person associations, and differences by ADHD group. The addition of structured residuals probed within-person year-to-year change in peer and personal alcohol use and their prospective associations.

Results: Perceived peer alcohol use and individuals heavy drinking frequencies changed together over time concurrently from ages 18 to 21 (piece 1) and 21 to 29 (piece 2). Prospectively, individuals who increased the most in heavy drinking from ages 18 to 21 reported more friends using alcohol at age 29, regardless of ADHD history. Within-person increases in personal alcohol use likewise predicted increased perceived peer use the subsequent year within each age group (piece), regardless of ADHD history. However, while decreasing perceived peer use from ages 21 to 29 was related to more frequent heavy drinking at age 29 for those without ADHD, increasing perceived peer use from ages 18 to 21 predicted more frequent heavy drinking at age 29 for those with ADHD.

Conclusions: Young adult heavy drinking changes in tandem with perceived peer alcohol use across individuals and predicts selection of alcohol-using peers from year to year within individuals, further into adulthood than previously documented. Findings suggest the centrality of relationships with alcohol-consuming friends in relation to one's heavy drinking, especially for young adults with ADHD histories, through the twenties

……..

……..

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.

Anesthesia and Analgesia. 2020;131:723-33.

EXPOSURE TO SURGERY AND ANESTHESIA IN EARLY CHILDHOOD AND SUBSEQUENT USE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATIONS.

Ing C, Ma X, Sun M, et al.

BACKGROUND: Some recent clinical studies have found that early childhood exposure to anesthesia is associated with increased risks of behavioral deficits and clinical diagnoses of attention deficit hyperactivity disorder (ADHD). While diagnoses in claims data may be subject to inaccuracies, pharmacy claims are highly accurate in reflecting medication use. This study examines the association between exposure to surgery and anesthesia and subsequent ADHD medication use.

METHODS: Longitudinal data for children enrolled in Texas and New York Medicaid from 1999 to 2010 were used. We assessed the association between a single exposure to anesthesia before age 5 years for 1 of 4 common pediatric surgical procedures (pyloromyotomy, inguinal hernia repair, circumcisions outside the perinatal period, and tonsillectomy and/or adenoidectomy) and persistent ADHD medication use (event defined as the initial ADHD medication prescription, and persistent use defined as filling 2 or more ΓëÑ30-day prescriptions between 6 months following surgery until censoring). Exposed children (n = 42,687) were matched on propensity score (ie, the probability of receiving surgery) estimated in logistic regression including sociodemographic and clinical covariates, to children without anesthesia exposure before age 5 years (n = 213,435). Cox proportional hazards models were used to evaluate the hazard ratio (HR) of ADHD medication use following exposure. Nonpsychotropic medications served as negative controls to determine if exposed children simply had higher overall medication use.

RESULTS: Children with a single exposure to surgery and anesthesia were 37% more likely than unexposed children to persistently use ADHD medication (HR, 1.37; 95% confidence interval [CI], 1.30-1.44). The estimated HRs for common nonpsychotropic medication use following a single anesthetic exposure were 1.06 (95% CI, 1.04-1.07) for amoxicillin, 1.10 (95% CI, 1.08-1.12) for azithromycin, and 1.08 (95% CI, 1.05-1.11) for diphenhydramine. In comparison, the risk of using other psychotropic medication to treat conditions besides ADHD was also significantly higher, with HRs of 1.37 (95% CI, 1.24-1.51) for sedative/anxiolytics, 1.40 (95% CI, 1.25-1.58) for antidepressants, 1.31 (95% CI, 1.20-1.44) for antipsychotics, and 1.24 (95% CI, 1.10-1.40) for mood stabilizers.

CONCLUSIONS: Medicaid-enrolled children receiving anesthesia for a single common pediatric surgical procedure under age 5 years were 37% more likely to require subsequent persistent use of ADHD medications than unexposed children. Because the increased use of ADHD medication is disproportionately higher than that of nonpsychotropic medications, unmeasured confounding may not account for all of the increase in ADHD medication use. By evaluating Medicaid data, this study assesses children who may be particularly vulnerable to neurotoxic exposures

……..

Appl Psychophysiol Biofeedback. 2020 Sep;45:165-73.

DIFFERENT SPECTRAL ANALYSIS METHODS FOR THE THETA/BETA RATIO CALCULATE DIFFERENT RATIOS BUT DO NOT DISTINGUISH ADHD FROM CONTROLS.

van Dijk H, DeBeus R, Kerson C, et al.

There has been ongoing research on the ratio of theta to beta power (Theta/Beta Ratio, TBR) as an EEG-based test in the diagnosis of ADHD. Earlier studies reported significant TBR differences between patients with ADHD and controls. However, a recent meta-analysis revealed a marked decline of effect size for the difference in TBR between ADHD and controls for studies published in the past decade. Here, we test if differences in EEG processing explain the heterogeneity of findings. We analyzed EEG data from two multi-center clinical studies. Five different EEG signal processing algorithms were applied to calculate the TBR. Differences between resulting TBRs were subsequently assessed for clinical usability in the iSPOT-A dataset. Although there were significant differences in the resulting TBRs, none distinguished between children with and without ADHD, and no consistent associations with ADHD symptoms arose. Different methods for EEG signal processing result in significantly different TBRs. However, none of the methods significantly distinguished between ADHD and healthy controls in our sample. The secular effect size decline

for the TBR is most likely explained by factors other than differences in EEG signal processing, e.g. fewer hours of sleep in participants and differences in inclusion criteria for healthy controls

……..

Arch Pediatr. 2020.

COMPARING THE PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN HEARING-IMPAIRED CHILDREN WITH NORMAL-HEARING PEERS.

Soleimani R, Jalali MM, Faghih HA.

Objectives: The most important aspect of hearing loss is its effect on the communication abilities of individuals. The aim of this study was to compare the prevalence of attention deficit hyperactivity disorder (ADHD) in hearing-impaired (HI) children with normal-hearing (NH) peers.

Methods: A total of 130 children (65 children with severe-to-profound hearing loss and 65 NH peers) participated in this cross-sectional study from November 2013 to May 2014. ADHD Rating Scale IV questionnaires were given to children's parents to collect data. Descriptive and analytical analyses were used in order to achieve the objectives of the study.

Results: The mean age of the HI children and NH peers was 14.1 and 13.3 years, respectively. In the case group, 52 children suffered from congenital hearing loss and 10 children had acquired hearing loss. In total, 19 cases (29.2%) and eight controls (12.3%) were diagnosed with ADHD. This difference was statistically significant (P = 0.017). The prevalence of ADHD in children with hereditary or acquired hearing loss was 30.7% and 20.0%, respectively. However, this difference was not significant (P = 0.71).

Conclusion: The prevalence of ADHD in school-aged children with hearing loss is higher than that in the general population of the same age. We could not find significant differences between the different subgroups due to the small sample size. Therefore, we recommend a further larger study to determine the interaction between hearing loss and ADHD

……..

Archivos Argentinos de Pediatria. 2020;118:E405-E409.

ISOLATED ATTENTION DEFICIT DISORDER WITH/WITHOUT HYPERACTIVITY IN CLINICAL PRACTICE. SERIES OF CASES.

Andres MM, S+ínchez AMG, Navarcorena ALMD, et al.

Attention deficit disorder with hyperactivity has a high prevalence affecting 5 % of school-age children. We present a case series of 82 children with said disorder not associated with neurological diseases or intellectual disability or autism spectrum disorder, treated during a period of 8 months in a neuropediatrics clinic: 57 cases of combined type, 23 of inattentive type and 2 of overactive predominance. Average follow-up time: 7 ± 2.8 years (range: 4-14.6); 16 patients shared follow-up with Psychiatry; 12 patients never received treatment by parental decision. Of the 70 who received it, in 20 there was a delay in the start of treatment. Average delay time: 20 months ± 1.6 years (range: 1 month and 6 years). Average treatment time: 44 months ± 2.6 years (range: 1 month and 10.5 years); 90 % of the patients (63) who started treatment were under treatment at the last control

……..

Asian J Psychiatry. 2020;54.

RESTLESS LEGS SYNDROME IN CHILDREN WITH ADHD: A COMMON AND TREATABLE CONDITION, BUT FORGOTTEN BY PSYCHIATRISTS?

Srifuengfung M.

……..

Autism Res. 2020.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN YOUNG CHILDREN WITH AUTISM SPECTRUM DISORDER.

Hong JS, Singh V, Kalb L.

The purpose of the current study was to examine the prevalence of attention deficit hyperactivity disorder (ADHD) symptoms among young children with autism spectrum disorder (ASD), child and parent-related demographic and clinical correlates of ADHD symptoms, and the relationships between co-occurring mental health problems and ADHD symptoms. Data for this cross-sectional study came from 979 toddlers and preschoolers, ages 1.5ΓÇô5 years, with ASD. The primary outcome, ADHD symptoms, was measured using the Child Behavior Check List 1.5-5 (CBCL). Additional information from the medical record included demographics, parenting stress, and Autism Diagnostic Observation Schedule Second Edition. Descriptive and bivariate (ANOVA, Chi-Square) statistics and multivariate, multinomial regression analyses were used to examine demographic and clinical differences between low, moderate, and high ADHD symptom groups, as defined by 2 ADHD-related subscales. There were 418 (43%) children in the low ADHD symptom group, 294 (30%) in the moderate ADHD symptom group, and 267 (27%) in the high ADHD symptom group. Those with high ADHD symptoms were less likely to be Black or Hispanic and less likely to have parents with a graduate-level education compared to those with low ADHD symptoms. Parenting stress and all CBCL DSM-oriented subscales were positively associated with increasing ADHD symptoms. Among young children with ASD, ADHD symptoms were highly prevalent. The presence of ADHD symptoms was associated with increasing parenting stress and greater levels of other psychopathologies. These data suggest that young children with ASD should be evaluated for ADHD, and mental health as a whole. Lay Summary: We investigated attention deficit hyperactivity disorder (ADHD) symptoms in toddlers and preschoolers with autism spectrum disorder (ASD) from a large sample with diverse race and socioeconomic background. In our study, we found that ADHD symptoms are highly prevalent in young children with ASD and are associated with increasing parenting stress and greater level of other psychopathologies, both internalizing and externalizing problems

……..

Basic Clin Neurosci. 2020;11:359-68.

DISCRIMINATION OF ADHD SUBTYPES USING DECISION TREE ON BEHAVIORAL, NEUROPSYCHOLOGICAL, AND NEURAL MARKERS.

Rostami M, Farashi S, Khosrowabadi R, et al.

Introduction: Attention-Deficit/Hyperactivity Disorder (ADHD) is a well-known neurodevelopmental disorder. Diagnosis and treatment of ADHD can often lead to a developmental trajectory toward positive results. The present study aimed at implementing the decision tree method to recognize children with and without ADHD, as well as ADHD subtypes.

Methods: In the present study, the subjects included 61 children with ADHD (subdivided into ADHD-I (n=25), ADHD-H (n=14), and ADHD-C (n=22) groups) and 43 typically developing controls matched by IQ and age. The Child Behavior Checklist (CBCL), Integrated Visual And Auditory (IVA) test, and quantitative EEG during eyes-closed resting-state were utilized to evaluate the level of behavioral, neuropsychology, and electrophysiology markers using a decision tree algorithm, respectively.

Results: Based on the results, excellent classification accuracy (100%) was obtained to discriminate children with ADHD from the control group. Also, the ADHD subtypes, including combined, inattention, and hyperactive/impulsive subtypes were recognized from others with an accuracy of 80.41%, 84.17%, and 71.46%, respectively.

Conclusion: Our results showed that children with ADHD can be recognized from the healthy controls based on the neuropsychological data (sensory-motor parameters of IVA). Also, subtypes of ADHD can be distinguished from each other using behavioral, neuropsychiatric and electrophysiological parameters. The findings suggested that the decision tree method may present an efficient and accurate diagnostic tool for the clinicians

……..

Basic Clin Neurosci. 2020;11:313-22.

THE RELATIONSHIP BETWEEN ANTIOXIDANTS AND INFLAMMATION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Namjoo I, Naeini AA, Najafi M, et al.

Introduction: Recent studies have identified Attention Deficit Hyperactivity Disorder (ADHD) as an inflammatory condition associated with immunological and oxidative responses. Therefore, it is necessary to examine these processes in these patients. The present study aimed at investigating the relationship between the dietary intake of antioxidants, Superoxide Dismutase (SOD) activity, and the serum levels of inflammatory factors in ADHD students.

Methods: This retrospective case-control study was conducted on 64 ADHD children aged 6 - 13 years. The demographic questionnaire, Food Frequency Questionnaire, and Baecke Physical Activity Questionnaire were used for data collection. SOD activity and the serum level of inflammatory factors (homocysteine, interleukin-6, and C-reactive Protein (CRP)) were measured in all patients. According to the CRP values, 32 patients were included in the case group (CRP 1 mg/L) and 32 patients in the control group (0 CRP<1 mg/L).

Results: There was no significant difference between the two groups in age, sex, weight, height, and body mass index. In the case group, the mean SOD activity (P=0.034), the physical activity (P=0.04), zinc intake (P=0.02), and homocysteine levels were higher than the control group (P=0.001). Of all studied variables, the best predictors were homocysteine (OR: 1.34, 95% CI: 1.082-1.670, P=0.029) and physical activity (OR: 0.85, 95% CI: 0.761-0.952, P=0.022) respectively, whereas other variables were not significant predictors.

Conclusion: The present study showed that the level of inflammatory factors in the case group was significantly higher than the control group. Homocysteine and physical activity can predict the inflammation status induced by CRP

……..

Behav Brain Res. 2021;397.

HETEROGENEITY IN BRAIN FUNCTIONAL CHANGES OF COGNITIVE PROCESSING IN ADHD ACROSS AGE: A SYSTEMATIC REVIEW OF TASK-BASED FMRI STUDIES.

Yap KH, Abdul Manan H, Sharip S.

This review aims to establish the cognitive processing of patients with attention-deficit hyperactive disorder (ADHD) across age. Functional magnetic resonance imaging (fMRI) studies on children and adult populations were conducted, thus delineating deficits that could have been maintained and ameliorated across age. This allowed for the examination of the correlation between patterns of brain activation and the corresponding development of functional heterogeneity in ADHD. A systematic literature search of fMRI studies on ADHD was conducted using the PubMed and Scopus electronic databases based on PRISMA guidelines. References and citations were verified in Scopus database. The present study has identified 14 studies on children, 16 studies on adults, and one study on both populations of ADHD consisting of 1371 participants. Functional heterogeneity is present in ADHD across age, which can manifest either as different brain activation patterns, intra-subject variability, or both. This is shown in the increased role of the frontal regions and the specialized network in adults with ADHD from inefficient non-specific activation in childhood. Functional heterogeneity may manifest when delayed maturation is insufficient to normalize frontal lobe functions

……..

Biomedical Signal Processing and Control. 2021;63.

COMPUTER AIDED DIAGNOSIS SYSTEM USING DEEP CONVOLUTIONAL NEURAL NETWORKS FOR ADHD SUBTYPES.

Ahmadi A, Kashefi M, Shahrokhi H, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a ubiquitous neurodevelopmental disorder affecting many children. Therefore, automated diagnosis of ADHD can be of tremendous value. Unfortunately, unlike many other applications, the use of deep learning algorithms for automatic detection of ADHD is still limited.

Method: In this paper, we proposed a novel computer aided diagnosis system based on deep learning approach to classify the EEG signal of Healthy children (Control) from ADHD children with two subtypes of Combined ADHD (ADHD-C) and Inattentive ADHD (ADHD-I). Inspired by the classical approaches, we proposed a deep convolutional neural network that is capable of extracting both spatial and frequency band features from the raw electroencephalograph (EEG) signal and then performing the classification.
Result: We achieved the highest classification accuracy with the combination of ±1, ±2, and ± bands. Accuracy Recall, Precision, and Kappa values were %99.46, %99.45, %99.48, and 0.99, respectively. After investigating the spatial channels, we observed that electrodes in the Posterior side had the most contribution.
Conclusions: To the best of our knowledge, all previous multiclass studies were based on fMRI and MRI imaging. Therefore, the presented research is novel in terms of using a deep neural network architecture and EEG signal for multiclass classification of ADHD and healthy children with high accuracy

……..

BJOG. 2020 Nov;127:1488.
MATERNAL ADHD AND PRETERM BIRTH: INTERPRET WITH CARE.
Lane S.

……..

BMC Neurosci. 2020;21.
ABERRANT FUNCTIONAL CONNECTIVITY IN RESTING STATE NETWORKS OF ADHD PATIENTS REVEALED BY INDEPENDENT COMPONENT ANALYSIS.
Zhang H, Zhao Y, Cao W, et al.
Background: ADHD is one of the most common psychiatric disorders in children and adolescents. Altered functional connectivity has been associated with ADHD symptoms. This study aimed to investigate abnormal changes in the functional connectivity of resting-state brain networks (RSNs) among adolescent patients with different subtypes of ADHD.
Methods: The data were obtained from the ADHD-200 Global Competition, including fMRI data from 88 ADHD patients (56 patients of ADHD-Combined, ADHD-C and 32 patients of ADHD-Inattentive, ADHD-I) and 67 typically developing controls (TD-C). Group ICA was utilized to research aberrant brain functional connectivity within the different subtypes of ADHD.
Results: In comparison with the TD-C group, the ADHD-C group showed clusters of decreased functional connectivity in the left inferior occipital gyrus ($p = 0.0041$) and right superior occipital gyrus ($p = 0.0011$) of the dorsal attention network (DAN), supplementary motor area ($p = 0.0036$) of the executive control network (ECN), left supramarginal gyrus ($p = 0.0081$) of the salience network (SN), middle temporal gyrus ($p = 0.0041$), and superior medial frontal gyrus ($p = 0.0055$) of the default mode network (DMN), while the ADHD-I group showed decreased functional connectivity in the right superior parietal gyrus ($p = 0.0017$) of the DAN and left middle temporal gyrus ($p = 0.0105$) of the DMN. In comparison with the ADHD-I group, the ADHD-C group showed decreased functional connectivity in the superior temporal gyrus ($p = 0.0062$) of the AN, inferior temporal gyrus ($p = 0.0016$) of the DAN, and the dorsolateral superior frontal gyrus ($p = 0.0082$) of the DMN. All the clusters surviving at $p < 0.05$ (AlphaSim correction).
Conclusion: The results suggested that decreased functional connectivity within the DMN and DAN was responsible, at least in part, for the symptom of inattention in ADHD-I patients. Similarly, we believed that the impaired functional connectivity within networks may contribute to the manifestations of ADHD-C patients, including inattention, hyperactivity/impulsivity, and unconscious movements

……..

BMC Psychiatry. 2020;20.

ADHD SUBTYPE-SPECIFIC COGNITIVE CORRELATES AND ASSOCIATION WITH SELF-ESTEEM: A QUANTITATIVE DIFFERENCE.

Molavi P, Nadermohammadi M, Salvat Ghojehbeiglou H, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) is a major neurodevelopmental disorder with heterogeneous symptoms, subtypes, and cognitive deficits. Cognitive deficits are central to ADHD pathophysiology and one potential source of heterogeneity in ADHD. Subtype-specific cognitive correlates are not, however, well-studied. We explored cognitive correlates of ADHD subtypes based on the Wechsler Intelligence Scale for Children (WISC-IV) scores. We also assessed subtype-specific self-esteem rating in ADHD subtypes and explored its association with cognitive correlates.

Methods: One hundred thirty-nine children with ADHD (80.6% boy, 19.4% girl) were categorized into the predominantly "hyperactive (ADHD-H)", "inattentive (ADHD-I)"and "combined (ADHD-C)"subtype based on their symptoms and scores on the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) and Conners Parent-Rating Scale (CPRS-RS). They were then individually administrated the WISC-IV and completed a self-esteem inventory. Group differences in the WISC-IV indices and their predictability in discriminating ADHD subtypes were analyzed.

Results: We found a quantitative differentiation of cognitive abilities among ADHD subtypes with "working memory as the most compromised cognitive domain. ADHD-I had the poorest cognitive profile while ADHD-H scored highest in all cognitive domains. Importantly, cognitive abilities were negatively correlated with inattention and positively correlated with hyperactive symptoms. Moreover, self-esteem ratings were positively correlated with the cognitive domains and were rated differently based on the subtypes. ADHD-H, with the highest cognitive strength, reported the highest level of self-esteem among all subtypes.

Conclusions: ADHD subtype-specific symptoms, cognitive deficits, and self-esteem problems should be considered for precise diagnosis and effective and personalized treatment in ADHD in light of further supporting evidence and assessments. Cognitive interventions might be more compatible with and effective in inattentive and combined subtypes of ADHD. Working memory improving-based interventions can benefit all ADHD subtypes. A supportive educational system in school and providing adjunct supportive interventions should be considered for children with ADHD as well

……..

BMC Psychiatry. 2020;20.

LONG-TERM MELATONIN TREATMENT FOR THE SLEEP PROBLEMS AND ABERRANT BEHAVIORS OF CHILDREN WITH NEURODEVELOPMENTAL DISORDERS.

Yuge K, Nagamitsu S, Ishikawa Y, et al.

Background: Clinical evidence is required about the long-term efficacy and safety of melatonin treatment for sleep problems in children with neurodevelopmental disorders (NDDs) who underwent adequate sleep hygiene interventions.

Methods: We conducted a 26-week, multicenter, collaborative, uncontrolled, open-label, phase III clinical trial of melatonin granules in children 6 to 15 years of age who had NDDs and sleep problems. The study consisted of the 2-week screening phase, the 26-week medication phases I and II, and the 2-week follow-up phase. Children received 1, 2, or 4 mg melatonin granules orally in the medication phases. Variables of sleep status including sleep onset latency (SOL), aberrant behaviors listed on the Aberrant Behavior Check List-Japanese version (ABC-J), and safety were examined. The primary endpoint was SOL in the medication phase I.

Results: Between June 2016 and July 2018, 99 children (80 males and 19 females, 10.4 years in mean age) were enrolled at 17 medical institutions in Japan - 74, 60, 22, 9, 6, and 1 of whom had autism spectrum disorder, attention-deficit/hyperactivity disorder, intellectual disabilities, motor disorders, specific learning disorder, and communication disorders, respectively, at baseline. Fifteen children received the maximal dose of 4 mg among the prespecified dose levels. SOL recorded with the electronic sleep diary shortened significantly (mean -¦ standard deviation [SD], - 36.7 -¦ 46.1 min; 95% confidence interval [CI], - 45.9 to - 27.5; $P < 0.0001$) in the medication phase I from baseline, and the SOL-shortening effect of melatonin persisted in the medication phase II and the follow-up phase. Temper upon wakening and sleepiness after awakening improved significantly ($P < 0.0001$ each) in the medication phase I from baseline and persisted in the follow-

up phase. The following subscales of the ABC-J improved significantly: stereotypic behavior (P = 0.0322) in the medication phase I; and irritability, hyperactivity, and inappropriate speech (P < 0.0001) in the medication phase II. Treatment-emergent adverse events did not occur subsequent to week 16 after medication onset, and NDDs did not deteriorate in the follow-up phase.
Conclusions: Long-term melatonin treatment in combination with adequate sleep hygiene interventions may afford clinical benefits to children with NDDs and potentially elevates their well-being. Trial registration: ClinicalTrils.gov, NCT02757066. Registered April 27, 2016

……..

BMC Psychiatry. 2020;20.
INTERACTION BETWEEN LEAD AND NORADRENERGIC GENOTYPES AFFECTS NEUROCOGNITIVE FUNCTIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CASE CONTROL STUDY.
Choi JW, Jung AH, Nam S, et al.
Background: Lead is known to be associated with attention-deficit/hyperactivity disorder (ADHD) even at low concentrations. We aimed to evaluate neurocognitive functions associated with lead in the blood and the interactions between lead and dopaminergic or noradrenergic pathway-related genotypes in youths with ADHD.
Methods: A total of 259 youths with ADHD and 96 healthy controls (aged 5-18 years) enrolled in this study. The Korean Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version was conducted for psychiatric diagnostic evaluation. Blood lead levels were measured, and their interaction with dopaminergic or noradrenergic genotypes for ADHD; namely, the dopamine transporter (DAT1), dopamine receptor D4 (DRD4), and alpha-2A-adrenergic receptor (ADRA2A) genotypes were investigated. All participants were assessed using the ADHD Rating Scale-IV (ADHD-RS). Participants also completed the continuous performance test (CPT) and Stroop Color-Word Test (SCWT). Analysis of covariance was used for comparison of blood lead levels between ADHD and control groups. A multivariable linear regression model was used to evaluate the associations of blood lead levels with the results of ADHD-RS, CPT, and SCWT; adjusted for intelligence quotient (IQ), age, and sex. A path analysis model was used to identify the mediating effects of neurocognitive functions on the effects of blood lead on ADHD symptoms. To evaluate the effect of the interaction between blood lead and genes on neuropsychological functions, hierarchical regression analyses were performed.
Results: There was a significant difference in blood lead levels between the ADHD and control groups (1.4 -¦ 0.5 vs. 1.3 -¦ 0.5 ++g/dL, p =.005). Blood lead levels showed a positive correlation with scores on omission errors(r =.158, p =.003) and response time variability (r =.136, p =.010) of CPT. In the multivariable linear regression model, blood lead levels were associated with omission errors (B = 3.748, p =.045). Regarding the effects of lead on ADHD symptoms, hyperactivity-impulsivity was mediated by omission errors. An interaction effect was detected between ADRA2A DraI genotype and lead levels on omission errors (B = 5.066, p =.041).
Conclusions: Our results indicate that neurocognitive functions at least partly mediate the association between blood lead levels and ADHD symptoms, and that neurocognitive functions are affected by the interaction between blood lead levels and noradrenergic genotype

……..

BMC Psychiatry. 2020 Oct;20:511.
THE IMMEDIATE EFFECT OF COVID-19 PANDEMIC ON CHILDREN AND ADOLESCENTS WITH OBSESSIVE COMPULSIVE DISORDER.
Nissen JB, HÃ¸jgaard DRMA, Thomsen PH.
BACKGROUND: Obsessive compulsive disorder (OCD) is a distressing psychiatric disorder. Traumas may trigger or aggravate OCD symptoms. COVID-19 pandemic has coursed a global crisis and has been associated with onset of psychiatric disorders in adults. Little is known about children/adolescents with OCD. The present study aimed to examine how children/adolescents with OCD react towards COVID-19 crisis.

METHODS: A questionnaire was distributed to two separate groups of children/adolescents. One group was a clinical group newly diagnosed at a specialized OCD clinic. All the children/adolescents had a current close contact to a therapist or doctor. The other group was a survey group identified through the Danish OCD Association. Most of these children/adolescents were diagnosed years ago, and their primary treatment was completed. For the clinical group, data from patient files was available.
RESULTS: In both groups, but most pronounced in the survey group, participants experienced a worsening of their OCD, anxiety, and depressive symptoms. The aggravation of OCD correlated with the worsening of anxiety, depressive symptoms, and the extent of avoidance behavior. For both groups, OCD aggressive symptoms predicted a significant worsening. Poor baseline insight showed a trend to predict a symptom worsening. The worsening was most pronounced in children with early age of onset and a family history of attention deficit hyperactivity disorder.
CONCLUSIONS: To our knowledge, this is one of the first studies examining the effect of COVID-19 in children/adolescents with OCD. The effect was examined in two separate populations strengthening the findings. The study points towards an influence of the OCD phenotype, baseline insight suggesting a continued vulnerability, and a family history of psychiatric disorders. TRIAL REGISTRATION: The study is approved by the Danish Data Protection Agency (1-16-02-147-20) registered 1st of April 2020. Oral and written information was given to parents and patients and written consent from patients over 15â€‰years and parents were received

……..

Brain Res. 2021;1750.

INVESTIGATING BRAIN ELECTRICAL ACTIVITY AND FUNCTIONAL CONNECTIVITY IN ADOLESCENTS WITH CLINICALLY ELEVATED LEVELS OF ADHD SYMPTOMS IN ALPHA FREQUENCY BAND.

Debnath R, Miller NV, Morales S, et al.

EEG measures such as power and connectivity have been widely used to investigate the neuronal underpinnings of ADHD. Traditionally, the fixed band analysis, in which a single frequency band is applied to all the subjects, has been used to estimate these EEG measures. However, there are important interindividual differences in the predominant frequency of alpha-band oscillations. In this study, we present an individualized estimate of EEG in the alpha band and compared the results with traditional fixed band analysis. We also examined the EEG profile separately in lower and upper alpha bands. We further examined the association between EEG measures and ADHD symptoms. Eyes closed resting EEG was collected from 21 adolescents with clinically elevated levels of ADHD and 21 age and gender matched control subjects. Spectral power and connectivity were computed in lower and upper alpha bands. Results revealed a dissociation between upper and lower alpha band power and connectivity in ADHD. The ADHD group showed reduced power and connectivity in the lower alpha band and an elevation of upper alpha power compared to the Control group. EEG power in the lower alpha band was negatively associated with ADHD severity. Our results, however, did not provide conclusive evidence for IAF as an overall greater measure of EEG compared to the traditional fixed band method

……..

Brain Sciences. 2020;10:1-17.

A NATURALISTIC STUDY OF YOUTH REFERRED TO A TERTIARY CARE FACILITY FOR ACUTE HYPOMANIC OR MANIC EPISODE.

Masi G, Berloffa S, Muratori P, et al.

Background: Bipolar Disorders (BD) in youth are a heterogeneous condition with different phenomenology, patterns of comorbidity and outcomes. Our aim was to explore the effects of gender; age at onset (prepubertal- vs. adolescent-onset) of BD; and elements associated with attention deficit hyperactivity disorder (ADHD) and Substance Use Disorder (SUD) comorbidities, severe suicidal ideation or attempts, and poorer response to pharmacological treatments.

Method: 117 youth(69 males and 57 females, age range 7 to 18 years, mean age 14.5±2.6 years) consecutively referred for (hypo)manic episodes according to the Diagnostic and Statistical Manual of Mental Disorders,54th ed (DSM 5) were included.
Results: Gender differences were not evident for any of the selected features. Prepubertal-onset BD was associated with higher rates of ADHD and externalizing disorders. SUD was higher in adolescent-onset BD and was associated with externalizing comorbidities and lower response to treatments. None of the selected measures differentiated patients with or without suicidality. At a 6-month follow up, 51.3% of the patients were responders to treatments, without difference between those receiving and not receiving a psychotherapy. Clinical severity at baseline and comorbidity with Conduct Disorder (CD) and SUD were associated with poorer response. Logistic regression indicated that baseline severity and number of externalizing disorders were associated with a poorer outcome.
Conclusions: Disentangling broader clinical conditions in more specific phenotypes can help timely and focused preventative and therapeutic interventions

……..

Can J Occup Ther. 2020 Oct;87:278-86.
CO-OP FOR CHILDREN WITH DCD: GOALS ADDRESSED AND STRATEGIES USED.
Schwartz SP, Northrup SRK, Izadi-Najafabadi S, et al.
Introduction: Developmental coordination disorder (DCD) is a neurodevelopmental disorder that impacts motor coordination and interferes with participation in everyday activities. Cognitive Orientation to Occupational Performance (CO-OP) is a client-centered treatment approach that focuses on skill acquisition through cognitive strategy use.
Objectives: To determine which types of goals a sample of children with DCD choose most frequently and which domain-specific strategies were most commonly used to address these goals.
Methods: Retrospective chart review of 50 children (8–12 years) with DCD who completed CO-OP intervention was conducted to identify goal types and strategy use.
Results: Leisure was the most common goal type. Supplementing task knowledge, body position, and task modification were the most frequently used strategies.
Conclusions: Results confirm the types of goals that are commonly selected by children with DCD and highlight commonly used strategies used to meet these goals. Findings will help guide occupational therapists in selecting appropriate strategies to meet children's goals

……..

Child Adolesc Psychiatr Clin North Am. 2020.
THE ASSOCIATIONS BETWEEN SLEEP AND EXTERNALIZING AND INTERNALIZING PROBLEMS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EMPIRICAL FINDINGS, CLINICAL IMPLICATIONS, AND FUTURE RESEARCH DIRECTIONS.
Dimakos J, et al.
Sleep problems are common in youth with attention-deficit/hyperactivity disorder (ADHD). Externalizing and internalizing problems contribute to dysfunction in youth with ADHD and are amplified by disrupted sleep. This objective of this article is to synthesize empirical studies that examined the associations between sleep and internalizing or externalizing problems in individuals with ADHD. The main findings are that sleep problems precede, predict, and significantly contribute to the manifestation of internalizing and externalizing behavior problems among children and adolescents with ADHD. Clinicians should assess sleep and integrate sleep interventions into the management of youth with ADHD

……..

Clin Exp Allergy. 2020.

ASSOCIATION BETWEEN CHILDHOOD ASTHMA AND ATTENTION DEFICIT HYPERACTIVITY OR AUTISM SPECTRUM DISORDERS: A SYSTEMATIC REVIEW WITH META-ANALYSIS.

Kaas TH, Vinding RK, Stokholm J, et al.

Background Children with asthma are at risk of depression and anxiety and growing evidence suggest they may also be at risk of attention deficit hyperreactivity disorder (ADHD) and autism spectrum disorder (ASD). Here, we conducted a systematic review with meta-analysis of studies investigating association between asthma and ADHD or ASD in children.

Methods A comprehensive search using PubMed, EMBASE and Cochrane Library databases was completed in March 2019. Observational human studies published in English, clinic-based or population-based with a healthy comparator group, evaluating asthma-ADHD or asthma-ASD overlap in children 18 years or younger using categorical diagnoses (yes/no) were considered for inclusion. Random effects meta-analysis models were used to analyse data. The Newcastle Ottawa Scale was used to evaluate risk of bias.

Results A total of 25 asthma-ADHD studies were included of which 17 showed significant positive associations and one a negative association: 17/25 studies were population-based, 19/25 were cross-sectional or cohort studies and 7/25 had a low risk of bias. We performed a meta-analysis of 23 of the studies, which showed a significant association between asthma and ADHD: odds ratio (OR) 1.52 (1.42-1.63), P < .001, I2 = 60%. All studies were adjusted for age and sex and a large proportion; that is, 19/23 were further adjusted for relevant confounders. Seventeen asthma-ASD studies were included, whereof 7 showed a positive association and 3 a negative association; 8/17 were population-based with a cross-sectional study design and 4/17 had a low risk of bias. We performed a meta-analysis of 14 of the studies, which did not show a significant association between asthma and ASD: OR 1.12 (0.93-1.34), P = .24, I2 = 89%. All studies were adjusted for age and sex and 10/14 were further adjusted for relevant confounders.

Conclusions This systematic review with meta-analyses shows a significant overlap between asthma and ADHD, but not between asthma and ASD in children. Clinicians taking care of children with asthma or ADHD should be aware of such association to aid an early diagnosis and treatment of such comorbidity.

……..

Clin EEG Neurosci. 2020.

QUANTITATIVE EEG IN CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER AND LEARNING DISABILITIES.

Chiarenza GA.

The clinical use of the quantitative EEG (QEEG) from the pioneering work of John has received a new impetus thanks to new neuroimaging techniques and the possibility of using a number of normative databases both of normal subjects and of subjects with definite pathologies. In this direction, the term personalized medicine is becoming more and more common, a medical procedure that separates patients into different groups based on their predicted response to the quantitative EEG. This has allowed the study of single subjects and to customize health care, with decisions and treatments tailored to each individual patient, as well as improvement of knowledge of the pathophysiological mechanisms of specific diseases. This review article will present the most recent evidence in the field of developmental neuropsychiatric disorders obtained from the application of quantitative EEG both in clinical group studies (attention deficit hyperactivity disorder, developmental dyslexia, oppositional defiant disorder) and in individual case studies not yet published

……..

Clinical Epidemiology and Global Health. 2020;8:1155-57.

STRESS AMONG THE CAREGIVERS OF MENTALLY DISABLED CHILDREN VISITING A REHABILITATION CENTRE IN CHENNAI, TAMIL NADU – A CROSS-SECTIONAL STUDY

Ramachandran A, Vyas N, Pothiyil DI.

Caregiving is a complex health care activity, from an informal family level activity; it is becoming a major part of health care. In India, family members are mostly caregivers for persons with mental disabilities. The present study assessed the stress among the caregivers of mentally disabled children (Autistic Spectrum

Disorder, Intellectual Disability, and Attention Deficit Hyperactivity Disorder) and found the association between stress and selected socio-demographic variables. This was an institutional based cross-sectional study with a duration of six months, i.e. from January 2019 to June 2019. This study was conducted among the caregivers availing services (therapies and follow-ups) at the National Institute for Empowerment of Persons with Multiple Disabilities, Chennai, Tamil Nadu. The level of stress was assessed using the Kingston Caregiver Stress Scale. This study was conducted with time-bound complete enumeration method, by which data from 101 participants were collected. The results of this study showed that 64.3% of the caregivers had the severe level of stress, 21.7% of the caregivers had a moderate level of stress and 13.8% of the caregivers had mild stress. Hence, it can be concluded that caregiver's stress is an important element to determine the burden and the unexplained psychological pressure a caregiver holds onto

……..

Clin Ther. 2020.

PYRIDOXINE AND MAGNESIUM ADMINISTRATIONΓÇôINDUCED HYPERACTIVITY IN TWO CHILDREN WITH AUTISM SPECTRUM DISORDER: CASE REPORTS FROM A CLINICAL TRIAL.

Debi Ann A, Udayakumar N, Senta C, et al.

Purpose: Pyridoxine hydrochloride and magnesium sulfate (pyridoxine-Mg) have been used for the management of autism spectrum disorder (ASD). We present a case report of 2 children with ASD who were administered pyridoxine-Mg for 2 months.

Methods: The Childhood Autism Rating Scale, Second Edition, was used to confirm the adverse reaction. The Naranjo Adverse Drug Reaction Probability Scale was used to assess causality.

Results: Children were reported by their parents as being hyperactive. Evaluation by the psychologist using the Childhood Autism Rating Scale, Second Edition, also confirmed the reaction. According to the Naranjo scale, hyperactivity had a possible and probable association with pyridoxine-Mg for child 1 and 2, respectively.

Implications: A probable to possible association exists between hyperactivity and pyridoxine-Mg.

Clinical Trial Registry India identifier: CTRI/2019/07/020102

……..

Cogn Ther Res. 2020.

PSYCHOTHERAPY, ATOMOXETINE OR BOTH? PRELIMINARY EVIDENCE FROM A COMPARATIVE STUDY OF THREE TYPES OF TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

David D, Dobrean A, et al.

Background The current study aimed to investigate using a superiority framework the efficacy of a combined treatment (cognitive-behavioral therapy based on behavioral components derived from classical behavioral therapy modifications and cognitive components mainly derived from rational emotive behavior therapy, plus an attention training component in a virtual environment (CBT/REBT + ATX, N = 20) as compared to psychotherapy alone (CBT/REBT, delivered over 16 weeks, N = 18—reference treatment) and non-stimulant medication alone (atomoxetine; ATX, N = 21—reference treatment) for children with Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods A three-arm pilot randomized controlled trial was conducted. Fifty-nine children (Mage = 8.46, SD = 1.57) were randomly allocated to one of the 3 conditions.

Results Our preliminary findings indicated a significant difference between the CBT/REBT + ATX and ATX group at post-treatment for the total ADHD symptoms rated by parent, d = 1.30, 95% CI [0.63, 1.98], p = 0.010.

Conclusions The combined treatment seems to be superior to the medication alone on parent ratings on ADHD symptoms, however, on clinical ratings on ADHD diagnosis and functioning there are no significant group differences between treatments. Future larger trials with follow-up assessments are needed to test the stability of the effects over time

……..

Complement Ther Med. 2020;53.

SUGAR CONSUMPTION, SUGAR SWEETENED BEVERAGES AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Farsad-Naeimi A, Asjodi F, Omidian M, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is a significant neurobehavioral disorder in children and adolescence which may be affected by diet. Objective: To evaluate the possible relationship between sugar consumption and the development of symptoms of ADHD.

Methods: In March 2020, an exhaustive systematic literature search was conducted using Google Scholar, PubMed, and Scopus. In this meta-analysis of observational studies, odds ratios, relative risks, hazard ratios, and their 95% confidence intervals, which was reported for ADHD regarding SSBS, soft drink consumption, and dietary sugars, were used to calculate ORs and standard errors. At first, a fixed-effects model was used to drive the overall effect sizes using log ORs and SEs. If there was any significant between-studies heterogeneity, the random-effects model was conducted. Cochran's Q test and I2 were used to measure potential sources of heterogeneity across studies. The Newcastle-Ottawa scale was used to assess the quality of the included articles.

Results: Seven studies, two cross-sectional, two case-control, and three prospective with a total of 25,945 individuals were eligible to include in the current meta-analysis. The association between sugar and soft drink consumption and the risk of ADHD symptoms were provided based on the random-effects model (pooled effect size: 1.22, 95%CI: 1.04-1.42, P = 0.01) (I-¦ = 81.9%, P heterogeneity< 0.0001).

Conclusion: This meta-analysis indicated a positive relationship between overall sugar and sugar-sweetened beverages consumption and symptoms of ADHD; however, there was heterogeneity among included studies. Future well-designed studies that can account for confounds are necessary to confirm the effect of sugar on ADHD

……..

Dev Med Child Neurol. 2020.

WHAT IS THE EFFECT OF PHARMACOLOGICAL TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH COMORBID TIC DISORDERS? A COCHRANE REVIEW SUMMARY WITH COMMENTARY.

Malmivaara A.

……..

Dokkyo J Med Sci. 2020;47:73-78.

TWO CASES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER(ADHD)IN A FAMILY.

Watanabe T, Furukori N, Shimoda K.

This is a case report of both of a father and his daugh-ter who contracted attention-deficit/hyperactivity disorder ADHD. Although the onset of ADHD is before the age of 12 years, the neurodevelopmental trajectory shows a various pattern in terms of clinical symptoms, comorbid disorders, social impairment. Some patients have persis-tence of ADHD-related symptoms and fulfill the complete ADHD criteria in adult, and the other patients, only in their childhood. Nevertheless, ADHD-related symptoms, together with relevant comorbid other psychiatric disor-ders can cause suffering as well. Recent genetic studies indicate many different genetic factors might be associated with ADHD. Occasionally there are several differences in main clinical symptoms, comorbid disorder, and drug treat-ment response in a family. These differences are interpret-ed by polygenic model

……..

Drug Metabolism and Pharmacokinetics. 2020.

POPULATION PHARMACOKINETIC AND EXPOSURE-RESPONSE ANALYSES OF D-AMPHETAMINE AFTER ADMINISTRATION OF LISDEXAMFETAMINE DIMESYLATE IN JAPANESE PEDIATRIC ADHD PATIENTS.

Tsuda Y, Matsuo Y, Matsumoto S, et al.

Lisdexamfetamine dimesylate, a prodrug of d-amphetamine, has been approved for treatment of attention-deficit/hyperactivity disorder (ADHD). The purposes of this study were constructing a population pharmacokinetic model of d-amphetamine after dosing of lisdexamfetamine dimesylate and assessing influential factors on the pharmacokinetics of d-amphetamine in Japanese pediatric patients with ADHD. Additionally, the exposure-response relationship was evaluated for Japanese pediatric patients with ADHD using a clinical rating scale, the ADHD Rating Scale IV (ADHD RS-IV, efficacy endpoint) total score as a response index. A total of 1365 points of plasma d-amphetamine concentrations from pediatric patients (6ΓÇô17 years) with ADHD in clinical studies conducted in Japan and the US were employed for the population pharmacokinetic analysis. The plasma concentrations of d-amphetamine in pediatric patients with ADHD were well described by a one-compartment model with first-order absorption and lag time. The effects of body weight and ethnicity (Japanese or non-Japanese) on apparent total body clearance and the effect of body weight on apparent volume of distribution were incorporated into the final model. No clear exposure-dependent reduction was evident from the ADHD RS-IV total score, whereas the reductions were greater for the lisdexamfetamine dimesylate treatment groups compared with the placebo group regardless of exposure to d-amphetamine

……..

Dusunen Adam. 2020;33:228-36.

EMOTIONAL REGULATION AND ATTACHMENT STYLE IN PREVIOUSLY UNTREATED ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Eyuboglu M, Eyuboglu D.

Objective: The aim of our study was to evaluate adolescents who have been diagnosed with attention deficit hyperactivity disorder (ADHD) for the first time, in terms of difficulties in emotion regulation and attachment characteristics and to compare them with healthy controls.

Method: The study is a cross-sectional with a healthy control group. A total of forty eight untreated adolescents with ADHD and 51 healthy subjects participated in the study. To determine the psychiatric disorders, all adolescents were assessed with a structural interview. All participants were assessed by WISC-R intellegence test. Emotion regulation and attachment characteristics were assessed by Difficulties in Emotion Regulation Scale and the Experiences in Close Relationships Scale. The ADHD symptoms of case group were evaluated by Conners' Parent Rating Scale which was competed by parents.

Results: Adolescents with ADHD displayed worse performance in emotion regulation. The avoidant attachment score was also higher in these adolescents. Furthermore, emotional regulation difficulties and attachment scores correlated with the severity of ADHD.

Conclusion: It has been shown that difficulty in emotion regulation and insecure-avoidant attachment styles have been more common in untreated adolescents with ADHD. The findings of our study support the view that ADHD is a heterogeneous condition and insecure attachment style and emotional regulation should be considered in the assessment and treatment of ADHD

……..

Dusunen Adam. 2020;33:289-95.

COMPARISON OF SOCIAL COGNITION IN ADOLESCENTS DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Dagdelen F.

Objective: The aim of this study was to analyze social cognition deficits of children with autism spectrum disorder (ASD) and attention deficit-hyperactivity disorder (ADHD) in their performance on explicit and applied measures of theory of mind (ToM) skills.

Method: This study comprised of 120 patients with ADHD and ASD according to DSM-5, between 12-16 ages, and 60 adolescents without any psychiatric diagnosis. Turkish version of Schedule for Affective Disorders and Schizophrenia for School-Age-Children Present and lifetime version were applied in order to assess psychopathology. Intelligence level of patients were assessed with Wechsler Intelligence Scale for Children-Revised. Reading the Mind in the Eyes test, Faus pax test and The Hinting task were used in patients to evaluate ToM skills.
Results: Adolescent patients with ADHD and ASD have difficulties in ToM skills. Adolescents diagnosed with ASD had more difficulty in ToM skills than adolescents with ADHD.
Conclusion: This study supports the idea that ADHD and ASD is related to deficits in social cognition skills. Therefore, interventions to improve social cognition skills may help improve the compliance with treatment and increase treatment effectiveness of ADHD and ASD cases

……

Duzce Med J. 2020;22:84-90.

EVALUATION OF THE INDICATORS OF INFLAMMATION IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER: EFFECT OF SEX AND SUBTYPE.

Aksu GGULER, et al.

Aim: It was aimed to evaluate the hematological inflammatory markers in treatment-naive and comorbidity-free children and adolescents with attention deficit and hyperactivity disorder (ADHD) in this study.
Material and Methods: One hundred sixty-nine children aged 6-18, who were diagnosed with ADHD according to DSM-5 criteria were included in the study. Age and sex-matched 59 healthy children without any psychiatric and/or medical disorder were included as a control group. The children who had an intellectual disability and/or autism spectrum disorder, acute, chronic or inflammatory diseases were excluded from the study. Smoking, obesity and using psychotropic medications and lack of data in records were other exclusion criteria. ADHD and control groups were compared in terms of sociodemographic characteristics, inflammatory markers and hematological parameters.
Results: Mean platelet volume (MPV) and Basophil (BASO) levels were significantly higher in the ADHD group compared to the control group and this statistical difference was only observed for boys. In hyperactivity subtype, red cell distribution width (RDW), lymphocyte (LYMPH) and monocytes (MONO) were higher; in attention deficit subtype mean platelet volume-to-lymphocyte ratio (MPVLR) was higher than all other subtypes and control group. MPV was similar in three subtypes, and were higher in all of them than the control group.
Conclusion: This study revealed that MPV and BASO tend to be higher in the ADHD group especially in boys. Hematological biomarkers may be useful for diagnosis of ADHD and determination of ADHD subtypes but data on this subject are insufficient and more comprehensive studies are needed

……

Environ Health Perspect. 2020;128:1-10.

EXPOSURE TO MANGANESE IN DRINKING WATER DURING CHILDHOOD AND ASSOCIATION WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A NATIONWIDE COHORT STUDY.

Schullehner J, Thygesen M, Kristiansen SM, et al.

BACKGROUND: Manganese (Mn) in drinking water may increase the risk of several neurodevelopmental outcomes, including attention-deficit hyperactivity disorder (ADHD). Earlier epidemiological studies on associations between Mn exposure and ADHD-related outcomes had small sample sizes, lacked spatiotemporal exposure assessment, and relied on questionnaire data (not diagnoses) shortcomings that we address here.
OBJECTIVE: Our objective was to assess the association between exposure to Mn in drinking water during childhood and later development of ADHD.
METHODS: In a nationwide population-based registry study in Denmark, we followed a cohort of 643,401 children born 1992-2007 for clinical diagnoses of ADHD. In subanalyses, we classified cases into ADHD-Inattentive and ADHD-Combined subtypes based on hierarchical categorization of International

Classification of Diseases (ICD)-10 codes. We obtained Mn measurements from 82,574 drinking water samples to estimate longitudinal exposure during the first 5 y of life with high spatiotemporal resolution. We modeled exposure as both peak concentration and time-weighted average. We estimated sex-specific hazard ratios (HRs) in Cox proportional hazards models adjusted for age, birth year, socioeconomic status (SES), and urbanicity.
RESULTS: We found that exposure to increasing levels of Mn in drinking water was associated with an increased risk of ADHD-Inattentive subtype, but not ADHD-Combined subtype. After adjusting for age, birth year, and SES, females exposed to high levels of Mn (i.e., >100 lg=L) at least once during their first 5 y of life had an HR for ADHD-Inattentive subtype of 1.51 [95% confidence interval (CI): 1.18, 1.93] and males of 1.20 (95% CI: 1.01, 1.42) when compared with same-sex individuals exposed to <5 lg=L. When modeling exposure as a time-weighted average, sex differences were no longer present.
DISCUSSION: Mn in drinking water was associated with ADHD, specifically the ADHD-Inattentive subtype. Our results support earlier studies suggesting a need for a formal health-based drinking water guideline value for Mn. Future Mn-studies should examine ADHD subtype-specific associations and utilize direct subtype measurements rather than relying on ICD-10 codes alone. https://doi.org/10.1289/EHP6391

……..

Epigenomics. 2020;12:813-23.
GENETIC AND EPIGENETIC MTHFR GENE VARIANTS IN THE MOTHERS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AFFECTED CHILDREN AS POSSIBLE RISK FACTORS FOR NEURODEVELOPMENTAL DISORDERS.
Piras IS, Costa A, Tirindelli MC, et al.
Aim: To assess promoter methylation levels, gene expression levels and 677C>T/1298A>C genotype and allele frequencies of the MTHFR gene in 45 mothers of attention-deficit/hyperactivity disorder affected child/children (ADHDM) and compare it with age matched healthy control mothers (HCM).
Materials & methods: High resolution melting analysis, quantitative real time PCR and PCR-RFLP were performed to assess methylation, gene expression and genotyping, respectively. Significance between ADHDM and HCM was assessed by linear (methylation and gene expression) and logistic regression (genotypes).
Results: MTHFR gene expression levels were significantly higher in the ADHDM compared with the HCM group (adj-p < 7.7E-04). No differences in MTHFR promoter methylation level and 677C>T/1298A>C genotype frequencies were detected between ADHDM and HCM.
Conclusion: We observed increased MTHFR expression levels not resulting from promoter methylation changes in ADHDM respect to HMC, potentially contributing to the ADHD condition in their children and deserving further investigation

……..

Erciyes Medical Journal. 2019;41:52.
INVESTIGATION OF CYP2D6 VARIANTS IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.
Akalin H, Erdem Y, Ozmen S, et al.
ADHD is a chronic condition that is constantly marked with inattention, hyperactivity and sometimes impulsivity. Stimulants such as methylphenidate and nonstimulants such as atomoxetine are commonly used drugs in ADHD treatment. Cytochrome P450 2D6 (CYP2D6) plays a role in the metabolism of up to 25% of clinically used drugs. Polymorphisms in this gene cause significant changes in CYP2D6 enzyme activity and serve as biomarkers that guide drug therapy. Our aim is to determine the effect of variants of CYP2D6 gene on the metabolism of drugs used in ADHD. For this purpose, Clinical Global Impression (CGI) scales of patients were evaluated. The severity of the disease (CGI-S) or the degree of improvement (CGI-I) was graded between 0 (not ill at all) and 7 (extremely ill). Forty-three children with ADHD and thirty-eight healthy children of similar age were included in the study. The patient group was divided into two according to drug use, thirty-five methylphenidate and eight atomoxetine users. DNA was isolated from 2ml of blood, which was collected from all the children in the study. The mutation analysis was performed by pyro-sequencing method to investigate the effect of five different CYP2D6-3, CYP2D6-4, CYP2D6-5, CYP2D6-6 and CYP2D6-

10 alleles on disease and treatment processes. In our preliminary study, Pearson correlation analysis was conducted between CYP2D6 variants and CGI scores of the patients and no statistically significant relationship was found (p>0.05). In order to fully demonstrate the association of CYP2D6 gene with methylphenidate, atomoxetine therapy, there is a need for more patients and studies with different groups

……..

Erciyes Medical Journal. 2019;41:37.

GENE EXPRESSION RESEARCH IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Akalin H, Erdem Y, Ozmen S, et al.

Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder that affects usually children and adolescents. Besides it also effects also adults. Especially, twin and adoption studies show ADHD to be highly heritable. Therefore, in this study, we aimed to explore expression analysis of particular genes and effects of different alleles of selected gene on children with ADHD which are highly suspicious genes. Besides, different children with ADHD use different drugs which are used for ADHD treatment were researched to explore of this expression and allele analysis studies. This study was comprised of three groups as control group without ADHD, children with ADHD treated with methylphenidate and atomoxetine. Samples were collected both pre-treatment and posttreatment for children with ADHD. SLC6A3, SLC6A4, SLC1A2, VMAT2, MAOA, COMT, GLYAT, GRM5, DRD4, TPH and ADRA2C genes, which are suspicious genes associated with ADHD, were selected for expression analysis. Besides CYP2D6−3, CYP2D6-4, CYP2D6-5, CYP2D6-6 and CYP2D6-10 alleles were analyzed and corelated with treatment of patient children. As a conclusion, expression analysis showed us there were significant differences for ADHD and treatment caused return to normal of the expression of determined genes. However, there is no any significance correlations among analysis of CYP2D6 alleles, cause of there was not enough sample for each combination of sample groups (pre-treated/post-treated ADHD samples with MHP/ATX and 5 different allele combinations). As further studies, larger group which include more patient children and children have more different allele group should be organized and studied to explain correlation between alleles, ADHD and treatment

……..

Eur Child Adolesc Psychiatry. 2020 Oct;29:1453-64.

CHARACTERISTICS OF CHILD PSYCHIATRIC OUTPATIENTS WITH SLOW PROCESSING SPEED AND POTENTIAL MECHANISMS OF ACADEMIC IMPACT.

Braaten EB, Ward AK, Forchelli G, et al.

While slow processing speed (PS) is well documented in youth with ADHD, growing evidence suggests that this difficulty affects children with other neuropsychiatric conditions. Clarifying the relationship between slow PS and different forms of psychopathology is important clinically, given the potential impact of PS on academic functioning, and conceptually. In 751 youth, ages 6-21, consecutively referred for neuropsychiatric evaluation, we examined the association between slow PS (i.e., Wechsler PS Index < 85) and seven neuropsychiatric diagnostic groups. In 492 of these youth, we also related slow PS to eight psychopathology symptom dimensions. Finally, we modeled the relationship between PS, other cognitive functions and academic achievement. Data are from the Longitudinal Study of Genetic Influences on Cognition. Analyses included one-sample t tests, ANOVA, logistic regression, mixed modeling, and structural equation modeling (SEM), controlling for age, sex, and medication. Compared to normative data, all clinical groups showed PS decrements. Compared to referred youth without full diagnoses and accounting for other psychopathology, risk for slow PS was elevated in youth with autism spectrum disorder (OR = 1.8), psychotic disorders (OR = 3.4) and ADHD-inattentive type (OR = 1.6). Having multiple comorbidities also increased risk for slow PS. Among dimensions, inattention (OR = 1.5) associated with slow PS but did not fully explain the association with autism or psychosis. In SEM, PS had direct effects on academic achievement and indirect effects

through working memory. Findings extend evidence that PS relates to multiple aspects of child psychopathology and associates with academic achievement in child psychiatric outpatients

……..

Eur Child Adolesc Psychiatry. 2020 Oct;29:1411-24.

THE PREMONITORY URGE FOR TICS SCALE IN A LARGE SAMPLE OF CHILDREN AND ADOLESCENTS: PSYCHOMETRIC PROPERTIES IN A DEVELOPMENTAL CONTEXT. AN EMTICS STUDY.

Openneer TJC, et al.

Premonitory urges are uncomfortable physical sensations preceding tics that occur in most individuals with a chronic tic disorder. The Premonitory Urge for Tics Scale (PUTS) is the most frequently used self-report measure to assess the severity of premonitory urges. We aimed to evaluate the psychometric properties of the PUTS in the largest sample size to date (n = 656), in children aged 3-16 years, from the baseline measurement of the longitudinal European Multicenter Tics in Children Study (EMTICS). Our psychometric evaluation was done in three age-groups: children aged 3-7 years (n = 103), children between 8 and 10 years (n = 253), and children aged 11-16 years (n = 300). The PUTS exhibited good internal reliability in children and adolescents, also under the age of 10, which is younger than previously thought. We observed significant but small correlations between the severity of urges and severity of tics and obsessive-compulsive symptoms, and between severity of urges and ratings of attention-deficit/hyperactivity disorder and internalizing and externalizing behaviors, however, only in children of 8-10 years. Consistent with previous results, the 10th item of the PUTS correlated less with the rest of the scale compared to the other items and, therefore, should not be used as part of the questionnaire. We found a two-factor structure of the PUTS in children of 11 years and older, distinguishing between sensory phenomena related to tics, and mental phenomena as often found in obsessive-compulsive disorder. The age-related differences observed in this study may indicate the need for the development of an age-specific questionnaire to assess premonitory urges

……..

Eur Child Adolesc Psychiatry. 2020.

ADHD SUBTYPES ARE ASSOCIATED DIFFERENTLY WITH CIRCADIAN RHYTHMS OF MOTOR ACTIVITY, SLEEP DISTURBANCES, AND BODY MASS INDEX IN CHILDREN AND ADOLESCENTS: A CASEΓÇôCONTROL STUDY.

Izquierdo-Pulido M, Carpio-Arias TV, Ferreira-Garc+¡a E, et al.

To date, few studies have examined the circadian pattern of motor activity in children and adolescents newly diagnosed with attention-deficit/hyperactivity disorder (ADHD). The objective was to study the circadian pattern of motor activity in subjects with ADHD (medication na+»ve) and to investigate the relationships between alterations in circadian patterns, the ADHD subtype (combined or inattentive), sleep disturbances and body mass index (BMI). One-hundred twenty children and adolescents (60 medication na+»ve ADHD and 60 controls) were included in a gender- and age-matched caseΓÇôcontrol study. ADHD was diagnosed according to the DSM-IV-TR, the Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version, and the ConnerΓÇÖs Parents Rating Scale-Revised. Circadian rhythms of motor activity and sleep parameters were measured using actigraphy and the Sleep Disturbance Scale for Children. BMI and dietary intake were also evaluated. ADHD patients showed a trend towards eveningness and greater sleep disturbances than controls. Additionally, patients with ADHD-combined had significantly higher mean values of motor activity and showed a significant delay in bedtime. Furthermore, among ADHD-C patients hyperactivity symptoms were significantly associated with the least 5-áh of activity. Regarding patients with ADHD-inattentive, increased fragmentation of the circadian pattern was associated with inattention symptoms, and they also showed a significant increase in BMI of 2.52-ákg/m2 [95% CI 0.31, 4.73] in comparison with controls. Our findings highlight the potential use of actigraphy as a clinical tool to aid in the diagnosis of ADHD. It should be noted that evaluating motor activity variables could also allow the differentiation between ADHD subtypes

……..

Eur Child Adolesc Psychiatry. 2020.
DEVELOPMENTAL PATHWAYS FROM CHILDHOOD ADHD TO ADOLESCENT DEPRESSION: INSIGHTS FROM THE ALSPAC STUDY.
Fairchild G.

……..

Eur J Pediatr. 2020.
ASSOCIATION OF ELEVATED NEONATAL THYROID-STIMULATING HORMONE LEVELS WITH SCHOOL PERFORMANCE AND STIMULANT PRESCRIPTION FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDHOOD.
Lain SJ, Wiley V, Jack M, et al.
Untreated severe newborn thyroid deficiency causes neurocognitive impairment; however, the impact of mild thyroid deficiency is not known. This study aimed to examine whether mildly elevated neonatal thyroid-stimulating hormone (TSH) levels are associated with poor school performance or stimulant prescription for attention deficit hyperactivity disorder (ADHD). This record-linkage study included 232,790 term-born infants in Australia with a TSH level below newborn screening threshold (< 15-ámIU/L). Among our cohort, as TSH levels increased, the proportion of infants born low birthweight via caesarean section and with disadvantaged socioeconomic status increased. Multivariable logistic regression analysis showed that, compared with infants with normal neonatal TSH level (< 5-ámIU/L), those with neonatal TSH 10-15-ámIU/L had an increased risk of being exempt from school testing (aOR 1.63 (95% CI 1.06-2.69)) or prescribed a stimulant for ADHD (aOR 1.57 (95% CI 1.10-2.24)), adjusted for perinatal and sociodemographic factors. Among a nested analysis of 460 sibling pairs, siblings with mildly elevated TSH levels were more likely to be exempt from school tests compared with siblings with normal TSH levels (aOR 2.53, 95% CI 1.01-6.33). Conclusion: In this population cohort and sibling analysis, mildly elevated neonatal TSH levels were associated with being exempt from school testing due to significant or complex disability. What is Known: Newborn screening for severe thyroid hormone deficiency has virtually eliminated congenital hypothyroidism-associated intellectual disability in developed countries. The impact of mild thyroid hormone deficiency in infants is unclear. What is New: Children with a mildly elevated neonatal TSH level below current newborn screening cut-offs have an increased likelihood of being exempt from school testing due to significant or complex disability compared with siblings and peers. This study includes a population-based and nested sibling analysis

……..

Eur J Pediatr. 2020.
THE CO-OCCURRENCE OF MENTAL DISORDERS AMONG DUTCH ADOLESCENTS ADMITTED FOR ACUTE ALCOHOL INTOXICATION.
de Veld L, van Hoof JJ, Wolberink IM, et al.
Adolescents with substance use disorders are often diagnosed with co-occurring mental disorders. However, it is unknown if adolescent hospital admission for acute alcohol intoxication is also associated with co-occurring mental disorders. Therefore, the primary aim of this study is to estimate the prevalence of co-occurring mental disorders among Dutch adolescents admitted for acute alcohol intoxication. Secondly, this study aims to explore the cross-sectional relationship between the co-occurrence of mental disorders and patient characteristics, such as sex, age and blood alcohol concentration at admittance. Data were retrospectively collected from 726 adolescents admitted for acute alcohol intoxication. Overall, 245 (34%) of the 726 adolescents treated for acute alcohol intoxication were diagnosed with a co-occurring mental health disorder, such as attention-deficit hyperactivity disorder (13%) or autism spectrum disorder (2.1%). Attention-deficit hyperactivity disorder in particular seems to be more prevalent in the study population than in the general Dutch adolescent population. Conclusion: This study demonstrates that among adolescents admitted for acute alcohol intoxication, the prevalence of co-occurring mental disorders is a common and a relevant issue for treatment and prevention strategies. What is Known: Alcohol consumption among adolescents has been associated with negative psychosocial effect. Among adolescents admitted for acute alcohol intoxication, risk factors for psychological dysfunction appear to be inadequately assessed, documented and followed up. What is New: The current study reports on the prevalence of co-occurring mental disorders

among a substantial sample of adolescents admitted for acute alcohol intoxication. Understanding the prevalence of co-occurring mental disorders is clinically relevant for the outpatient follow-up of adolescents admitted for acute alcohol intoxication

……..

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

AN INDIVIDUALIZED PROGRAM TO TREAT A CHILD WHO IS "GAMING THE SYSTEM:" A CASE REPORT.

Morrow AS, Baldivieso Gutierrez M, Gnagy EM, et al.

Children with disruptive behavior disorders (DBD) and callous-unemotional traits (CU; i.e., lack of guilt, uncaring) are at risk for a variety of negative trajectories (Frick & White, 2008), and frequently exhibit poorer response-to-treatment than children without CU traits (Haas et al., 2010; Hawes & Dadds, 2005). The current single-case design study describes the process of developing individualized modifications of a Daily Report Card intervention for a nine-year, eleven-month-old boy receiving treatment for disruptive behavior and CU traits in the context of a highly controlled, well-staffed Summer Treatment Program setting. After the child showed an initial non-response to the standard components of the behavior modification program, several treatment adaptations were attempted to maximize treatment response. During the 8-week program, one strategy emerged as superior in which the child was not told which target behaviors were being evaluated until immediately before the reward was given (ΓÇ£mysteryΓÇØ Daily Report Card targets). Results are discussed in the context of ways in which treatment can be maximized for children with both DBD and co-occurring CU traits. Our findings suggest that clinicians who are working with children who initially demonstrate an insufficient response to treatment should consider using iterative, data-driven treatment planning and progress monitoring strategies

……..

Expert Opinion on Emerging Drugs. 2020.

EMERGING DRUGS FOR THE TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).

Pozzi M, Bertella S, Gatti E, et al.

Introduction: Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting up to 5.3% of children and 2.5% of adults depending on the country considered. Current pharmacological treatments for ADHD are based on stimulant or non-stimulant medications, targeting dopaminergic and noradrenergic systems in the frontal cortex and dopaminergic system in the basal ganglia. These drugs are effective and safe for the majority of patients, whereas about 20% of treated patients do not tolerate current therapies or experience insufficient efficacy. The adequate treatment of ADHD is necessary to allow a proper social placement and prevent the acquisition of additional, more severe, comorbidities.

Areas covered: We conducted a review of the scientific literature and of unpublished/ongoing clinical trials to summarize the advances made in the last 10-áyears (2010ΓÇô2020) for the pharmacological treatment of ADHD. We found many pharmacological mechanisms beyond dopaminergic and noradrenergic ones have been investigated in patients.

Expert opinion: Some emerging drugs for ADHD may be promising as add-on treatment especially in children, amantadine to enhance cognitive functions and tipepidine for hyperactivity/impulsivity. Stand-alone emerging treatments for ADHD include viloxazine and dasotraline, which will soon have more clinical data available to support market access requests

……..

Frontiers in Genetics. 2018;9.

POLYMORPHISMS IN MANGANESE TRANSPORTERS SLC30A10 AND SLC39A8 ARE ASSOCIATED WITH CHILDREN'S NEURODEVELOPMENT BY INFLUENCING MANGANESE HOMEOSTASIS.

Wahlberg KE, Guazzetti S, Pineda D, et al.

Background: Manganese (Mn) is an essential element but at excessive levels, it is neurotoxic. Even a moderate increase in Mn has been suggested to interfere with neurodevelopment in children. Genetics influencing Mn concentrations and toxicity is unclear.

Objective: We assessed, in a cross-sectional study, whether common single-nucleotide polymorphisms in the Mn transporters SLC39A8 (influx) and SLC30A10 (efflux) are associated with neurodevelopment in children.

Design: We genotyped SLC39A8 (rs13107325 C/T) and SLC30A10 (rs1776029 G/A and rs12064812 T/C) in Italian children (n = 686, ages 11 14). We then used linear regression models to analyze associations between genotype, blood Mn concentrations, and neurodevelopmental outcomes including intelligence, behavior, motor function, and sway. Inferred causal relationships were evaluated using instrumental variables (IV) analysis.

Results: For SLC30A10 rs1776029, the minor allele (A) was associated with increased average blood Mn of 41% ($p < 0.001$), whereas minor alleles for rs12064812 (C) and rs13107325 (T) were associated with reduced blood Mn of 7% ($p = 0.002$) and 15% ($p < 0.001$), respectively. For children carrying genotypes associated with high blood Mn, we observed lower performance for certain IQ subtests, increased sway, and increased scores for behavioral problems. High Mn genotypes showed odds ratios of 2-4 (p 0.01) for high scores in tests assessing ADHD-related behavior. IV analyses suggested that several of the associations were mediated by blood Mn.

Conclusions: Our results suggest that common polymorphisms in SLC39A8 and SLC30A10 influence neurodevelopmental outcomes in children via differences in Mn homeostasis

……..

Front Human Neurosci. 2020 Sep;14.

A MACHINE-BASED PREDICTION MODEL OF ADHD USING CPT DATA.

Slobodin O, Yahav I, Berger I.

Despite the popularity of the continuous performance test (CPT) in the diagnosis of attention-deficit/hyperactivity disorder (ADHD), its specificity, sensitivity, and ecological validity are still debated. To address some of the known shortcomings of traditional analysis and interpretation of CPT data, the present study applied a machine learning-based model (ML) using CPT indices for the Prediction of ADHD. Using a retrospective factorial fitting, followed by a bootstrap technique, we trained, cross-validated, and tested learning models on CPT performance data of 458 children aged 6–12 years (213 children with ADHD and 245 typically developed children). We used the MOXO-CPT version that included visual and auditory stimuli distractors. Results showed that the ML proposed model performed better and had a higher accuracy than the benchmark approach that used clinical data only. Using the CPT total score (that included all four indices: Attention, Timeliness, Hyperactivity, and Impulsiveness), as well as four control variables [age, gender, day of the week (DoW), time of day (ToD)], provided the most salient information for discriminating children with ADHD from their typically developed peers. This model had an accuracy rate of 87%, a sensitivity rate of 89%, and a specificity rate of 84%. This performance was 34% higher than the best-achieved accuracy of the benchmark model. The ML detection model could classify children with ADHD with high accuracy based on CPT performance. ML model of ADHD holds the promise of enhancing, perhaps complementing, behavioral assessment and may be used as a supportive measure in the evaluation of ADHD

……..

Front Psychiatry. 2020;11.

OLIGOANTIGENIC DIET IMPROVES CHILDREN'S ADHD RATING SCALE SCORES RELIABLY IN ADDED VIDEO-RATING.

Dolp A, Schneider-Momm K, Clement C, et al.

Objectives: The influence of food intake on behavioural disorders was already described in the early 20th century. Elimination of individually allergenic food items from individual diets [oligoantigenic diet (OD)] showed promise to improve attention-deficit/hyperactivity disorder (ADHD) symptoms. However, only few of the positive results were evaluated by blinded symptom rating. Therefore the present study's purpose was to evaluate the reliability of a non-blinded rating of the ADHD Rating Scale IV (ARS) for the assessment of OD effects in comparison to a blinded rating of the ARS based on pseudonymized video recordings.

Methods: Ten children (8m/2f) aged 8 to 14 with ADHD according to ICD-10 participated in an uncontrolled, open-label dietary intervention study. Food items, commonly related to intolerances, were eliminated for four weeks. Participants with > 40% improvement in the ARS between T1 (before the diet) and T2 (after the diet) were defined as responders. Nutrients with individual relevance to ADHD symptoms were identified in a following reintroduction phase (T3ΓÇôT4) lasting 8-16 weeks. The ARS was completed by a non-blinded child and adolescent psychiatrist (T0-T4). Sessions were recorded on video, pseudonymized, and evaluated by three blinded raters. Complete data were captured for eight children. The inter-rater reliability between the non-blinded therapist and every blinded rater was determined by the intra-class correlation coefficient (ICC). Correlations according to Pearson and Spearman between the non-blinded and blinded rating were calculated for each rater.

Results: Two blinded raters and the non-blinded rater considered 5 of 8 (62.5%) children as responders, whereas one blinded rater disagreed as to the success of one case thus considering only 4 of 8 children as responders to the diet. Inter-rater reliability was assessed after each rater having scored 33 videos: The intra-class coefficients were >.9 for all raters (rater 1: ICC=.997, rater 2: ICC=.996, rater 3: ICC=.996) and the Spearman rho between the raters were high (n=33; rater 1: rho =.989, p<.0001, rater 2: rho=.987, p<.0001, rater 3: rho=.984, p<.0001), respectively.

Discussion: As both, blinded and non-blinded ratings of the ARS, revealed relevant significant improvement of ADHD scores in children following an OD in this uncontrolled trial, Randomized controlled trials appear as highly desirable in order to replicate these improvements and to establish reliable and unbiased effect sizes thereby fostering further more objective confirmatory measurements

……..

Front Psychiatry. 2020;11.

A FOUR-STEP METHOD FOR THE DEVELOPMENT OF AN ADHD-VR DIGITAL GAME DIAGNOSTIC TOOL PROTOTYPE FOR CHILDREN USING A DL MODEL.

Wiguna T, Wigantara NA, Ismail RI, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder among children resulting in disturbances in their daily functioning. Virtual reality (VR) and machine learning technologies, such as deep learning (DL) application, are promising diagnostic tools for ADHD in the near future because VR provides stimuli to replace real stimuli and recreate experiences with high realism. It also creates a playful virtual environment and reduces stress in children. The DL model is a subset of machine learning that can transform input and output data into diagnostic values using convolutional neural network systems. By using a sensitive and specific ADHD-VR diagnostic tool prototype for children with DL model, ADHD can be diagnosed more easily and accurately, especially in places with few mental health resources or where tele-consultation is possible. To date, several virtual reality-continuous performance test (VR-CPT) diagnostic tools have been developed for ADHD; however, they do not include a machine learning or deep learning application. A diagnostic tool development study needs a trustworthy and applicable study design and conduct to ensure the completeness and transparency of the report of the accuracy of the diagnostic tool. The proposed four-step method is a mixed-method research design that combines qualitative and quantitative approaches to reduce bias and collect essential information to ensure the trustworthiness and relevance of the study findings. Therefore, this study aimed to present a brief review of a ADHD-VR digital

game diagnostic tool prototype with a DL model for children and the proposed four-step method for its development

……..

Front Psychiatry. 2020;11.

COMORBIDITY MATTERS: SOCIAL VISUAL ATTENTION IN A COMPARATIVE STUDY OF AUTISM SPECTRUM DISORDER, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THEIR COMORBIDITY.

Ioannou C, Seernani D, Stefanou ME, et al.

Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) represent two common neurodevelopmental disorders with considerable co-occurrence. Their comorbidity (ASD + ADHD) has been included in the latest diagnostic guidelines (DSM-V, 2013). The present study focuses on social visual attention that i) is a main aspect of social attention reflecting social cognition and ii) its atypicalities have been suggested as a potential biomarker for ASD. Considering the possible shared background of both disorders and their comorbidity, it is important to compare such traits directly. Here, 73 children and adolescents paired for age and IQ diagnosed with ASD (N = 12), ADHD (N = 21), comorbid ASD + ADHD (N = 15), and ΓÇ£typically developingΓÇØ (TD) controls (N = 25), were shown static real-life social scenes while their gaze movements were recorded with eye-tracking. Scenes with two levels of social complexity were presented: low complexity (one person depicted) and high (four interacting individuals). Gaze fixation variables were investigated. Fixation duration on faces was significantly reduced only in ASD + ADHD which also required longer time to fixate all faces at least once. Fixation duration on faces in ASD was reduced, compared to TD, only when looking at scenes with high versus low social complexity. ADHD individuals did not differ from TD. Concluding, the observed alterations of social visual attention support the existence of possible dysfunctional particularities differentiating ASD, ADHD, and ASD + ADHD, which can be revealed with the new method of eye-tracking technique. The objective gaze measurements provided contribute to the development of biomarkers enabling early diagnosis, amelioration of care and further interventions specified for each group

……..

Gazi Medical Journal. 2020;31:603-08.

EVALUATION OF VISUAL ATTENTION COMPONENTS IN A GROUP OF PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Orgun LT, Acar ASS, Torun YT, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which is widely seen in school age children and adolescents. ADHD is seen in boys 2-10 times more frequent than girls. Attention processes are carried out by the neural network system which different brain regions form intense interconnections between them. Children with ADHD may have some difficulties in selective attention, sustained attention and visual-spatial attention functionality, which is one of the visual attention components. The purpose of this study was to investigate the selective attention, sustained attention and visual-spatial functions in boys with ADHD diagnosis.

Methods: The study sample included 80 boys, age range: 6-10 years, who met the DSM-V criteria for ADHD and consecutively referred to the Child and Adolescent Mental Health and Psychiatry Department and Child Neurology Department of Gazi University. As a control group, 73 healty boys included the study. Wechsler Intelligence Scale for Children - Revised Form (WISC-R) as administered to exclude comorbid diagnoses. Visual selective attention and sustained attention were measured with Cancellation Test (CT) and Raven Standard Progressive Matrices Test (RSPM), while visual spatial attention was measured with the Line Orientation Test (LOT).

Results: Patients with ADHD were defined as, 33 attention deficit, 24 hyperactivity-impulsivity, 23 combined type. In terms of age; there was no significant difference between the diagnostic group (7.89 -¦ 1.33 years) and the control group (8.14 -¦ 1.44 years) (p> .05). Children in the control group scored higher in all tests including at WISC-R, RSPM, CT and LOT tests than ADHD groups (p<.05).

Conclusion: Selective attention, sustained attention and visual-spatial attention functionality, which is one of the visual attention components, is affected in children with ADHD according to their healthy peers. Therefore, neuropsychological tests should be used to improve the quality of life and to evaluate the treatment follow-up in patients with ADHD

……..

Human Reproduction. 2020;35:1211-21.

MATERNAL SPONTANEOUS ABORTION AND THE RISK OF ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER IN OFFSPRING: A POPULATION-BASED COHORT STUDY.

Wang H, Li F, Miao M, et al.

STUDY QUESTION: Is a maternal history of spontaneous abortion (SA) associated with an increased risk of attention-deficit/hyperactivity disorder (ADHD) in offspring?

SUMMARY ANSWER: Our results suggest an association between maternal history of SA and ADHD in offspring, with the risk increasing with the number of maternal SA and highest in the firstborn children whose mothers had had recurrent SAs after adjusting for a number of potential confounders.

WHAT IS KNOWN ALREADY: A history of SA has been associated with more complications in next pregnancies and adverse childbirth outcomes, which are risk factors for ADHD in the offspring. However, no previous study has investigated whether maternal SA increases risk of ADHD in the offspring.

STUDY DESIGN, SIZE, DURATION: This population-based study included all live-born children in Denmark from 1 January 1995 to 31 December 2012 (n = 1 062 667). All children were followed from 3 years of age until the day of ADHD diagnosis, death, emigration or 31 December 2016, whichever came first.

PARTICIPANTS/MATERIALS, SETTING, METHODS: There were 130 206 (12.2%) children born to mothers who had at least one SA. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

MAIN RESULTS AND THE ROLE OF CHANCE: During a median follow-up of 9.4 years (interquartile range, 5.4-14.3), 25 747 children were diagnosed with ADHD. Overall, children of mothers with a history of SA had an increased rate of ADHD (HR, 1.11; 95% CI, 1.07 to 1.15). The HRs increased with the number of maternal SA, 1.09 (95% CI, 1.05 to 1.13) for one SA and 1.22 (95% CI, 1.12 to 1.33) for at least two SAs, respectively. These findings were consistent when we took into consideration a number of factors, such as maternal socioeconomic status, type of SA, birth order, parental history of psychiatric disorders, pregnancy characteristics and adverse birth outcomes.

LIMITATIONS, REASONS FOR CAUTION: Misclassification of SA was possible as we used population-based register data to capture maternal history of SA. However, any misclassification of maternal history of SA would be non-differential with regard to the diagnosis of ADHD in offspring, which generally leads to underestimation of the associations. Furthermore, probabilistic sensitivity analysis suggested that only 1% of change in the estimate may have been due to misclassification of SA.

WIDER IMPLICATIONS OF THE FINDINGS: SA is quite frequent (varying from 15 to 20%), and a small increase of neurodevelopmental problems in offspring could have major public health implications

……..

Indian J Pediatr. 2020.

TRAUMATIC STRESS OR ADHD? MAKING A CASE FOR TRAUMA INFORMED CARE IN PEDIATRIC PRACTICE.

Malhi P, Bharti B.

……..

Int Clin Psychopharmacol. 2020;300-04.

PHARMACOTHERAPY OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER: COMMON QUANDARIES, DILEMMAS AND CHALLENGES.

Mosheva M, Dar N, Rima Madi L, et al.

Multiple studies have shown that pharmacologic treatments for attention-deficit hyperactivity disorder (ADHD), especially stimulants, are generally effective. There is yet a paucity of empirical data, however, for some common clinical conditions overlooked in the ADHD treatment guidelines. Some examples include: in cases of first line treatment failure, it is unclear whether switching from one type of stimulant to another is beneficial. In cases of comorbid ADHD and severe aggressive/disruptive behavior in children, it is unclear whether the best first-line treatment is stimulants or atypical antipsychotics like risperidone. In cases of ADHD with comorbid anxiety disorders, there is no clear evidence regarding optimal treatment. The objectives of this article are to review these issues and propose possible answers for such clinical dilemmas

……..

Int J Behav Dev. 2020.

THE EFFECT OF MINDFULNESS-BASED INTERVENTIONS ON INATTENTIVE AND HYPERACTIVEΓÇÔIMPULSIVE BEHAVIOR IN CHILDHOOD: A META-ANALYSIS.

Vekety B, Logemann HNA, Takacs ZK.

Current research has reported the beneficial effects of mindfulness-based interventions (MBIs) on general domains of cognition and behavior among children. The present study is the first meta-analysis with controlled studies investigating the pre-post change effects of MBIs on two widely experienced behaviors in childhood education, namely inattentiveness and hyperactivity-impulsivity. With a special developmental focus on the early years, a total of 21 studies with 3- to 12-year-old children were included in the meta-analysis. Results indicated that MBIs decreased children's overall inattentive and hyperactive-impulsive behavior with a small but significant effect size (k = 21, g+ =.38, p <.001). However, this overall positive effect was only significant when teachers rated children's behavior and nonsignificant when parents and children themselves were the informants. Additionally, MBIs showed a moderate effect in reducing inattentiveness and hyperactivity-impulsivity for children at risk for such behavior. In conclusion, results indicate that MBIs, which are relatively easily applied in educational practice, have the potential to decrease inattentive and hyperactive-impulsive behavior and might contribute to childrenΓÇÖs overall better functioning at school

……..

Int J Environ Res Public Health. 2020;17:1-16.

CLINICAL APPLICATION OF MINDFULNESS-ORIENTED MEDITATION: A PRELIMINARY STUDY IN CHILDREN WITH ADHD.

Santonastaso O, Zaccari V, Crescentini C, et al.

Mindfulness-oriented meditation (MOM) is a self-regulatory training used for attentional and behavioral problems. With its focus on attention, MOM is a promising form of training that is gaining empirical support as a complementary or alternative intervention for attention deficit/hyperactivity disorder (ADHD). In this study, we tested the preliminary efficacy of MOM training in children with ADHD, by comparing its efficacy with an active control condition (Emotion Education Program, EEP). Twenty-five children with ADHD aged 7ΓÇô11 years participated in MOM training (n = 15) or EEP (n = 10) 3 times per week for 8 weeks. Neuropsychological and academic measures and behavioral, emotional, and mindfulness ratings were collected before and after the two programs. On average, MOM training had positive effects on neuropsychological measures, as evidenced by a significant mean improvement in all outcome measures after training. Moreover, positive effects on ADHD symptoms were found only in the MOM group. Although they are preliminary, our results documented that MOM training promotes changes in neuropsychological measures and in certain behavioral symptoms, suggesting it as a promising tool for ameliorating cognitive and clinical manifestations of ADHD

……..

International Journal of Pharmaceutical Research. 2020;12:2567-69.

EVALUATION OF PERCEPTUAL ABILITY IN CHILDREN WITH DELAYED LANGUAGE DEVELOPMENT (DLD)-A PILOT STUDY.

Ganapathy Sankar U, Monisha R.

Visual Perception plays an important role in processing information and coordinating inputs with appropri ate output to perform the activities in an organized and coordinated manner. Visual perception stores and feeds at immense information, that is greater than the brains processing speed. The most important feature behind perceptual efficiency is the ability to suppress the unwanted and irrelevant information. We aimed to evaluate visual Perceptual skills among children with delayed language developed [DLD]. Previous researchers were examined the clinical manifestations of delayed language development child, but the correlation of visual perceptual skill and language were not evaluated in detail and innumerous trouble exist in concluding these children's defect. We initiated the current study with 10 children. Were 5 children with Delayed Language Development (DLD) and 5 typically developing children were included. Children with visual impairment or with the presence of any other neurological disorder were excluded from the study. At baseline every child is requested to undergo screening test using IQ test, ADHD test and Illinois Test of Psycholinguistic Abilities (ITPA). Results of the study suggests that learning disorder developed among these children were more related to language than to the visual perceptual skill. We conclude that when planning intervention strategy for children with delayed language development, visual closure and visual memory task should be examined in detail

……..

Int J Res Pharm Sci. 2020;11:4800-06.

ROLE OF AYURVEDA IN UNMADA WITH REFERENCE TO ADHD ΓÇÔA CASE STUDY.

Khatana R, Rathi R, Khatana A.

Attention deficit hyperactive disorder (ADHD) is one of the most prevalent neurobehavioral disorders of childhood which affects the social, learning and behavioural abilities, Ayurveda explains almost all the Psychiatric and Behavioral disorders under the headings of Unmada and Apasmara where Unmada is a disease featured as unstable intellect, mind, knowledge, memory, conscious-ness, and bad manners. This case report is aimed at dissemination of role of Ayurveda in the management of ADHD (Unmada). This case study of 4.3 years male presented with complaints of hyperactivity, poor concentration, easily irritable, shouting, headbanging, unable to speak two words at a time and sen-tences since last one and half year. It has shown promising results. Rasayana is the source of achieving the excellent quality of rasadidhatus (body tissues) which increases life span, improves Medha (intelligence), stabilizes youthful-ness, cures disease, enhances complexion, lustre, and voice makes body strong and healthy. So Sarsawataarishta with gold is selected as a choice of drug as best rejuvenator as it promotes memory and intelligence, improves speech, and promotes health. It provides nourishment to body tissue and also acts on mind. It opened the door of the Ayurvedic approach with hope to deliver the good result in similar disorders. The case was successfully treated with the help of internal medications which were carminative, digestive and mild purgative in action, external oleation and medicated oil enemas suggested by Acharya in the treatment of Unmada. In the view of Ayurveda, ADHD can be named as Unmada due to the specific psycho-somatic clinical presentation

……..

J Med Internet Res. 2020 Oct;22:e22635.

NATURAL LANGUAGE PROCESSING REVEALS VULNERABLE MENTAL HEALTH SUPPORT GROUPS AND HEIGHTENED HEALTH ANXIETY ON REDDIT DURING COVID-19: OBSERVATIONAL STUDY.

Low DM, Rumker L, Talkar T, et al.

BACKGROUND: The COVID-19 pandemic is impacting mental health, but it is not clear how people with different types of mental health problems were differentially impacted as the initial wave of cases hit.

OBJECTIVE: The aim of this study is to leverage natural language processing (NLP) with the goal of characterizing changes in 15 of the world's largest mental health support groups (eg, r/schizophrenia, r/SuicideWatch, r/Depression) found on the website Reddit, along with 11 non-mental health groups (eg, r/PersonalFinance, r/conspiracy) during the initial stage of the pandemic.

METHODS: We created and released the Reddit Mental Health Dataset including posts from 826,961 unique users from 2018 to 2020. Using regression, we analyzed trends from 90 text-derived features such as sentiment analysis, personal pronouns, and semantic categories. Using supervised machine learning, we classified posts into their respective support groups and interpreted important features to understand how different problems manifest in language. We applied unsupervised methods such as topic modeling and unsupervised clustering to uncover concerns throughout Reddit before and during the pandemic.
RESULTS: We found that the r/HealthAnxiety forum showed spikes in posts about COVID-19 early on in January, approximately 2 months before other support groups started posting about the pandemic. There were many features that significantly increased during COVID-19 for specific groups including the categories "economic stress," "isolation," and "home," while others such as "motion" significantly decreased. We found that support groups related to attention-deficit/hyperactivity disorder, eating disorders, and anxiety showed the most negative semantic change during the pandemic out of all mental health groups. Health anxiety emerged as a general theme across Reddit through independent supervised and unsupervised machine learning analyses. For instance, we provide evidence that the concerns of a diverse set of individuals are converging in this unique moment of history; we discovered that the more users posted about COVID-19, the more linguistically similar (less distant) the mental health support groups became to r/HealthAnxiety (Ï• =-0.96, P<.001). Using unsupervised clustering, we found the suicidality and loneliness clusters more than doubled in the number of posts during the pandemic. Specifically, the support groups for borderline personality disorder and posttraumatic stress disorder became significantly associated with the suicidality cluster. Furthermore, clusters surrounding self-harm and entertainment emerged.
CONCLUSIONS: By using a broad set of NLP techniques and analyzing a baseline of prepandemic posts, we uncovered patterns of how specific mental health problems manifest in language, identified at-risk users, and revealed the distribution of concerns across Reddit, which could help provide better resources to its millions of users. We then demonstrated that textual analysis is sensitive to uncover mental health complaints as they appear in real time, identifying vulnerable groups and alarming themes during COVID-19, and thus may have utility during the ongoing pandemic and other world-changing events such as elections and protests

……..

JAMA Network Open. 2020;3.
ASSOCIATION OF EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS DURING ADOLESCENCE WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER-RELATED BEHAVIORS.
Shoaff JR, Coull B, Weuve J, et al.
Importance Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurobehavioral disorder. Studies suggest that prenatal and early childhood exposure to endocrine-disrupting chemicals may be associated with ADHD, but the association during adolescence has not been studied to date.
Objective To evaluate the association between exposure to select endocrine-disrupting chemicals during adolescence and ADHD-related behaviors.
Design, Setting, and Participants For this cross-sectional analysis, data were collected from 205 adolescents in the New Bedford Cohort, an ongoing prospective birth cohort, between June 18, 2011, and June 10, 2014. The adolescents provided spot urine samples and underwent neurodevelopmental testing. Statistical analyses performed from January 15 to December 31, 2019, used a repeated-measures analysis with multivariate modified Poisson models to estimate the adjusted relative risk of ADHD-related behaviors associated with exposure to endocrine-disrupting chemicals.
Exposures Urinary biomarker concentrations of endocrine-disrupting chemicals or their metabolites, including phthalates, parabens, phenols, and triclocarban, were quantified. Summary exposure measures were created, combining biomarker concentrations of chemicals with a shared mechanism of action, exposure pathway, or chemical class.
Main Outcomes and Measures Behaviors related to ADHD were assessed with up to 14 indices from self-, parent-, and teacher-completed behavioral checklists using validated and standardized instruments; specifically, the Conners Attention Deficit Scale and the Behavior Assessment System for Children, Second Edition. Scores on each index were dichotomized to identify those with evidence of a significant behavioral problem, defined by each scale's interpretive guidelines.

Results Among the 205 participants, the mean (SD) age at assessment was 15.3 (0.7) years, with 112 girls (55%) and 124 non-Hispanic White participants (61%). The median urine concentrations were 0.45 μmol/L of Σantiandrogenic phthalates, 0.13 μmol/L of ΣDEHP metabolites, 0.49 μmol/L of Σpersonal care product phthalates, 0.35 μmol/L of Σparabens, 0.02 μmol/L of Σbisphenols, and 0.02 μmol/L of Σdichlorophenols. A total of 82 (40%) had scores consistent with a significant behavioral problem, whereas 39 (19%) had an ADHD diagnosis. Each 2-fold increase in the sum of antiandrogenic phthalate concentrations was associated with a 1.34 (95% CI, 1.00-1.79) increase in the risk of significant ADHD-related behavior problems, whereas a 2-fold increase in the sum of dichlorophenols was associated with a 1.15 (95% CI, 1.01-1.32) increased risk. These associations tended to be stronger in male participants, but comparisons of sex-specific differences were imprecise.
Conclusions and Relevance Endocrine-disrupting chemicals are used in a wide variety of consumer products resulting in ubiquitous exposure. The study findings suggest that exposure to some of these chemicals, particularly certain phthalates, during adolescence may be associated with behaviors characteristic of ADHD

……..

JAMA Pediatr. 2020.

ASSOCIATION OF PRENATAL ACETAMINOPHEN EXPOSURE MEASURED IN MECONIUM WITH RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEDIATED BY FRONTOPARIETAL NETWORK BRAIN CONNECTIVITY.

Baker BH, Lugo-Candelas C, Wu H, et al.

Importance: Despite evidence of an association between prenatal acetaminophen exposure and attention-deficit/hyperactivity disorder (ADHD) in offspring, the drug is not contraindicated during pregnancy, possibly because prior studies have relied on maternal self-report, failed to quantify acetaminophen dose, and lacked mechanistic insight.
Objective: To examine the association between prenatal acetaminophen exposure measured in meconium (hereinafter referred to as meconium acetaminophen) and ADHD in children aged 6 to 7 years, along with the potential for mediation by functional brain connectivity.
Design, Setting, and Participants: This prospective birth cohort study from the Centre Hospitalier Universit de Sherbrooke in Sherbrooke, Quebec, Canada, included 394 eligible children, of whom 345 had meconium samples collected at delivery and information on ADHD diagnosis. Mothers were enrolled from September 25, 2007, to September 10, 2009, at their first prenatal care visit or delivery and were followed up when children were aged 6 to 7 years. When children were aged 9 to 11 years, resting-state brain connectivity was assessed with magnetic resonance imaging. Data for the present study were collected from September 25, 2007, to January 18, 2020, and analyzed from January 7, 2019, to January 22, 2020.
Exposures: Acetaminophen levels measured in meconium.
Main Outcomes and Measures: Physician diagnosis of ADHD was determined at follow-up when children were aged 6 to 7 years or from medical records. Resting-state brain connectivity was assessed with magnetic resonance imaging; attention problems and hyperactivity were assessed with the Behavioral Assessment System for Children Parent Report Scale. Associations between meconium acetaminophen levels and outcomes were estimated with linear and logistic regressions weighted on the inverse probability of treatment to account for potential confounders. Causal mediation analysis was used to test for mediation of the association between prenatal acetaminophen exposure and hyperactivity by resting-state brain connectivity.
Results: Among the 345 children included in the analysis (177 boys [51.3%]; mean [SD] age, 6.58 [0.54] years), acetaminophen was detected in 199 meconium samples (57.7%), and ADHD was diagnosed in 33 children (9.6%). Compared with no acetaminophen, detection of acetaminophen in meconium was associated with increased odds of ADHD (odds ratio [OR], 2.43; 95% CI, 1.41-4.21). A dose-response association was detected; each doubling of exposure increased the odds of ADHD by 10% (OR, 1.10; 95% CI, 1.02-1.19). Children with acetaminophen detected in meconium showed increased negative connectivity between frontoparietal and default mode network nodes to clusters in the sensorimotor cortices, which mediated an indirect effect on increased child hyperactivity (14%; 95% CI, 1%-26%).
Conclusions and Relevance: Together with the multitude of other cohort studies showing adverse neurodevelopment associated with prenatal acetaminophen exposure, this work suggests caution should be

used in administering acetaminophen during pregnancy. Research into alternative pain management strategies for pregnant women could be beneficial

……..

J Adolesc Health. 2020.

REMOTE LEARNING DURING COVID-19: EXAMINING SCHOOL PRACTICES, SERVICE CONTINUATION, AND DIFFICULTIES FOR ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Becker SP, Breaux R, Cusick CN, et al.

Purpose: This study examined remote learning practices and difficulties during initial stay-at-home orders during the COVID-19 pandemic in adolescents with and without attention-deficit/hyperactivity disorder (ADHD).

Methods: Participants were 238 adolescents (132 males; 118 with ADHD) aged 15.64-17.99 years and their parents. Adolescents and parents completed questionnaires in May/June 2020 when in-person schools were closed in the U.S.

Results: Twenty-two percent of families incurred financial costs to support remote learning, and only 59% of school-based services received before COVID-19 continued during COVID-19 remote learning. Adolescents with ADHD had fewer routines and more remote learning difficulties than adolescents without ADHD. Parents of adolescents with ADHD had less confidence in managing remote learning and more difficulties in supporting home learning and homeΓÇôschool communication. Thirty-one percent of parents of adolescents with ADHD with an Individualized Education Program (IEP) or receiving academic accommodations (504 Plan) reported remote learning to be very challenging, compared with 18% of parents of adolescents with ADHD without an IEP/504 Plan, and only 4% of parents of adolescents with neither ADHD nor an IEP/504 Plan. Fewer adolescent routines, higher negative affect, and more difficulty concentrating because of COVID-19 were each associated with greater adolescent remote learning difficulties only in adolescents with ADHD.

Conclusions: This study provides initial findings of the nature and impact of remote learning during the COVID-19 pandemic. It is imperative for schools and communities to provide the necessary supports to adolescents, particularly those with mental health and/or learning difficulties, and to their parents

……..

J Affective Disord. 2021;278:502-05.

PERSISTENCE OF DISRUPTIVE MOOD DYSREGULATION DISORDER IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Mulraney M, Silk TJ, Gulenc A, et al.

Disruptive mood dysregulation disorder (DMDD) is common in children with ADHD yet it is not known how persistent DMDD is in this population. As such we aimed to investigate the persistence of disruptive mood dysregulation disorder (DMDD) in a community sample of children with ADHD. The sample comprised children (n = 136) participating in a cohort study with data available at age 7 and age 10. DMDD status was ascertained using proxy items from the Diagnostic Interview Schedule for Children, Version IV. Of those with DMDD at age 7 (n = 30), eight (21.1%) had DMDD that persisted at age 10. In the first study investigating the longitudinal course of DMDD in ADHD one in five children with ADHD+DMDD at age 7 continued to meet diagnostic criteria for DMDD three years later

……..

J Affective Disord. 2021;279:59-65.

ASSOCIATION BETWEEN AFFILIATE STIGMA AND DEPRESSION AND ITS MODERATORS IN CAREGIVERS OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Chen YL, Chang CC, Chen YM, et al.

Background: This study aimed to determine the association between affiliate stigma and depression in caregivers of children with attention-deficit/hyperactivity disorder (ADHD) in Taiwan and evaluated the

moderating effects of perceived family support, self-esteem, and children's behavioral problems on the association.
Methods: The affiliate stigma and depressive symptoms of 400 caregivers of children with ADHD were assessed using the Affiliate Stigma Scale and Center for Epidemiological Studies Depression Scale, respectively. A general linear model (GLM) was used to examine the association between affiliate stigma and depression symptoms. The interaction models of the GLM and the Johnson-Neyman technique were used to examine the moderating effects of caregivers family support and self-esteem and children's internalizing problems and ADHD symptoms on the association.
Results: Affiliate stigma was positively associated with the depression level in caregivers of children with ADHD. The level of the association between affiliate stigma and depression symptoms was negatively associated with the levels of family support and self-esteem but positively associated with the levels of child's internalizing problems and ADHD symptoms.
Limitations: The cross-sectional design limited the possibility of determining the causal relationships among the variables. Conclusions: Prevention and intervention strategies should aim to reduce affiliate stigma and depression symptoms, as well as to target the moderators of the association

……..

J Altern Complement Med. 2020;26:701-07.
AN EVALUATION OF YOGA AND MEDITATION TO IMPROVE ATTENTION, HYPERACTIVITY, AND STRESS IN HIGH-SCHOOL STUDENTS.
Saxena K, Verrico CD, Saxena J, et al.
Objective: Problems with attention and stress are common in children and predict academic difficulties and other behavioral and emotional problems. Mind-body interventions such as yoga and meditation improve attention and reduce stress. In this study, we examined the impact of Hatha yoga on attention and stress in ninth graders.
Design: A total of 174 ninth graders from a Texas high school were enrolled in the study. Teachers assigned students to a yoga group (YG) or control group (CG) based on their class schedule. The YG participated in 25-min Hatha yoga classes twice weekly over 12 weeks (n = 123). The CG included 51 students. Student self-reports on measures of inattention and hyperactivity (the strengths and weaknesses of ADHD [attention-deficit/hyperactivity disorder] symptoms and normal behavior rating scale for ADHD) and stress (perceived stress scale) were obtained at baseline and at 12 weeks.
Results: There were no significant differences in baseline levels of inattention (p = 0.86), hyperactivity (p = 0.25), and perceived stress (p = 0.28) between the YG and CG. Regarding inattention scores, there was a significant interaction of group and time (b =-1.09, standard error [SE] = 0.30, p < 0.001). Pairwise t-tests showed a significant reduction in inattention for the YG (d = 0.27) but a significant increase in inattention for the CG. Regarding hyperactivity, there was no significant interaction of group and time (b =-0.43, SE = 0.26, p = 0.1). Pairwise t-tests demonstrated a significant reduction in hyperactivity for the YG (d = 0.22), but not the CG. The interaction of group and time was not significant in predicting the slope of change in perceived distress (b =-0.93, SE = 1.19, p = 0.43). Pairwise t-tests did not show a significant reduction in perceived distress for either group.
Conclusion: These findings suggest that Hatha yoga may improve attention and hyperactivity in high school students

……..

J Autism Dev Disord. 2020.
BRIEF REPORT: ASSOCIATIONS BETWEEN COGNITIVE CONTROL PROCESSES AND TRAITS OF AUTISM SPECTRUM DISORDER (ASD), ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND ANXIETY IN CHILDREN AT ELEVATED AND TYPICAL FAMILIAL LIKELIHOOD FOR ASD.
Godoy PBG, Shephard E, Milosavljevic B, et al.
Shared difficulties with cognitive control may play a role in co-occurring mental health problems frequently observed in autistic children. We investigated how different cognitive control processes (inhibitory control,

conflict resolution, cognitive flexibility) associated with traits of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and anxiety in 7-year-old children at elevated (n = 44) and typical (n = 37) familial likelihood for ASD. Poor inhibitory control was associated with higher ADHD traits. Better inhibitory control and poorer cognitive flexibility predicted higher anxiety traits. Cognitive control processes were not associated dimensionally with autistic traits, though better conflict resolution predicted greater likelihood of meeting diagnostic criteria for ASD in categorical analysis. These findings suggest that different cognitive control alterations are associated with ASD, ADHD and anxiety

……..

J Autism Dev Disord. 2020.

ASSOCIATIONS BETWEEN LIMBIC SYSTEM WHITE MATTER STRUCTURE AND SOCIO-EMOTIONAL FUNCTIONING IN CHILDREN WITH ADHD + ASD.

Stephens K, Silk TJ, Anderson V, et al.

Children with attention deficit/hyperactivity disorder (ADHD) combined with autism spectrum disorder (ASD) symptoms (ADHD + ASD) have poorer social and emotional functioning than those with ADHD alone. However, no studies have specifically examined the associations between ASD symptoms, measures of social and emotional functioning and limbic system white matter microstructure. Tractography on the cingulum, uncinate fasciculus and fornix were performed for 151 children with (N = 78) and without (N = 73) ADHD. Participants in the ADHD group who scored 11 or above on the Social Communication Questionnaire were classified as the ADHD + ASD group (N = 16). Significant differences in mean cingulum FA were present between the control group and the ADHD (all) group, however, no significant differences were seen between the ADHD and ADHD + ASD groups. Despite this, significant associations were seen between mean FA of the left cingulum and emotional problems for the ADHD + ASD group. Results give greater insights into the specific biological basis of emotional problems in the ADHD + ASD group, indicating that the cingulum may play a role

……..

J Child Adolesc Psychopharmacol. 2020;30:414-26.

EFFECTS OF EXTENDED-RELEASE METHYLPHENIDATE TREATMENT ON COGNITIVE TASK PERFORMANCE IN CHILDREN WITH AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Pearson DA, Santos CW, Aman MG, et al.

Objective: To examine the effectiveness of four doses of psychostimulant medication, combining extended-release methylphenidate (ER-MPH) in the morning with immediate-release MPH (IR-MPH) in the afternoon, on cognitive task performance.

Method: The sample comprised 24 children (19 boys and 5 girls) who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV-TR) criteria for an autism spectrum disorder (ASD) on the Autism Diagnostic Interview-R and the Autism Diagnostic Observation Schedule, and had significant symptoms of attention-deficit/hyperactivity disorder (ADHD). This sample consisted of elementary school-age, community-based children (mean chronological age = 8.8 years, SD = 1.7; mean intelligence quotient = 85; SD = 16.8). Effects of placebo and three dose levels of ER-MPH (containing 0.21, 0.35, and 0.48 mg/kg equivalent of IR-MPH) on cognitive task performance were compared using a within-subject, crossover, placebo-controlled design. Each of the four MPH dosing regimens (placebo, low-dose MPH, medium-dose MPH, and high-dose MPH) was administered for 1 week; the dosing order was counterbalanced across children.

Results: MPH treatment was associated with significant performance gains on cognitive tasks tapping sustained attention, selective attention, and impulsivity/inhibition. Dose/response was generally linear in the dose range studied, with no evidence of deterioration in performance at higher MPH doses in the dose range studied.

Conclusion: The results of this study suggest that MPH formulations are associated with significant improvements on cognitive task performance in children with ASD and ADHD

……..

J Child Adolesc Psychopharmacol. 2020;30:439-47.

PATTERNS OF LISDEXAMFETAMINE DIMESYLATE USE IN CHILDREN, ADOLESCENTS, AND ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN EUROPE.

Siffel C, Page M, Maxwell T, et al.

Objectives: Lisdexamfetamine dimesylate (LDX) is approved in some European countries for the second-line treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents when response to previous methylphenidate (MPH) treatment is considered clinically inadequate, and as a first-line treatment in adults. Limited evidence exists on the real-world use of LDX across Europe. This retrospective study evaluated LDX drug utilization patterns from eight European countries for up to 5 years.

Methods: Data were collected from national registries (Denmark, Finland, Norway, Sweden), electronic medical records (Germany, Spain, United Kingdom), and prescription databases (Switzerland) in eight European countries. Patients were included if they were prescribed LDX at least once since the LDX launch date in each country. Demographic and clinical characteristics, and LDX prescription data included patient age and gender, a recorded diagnosis of ADHD, the number of prescriptions per participant, previous MPH prescription recorded, average daily dose, treatment persistence, discontinuation, and switching of medications.

Results: Overall, information for 59,292 patients (437,272 LDX prescriptions) was analyzed. Most patients were male (58.1%-84.3%) and fewer than 1% were under 6 years of age. Extensive use of LDX in adults was observed in four countries (Denmark, Finland, Norway, and Sweden), including countries where LDX was not approved for this age group. Most patients had a recorded diagnosis of ADHD (61.9%-95.4%). The mean number of prescriptions per patient ranged from 5.4 to 10.0. At least 79.6% of patients with ADHD had a recorded previous MPH prescription. Mean duration of LDX exposure ranged from 233.1 to 410.8 days. The average daily dose of LDX was Γëñ70 mg/day for most patients (79.4%-99.7%). The 5-year discontinuation rate ranged from 22.8% to 70.6% and was below 40% for most countries. The proportion of patients switching from LDX to other medications was 33.8.

Conclusions: This study provides the first long-term, real-world information related to LDX use by children, adolescents, and adults in Europe in the 5 years since its first launch in the region. Most LDX prescriptions fulfilled label requirements regarding a recorded diagnosis of ADHD before treatment initiation, previous MPH use, and an average daily dose of Γëñ70 mg/day. LDX was largely prescribed within the indicated age range, although adult use of LDX was high in some countries where LDX is not approved for this population

……..

J Child Adolesc Psychopharmacol. 2020;30:448-55.

EPIDEMIOLOGY OF TREATMENT FOR PRESCHOOLERS ON KENTUCKY MEDICAID DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Davis DW, Feygin Y, Creel L, et al.

Objectives: The National Survey of Children's Health reported a concerning increase in children 2-5 years being diagnosed with attention-deficit/hyperactivity disorder (ADHD) in 2016. Concerns include both the increase in diagnosing and potential deviations from published guidelines for the treatment of ADHD in preschoolers. The present study aims to describe the epidemiology and factors associated with receiving the diagnosis and treatment types for low-income preschoolers.

Methods: Using Kentucky Medicaid claims from 2012 to 2017, a retrospective cohort study of children 2-5 years of age (n = 337,631) with a diagnosis of ADHD (n = 11,712) was completed. Trends in demographics, comorbidities, and treatment and provider types are presented. Multinomial logistic regression was used to determine predictors of receipt of the diagnosis and treatment type (a stimulant only, an alpha-2 agonist [A2A] only, both, or neither) based on nonmissing 2017 data (n = 2394).

Results: The number of children in the cohort diagnosed with ADHD and receiving a stimulant decreased from 2012 to 2017, but the use of A2As increased. Primary care physicians were the most frequent prescribers of both medications. The adjusted odds ratios (AORs) of receipt of an A2A alone, stimulant alone, or both medications over receiving no ADHD medication were associated with specific demographics and comorbid conditions for each medication regimen. Race/ethnicity is associated with receiving the diagnosis of ADHD and treatment with A2A. Comorbid mental health conditions and provider type are associated with treatment type.
Conclusion: Use of stimulants for preschoolers in Kentucky has decreased and A2A use has increased since 2012. Continued vigilance and long-term follow-up of preschoolers with ADHD are warranted. The appropriateness of the diagnosis and treatment type could not be determined

……

J Child Adolesc Psychopharmacol. 2020;30:456-64.
CHILD AND PARENTAL CHARACTERISTICS OF MEDICATION USE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Oerbeck B, Furu K, Zeiner P, et al.
Objectives: To investigate child and parental characteristics of medication use for attention-deficit/hyperactivity disorder (ADHD).
Methods: Participants were part of the prospective population-based Norwegian Mother, Father and Child Cohort study (MoBa) (n = 114,500 children, 95,000 mothers, and 75,000 fathers). This cohort was linked to the Norwegian Prescription Database (NorPD) and the Norwegian Patient Registry (NPR) to compare child and parental characteristics in children medicated and not medicated for ADHD during years 2008-2013.
Results: One thousand seven hundred and sixty-four children (74% boys) with ADHD (International Classification of Diseases [ICD-10]: F90 and F98.8) were identified. One thousand three hundred and sixty-two (77%) used medication. Boys and girls did not differ in the use of ADHD medication (both 77%). Mean age at first prescription was 9 years in both boys and girls, and age at ADHD diagnosis was 8 years in medicated and unmedicated children. Significantly more hyperkinetic conduct disorders (F90.1), and significantly fewer with attention-deficit disorder (F98.8) were found among the medicated children compared to the unmedicated children. The medicated children also had a significantly lower global functioning (Child Global Assessment Scale). Child disruptive symptoms reported in the MoBa child age 3 year questionnaire were significantly higher in children who used medication compared to the nonusers ($t = 2.2$, $p = 0.03$), and group differences in ADHD symptoms at age 3 years were close to significant ($t = 1.8$, $p = 0.07$). Other preschool child and parental characteristics were not significantly different in the two groups.
Conclusion: In this large birth cohort study, where a great majority of children with ADHD used medication, only child characteristics were significantly associated with the use of medication. We could not replicate previous findings suggesting that "environmental factors,"such as parental education and psychopathology, drive medication use. The small differences between medicated and unmedicated children in this cohort study, where a majority used medication, might be due to strong established clinical practices where medication is offered as a treatment option, particularly for hyperkinetic conduct disorder in an egalitarian high-income society

……

Journal of Child Science. 2020;10:E97-E103.
A CROSS-SECTIONAL STUDY OF 06 MILLION CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE UNITED STATES.
Rethemiotaki I.
Attention-deficit hyperactivity disorder (ADHD) is an increasingly recognized chronic neurodevelopmental disorder. This work aims at studying the prevalence and clinical characteristics of children with ADHD in the United States in the period between 2009 and 2018. Data from the National Health Interview Survey were analyzed by univariate and multivariate statistics to assess the role of socioeconomic factors in the development of ADHD. It has been studied 615,608 children, 51.2% male and 48.7% female. The prevalence

of ADHD was 9.13%, with males predominating over females. The number of children with ADHD increased from 2009 to 2018 by 14.8%. As specified by multiple logistic regression analysis, males (odds ratio [OR] 2.38) who have neither mother nor father (OR 1.76) are twice as likely to have ADHD compared with their peers. In addition, family income (OR 1.40) and parent's education (OR 1.12) were significantly associated with ADHD. It has been highlighted the significance of deprivation of both family and financial comfort as primary indicators for ADHD in children. Moreover, children with ADHD were more likely to be males in the age group of 12 to 17

……..

Journal of Clinical Investigation. 2020;130:3885-900.

HUMAN CRY1 VARIANTS ASSOCIATE WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Emre Onat O, Ece Kars M, G++l +, et al.

Attention deficit/hyperactivity disorder (ADHD) is a common and heritable phenotype frequently accompanied by insomnia, anxiety, and depression. Here, using a reverse phenotyping approach, we report heterozygous coding variations in the core circadian clock gene cryptochrome 1 in 15 unrelated multigenerational families with combined ADHD and insomnia. The variants led to functional alterations in the circadian molecular rhythms, providing a mechanistic link to the behavioral symptoms. One variant, CRY1+ö11 c.1657+3A>C, is present in approximately 1% of Europeans, therefore standing out as a diagnostic and therapeutic marker. We showed by exome sequencing in an independent cohort of patients with combined ADHD and insomnia that 8 of 62 patients and 0 of 369 controls carried CRY1+ö11. Also, we identified a variant, CRY1+ö6 c.825+1G>A, that shows reduced affinity for BMAL1/CLOCK and causes an arrhythmic phenotype. Genotype-phenotype correlation analysis revealed that this variant segregated with ADHD and delayed sleep phase disorder (DSPD) in the affected family. Finally, we found in a phenome-wide association study involving 9438 unrelated adult Europeans that CRY1+ö11 was associated with major depressive disorder, insomnia, and anxiety. These results defined a distinctive group of circadian psychiatric phenotypes that we propose to designate as ΓÇ£circiatricΓÇØ disorders

……..

J Consult Clin Psychol. 2020 Oct;88:871-85.

TREATMENT OF FRIENDSHIP PROBLEMS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: INITIAL RESULTS FROM A RANDOMIZED CLINICAL TRIAL.

Mikami AY, Normand S, Hudec KL, et al.

Objective: This study evaluated a novel intervention for friendship problems in children with attention-deficit/hyperactivity disorder (ADHD). Parental Friendship Coaching (PFC) teaches parents to coach their children in targeted friendship behaviors that are lacking in children with ADHD and that help children develop good quality friendships.

Method: Participants were 172 families of children with ADHD and social impairment (ages 6–11; 29.7% female) at two Canadian sites, randomized to PFC or to an active comparison intervention (Coping with ADHD through Relationships and Education; CARE) to control for common therapy factors. Questionnaire and observational measures assessing primary outcomes of children's friendship quality and secondary outcomes of children's friendship behaviors were collected at baseline, posttreatment, and 8-month follow-up.

Results: Across both treatment conditions, children showed improvements in positive friendship quality and in friendship behaviors. Relative to CARE, PFC was associated with somewhat more positive and less negative friendship behaviors at posttreatment and follow-up, but no difference between conditions was found in friendship quality. However, moderation analyses suggested that PFC may contribute to better friendship quality among families who had previous psychosocial treatment, as well as children with comorbid externalizing disorders.

Conclusions: Although PFC showed some efficacy for affecting children's friendship behaviors, these changes may not translate into friendship quality. Nevertheless, PFC may improve friendship quality for at-risk subgroups of children with ADHD. (PsycInfo Database Record (c) 2020 APA, all rights reserved)

What is the public health significance of this article?—The Parental Friendship Coaching intervention may improve children's friendship behaviors, and may improve friendship quality in some at-risk subgroups of children with ADHD

……..

J Indian Assoc Child Adolesc Ment Health. 2020;16:6-26.

A COMPARATIVE STUDY OF NEURO-COGNITIVE FUNCTIONING OF CHILDREN WITH AND WITHOUT ADHD ON COGNITIVE ASSESSMENT SYSTEM.

Satapathy S, Choudhary V, Sharma R, et al.

Background: Applicability of the Planning, Attention, Simultaneous and Successive (PASS) model of cognitive deficit in Attention Deficit Hyperactive Disorder (ADHD) has been widely discussed, and supporting evidence has been gathered on the cognitive assessment system (CAS). Examination of the hypothesis on CAS remains in infancy in India which further limits the clinical utility of the findings while planning neurocognitive interventions. The present study was thus conceived to assess neurocognitive functioning in young children between 6-11 years with a diagnosis of ADHD in comparison with those without ADHD.
Method: A cross-sectional research design was adopted. Using purposive sampling, 90 participants were included which consisted of two groups, ADHD (N=45) and Non- ADHD (N=45). Coloured Progressive Matrices (CPM) was used for screening intellectual functioning while primary outcome measures included CAS-II, Porteus Mazes Test (PMT), and ChildrenΓÇÖs Trail Making Test (TMT). Using SPSS 24.0, sociodemographic comparison across two groups on categorical variables was done using chi-square analysis while an independent sample t-test was applied to compare scores on primary outcome measures.
Results: Children with ADHD obtained significantly lower mean scores compared to children in the non-ADHD group across all domains of CAS-II. On PMT, the ADHD group committed a significantly greater number of errors and also took significantly more time to complete the test than the non-ADHD group. No significant group difference was obtained on TMT.
Conclusion: Supportive evidence for the PASS model deficit was obtained in the present study. The diagnostic utility study of CAS-II on a larger sample is further warranted to obtain norms for the Indian population

……..

J Indian Assoc Child Adolesc Ment Health. 2020;16:64-81.

SOLUBLE TRANSFERRIN RECEPTOR AND SFI INDEX- A NEW BIOMARKER TO IDENTIFY IRON DEFICIENCY IN DRUG NAÏVE CHILDREN WITH ADHD - A CASE-CONTROL STUDY.

Johnson Pradeep R, Sahu S, Raman V, et al.

Background: Children with Attention Deficit Hyperactivity Disorder (ADHD) have been associated with iron deficiency. Among several markers, serum ferritin and serum iron have been used frequently to identify iron deficiency; however, the results are inconclusive.
Aims: To compare soluble transferrin receptor levels (sTfR), sTfR/log ferritin index (SFI), and conventional markers of iron deficiency among drug naïve children with ADHD and healthy controls.
Methods: We conducted this study in a tertiary care setting with a case-control study design. Thirty-five children with ADHD compared with age-matched 35 controls. Children were assessed on clinical aspects, hematology profile, iron biomarkers, inflammatory markers, sTfR, and SFI.
Results: We found significantly reduced mean levels of serum iron and percentage transferrin saturation and an increase in the median levels of Erythrocyte sedimentation rate (ESR) in children with ADHD compared to healthy children. However, in a clinically meaningful categorical analysis, we found that socioeconomic strata, ESR, percentage transferrin saturation, and SFI were significantly different between the groups. Finally, we found that Children with SFI ΓëÑ1.5 were approximately four times more likely to be associated with ADHD as compared to the control group. However, the percentage transferrin saturation was not associated with ADHD, after controlling for socioeconomic strata and ESR
Conclusions: SFI is a new marker, which is feasible and a better marker than serum ferritin in the identification of latent iron deficiency in children with ADHD. Serum iron and percentage transferrin saturation

were also found to indicate an iron deficiency in children with ADHD. These findings must be explored in large community samples

……..

J Neural Transm. 2020.

EFFECTS OF AGMATINE, GLUTAMATE, ARGININE, AND NITRIC OXIDE ON EXECUTIVE FUNCTIONS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sari SA, Ulger D, Ersan S, et al.

In this study, we aimed to investigate the effects of agmatine, nitric oxide (NO), arginine, and glutamate, which are-the metabolites in the polyamine pathway, on the performance of executive functions (EF) in attention deficit hyperactivity disorder (ADHD). The ADHD group included 35 treatment-naive children (6ΓÇô14-áyears old)-áwho were ewly diagnosed with ADHD. The control group consisted of 35 healthy children with the same age and sex, having no previous psychiatric disorders. In the study groups, Stroop test (ST) and trail making test (TMT) were used to monitor EF, and blood samples were collected to measure agmatine with ultra-high-performance liquid chromatography and NO, glutamate, and arginine with enzyme-linked immunosorbent assay (ELISA). The EFs were significantly impaired in the ADHD group. The agmatine and arginine levels of the ADHD group were significantly higher than their peers. The NO and glutamate levels were also higher in the ADHD group compared to the control group, but these differences did not reach statistical significance. Children with ADHD had more difficulties during EF tasks compared to healthy children. The elevated NO and glutamate levels may be related with the impairment during EF tasks. Therefore, agmatine and arginine may increase to improve EF tasks through its inhibitory effect on the synthesis of NO and glutamate. Further studies are needed about polyamine pathway molecules to shed light on the pathophysiology of ADHD

……..

J Obsessive-Compulsive Relat Disord. 2020;27.

DEFICITS OF SUSTAINED ATTENTION IN PEDIATRIC OBSESSIVE-COMPULSIVE DISORDER COMORBID WITH TIC DISORDERS.

Xie IY, Lucke IM, F++rst N, et al.

Background: Pediatric obsessive-compulsive disorder (OCD) and Tourette syndrome/chronic tics (tic disorders, TD), are associated with attention-deficit hyperactivity disorder (ADHD). Deficits in sustained attention are a core deficit in ADHD which can be captured by continuous performance tests (CPT). CPT data are used to examine deficits in sustained attention in youth with OCD, TD or both, and OCD symptom factors, to characterize the deficits in sustained attention in OCD and TD, testing the hypothesis whether comorbid OCD + TD is distinct from OCD only or TD only.

Methods: A clinical registry of youth with OCD and/or TD included data on sustained attention, obtained with the Conner's CPT Test II (CPT-II). The CPT-II spans six time-blocks, capturing values for the capacity for sustained attention. The main outcome measure is the variability in the standard error (SE) of reaction time (RT) for correct responses (RT-SE), which is considered a core ADHD trait. Higher RT-SE values reflect a lack of uniformity in responses and is considered to reflect a deficit in sustained attention. Using generalized linear models (GLM), RT-SE is measured over the six time-blocks in three groups: OCD only, TD only and OCD + TS, with sex and age groups as moderators. Clinical ADHD diagnoses were contrasted between diagnostic groups while OCD dimensions (contamination-washing, aggressive-somatic, sexual-religious, counting-checking-repeating and hoarding) were tested for their effect on sustained attention.

Results: Deficits in sustained attention are significantly greater in the comorbid OCD + TD compared to OCD only and TD only, with the greatest differences apparent in blocks 5 and 6 ($p < .001$). While sex does not moderate sustained attention deficits, the higher RT-SE in blocks 5 and 6 is only seen in the younger age group (7-11 years), but not in adolescents (12-17 years). As expected, clinical ADHD is more prevalent in youth with comorbid OCD + TS (67%) compared to OCD only (21%) or TD only (33%) ($p = .0002$). The hoarding group, characterized by more frequent clinical ADHD diagnoses, has higher RT-SE for time blocks 3,4,5,6 compared to non-hoarders. Participants with contamination-washing symptoms, characterized by

more prevalent anxiety disorders, have higher RT-SE than those with no contamination-washing symptoms for time block 4.
Conclusion: Deficits in sustained attention are associated with comorbid OCD + TD compared OCD only or TD only, evident only in a younger age group. Sustained attention deficits are also more common in youth with ADHD, OCD hoarding and OCD contamination-washing symptoms. In summary, sustained attention deficits are intrinsic to the comorbid OCD + TD group, suggesting a compounded developmental insult specific to sustained attention which tends to resolve by adolescence. A mechanistic commonality to sustained attention, tic disorders and OCD-related extinction learning may be aberrant oscillatory brain phenomena

……..

Journal of Pediatric Research. 2020;7:257-63.
RELATIONSHIPS BETWEEN VITAMIN B12, FOLATE LEVELS AND CLINICAL FEATURES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER-NOT OTHERWISE SPECIFIED.
Utzurk Y, Topal Z, Demir N, et al.
Aim: In this study, we aimed to compare the levels of vitamin B12 and folate in children with Attention Deficit and Hyperactivity Disorder (ADHD) and Attention Deficit and Hyperactivity Disorder-Not Otherwise Specified (ADHD-NOS).
Materials and Methods: This study was planned as a cross-sectional, retrospective study. Patients were recruited between January 2012 and January 2013 and 205 case records were evaluated. The ADHD and ADHA-NOS groups were compared according to vitamin B12 and folate levels. Symptom severity was evaluated by the Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating scale. Anxiety symptom severity was assessed by The Screen for Anxiety Related Emotional Disorders.
Results: The average age of the children in the ADHD group was 10.88-¦3.02 (n=99) years, and the average age of the children in the ADHD-NOS group was 9.93-¦2.49 (n=106) years. There was no statistically significant difference between two groups in terms of Vitamin B12 level and folate level (p>0.05). A statistically significant negative correlation between the total number of diagnoses of a child and vitamin B12 levels was found. Folate levels correlated significantly with anxiety total scores generalized anxiety subscale.
Conclusion: Vitamin B12 levels may be affected in children with impairing ADHD symptoms and increased comorbidities. The results of the study should be supported by future studies

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S132.
5.3 TRIGEMINAL NERVE STIMULATION FOR ADHD: CLINICAL APPLICATIONS AND NEURAL MECHANISMS.
Loo SK.
Objectives: Although psychostimulant medications are the gold standard of treatment for ADHD, there has been increasing interest in nonmedication approaches to symptom management. Trigeminal nerve stimulation (TNS) is a minimal risk, noninvasive neuromodulation method that was recently FDA approved (April 2019) for the treatment of ADHD. The findings of the double-blind, sham-controlled trial of TNS will be presented as well as subsequent analyses that provide a mechanistic basis for understanding the effects of TNS in ADHD.
Methods: A total of 62 children, aged 8-12 years, with K-SADS diagnosed ADHD were randomly assigned to 4 weeks of nightly active or sham TNS treatment. The primary outcomes were clinician-rated ADHD Rating Scale (ADHD-RS) and Clinical Global Impression (CGI) scales. The secondary outcomes included baseline cognitive measures, weekly ratings of behavioral executive functions (Behavior Rating Inventory for Executive Function [BRIEF]), and EEG measures at baseline and posttreatment.
Results: ADHD-RS scores showed significant group-by-time interactions (F = 8.12, p = 0.005; week 4 Cohen's d = 0.5) and CGI-Improvement scores that favored active (vs sham) TNS treatment. Within the active treatment group, responders (RESP; n = 16) did not differ from nonresponders (NR; n = 14) in age, IQ, gender, or baseline ADHD-RS (all pΓÇÖs > 0.2). At baseline, several measures significantly differentiated TNS RESP from NR: lower spatial working memory accuracy (F = 4, p < 0.05), lower spelling achievement

(F = 4.8, p < 0.05), deficits on behavioral ratings of executive functions (F = 5.1-6.1, p < 0.05), and lower resting-state EEG power in the right frontal (F4) region (F = 4.4, p < 0.05). Compared to NR, RESP showed increased right frontal EEG power with TNS treatment, which was predictive of improved executive functions and ADHD symptomatology (b = 0.44; 95% CI, 0.3-1.2; p = 0.003).
Conclusions: Results from this first double-blind sham-controlled trial of TNS demonstrates efficacy in ADHD symptom reduction and provided the basis for the first FDA approval of a nonmedication therapy for ADHD. Our current analyses provide a mechanistic basis for understanding the TNS effects in ADHD and suggest that both executive function and EEG baseline profiles might serve as biomarkers predictive of positive treatment outcomes, consistent with the aims of personalized medicine. ADHD, NM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S149-S150.

5.4 ADHD DETECTION QUALITY IMPROVEMENT INITIATIVE: PROMISING AOUTCOMES AT 10 MONHS.

Loubeau K, Hasan ST, Doss M, et al.

Objectives: ADHD is the most common neurobehavioral disorder in children. When left untreated, ADHD can lead to significant lifelong functional impairment. The purpose of this quality improvement (QI) initiative was to improve detection and evaluation of ADHD in school-age children seen at our urban safety-net hospital-based pediatric primary care clinic.
Methods: During their annual well-child visit, children aged 6 to 11 years are screened for mental health symptoms with the Pediatric Symptom Checklist-17 (PSC-17), which includes a PSC Attention Scale (PSC-AS) that identifies children with probable ADHD. We sought to improve the recognition of positive PSC-AS screens and the use of follow-up standard scales for ADHD diagnostic evaluation (Parent and Teacher Vanderbilt Diagnostic Rating Scales) with a multicomponent intervention including: 1) a provider decision-making algorithm; 2) clinic workflow adjustments; and 3) electronic medical record (EMR) changes to highlight positive scores and facilitate diagnostic questionnaire distribution and return. We used driver diagrams and Plan-Do-Study-Act (PDSA) cycles to iteratively improve intervention implementation. To evaluate the effectiveness, we tracked 4 expected outcomes following positive PSC-AS: 1) documented provider acknowledgment; 2) documented provider plan; 3) percentage of diagnostic questionnaires distributed; and 4) percentage of diagnostic questionnaires returned. We compared these outcomes in the 10 months following the intervention to the previous year.
Results: There was a 46% increase in provider acknowledgment of a positive PSC-AS screening result in the intervention vs control condition (66% vs 45%), and a 12% increase in documentation of a plan for further evaluation following a positive PSC-AS (72% vs 64%). There was a 65% increase in diagnostic questionnaire distribution in the intervention vs control condition (31% vs 19%) and a 64% increase in return of at least 1 diagnostic questionnaire (15% vs 9%).
Conclusions: Our QI initiative led to significant improvements in the detection and evaluation of ADHD by providing an algorithm facilitating the subtle internal workflow adjustments, ease of questionnaire administration, and provider decision-making algorithm. ADHD, RI, DIAG

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S164-S165.

6.17 STRUCTURAL BRAIN ABNORMALITIES IN CHILDREN AND ADOLESCENTS WITH COMORBID AUTISM SPECTRUM DISORDER AND ADHD.

Mizuno Y, Jung M, Makita K, et al.

Objectives: Autism spectrum disorder (ASD) and ADHD share high rates of comorbidity, with the DSM-5 now acknowledging the comorbid diagnosis of ASD and ADHD. Although structural abnormalities in the prefrontal cortex, cerebellum, and basal ganglia occur in both ASD and ADHD, no structural studies have focused exclusively on patients with comorbid ASD and ADHD. We thus aimed to clarify the structural features and developmental changes in patients with comorbid ASD and ADHD in a relatively large sample from 2 sites.

Methods: Ninety-two patients were age-matched to 141 typically developing (TD) controls (age range: 5-16 years) and assessed for volumetric characteristics using structural MRI (ie, surface-based morphometry).
Results: While there were no significant differences in prefrontal cortex, cerebellum, and basal ganglia volumes, patients with ASD and ADHD exhibited significantly lower left postcentral gyrus volumes than TD controls. We observed significantly lower postcentral gyrus volumes exclusively in children and preadolescents, and not in adolescents.
Conclusions: Our findings suggest that abnormal somatosensory development, attributed to delayed maturation of the left postcentral gyrus, leads to the core symptoms experienced by patients with comorbid ASD and ADHD. ADHD, ASD, IMAGS

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S251.

51.2 CHALLENGES WITH MANAGING CHILDREN AND ADOLESCENTS WITH ADHD DURING THE COVID-19 PANDEMIC: A REVIEW OF THE LITERATURE.

McGowan G, Conrad R, Potts H.

Objectives: The COVID-19 pandemic has significantly altered the lives of children and families. Children with ADHD, one of the most common neurodevelopmental disorders, are vulnerable to the effects of the pandemic. This literature review examined the potential challenges of management and risks to children with ADHD and their families during the pandemic.
Methods: A literature review was conducted on the topic of children with ADHD during the pandemic. We searched the following online databases: PubMed, Google Scholar, PsycINFO, and Web of Science using keywords related to ADHD and COVID. All article types were included and published in English. PubMed and Google Scholar yielded 9 articles that met the relevance criteria.
Results: The literature indicates that externalizing behaviors significantly increased in children with ADHD during the pandemic and that both children and parents' overall mood state significantly predicted those behaviors. Impulsivity was found to interfere with compliance with public health guidelines, such as hygiene and social distancing. Hyperactivity was difficult to manage during quarantine restrictions that reduced access to physical activity outdoors. Social isolation could exacerbate underlying social vulnerability. Emotional dysregulation and oppositional behavior increased strain on families. Parents of children with ADHD have increased child-rearing stress, which may be amplified during the pandemic. Finally, school closures and reduced primary care visits have decreased access to mental health care and reduced referral rates. Guidelines were published to help navigate remote management and treatment of this population during the pandemic.
Conclusions: This review identified children with ADHD as a vulnerable population that requires research and clinician attention during the pandemic. The risk for worsening ADHD symptoms under quarantine highlighted the need for more home-based interventions and symptom monitoring by families and providers. There is a need to identify interventions to address challenges associated with parenting children with ADHD under quarantine and to assess the efficacy of telehealth in this population during a pandemic. Additional studies are warranted to better understand the impact of the pandemic on children and adolescents with ADHD. ADHD, OTH

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S156-S157.

5.24 SEX DIFFERENCES IN EXTERNALIZING AND INTERNALIZING SYMPTOM IN ADHD, AUTISM SPECTRUM DISORDER, AND GENERAL POPULATION SAMPLES.

Jolly TS, Mayes S, Castagna P, et al.

Objectives: Externalizing and internalizing symptoms are prevalent in ADHD and autism spectrum disorder (ASD). Specifically, oppositional behavior, irritability, and aggression are common in ADHD-Combined and in ASD (but less frequent in ADHD-Inattentive), and children with ASD are at high risk for anxiety symptoms. No study has simultaneously compared sex differences in externalizing and internalizing symptoms between ADHD-Combined, ADHD-Inattentive, ASD, and general population samples.

Methods: The samples comprised 1,436 children with ASD (with or without ADHD), 1056 with ADHD without ASD, and 665 from a general population sample aged 2-17 years. Externalizing, internalizing, and somatic symptoms were rated by mothers on the Pediatric Behavior Scale (PBS).
Results: PBS scores on 9 externalizing, 4 internalizing, and 9 somatic symptoms did not differ significantly ($t = 0.1$-2.8; Bonferroni $p > 0.05$) between girls and boys in the ASD, ADHD-Combined, and ADHD-Inattentive samples. In the general population sample, boys had higher externalizing problem scores than girls (particularly hyperactivity, inattention, and aggression; $t = 3.0$-3.6; $p < 0.05$), whereas anxiety, depression, and somatic complaints did not differ ($p > 0.05$), with the exception of more stomach aches in girls ($t = 3.5$; $p < 0.05$).
Conclusions: The finding that boys have more externalizing problems than girls in the general population has implications for the interpretation of rating-scale scores. Raw score to standard score conversions for most rating scales are based on general population age- and sex-specific norms. Therefore, standard scores (eg, T-scores) mask sex differences, and the same standard score for a girl and a boy does not represent equivalent symptom severity. By using standard scores to help in determining diagnoses, girls who are significantly impaired relative to other girls are not underidentified and boys are not overidentified. However, a boy must have more severe externalizing problems to earn the same elevated standard score as a girl. When making diagnostic and treatment decisions, it is important for clinicians to take into consideration both symptom raw scores (eg, often a problem reflecting symptom severity and the DSM threshold for clinical significance) and standard scores (symptom severity adjusted for sex and age effects). ADHD, ASD, IMD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S325.
ADHD NEUROFEEDBACK 25-MONTH FOLLOW-UP, MODERATION OF RESPONSE, AND NEUROCOGNITIVE SUBTYPING.
Arnold LE, Loo SK .
Objectives: The objective of this presentation is to relate delayed response at a 25-month follow-up of the International Collaborative ADHD Neurofeedback (ICAN) RCT to comorbidity and other moderators and mediators with practical clinical implications.
Methods: L. Eugene Arnold, MD, presents 25-month follow-up primary and key secondary outcomes. Michelle Roley-Roberts, PhD, presents moderation by mental health comorbidity and ADHD subtype, and the relationship between them. Cynthia Kerson, PhD, presents neurocognitive results of the Integrated Visual and Auditory (IVA) test and the Timed Arithmetic Task as outcome and moderator/mediator. Nadja Ging-Jehli, MA, presents computational psychiatry results from the IVA test, defining decisional subtypes as moderators and outcomes/mediators. Sandra K. Loo, PhD, discusses the implications of the results.
Results: Preliminary results here are from 13-month analyses, while the last 20 of the 25-month follow-ups are collected. Full 25-month data will be presented. There appears to be a delayed specific benefit of neurofeedback (NF), with significantly more remitters in the NF group (39%) than in the control group (19%). By 13 months, 15% of those who had received active NF and 7% of controls reduced or stopped medication, whereas 17% of the NF group and 38% of the control group increased medication ($p = 0.01$). Comorbid anxiety disorder without disruptive behavior comorbidity negatively moderated response during treatment (significantly worse with NF than control treatment). Following treatment, externalizing comorbidity positively moderated delayed response (significantly better with NF). Diffusion-model analyses revealed subtype-specific differences in multiple cognitive components.
Conclusions: Children with ADHD and anxiety disorder as their only comorbidity should not be given theta-beta NF. Improvement during treatment seems mainly due to nonspecific effects, but a specific benefit of NF seems to emerge at follow-up, significantly so for those with comorbid ODD or conduct disorder. NF may reduce the need for medication. Diffusion-model computations may identify biomarkers of subtypes of ADHD. ADHD, TREAT, NM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S157.

5.25 STARS-ADJUNCT: A HOME-BASED, DIGITAL TREATMENT FOR PEDIATRIC ADHD AS ADJUNCT TO STIMULANT MEDICATION: INSIGHTS ON REPEAT ADMINISTRATION AND THE STABILITY OF EFFECTS.

Kollins SH, Heusser A, Lutz J.

Objectives: AKL-T01 is an investigational digital treatment delivered through a video game-like experience, designed to improve attention functioning. A previously reported RCT in children with ADHD (STARS-ADHD) found that 1-month treatment with AKL-T01 significantly improved an objective measure of attention. However, that trial excluded children on ADHD medication and only examined a 4-week treatment period. The current study explored the effects of AKL-T01 as an adjunct to stimulant medication in children with ADHD. Further, we studied the stability of effects 1 month after treatment cessation and the effect of an additional treatment cycle both in children on and off ADHD medication.

Methods: STARS-Adjunct was a multicenter, open-label study conducted in children with ADHD (8-14 years old) on stimulant medication (n = 130, on meds) or not on any ADHD medication (n = 76, off meds). Participants used AKL-T01 for 1 month (days 0-28), followed by a treatment break of 1 month (days 29-56) and then a second 1-month treatment cycle (days 57-84). Primary outcomes were within-group changes in the ADHD Impairment Rating Scale (IRS) overall severity from baseline to day 28 in each cohort. Secondary/exploratory outcomes included changes in the IRS at days 56 and 84, and in the ADHD Rating Scale (ADHD-RS) and Clinical Global Impression (CGI) scale at days 28, 56, and 84.

Results: IRS improvements after the first treatment cycle were significant for cohorts who were on meds (mean +ö: 0.7; $p < 0.001$) and off meds (mean +ö: 0.5; $p < 0.001$). Changes from baseline to days 56 and 84 remained significant and became numerically larger: on meds (day 56: 0.9; day 84: 1), off meds (day 56: 0.8; day 84: 1), and both ($p < 0.001$). We observed a similar pattern for ADHD-RS and CGI in both cohorts.

Conclusions: The STARS-Adjunct trial showed similar improvements on ADHD-related impairment and symptoms after 4 weeks of AKL-T01 independent of medication status. Improvements were also comparable to data from STARS-ADHD. Together, the findings extend the generalizability of our results to a more diverse pediatric population with ADHD. Improvements remained stable 1 month after treatment, and a second month of treatment further increased the improvements. Within the caveats of an open-label trial, these findings imply positive effects on attention functioning beyond the treatment phase and suggest the value of an additional treatment cycle. ADHD, SAC, MCS

……..

J Am Acad Child Adolesc Psychiatry. 2020.

INCREASED FUNCTIONAL SEGREGATION RELATED TO THE SALIENCE NETWORK IN UNAFFECTED SIBLINGS OF YOUTHS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lin HY, Kessler D, Tseng WYI, et al.

Objective: Although there are frequent reports of shared neurofunctional and neurostructural alterations among probands with attention-deficit/hyperactivity disorder (ADHD) and their unaffected siblings, there is little knowledge regarding whether abnormalities in the resting-state functional connectivity of ADHD probands is also expressed in unaffected siblings, or whether this unaffected (but at-risk) cohort manifests distinct patterns.

Method: We used a multivariate connectome-wide association study examining intrinsic functional connectivity with resting-state functional magnetic resonance imaging (MRI) in a sample (aged 8-17 years) of medication-naive ADHD probands (n = 56), their unaffected siblings (n = 55), and typically developing (TD) youths (n = 106).

Results: ADHD probands showed, relative to TD youths, increased connectivity between the default-mode network (DMN) and task-positive networks. Relative to ADHD and TD groups, respectively, unaffected siblings showed increased connectivity within the salience network and reduced connectivity between the DMN and salience network. No shared alterations in functional connectivity among ADHD probands and their unaffected siblings were identified. These findings were largely confirmed by complementary pairwise connectomic comparisons. However, the main connectivity differences between ADHD and unaffected siblings were not replicated in a tightly age- and sex-matched subsample (20 proband-sibling pairs and 60 TD youths).

Conclusion: Our findings suggest that increased functional segregation related to the attention networks, especially the salience (ventral attention) system, may be a potential feature of at-risk siblings who remain unaffected by ADHD expression. Further replications are needed in other larger and sex-matched samples.
Clinical trial registration information: Structural and Functional Connectivity of Frontostriatal and Frontoparietal Networks as Endophenotypes of ADHD; https://clinicaltrials.gov/; NCT01682915

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S149.

5.3 ADHD AND CHILDHOOD ASTHMA: A SYSTEMATIC REVIEW OF COMORBIDITY.

Mirza SH, Obianyo-Onwuagha J, Baig B.

Objectives: ADHD and asthma are both common diseases of childhood. Studies have shown that there is a significant association between the 2 conditions. This systematic review aims to assess the consistency of, and possible hypotheses for, an association.
Methods: The systematic search was conducted by 2 independent researchers using MEDLINE and PsycINFO and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting systematic reviews. A total of 30 eligible studies examining the link between ADHD and asthma in children and adolescents were identified.
Results: Of these eligible studies, 24 found an association between ADHD and asthma, while 6 did not. Multiple outcomes were used in the studies to show the association, including rates that varied from 1.59%-36.6% in the ADHD and asthma group, compared to 0.39%-24.6% in controls, and ORs that ranged from 1.38 to 4.12.
Conclusions: Results suggest that younger male patients appear to be at a higher risk of comorbidity. ADHD, CM, PYI

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S153.

5.14 IMPROVING OBJECTIVE MEASURES OF ATTENTION IN TEST OF VARIABLES OF ATTENTION (T.O.V.A.) INTO NORMATIVE RANGERS WITH AKL-T01, A DIGITAL TREATMENT FOR ATTENTION IN PEDIATRIC ADHD.

Melmed RD, Lutz J, Jina A.

Objectives: Attention problems have detrimental effects on children with ADHD and often persist despite medication management. AKL-T01 is an investigational digital treatment designed to improve attention delivered through a video game interface. A key endpoint across AKL-T01 trials was the Test of Variables of Attention (T.O.V.A.), an FDA-cleared objective test of attention, which can aid in the evaluation of ADHD treatments. Clinically meaningful response on the T.O.V.A. can be defined as moving from an impaired into a normative range, that is, performing in a manner consistent with an age- and gender-matched non-ADHD normative sample. We investigated the number of children moving into the normative range on T.O.V.A. after 4 weeks of AKL-T01 treatment across our clinical trials in pediatric ADHD.
Methods: T.O.V.A. provides several objective measures of attention: the Attention Performance Index (API, a composite score measuring global attention), and subcomponents including Reaction Time Mean First Half (RT Mean H1, measuring selective and sustained attention) and Reaction Time Variability (RT Var, measuring attentional consistency). Normative range on the API is defined as a score of ΓëÑ0, and on RT Mean H1 and RT Var as being within 1 SD of T.O.V.A. norms (T.O.V.A. manual, Greenberg, 2018). Analyses included 296 children aged 8 to 15 years old with ADHD and T.O.V.A. impairment at baseline (API Γëñ0) across 4 clinical trials. We calculated the percentage of children moving from an impaired into a normative range on each of the 3 domains along with the pooled responses.
Results: The percentage of children moving into the normative range was 11% to 45% on T.O.V.A. API, 25% to 37% on RT Mean H1, and 20% to 40% on RT Var. Overall, 34.5% (102/296) of children moved into the normative range on at least 1 of these objective measures of attention across all studies.
Conclusions: After 4 weeks of AKL-T01 treatment across 4 studies, over one-third of children with ADHD and impaired attention no longer fell into the impairment range on at least 1 objective measure of global inattention, selective attention, sustained attention, or attentional consistency on the T.O.V.A. Movement into

normative ranges appear relatively consistent across studies. T.O.V.A. is an objective, complementary measure of inattention in children with ADHD. Movement into normative ranging on T.O.V.A. is a meaningful improvement on this measure. ADHD, R, RI

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S14-S15.

9.3 ENGAGEMENT STRATEGIES TO PROMOTR TREATMENT ADHERENCE AND LONG-TERM SUCCESS IN ADOLESCENTS WITH ADHD.

Sibley MH.

Objectives: There is a noted age-based disparity in the delivery of pediatric ADHD treatments, with adolescents receiving far fewer services than children. The source of this disparity is clear-unlike children, adolescents self-advocate to desist their ADHD medication-claiming problems with palatability (ie, stigma, side effects, perceived ineffectiveness). Furthermore, families of teenagers with ADHD often experience barriers to successful engagement in behavior therapy that include motivation deficits, inconsistent family routines, intrusive parenting, regulating electronics, and skepticism about the efficacy of behavioral techniques.

Methods: In this presentation, we will provide an overview of an evidence-based behavior therapy for adolescents with ADHD that emphasizes youth engagement (Supporting Teens Autonomy Daily [STAND]). We will discuss specific techniques that clinicians can use to increase medication and psychosocial treatment engagement among adolescents with ADHD.

Results: We will review key engagement strategies for adolescents with ADHD and discuss recent longitudinal findings on the complementary effects of medication and evidence-based psychosocial treatment. These findings are from the ADHD Teen Integrative Data Analysis Longitudinal (ADHD-TIDAL) study (N = 854), a recent RCT (N = 278) of STAND compared to community-based usual care, and 4-year follow-up.

Conclusions: We will summarize key goals when treating teenagers with ADHD and discuss why adolescence may be an excellent window for promoting long-term treatment effects. We will share resources with attendees to promote application of the presented material in their daily practice. ADHD, P, ADOL

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S299.

22.1 THE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD AND FOLLOW-UP: WHAT HAVE WE LEARNED AFTER TWO DECADES?

Jensen PS.

Objectives: The objective of this presentation is to present key important clinical findings from the Multimodal Treatment Study of Children with ADHD (MTA) and its follow-up study. Given the vast scope of the MTA's actual findings, many misinterpretations and much misinformation have circulated.

Methods: Key clinical findings from the MTA and follow-up study will be presented, which will guide practice and further research directions.

Results: Key findings are reviewed and include the following: 1) the relative effectiveness of the MTA's medication management strategy (MedMgt) vs treatment as usual (TAU); 2) the incremental benefits of intensive behavioral therapy when combined with medication (COMB); 3) specific components of the MedMgt strategy that rendered it more than twice as effective as TAU medication treatment delivered by community providers; 4) specific findings allowing providers to individualize and target treatment choices for children with internalizing and/or externalizing comorbidities; 5) findings concerning the frequency of children's needs for ongoing medication dose adjustment in the first year, even after careful initial titration; 6) the impact of carefully monitored MedMgt and COMB in reducing ODD symptoms and preventing new-onset ODD during the next 14 months; 7) the loss of benefits of ADHD treatments over time, if intensive follow-up is not maintained; 8) the finding that, over longer-term follow-up, children with ADHD do not appear to be at significant risk for bipolar disorder, hypertension, or psychosis, 9) long-term follow-up data indicate that ADHD is not a one-size-fits-all disorder; at 3 years after randomization, children with ADHD in the MTA had

3 different trajectories; and 10) children with ADHD in the MTA appear to be at increased risk of substance use in late adolescence and adulthood, but most children with ADHD do not suffer from significant substance abuse or substance dependence.
Conclusions: Despite the importance of these findings, recent national studies of ADHD care quality suggest that many of the MTA's lessons, even if learned, have not been applied. Future studies are needed to determine how to best translate research findings from studies such as the MTA into day-to-day practice. ADHD, LONG, RCT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S61-S62.
40.3 SLEEP AND CIRCADIAN CHANGES IN ADHD: EVALUATION AND TREATMENT.
Ivanenko A.
Objectives: Sleep problems occur in 25% to 50% of children and adolescents with ADHD and include difficulty falling asleep, night awakenings, sleep-disordered breathing, restless sleep, and excessive daytime sleepiness. Sleep difficulty is often caused by circadian rhythm disruption associated with sleep phase delay. This presentation will review common sleep disorders comorbid with ADHD, outline a stepwise approach to evaluation, and introduce empirically supported behavioral and pharmacological treatments of ADHD-associated insomnia.
Methods: This presentation will include a comprehensive literature review, lecture and discussion, and care presentations.
Results: Overall, children and adolescents with ADHD who report sleep difficulties may have poorer sleep hygiene, altered sleep drive, sleep phase delay, and impaired wakefulness due to arousal dysfunction or increased daytime sleepiness. Sleep disorders such as obstructive sleep apnea and restless legs syndrome are common comorbidities in children with ADHD and may either exacerbate ADHD symptoms or in some cases be the primary cause of ADHD symptoms. Evening chronotype with nocturnal rise in melatonin and early morning rise in cortisol were identified in patients with ADHD. These findings provide biological evidence of circadian dysfunction in youth with ADHD. Treatments of delayed sleep phase disorder include education, possible medication adjustments, chronotherapy, and light therapy. When presented with the common clinical scenario of sleep complaints in a child or adolescent with ADHD, the mental health provider must adopt an organized and stepwise approach to evaluation and management, and the treatment should be diagnostically driven. Additional considerations involve an assessment of the relative contributions of sleep practices (ie, bedtime routine, sleep-wake schedules, electronic use at bedtime), comorbid anxiety and mood symptoms, evening symptoms of ADHD, concomitant medication use, and comorbid primary sleep disorders.
Conclusions: The current status of knowledge regarding sleep and circadian characteristics in children and adolescents with ADHD will be reviewed. A practical approach to addressing sleep problems in children and adolescents with ADHD using a systematic, evidence-based approach will be presented. TREAT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S154.
5.16 LIFESTYLE ENHANCEMENT FOR ADHD PROGRAM (LEAP): HEALTH-FOCUSED PARENT TRAINING INTERVENTION EFFECTS ON PHYSICAL ACTIVITY AND SCREEN TIME BEHAVIORS AMONG CHILDREN WITH ADHD.
LaCount PA, Kuhn M, et al.
Objectives: Children with ADHD are more likely to be sedentary and less likely to meet recommendations for physical activity (PA), both of which can exacerbate ADHD and the risk for obesity and other poor health outcomes. We evaluated the initial effects of a parent behavior management training program enhanced to target health behaviors (eg, PA, screen time) Lifestyle Enhancement for ADHD Program (LEAP).
Methods: We conducted an open trial that focused on the feasibility and acceptability of LEAP. Our sample consisted of 33 predominantly White (64%) and female (57%) children with ADHD (mean age = 7.6 years) whose parents attended 8 weekly LEAP group sessions. Parents and children also received Garmin activity-tracking watches, and the parents joined a private motivational Facebook group. Child PA and screen time

behaviors were characterized by parents on a health behavior survey (HBS). We also collected an objective measure of PA using hip-worn accelerometers, and classified data into light PA (LPA) and moderate-to-vigorous PA (MVPA) intensities. Posttreatment improvements in child participants pre- to post-LEAP health behaviors were evaluated using multiple paired samples t tests.
Results: On the HBS, parents reported that children significantly increased their exposure to green spaces ($p = 0.04$; $d = 0.30$), required less one-on-one supervision when engaging in PA ($p = 0.02$; $d = 0.49$), increased their use of family rules to limit screen time ($p = 0.004$; $d = 0.57$), and reduced their children's weekday screen time ($p = 0.002$; $d = 0.30$). Parents' reported reduction in children's weekend screen time approached significance ($p = 0.08$; $d = 0.24$). Parents and children wore the provided watches to self-monitor their physical activity most days during the intervention period (child = 97%; parent = 88%). However, accelerometry data did not show significant pre- to posttest changes in PA, although seasonal cohorts (spring/summer and fall/winter) evidenced distinctive change patterns.
Conclusions: A health promotion-focused behavioral intervention for ADHD was acceptable and feasible, and it was associated with reduced screen time behaviors and some promising PA behavior changes. Objective measures of PA did not increase, suggesting that more focused targeting and weather-independent PA strategies may be warranted to increase PA among children with ADHD. ADHD, CAM, PAT

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S311.

29.3 EEG PREDICTORS AND CORRELATES OF METHYLPHENIDATE, GUANFACINE, AND COMBINED TREATMENT RESPONSE IN YOUTH WITH ADHD.

Michelini G.

Objectives: The combination of methylphenidate and guanfacine (an ±2A adrenergic receptor agonist) has been shown to be more effective than monotherapy in children with ADHD, but it is unclear what predicts and drives response to these treatments. This study is the first to investigate potential brain biomarkers as predictors and correlates of methylphenidate, guanfacine, and combined treatment response, consistent with a precision medicine approach.
Methods: In this study, 179 participants with ADHD (aged 7-14 years; n = 113 boys) were randomized to 3 conditions in an 8-week controlled, double-blind, comparative study: guanfacine, methylphenidate, or their combination. EEG was recorded during a spatial working memory task with encoding, maintenance, and retrieval phases before and after treatment. Linear mixed models examined the association between pretreatment EEG with ADHD symptom change, and between change in EEG and in ADHD symptoms. Pearson correlations further examined the association of pretreatment EEG measures with pretreatment ADHD symptoms and task performance.
Results: In terms of predictors, higher frontal theta (4-7 Hz) power during encoding and lower occipital theta and higher occipital beta (13-25 Hz) power during maintenance predicted ADHD symptom reduction across all treatments (all $p < 0.05$). Predictors specific to individual treatments were also observed. Higher pretreatment frontal beta power during encoding and maintenance predicted a greater ADHD symptom reduction following combined treatment than following monotherapies (all $p < 0.05$). Lower frontal theta power during maintenance and retrieval and lower occipital theta during encoding predicted greater ADHD symptom reduction with guanfacine than with methylphenidate (all $p < 0.05$). Greater treatment-related change in occipital theta during maintenance ($\pm = 0.18$; $p = 0.01$) and retrieval ($\pm = 0.16$; $p = 0.02$) were associated with greater ADHD symptom reduction across all treatments. Among measures emerging as predictors or correlates of treatment response, higher pretreatment occipital theta during maintenance ($r = 0.24$; $p < 0.01$) was associated with higher ADHD symptoms, whereas higher occipital beta during maintenance ($r = 0.18$; $p = 0.04$) and occipital theta during retrieval ($r = 0.21$; $p = 0.01$) were associated with poorer task accuracy.
Conclusions: We found treatment-specific and shared neural predictors and correlates of pharmaco-treatment response in children with ADHD. The identified biomarkers may offer promising future ways to aid personalized treatment decisions and to apply precision medicine approaches to child and adolescent psychiatry. ADHD, ATA, STIM

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S156.

5.23 QUANTITATIVE ELECTROENCEPHALOGRAPHY SUBTYPES AS AUXILIARY TOOLS TO ASSESS ADHD.

Young Choi T, Kim JW, Won GH, et al.

Objectives: This study investigated quantitative electroencephalography (QEEG) subtypes as auxiliary tools to assess ADHD.

Methods: A total of 74 subjects (58 males and 16 females) were assessed using the Korean version of the DISC-IV and were assigned to one of 3 groups: ADHD, ADHD-NOS, and normal control (NC). We measured EEG absolute and relative power in 19 channels and conducted an auditory continuous performance test. We analyzed QEEG according to the Hz range: delta (1-4 Hz), theta (4-8 Hz), slow alpha (8-10 Hz), fast alpha (10-13.5 Hz), and beta (13.5-30 Hz). The subjects were then grouped by Wardəs method of cluster analysis using the squared Euclidian distance to measure dissimilarities.

Results: There was no significant difference between the mean ages of the males and females ($t = 0.645$; $p = 0.521$) at 8.9 ± 1.2 years and 8.7 ± 1.2 years, respectively. We discovered 4 QEEG clusters, which were characterized by: 1) elevated delta power with less theta activity; 2) elevated alpha; 3) elevated theta with deficiencies of alpha and beta; and 4) elevated fast alpha and beta. Groups 1 and 3 had the largest proportion of the ADHD group (46% and 47% to ADHD, 33% and 40% to NOS, respectively). On the other hand, group 2 had the largest proportion of the NOS group (59% to NOS group, 30% to ADHD), whereas group 4 had the largest proportion of the NC group (62% to NC group, 13% to ADHD). The z score of absolute alpha and beta was elevated in the NC group more than the others ($p < 0.05$).

Conclusions: These results indicate that children with ADHD do not neurophysiologically constitute a homogenous group. We also discovered a new subtype: group 4 with increased alpha power in addition to those commonly reported in ADHD. Given the QEEG characteristics with increased alpha power, we should consider the possibility that this subtype may be caused by childhood depression. In conclusion, we believe that these novel QEEG subtypes of ADHD are expected to provide valuable information for accurately diagnosing ADHD and finding masked depression in childhood. ADHD, DIAG, IMAGS

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S150.

5.5 ADOLESCENT PERCEPITIONS OF FACTORES RELATED TO ENGAGEMENT IN ADHD CARE: A QUALITATIVE STUDY AT AN URBAN SAFETY NET HOSPITAL.

Zolli N, Spencer AE, Sikov J, et al.

Objectives: There is a noticeable gap in the literature on the treatment engagement experiences of adolescents from diverse backgrounds with a diagnosis of ADHD. Guided by the existing research on ADHD in adolescence and on how adolescents engage in ADHD care, the present study explored the factors and experiences that adolescents in treatment for ADHD at an urban safety-net hospital in Boston perceived as affecting their engagement with care.

Methods: As part of a larger and currently unpublished mixed-methods study, a cross-case, secondary thematic analysis of 11 interviews with adolescents from underserved and minority families was conducted. The majority of these adolescents were male (9; 81.2%), identified as African American (7; 63.6%), and were from Hispanic, Latino, or Spanish backgrounds (5; 45.5%). Most of the adolescents (63.6%) experienced financial hardship at least somewhat often.ΓÇØ In addition to their ADHD diagnosis, 7 (63.6%) participants had been diagnosed with a comorbid learning disability and 3 (27.3%) with a comorbid mental health condition.

Results: Thematic analysis delineated by Braun and Clarke (2006) revealed that engagement in care, as it is traditionally defined, ought to be redefined to incorporate the unique life circumstances and self-esteem and insight levels of adolescents. Four styles of engagement–proactive, anxious, apathetic, and actively rejecting engagement-emerged from the intersection of self-esteem and insight. Clinical implications included how providers can identify adolescents at risk for discontinuing treatment into adulthood and cultivate adolescents willingness to engage with treatment.

Conclusions: These findings confirm the importance of treating adolescents as a population with unique clinical needs and invite future researchers to investigate how to optimally transition adolescents with ADHD into adult care. ADHD, ADOL, MDM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S250.

50.1 ASSESSING HOSPIDALIZED ADOLESCENTS' READINESS TO ENGAGE IN THERAPY: RELATIONSHIPS WITH PSYCHOPATHOLOGY RATINGS, AVERALL FUNCTIONING, AND PATIENT-REPORTED TREATMENT ALLIANCE.

Nicotra C, Azizi M, Haggerty G, et al.

Objectives: Inpatient hospitalization for adolescents is the most expensive treatment modality, and inpatient beds have been reduced. Additionally, many mental health inpatient services, because of economic pressures, are not able to provide all patients with individual psychotherapy. Providers are in need of a measure that is easy to use and score and that could reliably assess patients ability to engage in inpatient psychotherapy.

Methods: We obtained consent from 72 adolescents admitted to an acute inpatient setting, of whom 52.8% were male, with an average age of 15.7 (SD = 1.18) years. In this group of adolescents, 40.8% were White, 25.4% were African American, 25.4% were Hispanic/Latino, 2.8% were Asian, and 5.6% identified as other. The main primary diagnosis was mood disorder (60%) followed by conduct disorder/ODD (30%). Patients completed the Inpatient-Treatment Alliance Scale. The unit psychiatrist completed the Readiness for Inpatient Psychotherapy Scale (RIPS) after their initial mental health evaluation. The consenting patient's individual and group therapists completed clinical ratings blind to each other, and the average of their ratings was used in this study. The clinicians were asked to rate the patients using the Overall Functioning Scale and Adolescent Psychopathology Prototypes.

Results: Results revealed that the RIPS was correlated with the clinician-rated Overall Functioning Scale ($r = 0.55$; $p < 0.001$), psychopathology prototypes for ADHD ($r = 0.37$; $p < 0.01$), conduct disorder, ($r = 0.56$; $p < 0.001$), and MDD ($r = 0.43$; $p < 0.001$). The RIPS was also correlated with self-reported alliance ($r = 0.25$; $p = 0.05$) and shorter length of stay ($r = 0.29$; $p = 0.02$).

Conclusions: The results show that those patients who are assessed as more ready to engage in therapy also reported better alliances at discharge and had a shorter length of stay. Lower readiness scores were related to higher ratings on ADHD and conduct disorder prototypes, as people with these diagnoses generally do not make use of therapy. Those who were rated higher on the MDD prototype also were rated higher on readiness. Depressed individuals may be more apt to take responsibility for their behavior and engage socially with the practitioners. ADOL, TREAT, P

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S14.

9.2 CHALLENGES IN PRESCRIBING AND OPTIMIZING PHARMACOTHERAPY IN ADOLESCENTS WITH ADHD.

Newcorn JH.

Objectives: Medication treatment in adolescents with ADHD poses unique challenges. Similar to, but also different from, treatment of both children and adults, pharmacotherapy of adolescents is less often studied. Moreover, developmental issues related to psychological independence and control significantly impact provision of care, as do increasing rates of comorbid mood, anxiety, and substance use disorders, and the need to cover a longer period of time each day. Most importantly, the need to shift from a parent-centered to an adolescent-centered approach has major implications for treatment adherence. This presentation will provide a mix of clinical and research-informed expertise on the use of medication in adolescents with ADHD.

Methods: A review of recent literature and experience in conducting clinical trials with adolescents will be utilized to generate specific recommendations, which will then be applied to the case examples put forward by the session chair.

Results: Effect sizes in clinical trials with adolescents are often lower for both stimulants and nonstimulants. Adolescents typically require higher absolute doses and lower weight-based doses of stimulants than do children. Effect sizes for ±-2 agonists are smaller, and dosing needs to be adjusted upward to account for

weight. Similar issues impact treatment with atomoxetine. Combining treatment with medications that target comorbidity offers opportunities but also complicates the therapeutic approach. Risks related to abuse and/or diversion of drugs are often not considered well enough.
Conclusions: Treatment of adolescents with ADHD requires sensitivity to myriad psychological, developmental, diagnostic, and pharmacokinetic considerations that impact treatment response. The art of managing these issues to therapeutic advantage will be illustrated in this presentation. PPC, ADOL, ADHD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S15.
9.4 WHEN SUBSTANCE USE DISORDER STRIKES YOUNG PEOPLE WITH.
Wilens TE.
Objectives: ADHD increases the risk for substance misuse and substance use disorder (SUD), with much of that risk occurring during the teenage and young adult years.
Methods: A clinically relevant review of the literature focused on the comorbidity of SUD in ADHD was undertaken. Recently published or completed findings on stimulant misuse were also examined.
Results: Data show important influences on the risk for SUD in teenagers with ADHD, including mental health comorbidity, characteristics, and early treatment of ADHD influencing the risk. Recent data on the epidemiology show stimulant misuse as a major issue, particularly on college campuses, with the context of stimulant misuse in this age group seemingly for performance enhancement. Studies on the treatment of ADHD in the context of SUD will be reviewed.
Conclusions: While ADHD increases the likelihood for the development of SUD, important modifiers of SUD risk exist. Treatment considerations and monitoring for SUD risk in high-risk teenagers with ADHD are recommended. SUD, ADOL, ADHD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S129.
4.1 WHAT'S NEW IN ADHD AND SUBSTANCE USE DISORDERS?
Wilens TE.
Objectives: Substance use disorders (SUDs) and ADHD are among the most prevalent disorders that child and adolescent psychiatrists treat. This talk provides a timely update on contemporary data related to the care of youth with these disorders.
Methods: A selected review of the literature focused on ADHD and SUDs was undertaken. Studies and editorials focused on relevant issues related to the prevention and care of young people with these disorders were reviewed.
Results: This talk will focus on the use of new formulations of stimulants and selected components of the guidelines from AAP on the treatment of ADHD. Work related to caffeine use, nonmedical use of prescription medications, and the clinical utility of toxicology testing in young people will be presented.
Conclusions: Emerging findings related to ADHD and to SUDs will be presented. ADHD, SUD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S159.
5.31 THE EFFICACY AND SAFETY OF SPN-812 (VILOXAZINE EXTENDED-RELEASE) FOR THE TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS.
Nasser A, Hull JT, Chaturvedi S, et al.
Objectives Four phase 3 RCTs evaluated the efficacy and safety of SPN-812, a serotonin norepinephrine modulating agent, for the treatment of ADHD, including 2 in children (aged 6-11 years; P301/3) and 2 in adolescents (aged 12–17 years; P302/4).
Methods Inclusion criteria included a DSM-5 ADHD diagnosis, ADHD-Rating Scale (RS)-5 Total Score (TS) ≥28, a Clinical Global Impression–Severity (CGI-S) score ≥4, and free of ADHD medication ≥1 week before randomization. Subjects were randomized 1:1:1 to placebo or 1 of the 2 SPN-812 treatment groups (100 mg

or 200 mg [P301]; 200 or 400 mg [P302/3]; 400 or 600 mg [P304]). The change from baseline (CFB) at end of study (EOS) in ADHD-RS-5 TS was the primary endpoint. CFB at EOS in CGI-I was the secondary endpoint. Safety assessments were included.
Results The reduction in the CFB at EOS in ADHD-RS-5 TS was significantly greater in the SPN-812 groups compared to placebo (difference of least squares [LS] mean ± SE [p -value]) in both trials in children (P301: 100 mg, –5.8 ± 1.61 [0.0004] and 200 mg, –6.9 ± 1.58 [<0.0001]; P303: 200 mg, –6.0 ± 2.05 [0.0038] and 400 mg, –5.8 ± 2.11 [0.0063]) and 1 trial in adolescents (P302: 200 mg, –4.5 ± 1.98 [0.0232] and 400 mg, –5.1 ± 1.93 [0.0091]; P304: 400 mg, –5.1 ± 1.93 [0.0082] and 600 mg, –3.5 ± 1.93 [0.0712]). The reduction in CGI-I at EOS was significantly greater in the SPN-812 groups compared to placebo in both trials in children (P301: 100 mg, –0.4 ± 0.14 [0.0020] and 200 mg, –0.6 ± 0.13 [<0.0001]; P303: 200 mg, –0.5 ± 0.17 [0.0028] and 400 mg, –0.4 ± 0.17 [0.0099]) and 1 trial in adolescents (P302: 200 mg, –0.5 ± 0.17 [0.0042] and 400 mg, –0.6 ± 0.16 [0.0003]; P304: 400 mg, –0.5 ± 0.17 [0.0051] and 600 mg, –0.3 ± 0.17 [0.0995]). A post hoc band-pass filter analysis found that the distribution of placebo response was similar among the P301-3 trials, but not in the P304 trial where it was higher by 44%, 73%, and 62%, respectively, compared to the P301-3 trials. The mixed-effect model repeated measure (MMRM) confirmed that the CFB in ADHD-RS-5 TS at EOS was statistically significant for all SPN-812 doses (100-600 mg; $p < 0.05$). Across the 4 studies, somnolence, decreased appetite, and headache were the most common adverse events (AEs) reported. The AE-related discontinuation rate for SPN-812 was <5%.
Conclusions Once-daily dosing of SPN-812 was effective in significantly reducing ADHD symptoms in children and adolescents. The low AE-related discontinuations indicate that SPN-812 treatment was well tolerated

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S149.

5.1 A COMPARATIVE STUDY ON COGNITIVE ABILITIES BY AGE GROUP IN ADOLESCENT AND ADULT PATIENTS WITH ADHD AND HEATHY CONTROLS.

Hwang H, Hong J, Kim SM, et al.

Objectives: Recently, there has been an updated conceptualization of whole-lifespan ADHD trajectories, promoted by increased awareness of persisting impairment from childhood into adulthood. Cognitive developments of ADHD have rarely been studied across whole lifespans. This study investigated age-related cognitive trajectories from adolescence to mid-adulthood in subjects with ADHD.
Methods: Data from 240 patients with ADHD and 244 healthy controls (HCs) were obtained from 8 Korean university hospitals and were separated into 4 age groups: 15 to 17, 18 to 24, 25 to 34, and 35 to 44 years. Clinical symptoms were assessed using the Korean ADHD Rating Scale for adolescents and the Korean Adult ADHD Self-Report Scale for adults. Neuropsychological functions were assessed using Korean versions of the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV), Wechsler Adult Intelligence Scale 4th Edition (WAIS-IV), and the Comprehensive Attention Test (CAT).
Results: Compared to HCs, patients with ADHD from the 15 to 17, 18 to 24, and 25 to 34 age intervals showed significant ($p < 0.05$) lower full scale IQ ($t = 5.18$, $t = 5.69$, and $t = 3.50$, respectively). Further analysis showed that patients with ADHD have decreased verbal comprehensive scores in the 15 to 17, 18 to 24, and 25 to 34 age intervals ($t = 4.91$, $t = 4.05$, and $t = 2.33$, respectively), perceptual organization scores only in the 15 to 17 age interval ($t = 3.93$), processing speed scores in the 15 to 17 and 18 to 24 age intervals ($t = 4.13$ and $t = 4.27$, respectively), and working memory scores in all age intervals ($t = 3.76$, $t = 4.94$, $t = 3.87$, $t = 2.38$). In the CAT, only the 15 to 17 age group of patients with ADHD and HCs showed significant differences in the errors of simple visual and auditory sections. However, differences in the errors of interference selection between the 2 groups were significant in the 15 to 17 and 18 to 24 age intervals. Differences in the errors of continuous inhibition were significant in all age intervals except for the 35 to 44 age interval. Finally, differences in the errors of divided attention, and forward and backward working memory were significant in all age intervals except for the 15 to 17 age interval.

Conclusions: Unlike adolescents with ADHD, adults with ADHD may not have deficits in simple attention, and their IQ may normalize after their mid-30s. However, they may have difficulties in complex attention including divided attention and working memory. ADHD, COG, DEV

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S113.

74.4 HOW MINDFUL PARENTING CAN SUPPORT CAREGIVERS IN MANAGING THEIR YOUNG CHILDREN WITH ADHD.

Kurahashi M, Reichert E.

Objectives: Young children with ADHD present unique challenges to caregivers, which can often lead to increased stress. Interventions to support caregiver well-being are gaining more attention as an important component in the treatment process. Mindful parenting involves intentionally having nonjudgmental awareness of the parents experience as well as greater awareness and acceptance of the child's unique nature, feelings, and needs. This intervention aims to reduce parentsΓÇÖ reactivity and increase their ability to respond with more presence and wisdom. In turn, this can decrease caregiver burnout and help parents be more effective in managing their childΓÇÖs ADHD symptoms. This presentation is designed to provide clinicians with current knowledge of mindful parenting in the context of caregiver stress and young children with ADHD.

Methods: Presenters will review current empirical evidence on mindful parenting interventions and their impact on caregiver stress. Evidence will be reviewed in the context of stress as a factor impacting treatment of young children with ADHD. Case examples will be used to enhance learning.

Results: Participants will learn the definition of mindful parenting and gain an understanding of how mindful parenting can potentially decrease caregiver stress, which can be a factor in overall treatment outcomes for young children with ADHD.

Conclusions: Given the nature of ADHD symptoms (eg, hyperactivity, impulsivity, challenges with emotion regulation), caregiversΓÇÖ stress can be increased. There is emerging empirical evidence supporting mindful parenting as an important intervention to improve caregiver well-being in the treatment of young children with ADHD. Enhancing cliniciansΓÇÖ understanding of the impact of mindful parenting practices when treating young children with ADHD can have important implications for treatment outcomes. PAT, EC, WL

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S316-S317.

33.1 ADHERENCE TO STIMULANT MEDICATION AMONG CHILDREN AND YOUTHS WITH ADHD: AN ELECTRONIC HEALTH RECORDS STUDY.

Biederman J.

Objectives: The objective of this study was to evaluate rates and correlates of stimulant medication adherence in pediatric samples using data derived from electronic medical records (EMRs) from a large metropolitan health care organization. Using the electronically recorded issuance of a stimulant prescription in the EMR, medication adherence was operationalized as a timely renewal of an index stimulant prescription.

Methods: Prescription and sociodemographic data were extracted from the Research Patient Data Registry to calculate adherence to stimulant medication treatment.

Results: We identified 2206 patients with prescriptions for central nervous system (CNS) stimulant medication. results showed that 46% of patients refilled their index prescriptions within a time frame to be considered consistently medicated. A multivariable logistic regression model predicting medication adherence from demographic and treatment characteristics yielded an area under the curve (AUC) statistic of 0.57, indicating that these characteristics were only modestly better than chance.

Conclusions: Data from EMRs from a large health care organization show that 46% of pediatric patients are adherent to treatment with stimulants. Rates of medication adherence were worse in the primary care than in the mental health setting, in older patients, and in female patients, and do not appear to be influenced by ethnicity, social class, stimulant type, or medication formulation (short- or long-acting). These findings provide

compelling new evidence of low rates of medication adherence in children with ADHD, calling for active efforts aimed at improving this state of affairs. ADHD, TREAT, STIM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S300.

22.3 CLINICAL CHALLENGES ARISING FROM THE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD FOLLOW-UP: POSSIBLE APPROACHES.

Hechtman L.

Objectives: This presentation aims to outline important clinical challenges and possible approaches that come out of the Multimodal Treatment Study of Children with ADHD (MTA) follow-up.

Methods: The MTA followed 576 children with ADHD (mean age = 8 years) from a 14-month RCT for 16 years after baseline. At 2-year follow-up, a local normative comparison group (LNCG, N = 286) was recruited from schools of the subjects with ADHD, and matched for age and sex. Retention was 80% and 90%, respectively.

Results: There are many important challenges arising from the follow-up. 1) Symptoms: symptoms are often syntonic and not reported or addressed even though they are present and impairing. Collateral input from a significant other who sees the person on a regular basis is critical. The study used self-report and/or reports of significant others, for example, parents or spouses to monitor symptomatology and impairment at follow-up. 2) Treatment: ADHD is often chronic, continuing into adolescence and adulthood. However, medication and psychosocial treatment are often discontinued; less than 10% are still medicated in adulthood. The numerous possible reasons include the lack of community treatment resources for adolescents and adults. Medication management may have little or no titration or systematic follow-up to adjust the dose and manage the side effects. Adolescents and young adults themselves may not wish to take medication or prefer to experiment with drugs and alcohol. Interventions other than medication (organization, time management, study skills, anger management, mood regulation) are often not perceived as needed by patients and are not readily available in the community. The challenge remains of informing patients and clinicians of the need for long-term follow-up and developing optimal community medication and psychosocial treatment approaches. 3.) Comorbidity: comorbidity is common, with 70% in childhood and adolescence and 85% in adulthood. However, comorbidities often go unrecognized and untreated. Anxiety, depression, and substance abuse are frequent in adulthood. Adults presenting with these disorders may have underlying ADHD or a learning disorder that is undetected and untreated.

Conclusions: Challenges arising from the MTA follow-up include ego-syntonic symptoms, the need to develop ongoing effective medication and psychosocial treatments as well as follow-up in the community, and the complexity of frequent comorbidities that also need to be diagnosed and treated. ADHD, LONG, RF

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S286.

INFECTIONS, IMMUNE FUNCTION, AND PSYCHOPATHOLOGY IN YOUTH.

Williams KA, Geller DA.

Objectives: The contribution of infections and immune function to childhood psychopathology has been investigated and debated for many years. Recently, a number of large-scale analyses using the Scandinavian Health Registries have shown increased associations between infections and childhood mental health conditions, such as anorexia nervosa, OCD, and tic disorders. Advances in the technology of metabolomics and immune system profiling have also shed new light on the potential immune system alterations that underlie these associations. The objective of this Symposium is to discuss the emerging data linking infections, immune dysregulation, and psychopathology on both an epidemiological level and a molecular level in order to discuss the future directions needed to make these suspected associations clearer.

Methods: The research presented in this Symposium will discuss results from the following: 1) a retrospective chart review of medical records assessing immune deficiencies in patients with OCD and other childhood-onset mental health disorders; 2) an analysis of immunogenetics and immune markers from patients with PANS; 3) an analysis of multimodal MRI neuroimaging from patients with PANDAS; 4) a report

of altered immune and metabolic markers in patients with anorexia nervosa compared to healthy controls; and 5) a report of metabolomic and genomic associations in patients with PANS compared to controls.
Results: The results from these studies suggest that: 1) children with OCD display higher rates of IgA deficiency than children with other common mental health disorders, such as ADHD; 2) children with PANS display a unique array of immunogenetic and immune markers; 3) children with PANDAS display unique abnormalities on MRI compared to healthy controls; 4) patients with anorexia nervosa display specific alterations in metabolic and immune plasma markers; and 5) patients with PANS show characteristic changes in immune cell activation compared to healthy controls.
Conclusions: This Symposium will discuss the results from a number of recent studies that suggest that infections and immune dysregulation are associated with childhood mental health disorders such as OCD, tics, and anorexia. The results presented here will provide further evidence that immune dysregulation may represent either a consequence of, or pathogenic mechanism for, childhood psychopathology. NI, AXN, OCD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S145.
1.20 THE PREVALENCE OF MENTAL ILLNESS AND ASSOCIATED PSYCHOSOCIAL FACTORS IN HOMELESS ADOLESCENT.
Zemanek CE, Kayne AN, Downen JM, et al.
Objectives Homelessness is a major social determinant of mental health. We set out to determine the prevalence of mental illness in an adolescent homeless population and to report on the prevalence of psychosocial factors that could be associated.
Methods This is a retrospective, cohort study of patients who underwent state-mandated physicals at a homeless adolescent shelter in Pennsylvania from February 19, 2015 to September 5, 2019. Demographics and mental health and social histories were extracted. Categorical data were reported using frequencies and percentages. To test the study hypothesis that social history components were associated with mental illness, a χ 2 test of independence was conducted.
Results A total of 435 charts was reviewed in the study cohort. The age range was 11 to 20 years with a mean age of 15.32 ± 1.62 years. Among these patients, 42.5% (N = 185) of the patients were male, 55.6% (N = 242) were female, and 1.8% (N = 8) were transgender. A mental health history was reported in 54.9% (N = 239) of the patients, some of whom had multiple diagnoses. Of these, the top 3 diagnoses reported were depression (55.2%, N = 132), ADHD (43.5%, N = 104), and anxiety (30.1%, N = 72). Regarding social history, 26.5% (N = 114) reported trauma, 39.5% (N = 170) reported self-injurious behavior, and 52.6% (N = 226) reported aggression. In addition, 47.1% (N = 205) reported illicit drug use, 12.0% (N = 52) reported alcohol use, and 27.6% (N = 120) reported tobacco use. A relationship existed between a mental health diagnosis and the following: previous self-injurious behavior (χ 2 [1, N = 432] = 30.4; p = 3.53); a history of aggression (χ 2 [1, N = 433] = 4.0; p = 0.046), and a history of trauma (χ 2 [1, N = 434] = 4.5; p = 0.034). There was a relationship between a mental health diagnosis and tobacco use (χ 2 [1, N = 434] = 6.1; p = 0.014). No relationship existed between a mental health diagnosis and alcohol use (χ 2 [1, N = 433] = 0.32; p = 0.569), or illicit drug use (χ 2 [1, N = 434] = 0.41; p = 0.524).
Conclusions In our single-site study, over half of the homeless adolescents reported a mental health diagnosis, most commonly depression. Histories of trauma, past aggression, and self-injurious behavior were present in a clinically substantial portion of the population. A mental health diagnosis was associated with a history of self-injurious behavior, trauma, aggression, and tobacco use. The proportion of patients who reported a mental health diagnosis did not differ by alcohol or illicit drug use. SP, RF, ADOL

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S155.
5.20 PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF SHP465 MIXED AMPHETAMINE ALTS AFTER MULTIPLE DAILY DOSES IN CHILDREN AGED 4-5 YEARS WITH ADHD.
Ilic K, Kugler AR, Yan B, et al.

Objectives: The pharmacokinetics (PK), safety, and tolerability of SHP465 mixed amphetamine salts (MAS) were evaluated in preschool children with ADHD after multiple once-daily (QD) doses of SHP465 MAS 6.25 mg (half the lowest FDA-approved dose of Mydayis).
Methods: In this open-label, multicenter study, 4- to 5-year-old children with DSM-5-defined ADHD, baseline ADHD-RS-5 total score 28 (boys) or 24 (girls), and baseline Clinical Global Impression-Severity (CGI-S) score 4 were administered SHP465 MAS 6.25 mg QD for 28 days. Blood samples were collected predose on Day 1 of Week 1 (D1W1), D7W4 (predose; 2, 5, 8, 12, 16 hours postdose), 24 hours and 48 hours postdose (D8W4 and D9W4) in the PK-rich group; and on D1W1, D1W2, and D1W3 (predose) and 24 hours post-D7W4 dosing (D8W4) in the PK-sparse group. The primary PK parameters included Cmax, Ctrough,ss, Tmax, AUC0-t, AUClast, AUCtau,ss, lz, t1/2, CL/F, and Vss/F. Safety endpoints included treatment-emergent adverse events (TEAEs) and vital signs.
Results: The mean age and BMI of 24 participants (66.7% males) were 4.8 ± 0.41 years and 17.2 ± 3.18 kg/m2. On D7W4, plasma geometric mean peak steady-state (SS) exposure for both d- and l-amphetamine was achieved at 7.92 hours postdose (median Tmax) and thereafter declined monoexponentially with a geometric mean half-life (t1/2) of 10.4 hours and 12.3 hours for d- and l-amphetamine, respectively. Plasma d- and l-amphetamine SS was attained by D8, consistent with the half-life. Peak and overall SS exposure (Cmax and AUCtau,ss) were comparable between 4- and 5-year-old children (n = 3 vs 8) regardless of sex for both d- and l-amphetamine. In total, 14 TEAEs were reported by 45.8% (11/24) participants; 5 TEAEs reported for 4 (16.7%) participants were considered treatment related; affect lability occurred in 2 (8.3%) participants, and insomnia, accidental overdose, and blood pressure increased (each TEAE occurred in 1 [4.2%] participant).
Conclusions: In 4- to 5-year-old children with ADHD, following multiple QD administration of 6.25 mg SHP465 MAS, plasma d- and l-amphetamine steady-state was attained by Day 8. Between-subject variability of plasma d- and l-amphetamine steady-state exposure was low to moderate. SHP465 MAS was generally well tolerated. Observed adverse events (AEs) of insomnia, increased blood pressure, and affect lability are AEs listed on the drug labels of prescription amphetamines. ADHD, PKS, STIM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S78.
51.3 ADHD IN AUTISM SPECTRUM DISORDER.
Handen BL.
Objectives: The objectives are to review our present knowledge of ADHD in autism spectrum disorder (ASD), including prevalence, developmental trajectory, diagnosis, and treatment.
Methods: This presentation will review relevant literature, including a summary of controlled treatment trial results.
Results: Until the publication of the DSM-5, clinicians were not permitted to diagnose ADHD in children and adults with ASD. While clinicians are now allowed to make concurrent ADHD and ASD diagnoses, the determination of an ADHD diagnosis in this population remains challenging. Prevalence estimates range from as low as 7% to as high as 75%, depending on the assessment tool used, cohort (eg, community, clinical), and respondent (eg, teacher, parent). As with the general population, there appears to be a reduction in reported rates of ADHD from childhood into adulthood. In general, pharmacologic treatment of ADHD in children and adolescents with ASD is effective. However, response rates tend to be lower than those documented in the literature involving typically developing children with ADHD, and the rate of reported side effects is often higher. For example, RCTs of stimulant medications, such as methylphenidate, have documented response rates of approximately 50% (vs 73% in the general population). Slightly lower response rates have been reported in RCTs with nonstimulant alternative medications, such as guanfacine and atomoxetine. Psychosocial treatments, such as parent training, have shown some effectiveness in children and also have an important role to play in meeting the needs of this population. However, we are unaware of any controlled trials of behavioral treatments for adults with ADHD and ASD.

Conclusions: Children and adults with ASD can now be diagnosed with concurrent ADHD. Research evidence supports the efficacy of psychostimulants, alpha-2 agonists, and atomoxetine in this population, although response rates are lower than in the general population. ASD, ADHD, CM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S260.

RESTING-STATE FMRI CORRELATES OF CLINICAL RESPONSE TO STIMULANTS IN CHILDREN AND ADOLESCENTS WITH ADHD.

Pereira-Sanchez V, Franco AR, Castro-Manglano PD, et al.

Objectives: Little is known about the brain mechanisms of action of pharmacological treatments for ADHD and the heterogeneity of responses across patients. Our objective was to analyze potential differences in resting-state brain functional connectivity across networks between patients with a good response to stimulants vs patients who are treatment-naïve.

Methods: We recruited 65 boys and girls (ages 7-17 years) with ADHD in an outpatient setting. We defined 3 different pharmacological treatment-response status groups: clinical responders to methylphenidate (n = 21; mean duration of treatment = 32 months; SD = 30); methylphenidate nonresponders treated with lisdexamfetamine (n = 21; mean duration of treatment = 23 months; SD = 14); and treatment-naïve (n = 23). Sociodemographic, neuropsychological, clinical data, and blood samples were collected from participants, who also underwent a resting-state fMRI scan. Neuroimaging data were preprocessed using CPAC v1.6.1, including artifact and motion correction. All data passed visual quality assessments. We performed dual regression of 10 resting-state brain networks. Group analyses were performed with a network-based false-discovery rate correction.

Results: Fifty-five patients were included in final analyses after excluding those with high head motion and significant artifacts (data analyzed consisted of 17 individuals on methylphenidate, 18 on lisdexamfetamine, and 20 treatment-naïve). Across-network functional connectivity between groups revealed a significant reduction in functional connectivity between lateral visual and executive control networks in patients on either stimulant vs treatment-naïve individuals; this difference was also observed when comparing lisdexamfetamine vs treatment-naïve, but was not significant for methylphenidate.

Conclusions: Our findings, which should be interpreted as preliminary due to the study limitations (sample size, naturalistic treatment), suggest a potential effect of stimulants in increasing an anticorrelation between visual and executive control networks. This strengthened anticorrelation implies that clinical response may be associated with reduced abnormal cross-network interference in patients with ADHD. ADHD, IMAGS

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S112.

73.3 LEVERAGING PROJECT ECHO FOR EXPANDING PRIMARY CARE CAPACITY TO TREAT PEDIATRIC ADHD.

Ochoa-Lubinoff C.

Objectives: The prevalence of ADHD has risen steadily among children in Illinois from 6% in 2003 to 9% in 2011. Due to a shortage of specialists, children from underserved Chicago communities have to wait 6 months to be seen. Community-based primary care providers (PCPs) are well-positioned to help close this gap, but they often do not diagnose and manage children with ADHD because of limited knowledge and confidence. The Extension for Community Healthcare Outcomes (ECHO)-Chicago ADHD series provides PCPs and other health care providers with the skills and knowledge to diagnose and treat ADHD in children, thus improving their health outcomes.

Methods: The ECHO-Chicago ADHD series curriculum focuses on providing PCPs with the knowledge and skills they need to implement clinical guidelines and to manage diverse patients in real-practice situations. This series includes 13 weekly hourly sessions that combine a 20-minute didactic with participant-led case presentations, modeled as virtual rounds. Key topics include diagnostic criteria, rating scales, differential diagnoses, and comorbidities; educational supports and school advocacy; behavior management and parent resources; medication management; and complementary-alternative therapies. Participants are expected to attend at least 70% of the sessions and to present 1-2 de-identified complex patient cases during the series.

Continuing Medical Education (CME) and Continuing Education Unit (CEU) credits are provided at no cost. Pre- and postseries surveys are used to measure changes in provider self-efficacy, provider knowledge, and self-reported provider behavior changes.
Results: Since 2011, this series has trained 280 PCPs and health care professionals. Participants largely represent federally qualified health centers (FQHCs), safety net hospitals, and free and charitable clinics. Pre-post survey data indicates a consistent significant increase in provider self-efficacy among 90% of participants following participation in the series. Mean self-efficacy rose by 1.3 points on a 7-point Likert scale. Participants have reported making structural practice-level changes and a decrease in referrals to specialists.
Conclusions: Currently in its 14th cohort, this series has proven to be quite effective in terms of expanding PCP self-efficacy to treat ADHD. We are working on developing a Quality Improvement component to the series. ADHD, EBP, TVM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S299.
FIDINGS FROM THE MULTISITE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD AND FOLLOW-UP: CLINICAL PEARLS AND CHALLENGES.
Hechtman L, Sonuga-Barke E.
Objectives: The aim of this Symposium is to describe key clinical findings in the Multimodal Treatment of ADHD (MTA) and follow-up study (Pearls), medication use and adult ADHD outcome, and the clinical challenges that remain.
Methods: Peter S. Jensen, MD, will present some of the key clinical findings from the MTA and follow-up study. James M. Swanson, PhD, will present the different patterns of medication use and adult ADHD outcome. Lily Hechtman, MD, will outline clinical challenges and possible approaches arising from the MTA follow-up.
Results: Findings from the MTA and follow-up study suggest that outcomes have at least 3 different patterns or trajectories, with some patients improving during treatment and remaining improved, others improving during treatment and then deteriorating when treatment stops, and a third group showing a very gradual improvement over time. Medication monitoring and adjustment are needed for it to remain effective. Children with ADHD have an increased risk of substance use in late adolescence and adulthood, but most do not have significant substance abuse or dependence, and ADHD does not increase the risk of bipolar disorder or psychosis. Patterns of medication use are often episodic, with only 7% using medication continuously over time. The impact of medication use patterns on adult ADHD outcome will be presented. Challenges that remain include the following: 1) the syntonic nature of symptoms, which often go unreported and untreated despite impaired functioning; 2) treatment (medication and psychosocial) being less than optimal and unavailable in the community or rejected by the patients; and 3) comorbidities that are often undiagnosed and untreated, or treatment of the comorbidities may be addressed without diagnosing or treating the underlying ADHD or learning disorder.
Conclusions: The Symposium addresses key clinical findings in the MTA and follow-up study and treatment approaches needed for a more positive outcome. It also reports an increase in substance use, although most do not abuse substances. No increased risk for bipolar disorder or psychosis was seen. The impact of the pattern of medication use on long-term outcomes is described. Challenges include syntonic symptoms, the availability and use of optimal medication and psychosocial treatment, and identifying and treating comorbidities. ADHD, LONG, RF

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S331.

42.3 DEVELOPMENT OF A WEB-BASED TRAINING PLATFORM FOR SCHOOL CLINICALS IN EVIDENCE-BASED PRACTICES FOR ADHD.

Pfiffner LJ, Dvorsky MR, Haack LM, et al.

Objectives: Web-based technology and videoconferencing are increasingly applied to scale-up and/or disseminate interventions to populations that may not otherwise have access to evidence-based services. We describe the development and outcomes of a web-based clinician training platform for school clinicians to gain skills in evidence-based practices for youth (ages 7-11 years) with ADHD.

Methods: The clinician training platform is adapted from an empirically supported in-person training for a school-home behavioral intervention (Collaborative Life Skills program), and it includes skill modules for working with teachers, parents, and students. Training methods include web-accessed manuals/handouts, skill example video clips, automated progress monitoring tools, supervision/in-session coaching via videoconferencing, online help desk, and social media groups. We gathered stakeholder (school clinician, trainer) qualitative, and quantitative feedback during the discovery and design phases of the iterative development. Following completion of the platform, we gathered usability, acceptability, feasibility, and fidelity data from open trials (4 clinicians, 24 students/parents/teachers) and a pilot randomized trial (10 clinicians, 60 students/parents/teachers) comparing remote vs in-person training.

Results: Focus group themes and qualitative feedback during the trials identified clinician preferences for remote training features (eg, interactive, brief, role-plays/coaching methods), video tools (recorded samples of skills and therapy sessions), and progress monitoring tools (eg, clear, easy to use). Clinician ratings of the platform were above average (scores 68) on the System Usability Scale with most components rated as slightly to very useful/easy to use. Iterative adaptations improved acceptability and usability to address clinician time constraints and varying comfort with technology. Rates of clinician fidelity implementing the treatment, engagement, and youth outcomes were favorable and similar to our in-person training (all $p > 0.05$; all $D = 0.09$-0.14).

Conclusions: Results document acceptability, feasibility, usability, and utility of remote, web-based clinician training and support the promise of this approach for the dissemination of evidence-based practices. ADHD, SC, TVM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S122.

1.1 PHARMACOLOGICAL STRATEGIES IN ADHD: FOCUS ON COMORBID MOOD DYSREGULATION.

Wilens TE.

Objectives: Increasingly complex cases of children with ADHD are presenting to child and adolescent psychiatrists, requiring practitioners to learn new strategies for sequencing treatment, the management of refractory core ADHD symptoms, and the treatment of comorbidity(ies), especially in the context of mood dysregulation.

Methods: A systematic review of the literature from historic, recently completed, and ongoing trials was reviewed to elucidate data on stimulant and nonstimulant treatments for ADHD. Data on treatment of mood dysregulation in ADHD were reviewed.

Results: The literature combined with the clinical experience indicates that alterations in the use of traditional stimulants in existing and novel release forms, atomoxetine, alpha agonists, the use of alternative agents, and combinations of medications can enhance a patient's ADHD response. Treatment of mood dysregulation often necessitates combined strategies.

Conclusions: Pharmacological strategies will be reported for those who: 1) have not responded to traditional agents; and 2) present with comorbidity(ies), with a focus on mood dysregulation. Both empirically derived data and illustrative cases will be used in the presentation. ADHD, PKS, STIM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S316.

ASSESSING THE IMPACT OF STIMULANTS ON FUNCTIONAL OUTCOMES IN ADHD.

Biederman J, Newcorn JH.

Objectives: Despite data documenting that stimulants are safe and highly effective in the treatment of ADHD and could help mitigate many of its adverse complications, we document the extent of nonadherence to stimulant treatment in ADHD and provide both a qualitative review and meta-analysis of the effects of stimulant treatment on ADHD-associated functional outcomes.

Methods: We first analyzed data from a large electronic medical record to document the rate of adherence to stimulant medication in children with ADHD. Next, using a qualitative review and meta-analysis of the present literature, we examined the effect of pharmacological treatments for ADHD on various functional outcomes. We then quantified the protective effects of stimulant treatment on important functional outcomes in ADHD using the number needed to treat (NNT) statistic.

Results: Our results further document that the rate of adherence to stimulant medication in ADHD is quite low. Our qualitative review demonstrated a robust protective effect of ADHD medication treatment on ADHD-associated functional outcomes, including mood disorders, suicidality, criminality, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes. Our meta-analysis showed similar findings. The NNT statistics we calculated were very low, ranging from 3 to 10, indicating that stimulants have strong protective effects on important functional outcomes.

Conclusions: These findings suggest that ADHD stimulant medication treatments are associated with decreases in the risks for a wide range of ADHD-associated functional outcomes and that the NNT statistic is quite low for each outcome, yet nonadherence to stimulant medication remains very high for children diagnosed with ADHD, thus supporting efforts aimed at early diagnosis and treatment of individuals with ADHD. ADHD, STIM, TREAT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S155-S156.

5.21 POST HOC META-ANALYSIS OF MORNING AND EVENING BEHAVIORS IN CHILDREN WITH ADHD TREATED WITH DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE FROM TWO PHASE 3 STUDIES.

Pliszka SR, Childress AC, Cutler AJ, et al.

Objectives: The Parent Rating of Evening and Morning Behavior Scale, Revised (PREMB-R) is a validated 11-item, clinician-rated scale based on a structured parent interview that evaluates functional impairment in the early morning (AM subscale, 3 items) and late afternoon/evening (PM subscale, 8 items). Items assess the extremes of the waking day, from getting out of bed to falling asleep. In 2 phase 3 trials of children with ADHD, delayed-release and extended-release methylphenidate (DR/ER-MPH) significantly improved PREMB-R AM and PREMB-R PM scores vs placebo. Because neither study was designed to assess the effect of DR/ER-MPH on functional impairments at an item level, a post hoc meta-analysis of individual PREMB-R items was conducted on pooled data from both studies.

Methods: Data were pooled from 2 randomized, double-blind, placebo-controlled, phase 3 trials of DR/ER-MPH in children with ADHD (NCT02520388 and NCT02493777). Individual PREMB-R item scores in the DR/ER-MPH and placebo groups at the endpoint of each trial were assessed in the intention-to-treat population. The fixed-effects model included the PREMB-R subscale and item scores as the dependent variable; study, treatment, and study/treatment interactions were included as main effects; and the baseline PREMB-R score was a covariate. The study sites were included as a random effect.

Results: A total of 271 participants had endpoint PREMB-R scores (143 DR/ER-MPH; 128 placebo). Baseline demographics and clinical characteristics were similar between the placebo and DR/ER-MPH groups. All 3 PREMB-R AM items significantly improved with DR/ER-MPH compared to placebo (p 0.001). Seven of the 8 PREMB-R PM items, including settling down and getting ready for bed significantly improved with DR/ER-MPH compared to placebo (p 0.05). Falling asleep was improved with DR/ER-MPH compared to placebo, but the improvement was not statistically significant (p = 0.145).

Conclusions: In a pooled post hoc analysis, DR/ER-MPH significantly improved 10/11 PREMB-R items vs placebo (from getting out of bed to settling down and getting ready for bed), suggesting an improvement in functional impairment that starts in the early morning and lasts into the evening. These results are worth further exploration. ADHD, IMP, RI

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S326-S327.

39.4 NEUROCOGNITIVE SUBTYPING OF ADHD BY COMPUTATIONAL PSYCHIATRY.

Ging-Jehli N, Eugene Arnold L, Childers R, et al.

Objectives: The objectives of this presentation are to improve distinction of endophenotypes of ADHD and to explore biomarkers that may help in the selection of effective treatments.

Methods: We examined differences in cognitive processing between children with ADHD (n = 136, from the International Collaborative ADHD Neurofeedback [ICAN] study) and without ADHD (n = 57). To do so, we fit the diffusion decision model (DDM) to the Integrated Visual and Auditory (IVA) 2.0 neurocognitive test data. This allowed us to decompose performance into 4 cognitive components, namely: prior expectation (z); quality of information integration (v); required amount of information to reach a decision (a); and time for perceptual encoding and response execution (Ter). We also examined whether the source of any cognitive deficits in v and/or Ter predicted improvements in inattention ratings (composite ratings by parents and teachers) from baseline to treatment end in the RCT of neurofeedback for ADHD.

Results: Children with ADHD had significantly poorer information integration (lower v) compared to children without ADHD ($p < 0.001$). We also found differences between DSM-5 ADHD presentations (Combined [ADHD-C] vs Inattentive [ADHD-I]). Children with ADHD-I were slower in perceptual encoding and response execution (longer Ter) than children with ADHD-C ($p = 0.04$). Comparing EEG frequency bands collected in unrelated tasks, we found that higher theta/beta ratios were associated with lower v ($r = 0.178$; $p = 0.04$). The source of cognitive deficits significantly predicted improvements in inattention ratings on a 0-to-3 scale ($p = 0.004$). Specifically, children with mild deficits in v and in Ter improved the least (0.38), followed by those with greater deficits in Ter only (ΓêÆ0.56), and those with greater deficits in v only (0.59); children with greater deficits in both Ter and v improved the most (ΓêÆ0.66).

Conclusions: Neurocognitive testing, in conjunction with computational models, may be used to characterize differences in cognitive processing between ADHD subtypes. Combining computational modeling and neural measures may distinguish a broader set of phenotypes associated with neurocognitive biomarkers. ADHD, COG, CM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S158-S159.

5.30 THE EFFECT OF CLOSED-LOOPED ACOUSTIC STIMULATION DURING SLEEP IN CHILDREN WITH AND WITHOUT ADHD: ENHANCING THE CONSOLIDATON OF REWARDED MEMORIES BY INCREASING SLOW-WAVE ACTIVITY?

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

Objectives: Slow oscillations (SO) during slow-wave sleep foster the consolidation of declarative memory. Children with ADHD display deficits in the sleep-associated consolidation of declarative memory, possibly due to an altered function of SO. A recent study showed that the external induction of SO by transcranial direct current stimulation (tDCS) can normalize the sleep-dependent consolidation of declarative memory in children with ADHD. The present study aimed at enhancing SO activity using closed-looped acoustic stimulation during slow-wave sleep in children with ADHD. This method was proven to enhance endogenous SO activity during sleep and to foster sleep-dependent consolidation of declarative memory.

Methods: Fourteen children with ADHD (aged 9-12 years) and 15 healthy children (same ages) participated in a double-blind, placebo-controlled study. Besides an adaptation night, children spent 2 experimental nights in a sleep lab, including 1 stimulation night and 1 sham night. Before sleep, children learned a set of word pairs; half of the word pairs were declared as high-rewarded (yielding a high monetary reward), while the other half was declared as low-rewarded (yielding only little monetary reward). In addition, a motor learning (serial reaction time) task was applied. After sleep, the retrieval took place on the next morning.

Results: There were no differences in memory performance between children with and without ADHD in the sham condition. After stimulation, however, healthy children performed significantly better on high-rewarded memory items, compared to children with ADHD. In contrast, children with ADHD performed better on the motor learning task than healthy children.
Conclusions: Here, we observed that the improvement of endogenous SO activity during sleep supported the consolidation of rewarded declarative memories in healthy children. No such effect was observed in children with ADHD. These data support the hypothesis that the function of slow-wave activity in memory consolidation is altered in ADHD. ADHD, SLP, COG

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S156.

5.22 PREDICTORS OF GROWTH SUPPRESSION IN CHILDREN WITH ADHD TREATED WITH CENTRAL NERVOUS SYSTEM STIMULANTS.

Waxmonsky JG, Pelham WE, Baweja R.

Objectives: In this poster, we will examine predictors of BMI loss and growth suppression in children with ADHD initiating central nervous system (CNS) stimulants.
Methods: A total of 230 children aged 5 to 12 years with ADHD who were medication naïve and had a BMI between the 5th to 95th percentiles were randomized to extended-release CNS stimulants (80%) or behavior therapy (20%) over 30 months. All medication was provided through the study and was predominantly OROS methylphenidate (MPH). After month 6, any participant whose BMI z score dropped 0.5 units (one z unit if BMI 85th percentile) was randomized to 1 of 3 weight-recovery treatments (WRT: drug holiday, caloric supplementation, or monthly monitoring). After month 6, children with moderate or worse impairment could cross treatment arms. Growth, ADHD symptoms, caloric intake, and medication use were measured every 2 to 4 weeks.
Results: A total of 165 participants used medication, 71 (43%) of whom entered WRT at a mean time of 12.7 (SD = 6.4) months. WRT youth had statistically significant declines in z-height and z-weight over 30 months. The following were correlated ($p < 0.05$) with WRT entry (ie, BMI loss): mg of MPH pre-WRT ($r = 0.046$), baseline z-height ($r = 0.22$), weight ($r = \Gamma\text{Ç}\hat{o}0.39$) and BMI ($r = 0.35$), raw height ($r = 0.18$), and weight ($r = 0.22$). Heavier and taller children and those with lower medication exposure were less likely to enter WRT. The following were correlated ($p < 0.05$) with change in z-height at month 6: parent ratings of appetite loss on optimal dose ($r = 0.34$), age ($r = 0.32$), raw weight ($r = 0.28$), and height ($r = 0.27$). For the 35 WRT participants with calorie logs before and after medication, change in calories was moderately correlated with z-height ($r = 0.24$) and mildly correlated with WRT entry ($r = 0.14$). There was no significant association with gender, puberty status, ADHD, or ODD symptoms.
Conclusions: The amount of medication used robustly predicted BMI loss. Adjusting the dose or frequency of use may be a way to lower risk. Smaller, lighter children were at increased risk for BMI decline and growth suppression and should be closely monitored when initiating CNS stimulants. Parent ratings of appetite suppression may indicate future growth suppression. ADHD, PPC, STIM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S261-S262.

CAN AUTISM SPECTRUM DISORDER (ASD) AND ADHD BE ON THE SAME SPECTRUM: CROSS-SECTONAL STUDY ANALYZING THE SUBTYPES OF ASD WITH COMORBID SUBTYPES OF ADHD.

Ghumman U, Kirkham C, Ghumman MZ, et al.

Objectives: Neurodevelopmental disorders (NDDs) are a group of disorders with impairment in growth, development, and function of the brain, which negatively impact memory, learning ability, and emotions. Both ADHD and autism spectrum disorder (ASD) are in the NDD group that have similarities such as increased prevalence in boys, difficulties in social communication, stereotyped behavior, aberrations in brain structures, and similar neurotransmitters involved in the disorders.
Methods: In this cross-sectional study, we were interested in the prevalence of ADHD presentations with comorbid ASD among children at the US-Mexico border. ICD-9 codes were used to query the electronic

medical record database. Patients at the Texas Tech Child Psychiatry Clinic, from 2010 to 2018, were included in the study. Inclusion criteria included a mental health interview, a Social Communication Questionnaire (SCQ), Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2), and the Vanderbilt ADHD Diagnostic Rating Scale.
Results: Revision of 1203 patients' charts yielded 31 patients who had combined diagnosis of ADHD and ASD with testing via ADOS-2/SCQ and the Vanderbilt Scale. Out of the 31 patients, 23 are male and 8 are female. All ADHD presentations had similar interquartile ranges for the SCQ and ADOS: Restricted and Repetitive Behaviors (RRB), Social Affect (SA), and Comparison scores. There was a stronger correlation between ADOS-RRB and the Vanderbilt inattentive and total scores (r = ΓÇô0.0255, p = 0.165; r = 0.222, p = 0.23, respectively) than between ADOS-SA and Vanderbilt scores (r = ΓÇô0.027, p = 0.886). Gender differences in ADOS scores were higher in male scores on the SCQ, ADOS SA, and ADOS-2 comparison scores (p = 0.156, p = 0.152, p = 0.412, respectively). Females had higher scores in ADOS-RRB (p = 0.220).
Conclusions: All ADHD presentations received similar scores for all sections of the ADOS-2. Higher scores for RRB in females could mean that, even though the prevalence for both ASD and ADHD is higher in males, RRB is more severe when diagnosed in females. Similarities between ADHD and ASD exist, and there is a possibility that both can be considered as a different presentation of the same illness. The limitation of the study was a small number of participants who had an ADOS-2. With a small sample size, statistical insignificance is to be expected, but trends in the data are important. ADHD, ASD, EPI

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S158.

5.28 STRENGTHS AND CHALLENGES AT SCHOOL FOR CHILDREN WITH ADHD: INSIGHTS FROM PUPILS AND THEIR TEACHERS.

Rhodes SM, McDougal E, Stewart T, et al.

Objectives: Children with ADHD can struggle at school and are more at risk for academic underachievement or dropping out of school. The current study aimed to investigate their greatest strengths and challenges at school, as well as how these can be supported.
Methods: The sample comprised 17 participants. Ten primary school pupils with ADHD (aged 6 to 11 years) were recruited from a clinical population to take part in face-to-face semi-structured interviews. Following participation, each child's teacher was contacted to ask if they would be willing to take part. Seven teachers were recruited. The semi-structured interviews focused on: 1) the child's strengths; 2) the child's biggest challenges at school; 3) strategies in place for support and their efficacy; and 4) any gaps where support is still needed. Interview transcripts were analyzed qualitatively using thematic analysis to identify key themes.
Results: A range of strengths and challenges that pupils with ADHD face at school were identified, including both academic (eg, math, literacy, art) and nonacademic (eg, attention, social skills, motivation) factors. Importantly, we were able to consider these issues from the perspectives of both children and their teachers. Further, strategies of support for specific challenges were discussed in the context of how effective or useful children found these strategies. The focus of these strategies for both children and teachers tended to be on external aids (eg, visual aids, planners). Some participants did also refer to cognitive strategies (eg, rehearsal, chunking), but these were mentioned less frequently.
Conclusions: The findings have important implications for the development and focus of interventions focused on improving learning in children with ADHD, particularly in relation to the need to focus on cognitive skills. SC, ADHD, EDUC

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S325-S326.

39.1 A 25-MONTH FOLLOW-UP OF A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL OF NEUROFEEDBACK FOR ADHD.

Eugene Arnold L, deBeus RJ, Pan J, et al.

Objectives: This presentation aims to examine the delayed and enduring effect of neurofeedback (NF) for ADHD.

Methods: In a double-blind parallel-design study, 142 children aged 7-10 years with DSM-5 ADHD and a theta:beta ratio (TBR) greater than 4.5 were randomized 3:2 to NF training down EEG theta band power and training up beta power vs a control treatment (Tx) of equal appearance, intensity, duration, and reinforcement for 38 sessions 3 times per week. Because the expense and effort of NF are justified only by enduring benefit, follow-up (FU) assessments were among the chief aims. Effect on medication use was another chief aim. Assessments were at baseline, mid-Tx, Tx end, 6 months, 13 months, and 25 months. Blinding check at Tx end found that only one-fourth of children, parents, and trainers were able to guess the Tx assignment; blinding is maintained through 25-month FU. At Tx end, both Tx groups showed large within-group improvement (d = 1.5; p < 0.001) but no significant difference between them. All 13-month FUs and 107 of the 25-month FUs are complete, with the remainder being completed by June 2020.
Results: Tx groups started separating at 13 months, although not significantly, on primary outcome (composite of inattention ratings by parents and teachers), as NF continued improving (d = 0.1), while controls deteriorated slightly (d = ΓÇô0.07) from Tx end. At 13 months, the response rate (Clinical Global Impression-Improvement [CGI-I] of 1 or 2) was 63.0% of NF and 53.7% of controls; the remission rate (Clinical Global Impression-Severity [CGI-S] of 1 or 2) was 26.0% of NF and 14.8% of controls; and the symptomatic remission rate (item mean < 1.00 on ADHD symptoms by parent and teacher) was 39.4% of NF and 18.5% of controls (p = 0.011). Medication stopped or decreased in dose from baseline to 13 months for 15% of NF vs only 7% of controls, and it started or increased in dose from baseline for 38% of controls vs only 17% of NF (p = 0.01). We will present 25-month data for the whole sample with group comparisons on the primary outcome and key secondary outcomes.
Conclusions: There may be a delayed specific benefit (sleeper effect) of NF, including a significantly reduced need for medication compared to controls. ADHD, TREAT, CAM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S326.

39.2 MODERATING EFFECTS OF MENTAL HEALTH DIAGNOSES ON NEUROFEEDBACK FOR ADHD.

Roley-Roberts ME, Bergman R, Hendrix K, et al.

Objectives: Over 50% of children with ADHD have at least 1 comorbid diagnosis. ADHD treatments should consider co-occurring mental health complexities. FDA-approved medications are proven effective for only up to 2 years, highlighting the need for treatments with enduring effects. A 2-site, double-blind RCT comparing active neurofeedback (NF) to double-blind control NF found a delayed benefit. We examined whether comorbid mental health diagnoses or ADHD subtypes enhanced or impaired NF effects.
Methods: Children aged 7-10 years with ADHD inattentive or combined type participated in either NF (n = 84) or double-blind control treatment (n = 58) for up to 38 treatments in a 3-month period, and their ADHD inattentive symptoms were rated by parents and teachers on a 0-3 scale at baseline, midtreatment, treatment end, and 6-, 13-, and 25-month follow-ups. Of these children, 70% had at least 1 comorbid diagnosis: 50% met criteria for ODD, 27% for specific phobias, 23% for generalized anxiety, and 16% for separation anxiety. These comorbidities were grouped into internalizing disorders (ID) alone, ODD alone, neither, or both, to assess whether comorbidity moderated outcomes.
Results: Of 142 children, 91 had combined presentation, 51 had inattentive presentation; 29 had ID alone, 33 had ODD alone, 38 had both, and 42 had neither. Youth with ID alone had less inattention improvement from baseline to treatment end (item mean difference ΓÇô0.547; CI, 0.996 to 0.127; p = 0.011) and also from baseline to 13-month follow-up (item mean scale difference 0.467; CI, ΓÇô0.909 to 0.025; p = 0.038) than other comorbidity groups. A time*treatment*comorbidity interaction (p = 0.0336) was found. From baseline to treatment end, those with ID alone improved less with NF than with control treatment (item mean difference 0.410; CI, ΓÇô0.029 to 0.791; p = 0.035). In contrast, those with ODD alone improved more with NF than control (0.378; CI, 0.027 to 0.729; p = 0.035) from baseline to 13 months. Presentation had no significant effect. We will present 25-month data, still being collected, at the conference.
Conclusions: Results suggest that theta-beta NF is contraindicated for youth with comorbid anxiety without ODD, but it has a delayed specific benefit for youth with comorbid ODD. ADHD, TREAT, CM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S198.

23.5 NEUROFUNCTIONAL DIFFERENCES TO REWARD AND LOSS BETWEEN CHILDREN WITH ADHD + EMOTIONAL DYSREGULATION VS ADHD ONLY.

Blader JC, Garrett AS, Pliszka SR.

Objectives: Approximately 30% of children with ADHD also display emotion dysregulation with aggression (ADHD+EDA), and are prone to rageful outbursts and aggressive reactions to emotional upsets. It is uncertain if these affective disturbances reflect a more severe form of ADHD or if they arise from a distinct pathophysiology that is synergistic with ADHD.

Methods: We acquired fMRI data from 8- to 12-year-old children and adolescents during a guessing game in which each trial culminated in a monetary reward or loss; participant groups comprised those with ADHD+EDA (n = 16), ADHD only (n = 11), and typically developing controls (n = 10). ADHD groups did not receive stimulant medication on the day of these scans. A whole-brain voxel-wise ANOVA was conducted to examine the neurofunctional differences between groups across the win and loss conditions. After the initial scan, the ADHD+EDA group received stimulant treatment individually titrated to an optimal regimen and family-based behavioral therapy; they were rescanned on medication 10 weeks after their baseline fMRI.

Results: Only the ADHD+EDA group demonstrated hypoactivation in several cortical (medial, orbitofrontal, and anterior cingulate cortex) and limbic areas (amygdala and ventral striatum) to both reward and loss, whereas the ADHD-only and TDC groups showed activation in these areas ($p < 0.05$, family-wise error [FWE] corrected). The ADHD-only group showed greater activation for win relative to loss trials, whereas in the TDC group the win-loss difference was smaller. From pretreatment to posttreatment, in the ADHD+EDA group, activation in the medial and orbitofrontal cortex increased for loss trials, becoming more similar to the TDC group. However, activation did not change for reward trials.

Conclusions: Findings suggest a distinctive abnormality in neural response to reward and loss among those with ADHD+EDA that is not shared by those with ADHD only. Specifically, several brain areas implicated in the generation and regulation of emotion showed diminished reactivity in children with EDA. Stimulant treatment appears to heighten activation during loss in these patients. Results therefore suggest neurofunctional features that: 1) distinguish ADHD+EDA from ADHD-only; and 2) may represent a target that potentially mediates the therapeutic effects of stimulant pharmacotherapy. ADHD, DMDD, IMAGS

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S113.

74.2 TREATMENT GUIDELINES EVIDENCE FOR DISRUPTIVE BEHAVIORS IN KIDS WITH ADHD.

Romanowicz M.

Objectives: There is a high comorbidity of ADHD and disruptive behavior problems in young children. The AAP recommends behavioral parent training and/or behavioral therapy as a first-line treatment of preschool-aged children with ADHD. Based on a literature review, behavioral therapy in young children is the most efficacious in the treatment of ADHD symptomatology, particularly when it is comorbid with disruptive behaviors; however, if it fails or is inadequate in managing symptomatology, stimulant medications can be considered. Dextroamphetamine is FDA approved for the treatment of ADHD in children aged 3 years and older, vs methylphenidate, which has a warning to not be used in children younger than 6 years old. Data on medication use in this patient population are limited and risk assessment is complex due to a lack of full appreciation of the potential long-term side effects and consequences on the developing brain. It is also unclear which children would respond better to therapy and which to medication management. There are also no guidelines for combined medication and psychotherapy for children with severe symptomatology.

Methods: This presentation will focus on a literature review of studies discussing various treatment modalities for disruptive behaviors in young children with ADHD. It will discuss the challenges of combined treatment and will focus on the available literature on the use of psychotropic medications in children aged 2-7 years. It will review available treatment guidelines and offer provisional guidelines, based on the available literature on when to use behavior treatment alone vs in combination with medication.

Results: Participants will learn treatment recommendations for young children with ADHD and disruptive behaviors. They will gain an understanding of the pros and cons of using medications in this patient population. They will have an opportunity to present their challenging cases and ask questions.

Conclusions: Although first-line treatment for disruptive behaviors in young children with ADHD is behavioral therapy, participants will appreciate the research data on medication use in this population. DBD, EC, TREAT

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S301.

23.3 TREAT THE TICS OR TRET THE BEHAVIOR? HOW TO APPROACH TIC DISORDER TREATMENT AMONG YOUTH WITH DISRUPTIVE BEHAVIOR.

Espil F.

Objectives: Tourette's disorder (TD) and persistent tic disorders are neurodevelopmental disorders characterized by sudden, rapid, and involuntary vocalizations and/or motor movements. Studies of individuals with tic disorders indicate lifetime prevalence rates of comorbid disorders as high as 90%, with higher rates of impulse control issues than those in the general population. Individuals with comorbid diagnoses often represent a more clinically severe presentation of tic frequency, intensity, and greater overall impairment. Although OCD and ADHD are the most common comorbid mental health disorders, preliminary data suggest rates of disruptive behavior disorders ranging from 20% to 30% in females and males, respectively. Further, when disruptive behaviors are present, they may interfere with successful treatment of tics among families seeking services. To this end, clinical considerations to address these behaviors may need to be incorporated into successful treatment of youth with such comorbidities.

Methods: This presentation will provide overall recommendations on how to approach disruptive behaviors and tics among youth who present for treatment.

Results: Preliminary data on the prevalence, course, and implications of disruptive behaviors will also be presented. In addition to these data, the author will present a case study of a young child diagnosed with TD, ADHD, and ODD.

Conclusions: Considerations with respect to delineating treatment decisions, sequencing of techniques, and relevance within the treatment literature more generally will be discussed. TD, DBD

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S113.

74.3 LONG-TERM OUTCOMES OF PARENT CHILD INTERACTION THERAPY ON ADHD SYMPTOMS: NEW RESEARCH FINDINGS.

Bussing R, Eyberg S, Guzick A, et al.

Objectives: This study examines the long-term effects of parent-child interaction therapy (PCIT) on female and male caregiver ratings of ADHD symptoms, as well as on observational interaction measures in preschoolers randomized to individual or group PCIT.

Methods: Data from 128 children (mean age at study entry = 4.8 years) participating in treatment were examined. Children with ADHD, half of which also met criteria for disruptive behavior disorder (DBD), were randomized to group or individual PCIT, and outcomes were assessed posttreatment as well as 1 and 2 years after treatment completion. Pre- and posttreatment measures included: 1) parent rating scales, like the Child Behavior Checklist (CBCL) Externalizing Problems Subscale; the SNAP-IV; the Eyberg Child Behavior Inventory (ECBI) Intensity Score; and the Columbia Impairment Scale (CIS); and 2) observations of the parent-child interaction using the Dyadic Parent-Child Interaction Coding System (DPICS).

Results: PCIT results in clinically and statistically significant improvements in ADHD symptoms and reductions in impairment as rated by female and male caregivers. There are no differences in outcomes at posttreatment between children with and without DBD, or between those in individual or group PCIT. For both PCIT treatment formats, improvements are maintained at 1- and 2-year follow-up on all caregiver measures, including ADHD-specific ratings, externalizing behavior ratings, CIS scores, and observational measures of parent-child interactions.

Conclusions: ADHD symptom reduction is not an original goal of PCIT intervention, yet significant improvements occur in ADHD symptoms based on both caregivers reports and observational data. These findings suggest that PCIT may be an effective treatment for the behavioral and attentional symptoms of

ADHD in preschoolers with or without DBD and that PCIT merits further study as a promising intervention for preschoolers with ADHD. ADHD, PSC, PAT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S155.

5.19 PERCEPTIONS OF ADHD THROUGHOUT THE DAY AMONG HEALTH CARE PREVIDERS, ADULT PATIENTS, AND CAREGIVERS OF DIAGNOSED CHILDREN AND ADOLESCENTS.

Sallee FR, Warrington LE, Incledon B.

Objectives: ADHD impacts patients not only during school/work hours but throughout the waking day. Long-acting stimulants are recommended as first-line pharmacotherapy for ADHD; however, treatment effect over the whole day remains an unmet need for many patients on stimulant monotherapy. It is unclear whether health care provider (HCP) perceptions of the importance of ADHD treatment duration match those of patients and caregivers. This survey explored such perceptions throughout all parts of the day among HCPs, adult patients, and caregivers of children/adolescents with ADHD.

Methods: Two cross-sectional, self-administered, online surveys were conducted (patient/caregiver survey, N = 800; and HCP survey, N = 423). HCPs were required to be treating Γ ëÑ30 patients/month with ΓëÑ15 ADHD patients, and to be actively prescribing and managing ADHD pharmacotherapy. Adults, adolescents, and children with ADHD were required to be taking prescription medication, with a recruitment quota of ΓëÑ50% having to be on long-acting stimulants. Survey questions inquired about 4 day parts: early morning, school/work, after school/work, and dinner/bedtime. Respondents were blinded to the research sponsor. Results were reported using quantitative measures.

Results: Each of the 4 day parts queried were reported as challenging due to their/their childΓÇÖs ADHD (rated ΓëÑ5 on a 7-point scale) by over half of adult patients (53%-73%) and caregivers (62%-77%). For each of the 4 day parts, over half of respondents reported it was important for ADHD medication to control symptoms (rated ΓëÑ5 on a 7-point scale) (HCPs [54%-95%], adults [60%-89%], and caregivers [68%-95%]). However, the majority of HCPs (60%-91%) reported questioning patients/caregivers about school/work and after school/work parts of the day at most visits, while the early morning and dinner/bedtime parts of the day were only queried occasionally (33%-43%).

Conclusions: HCPs may continue to prioritize improvements during the school/work and after school/work parts of the day despite reporting that symptom control is important for all day parts. This suggests that to meet the needs of their patients, HCPs should focus on the whole day, especially given the availability of treatments that are efficacious at the extremes of the day. ADHD, MDM, STIM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S209.

29.8 PREVALENCE OF MENTAL DISORDERS IN CARGIVERS OF CHILDREN AND ADOLESCEBTS UNDER AMBULATORY PSYCHIATRIC FOLLOW-UP IN A TEACHING HOSPITAL.

Samara Rodrigues Almeida JR, Marques Filho AB, Takaki Konno Y.

Objectives: The main objective of this study was to identify the prevalence of mental disorders in the caregivers of children who have been attending the children's psychiatry outpatient clinic of the Medical School of S+úo Jos+® do Rio Preto (FAMERP)-SP.

Methods: A cross-sectional study was conducted in which 50 caregivers were randomly selected from the population who were attended in this outpatient clinic over the past 3 years. Participants were interviewed by signing an informed consent form, after approval of the research project by the Research Ethics Committee. In the clinic rooms, the caregivers were received and were submitted to short and structured interviews that used the Mini International Neuropsychiatric Interview (MINI) tool, which provides the detection of mental disorders in clinical practice.

Results: The results pointed to a significant prevalence of mental disorders among these caregivers. There was a statistically significant association between sociodemographic factors and some mental disorders: intellectual disability in children and adolescents associated with the age and caregivers' level of education (p = 0.016); and ADHD in children associated with the marital status of the caregivers (p = 0.042).

Conclusions: We conclude that mental disorders in caregivers may be related to the presence of mental disorders in children and adolescents. RF, PAT, FT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S154.

5.17 OUT-OF-HOME CARE PLACEMENTS IN CHILDREN WITH ADHD AND DISRUPTIVE BEHAVIOR DISORDERS: A PROSPECTIVE COHORT STUDY.

Vuori M, Tiiri E, Ollila H, et al.

Objectives: There is a need for updated population-based epidemiological data that address mental health disorders among children and adolescents in the child welfare system in order to develop social and mental health services. We fill the gap in the literature by examining: 1) the prevalence of ADHD and disruptive behavior disorders (DBDs) such as ODD or conduct disorder; and 2) the impact of the degree of ADHD vs ADHD and co-occurring DBDs on the likelihood for out-of-home care placements in children.

Methods: The Southwest Finland Birth Cohort (SFBC) consists of all live-born children in the Hospital District of Southwest Finland born from January 2008 to December 2010 (N = 14,946; 51.2% males). The data originated from the following national registers: the Care Register for Health Care and the Register of Child Welfare (maintained by the Finnish Institute for Health and Welfare), and the Prescription Register (maintained by the Social Insurance Institution). The follow-up ended on May 31, 2019.

Results: The cumulative prevalence of ADHD in SFBC children was 5.5%. In addition, 0.7% of the cohort children were diagnosed with ADHD and co-occurring DBD, or DBD only. A total of 360 children had been placed into out-of-home care during the follow-up (2.4%). Compared with the cohort children without ADHD or DBD, the crude OR for out-of-home care in children with ADHD was 4.6 (95% CI, 3.5-6.1; $p < 0.001$), and for those with ADHD and co-occurring DBD or DBD only, the OR was 22.0 (95% CI, 14.4-33.6; $p < 0.001$).

Conclusions: In this total population cohort study, we discovered that ADHD and co-occurring DBD, or DBD only, in particular, is related to the likelihood for out-of-home care in children. Further research is needed to better understand the extent to which different symptom dimensions (eg, irritability) increase the risk for out-of-home care in children with ADHD in order to inform treatment planning. SAC, DBD, ADHD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S290.

16.3 THE ROLE OF ADHD IN YOUTH SUBSTANCE MISUSE AND DELINQUENT BEHAVIOR AMONG COURT-INVOLVED ADOLESCENTS: THE IMPORTANCE OF PROMOTIVE AND PROTECTIVE MECHANISMS.

Dvorsky MR, Folk JB, Tolou-Shams M.

Objectives: Adolescents with ADHD are at high risk for delinquency, substance misuse, and justice involvement. Growing evidence indicates that substance use risk increases as a function of ADHD symptom severity. However, there is substantial variability among youth, and little is known about promotive and protective factors. The current study examined: 1) the role of ADHD in predicting patterns of youth substance use and delinquency during the 2 years following first court contact; and 2) how individual (eg, self-esteem, emotional self-control), family (eg, parent relationships, parental monitoring), and social (eg, school engagement, prosocial involvement) promotive and protective factors impact these patterns.

Methods: Participants included 400 first-time court-involved youth (Mage = 14.5 years, 57% male, 46% non-Latinx White, 42% Latinx) assessed every 4 months, and 40% to 53% of youth had elevated parent-rated ADHD symptoms (t scores > 60) at each wave. Using a developmental cascades approach, a series of autoregressive cross-lagged models were used to examine the interactional and reciprocal effects of ADHD in predicting alcohol and marijuana misuse, delinquency, and academic outcomes (grade point average [GPA], suspensions).

Results: Models revealed that inattention and hyperactivity/impulsivity were associated with higher levels of youth delinquency, greater likelihood of alcohol and marijuana misuse, and poor grades. Adolescent's self-efficacy, presence of supportive family relationships, and school engagement demonstrated significant promotive effects, buffering against the risk of ADHD in predicting subsequent substance use risk.

Conclusions: This study addresses several gaps in the extant literature by: 1) considering the domain-specific influence of ADHD on multiple risk outcomes; and 2) examining the role of individual, family, and social-level promotive/protective factors in these associations over time. We will discuss implications for assessing risk and protective mechanisms early following first court contact and identifying when (ie, critical periods to intervene) and how (ie, target mechanisms to engage) to intervene for the prevention of future delinquency, substance misuse, and poor academic outcomes. ADHD, SUD, JJS

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S305.

25.4 RISK OF DEVELOPING BIPOLAR DISORDER OR OTHER COMORBIDITY AMONG YOUTH WITH ADHD.

Van Meter A, Eugene Arnold L, Fristad MA, et al.

Objectives: Cross-sectional studies of youth often report higher rates of comorbid ADHD among youth with bipolar disorder (BD) relative to their peers, and some consider ADHD a risk factor for the development of BD. This study examined the development of BD and other disorders in prospectively followed children with ADHD in order to assess whether ADHD confers risk for BD.

Methods: In the Longitudinal Assessment of Manic Symptoms (LAMS) study, 531 of 685 participants had ADHD at baseline. Of these 531 participants, 112 had BD, and 419 did not. At baseline, participants were aged 6-12 years, and most were recruited based on elevated symptoms of mania. They were followed annually for 8 years. 2 analyses compared the rate of new BD and other comorbidities between those with ADHD vs without baseline ADHD. Cox regression tested factors influencing the speed of BD onset. Additionally, we examined differences over the follow-up between youth who continued to meet criteria for ADHD over the follow-up and those who lost the diagnosis.

Results: Of 419 participants with baseline ADHD but not BD, 52 (12.4%) developed BD, compared to 16 of 110 (14.5%) without either diagnosis at baseline. Those who developed BD had more nonΓÇômood comorbidity over the follow-up than those who did not develop BD (p = 0.0001). Of those who developed BD, speed of onset was not significantly related to ADHD, anxiety, depression, or disruptive behavior disorder at baseline, nor was speed of onset related to age, maternal mania, or paternal mania. Those who started with both ADHD and BD had more severe symptoms/impairment than those who developed BD and reported having ADHD first.

Conclusions: In a cohort selected for symptoms of mania at age 6-12 years, baseline ADHD was not a significant prospective risk factor for developing BD. However, persistence of ADHD may marginally mediate the risk of BD, and early comorbidity of both diagnoses increases severity/impairment. ADHD, BRD, CM

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S152.

5.11 EFFICACY OF MINDFULNESS-BASED PARENTING PROGRAMS IN REDUCING PARENTING STRESS IN PARENTS OF CHILDREN AND ADOLESCENTS WITH ADHD: SYSTEMATIC REVIEW AND META-ANALYSIS.

Tumthammarong C, Pornnoppadol C, Atsariyasing W.

Objectives: The objective of this presentation is to systematically evaluate the effectiveness of mindfulness-based parenting programs in reducing parenting stress in parents of children and adolescents with ADHD.

Methods: Studies written in English or Thai until February 2020 were identified through Ovid, Embase, and Thai Citation Index (TCI) databases. The main search keywords were: 1) mindfulness OR meditation in Ovid; 2) parent OR parenting in Ovid; 3) mindfulness OR mindfulness-based stress reduction OR mindfulness-based therapy OR meditation in Embase; and 4) parent OR parenting in Embase. Studies that used mindfulness-based parenting interventions in parents of children and adolescents with ADHD and measured parental stress were included. The risk of bias was assessed with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials and with the ROBINS-I tool for nonrandomized studies.

Results: Six studies were included in this study. Two randomized controlled trials reported a significant reduction in parenting stress in the intervention group compared with the control group at posttest, and this effect was maintained at 8-week follow-up for 2 studies. Four pre-experimental studies reported conflicting results. Two of them reported a significant reduction in parenting stress from pre- to postintervention, and 1

study reported a further reduction in parental stress at 6-week follow-up. Another study reported a significant reduction in parental stress from pre- to postintervention in fathers, not mothers, and this effect was maintained at 8-week follow-up. The other study reported no significant changes in parental stress from pre- to postintervention. A meta-analysis of 3 studies demonstrated no significant changes in parental stress from pre- to postintervention.
Conclusions: The efficacy of mindfulness-based parenting programs in reducing parenting stress in the parents of children and adolescents with ADHD is still inconclusive, although promising. Further studies are needed in this field. ADHD, PAT, STRESS

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S157-S158.

5.27 STARS-ADJUNCT: AKL-T01, A HOME-BASED DIGITAL INTERVENTION AS AN ADJUNCT TO STIMULANT MEDICATION FOR PEDIATRIC ADHD: ACADEMIC PERFORMANCE AND RELATION TO OBJECTIVE MEASURES OF ATTENTION.

Davis N, Lutz J, Kollins SH.

Objectives: AKL-T01 is an investigational digital intervention targeting attention in children with ADHD, delivered through a video game interface. In the previously reported randomized controlled trial (STARS-ADHD), AKL-T01 significantly improved objective attention (Test of Variables of Attention [T.O.V.A.] Attention Comparison Score [ACS]/Attention Performance Index [API]) in children without ADHD medication after 1 month. Objective measures of attention like the T.O.V.A. have been associated with academic performance measures. However, the relationship between T.O.V.A. and academic performance measures during treatment with AKL-T01 is unknown. The STARS-Adjunct study explored the effects of repeated administration of AKL-T01 in both medicated and unmedicated children with ADHD. Here, we examine the association between attention functioning and academic performance measures over the course of the study.
Methods: A total of 236 children with ADHD (8-14 years old) enrolled in the open-label STARS-Adjunct study: 130 on stimulant medication, and 76 off any ADHD medication. Children completed 1 month of treatment with AKL-T01, followed by a 1-month pause and then another 1-month treatment with AKL-T01. Academic performance measures related to reading skills (Test of Silent Reading Efficiency and Comprehension [TOSREC]) and the Mathematics Fluency and Calculation Tests skills (MFaCTS), and the T.O.V.A. ACS/API were assessed at baseline, and after 1, 2, and 3 months. Correlations between T.O.V.A. ACS/API and academic measures were calculated for each time point. Further, we calculated the relationship between ACS/API improvement and improvement in TOSREC and MFaCTS after 1 month.
Results: At each of the 4 study visits, both MFaCTS and TOSREC were significantly correlated with T.O.V.A. ACS/API (TOSREC: all p s < 0.001, Pearson's r range: 0.26-0.29; MFaCTS: all p s < 0.017, Pearson's r range: 0.17-0.27). Improvement in T.O.V.A. ACS/API was related to improvements in academic performance measures across both cohorts at day 28.
Conclusions: In the STARS-Adjunct trial, objective attention assessments with T.O.V.A. were consistently related to measures of academic performance measures (reading and math skills), adding further support for the clinical meaningfulness of T.O.V.A. Additionally, improvements in objective attention were related to improvements in these academic performance measures, suggesting that gains in attention functioning with AKL-T01 have the potential to impact children's academic functioning. ADHD, OLT, R

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S317.

33.3 QUANTIFYING THE PROTECTIVE EFFECTS OF STIMULANTS OF FUNCTIONAL OUTCOMES IN ADHD: A FOCUS ON NUMBER-NEEDED-TO-TREAT STATISTIC AND SEX EFFECTS.

DiSalvo M.

Objectives: The objective of this study was to help quantify the protective effects of stimulant treatment on important functional outcomes in ADHD using the number needed to treat (NNT) statistic and to examine whether these effects are moderated by sex.

Methods: Subjects were derived from 3 independent samples, 2 similarly designed case-control, 10-year prospective follow-up studies of boys and girls with and without ADHD grown up, and a cross-sectional RCT of lisdexamfetamine on driving performance and behavior. For all studies, subjects were evaluated with structured diagnostic interviews. To measure psychopharmacological treatment in the follow-up studies, we collected information about each subject's stimulant medication use, age at onset, and age at termination of treatment. Subjects in the driving study underwent 2 driving simulation assessments (premedication and after 6 weeks of treatment on lisdexamfetamine or placebo). Outcomes included disruptive behavior disorders, mood disorders, anxiety disorders, addictive disorders, repeating a grade in school, and motor vehicle collisions. For each outcome, we ran a logistic regression model that included an interaction between sex and treatment status. Lifetime rates were used to calculate the NNT statistic. We also calculated adjusted NNT statistics that accounted for sex, age, socioeconomic status, and family intactness.
Results: The NNTs were very low, ranging from 3 for disruptive behavior disorders and anxiety disorders, to 10 for any substance use disorders. No interaction effects with sex were detected (all $p > 0.05$). The adjusted NNTs mostly remained the same, with the exception of any substance use disorder that increased after controlling for age.
Conclusions: Stimulants have strong protective effects on functional outcomes in youth with ADHD that are not moderated by sex. These results support the critical importance of early identification and treatment of children of both sexes with ADHD. ADHD, STIM, PPC

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S152-S153.

5.12 ELECTRONICALLY MONITORED ADHERENCE RATES WITH EVENING-DOSED DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE IN CHILDREN WITH ADHD.

Childress AC, Pliszka SR, Cutler AJ, et al .

Objectives: HLD200, a delayed-release and extended-release methylphenidate (DR/ER-MPH), is the first evening-dosed stimulant designed to provide an all-day treatment effect from waking into the evening. In 2 pivotal phase-3 trials in children (6 to 12 years old) with ADHD, DR/ER-MPH was well tolerated and demonstrated symptomatic and functional improvement vs placebo throughout the day and into the evening. Here, we report the medication adherence rates from these trials.
Methods: HLD200-107 (NCT02493777) included a 6-week, open-label, DR/ER-MPH titration phase (dose: 20-100 mg/d; dosing time: 8:00 PM -¦ 1.5 h) followed by randomization to double-blind, treatment-optimized DR/ER-MPH or placebo for 1 week ending with a laboratory classroom test day. HLD200-108 (NCT02520388) was a 3-week, randomized, double-blind, placebo-controlled, forced-dose titration trial (dose: 40-80 mg/d; dosing time: 8:00 PM ± 1.5 h). In both trials, adherence was measured with the Medication Event Monitoring System (MEMS-«), a device that records the date/time of cap openings. Participants were categorized as daily adherent if a cap opening occurred at least once in a 24-hour period and were categorized as timing adherent if an opening occurred within 30 minutes of the prescribed dosing time interval. Mean rates of adherence in each week were reported.
Results: During the open-label DR/ER-MPH titration phase of HLD200-107, mean daily adherence (N = 117) ranged from 96% to 98%, and mean timing adherence ranged from 80% to 90%. During the double-blind phase, mean daily adherence was 99% for DR/ER-MPH (n = 64) and 98% for placebo (n = 53), and mean timing adherence was 93% and 89%, respectively. In HLD200-108, mean daily adherence ranged from 89% to 94% for DR/ER-MPH (n = 81) and placebo (n = 80), and mean timing adherence ranged from 67% to 73% for DR/ER-MPH and 64% to 71% for placebo.
Conclusions: In 2 trials, daily adherence to evening-dosed DR/ER-MPH was >89% in all weeks, and the mean timing adherence rates ranged from 67% to 93%. These timing adherence rates were greater than those previously reported with once-daily morning-dosed stimulants in children and adults with ADHD. Although caution should be taken when making comparisons across trials, these data suggest that evening dosing of DR/ER-MPH is well accepted by parents and children. ADHD, STIM, TREAT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S47.

30.3 THE UTILITY OF PARENT-REPORT SCREENING TOOLS IN DIFFERENTIATING AUTISM SPECTRUM DISORDER VS ADHD IN SCHOOL-AGE CHILDREN.

Di Martino A.

Objectives: Although autism spectrum disorder (ASD) and ADHD are defined as distinct neurodevelopmental conditions, they often present with overlapping symptoms; this often delays accurate diagnosis and challenges clinical care. Here, we assessed the performance of 3 parent-report measures in discriminating ASD from ADHD-only in verbal and intelligent school-aged children.

Methods: We examined the Autism Symptom Interview (ASI), School-Age, a recently validated brief interview of ASD, along with widely used parent questionnaires, including the Social Responsiveness Scale-2nd Edition (SRS-2) and Social Communication Questionnaire (SCQ)-Lifetime. We analyzed data from a convenience sample of 176 children (n = 74 with ASD and n = 102 with ADHD; aged 6-11 years) enrolled in an ongoing neuroimaging study. Clinicians best-estimate diagnoses were based on DSM-5 criteria supported by parent interviews and direct child assessment by 2 independent evaluators, review of available parent and teacher questionnaires, and prior records. Receiver operating characteristic curves assessed each instrument's performance against the best-estimate clinician DSM-5 diagnosis of ASD or ADHD-only. Secondary analyses in children incorrectly classified as ASD or non-ASD examined a range of demographics and metrics of ASD and psychopathology, using measures distinct from the original screenings.

Results: Although all 3 screenings yielded moderate-to-high accuracy (area under the curve [AUC] = 0.79, 0.78, 0.85, for ASI, SRS-2, and SCQ, respectively), the AUC of the SCQ was larger relative to both ASI and SRS-2, reaching a statically significant difference relative to the SRS-2. Although misclassified children did not differ from children correctly classified in demographics and clinician-based measures, parent ratings were more severe for ASD false positives and less severe for ASD false negatives.

Conclusions: Although the ASI, SRS-2, and SCQ are valid options to correctly classify ASD vs ADHD-only, the SCQ may be preferable in clinically complex presentations. However, given the degree to which parent concerns impacted the classification accuracy of these instruments, soliciting multiple independent sources of information is essential to best characterize children with ASD and ADHD. ASD, ADHD, RI

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S149.

5.2 A RANDOMIZED, PLACEBO-CONTROLLED STUDY OF LISDEXAMFETAMINE DIMESYLATE IN 4- TO 5-YEARS OLD CHILDREN WITH ADHD.

Childress AC, Lloyd E, Jacobsen L, et al.

Objectives: In this poster, we aim to evaluate the acute efficacy, safety, and tolerability of lisdexamfetamine dimesylate (LDX) vs placebo (PBO) in children diagnosed with ADHD.

Methods: This phase 3, double-blind, fixed-dose study randomized children (aged 4 to 5 years) to 6 weeks of treatment with LDX (5, 10, 20, or 30 mg) or PBO. Participants were required to meet DSM-IV, Text Revision criteria for a primary ADHD diagnosis and to have ADHD Rating Scale-IV Preschool version total scores (ADHD-RS-IV-PS-TS) 28 (for boys) or 24 (for girls) and Clinical Global Impression-Severity (CGI-S) scores 4 at baseline. Prespecified analyses for the primary efficacy endpoint, ADHD-RS-IV-PS-TS, change from baseline at week 6, and the key secondary efficacy endpoint, Clinical Global ImpressionΓÇôImprovement (CGI-I) score at week 6, were conducted in the full analysis set (FAS) using linear mixed-effects models for repeated measures and compared pooled LDX doses (10, 20, and 30 mg) to PBO. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs) and changes in pulse and blood pressure (BP) in the safety analysis set.

Results: Of 191 participants in the safety analysis set (all LDX, n = 146; PBO, n = 45), 187 were included in the FAS (all LDX, n = 142 [pooled 10-30 mg LDX, n = 103]; PBO, n = 45). At week 6, the least squares mean (95% CI) treatment differences (pooled LDX doses PBO) were statistically significant for ADHD-RS-IV-PS-TS change from baseline (5.9 [11.01, 0.78], p = 0.0242; effect size, 0.43) and for CGI-I score (0.6 [1.03, 0.16], p = 0.0074; effect size, 0.52). The frequency of TEAEs was 46.6% across all LDX doses and 42.2% with PBO. The most frequently reported TEAEs (all LDX doses vs PBO) were decreased appetite (13.7% vs 8.9%) and irritability (9.6% vs 0%). Mean ± SD changes from baseline (all LDX doses vs PBO) at week

6/early termination were 2.7 ± 10.79 vs 1.2 ± 9.90 bpm for pulse, 1.0 ± 7.51 vs 0.3 ± 6.06 mmHg for systolic BP, and 1.7 ±5.90 vs 0 ± 6.88 mmHg for diastolic BP.
Conclusions: In children aged 4 to 5 years diagnosed with ADHD, LDX was more efficacious than PBO in treating ADHD symptoms and had a safety and tolerability profile consistent with previous LDX studies in children and adolescents. ADHD, STIM, PSC

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S332.
43.1 THE SNOWBALL: EXPERIENCES OF DIVERSE CAREGIVERS SEEKING TREATMENT FOR CHILDREN WITH ADHD.
Spencer AE.
Objectives: We sought to understand barriers and facilitators to engagement in services for children with ADHD, experienced by families that are socioeconomically disadvantaged and belong to minority groups.
Methods: We conducted semi-structured, in-depth interviews with legal guardians of children aged 3-17 years in treatment for ADHD, recruited from specialty and primary care pediatric clinics at an urban safety-net hospital. Participants were questioned about: 1) knowledge and experience with ADHD diagnosis and treatment; 2) barriers and facilitators to ADHD diagnosis and treatment; 3) stigma and attitudes about ADHD; 4) environmental influences on symptoms; and 5) intervention preferences. Thematic analysis was performed on double-coded data.
Results: Caregivers of 41 children in treatment for ADHD (36.6% Hispanic and 56.1% African American) were recruited. Caregivers were 92.7% female from 10 different countries (41.5% born outside the United States) with a mean age of 40.8 years (SD = 7.61). Nine interviews were conducted in Spanish, 1 in Haitian Creole, and the rest in English. Caregivers described the process of engaging in care as a snowball, with worsening dysfunction over time, leading to increasing appreciation of the problem and escalation of services. Caregivers described 4 main themes within this process: 1) the snowball was often described as out of control and unnecessary, accompanied by others' dismissiveness of caregiver concerns and resistance to early intervention; 2) on the other hand, caregivers also described the snowball as a necessary path to accepting the problem and obtaining needed services; 3) caregivers perceived themselves as the singular advocate for their child's treatment, which was described as both empowering and isolating; and 4) acquiring a team of providers was perceived as necessary and supportive, yet overwhelming to coordinate without assistance.
Conclusions: Caregivers describe a snowball of worsening dysfunction as fueling the path toward ADHD treatment, because it gathers the considerable momentum needed to propel a team of providers to action long after caregivers first recognize a problem. Parents see themselves as the central drivers of care but report that help navigating complex systems is essential in order to appropriately support their child with ADHD. ADHD, CC, ETHN

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S263.
ANALYSIS OF GROWTH VELOCITY IN CHILDREN TREATED FOR UO TO 12 MONTHS WITH KP415, AND INVESTIGATIONAL ADHD PRODUCT CONTAINING THE PRODRIUG SERDEXMETHYLPHENIDATE (SDX).
Childress AC, Braeckman R, Guenther S, et al.
Objectives: KP415 is an extended-duration, investigational ADHD product containing serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), co-formulated with d-MPH hydrochloride (HCl) in fixed molar dose ratios of 70% SDX:30% d-MPH HCl. ADHD products with central nervous system (CNS) stimulant activity have been associated with a slowing of growth velocity in children. The objective of this analysis was to quantify the effects of KP415 on expected gains in weight and height in children treated for up to 12 months.
Methods: The effects of KP415 on body weight and height were examined in children (6-12 years of age) treated once-daily with KP415 during a phase 3, open-label, dose-optimized safety study. Body weight and height were recorded at baseline and at each monthly visit. A z score was calculated for each subject at each visit based on age and sex using the LMS parameters developed for the US 2000 CDC Growth Charts.

Results: Of 282 enrolled subjects (mean weight and height at baseline: 38.6 kg [z = 0.74] and 139.6 cm [z = 0.54]), 189 (67%) and 155 (55%) completed 6 and 12 months of treatment, respectively. On average, observed weight decreased slightly from baseline (0.45% to 1.3%) in the first 1-3 months of treatment but increased steadily thereafter for the remainder of the study. Mean weight z scores decreased from 0.74 to 0.53 (mean change from baseline of Γ Çô0.22) during the first 3 months but remained relatively unchanged through the end of the treatment phase. Subjects with a higher baseline BMI had a larger initial weight decrease or reduction in weight gain vs subjects with a lower baseline BMI. Observed height increased steadily across the study. Mean height increased 1.51% and 3.55% from baseline at months 6 and 12, respectively. The mean height z score decreased from 0.54 to 0.39 (change from baseline of 0.14) after 6 months and to 0.24 (change from baseline of 0.21) after 12 months. The z score trajectories for weight and height were similar in the subset of subjects who completed 12 months of treatment.
Conclusions: Consistent with prior studies of MPH products, long-term treatment with KP415 can lead to reductions in expected weight and lower-than-expected increases in height based on individual subject age and sex. However, such weight reductions and height deficits relative to children in the general US population diminish or plateau later in treatment. STIM, ADHD

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S14.

9.1 A SHARED DECISION-MARKING APPROSCH TO EVALUATING, SEQUENCING, AND COMBINING INTERVENTIONS IN TEENAGERS WITH ADHD.

Stein MA.

Objectives: The diagnostic evaluation of adolescents includes similar measures and methods that are used in evaluating ADHD in children. We wish to provide an overview of threats to reliability and validity of ADHD diagnosis in teenagers and to provide practical recommendations for clinicians.
Methods: A review of recent literature and experience in conducting clinical trials with adolescents will be utilized to generate specific recommendations for diagnosis and treatment outcome measures, which will then be applied to case examples.
Results: The reliability and validity of self-reporting of ADHD symptoms in adolescents is highly variable and often discordant from parent and teacher ratings. Age, family, and school contextual factors, as well as comorbidity, can impact the reliability and validity of measures and contribute to diagnostic dilemmas. Reconstructing the longitudinal record of ADHD and comorbidity-related impairment is essential along with careful review of social and medical mimic conditions and evaluation of comorbidity, which can be facilitated by judicious use of psychological or neuropsychological test data.
Conclusions: Following an evaluation, a shared decision-making approach to developing a treatment plan for sequencing and combining psychosocial and pharmacological interventions and measuring response is recommended. ADHD, CM, DIAG

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S157.

5.26 STARS-ADJUNCT: AKL-T01, A DIGITAL TREATMENT FOR PEDIATRIC ADHD AS AN ADJUNCT TO STIMULANT MEDICATION: RESPONSE RATES WITH REPEAT ADMINISTRATION.

Childress AC, Lutz J, Kollins SH.

Objectives: AKL-T01 is an investigational digital treatment designed to improve attention in ADHD delivered through a videogame interface. In a previous study (STARS-ADHD, RCT), AKL-T01 improved measures of attention, ADHD symptoms, and impairment in children without ADHD medication after 1 month. The subsequent STARS-Adjunct trial explored the effects of an additional treatment month in children both on and off ADHD medication. Here, we report response rates in symptoms and impairment after the first and second months of treatment from the STARS-Adjunct trial and draw comparisons with STARS-ADHD.
Methods: The open-label STARS-Adjunct trial enrolled 236 children with ADHD (8-14 years old) in 2 cohorts: 130 on stimulant medication, and 76 off any ADHD medication. Children used AKL-T01 for 1 month, followed by a 1-month treatment pause and then a second treatment month with AKL-T01. Clinically meaningful

response was defined as: at least 30% improvement on the ADHD-RS Total and Inattentive subscale compared to baseline; improvement in ADHD-related impairment (Impairment Rating Scale [IRS]) of at least 1 point; and a score of 2 (very much or much improved) on the Clinical Global Impression-Improvement scale (CGI-I). The percentage of children meeting these cutoffs was calculated for day 28 (end of first treatment month) and day 84 (end of second treatment month).
Results: Overall, 50% of parents reported improvements on the IRS. This response was similar to STARS-ADHD (48%) and further increased after a second AKL-T01 treatment month (68.3%). Response rates on ADHD symptoms were 27.2% for ADHD-RS Total and 28.2% on the Inattentive subscale, and both improved further after the second treatment month (ADHD-RS Total: 45.3%; Inattentive subscale: 40.3%). CGI-I responders after 1 month were similar to STARS-ADHD (17% STARS-Adjunct vs 15% STARS-ADHD) and increased to 27.6% at the end of the second treatment month. Response rates were similar for children on and off ADHD medication.
Conclusions: Responder rates from our STARS-Adjunct open-label trial in children on or off ADHD medication replicated response rates we saw in our STARS-ADHD, suggesting comparable effects independent of medication status and trial design. A second month of treatment with AKL-T01 increased response rates in ADHD symptoms and impairment, with the highest response rate of nearly 70% in ADHD-related impairment. ADHD, R, SAC

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S213.

31.8 REAL-WORLD SAFETY PROFILE OF DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE FOR ADHD IN CHILDREN, ADOLESCENTS, AND ADULTS.

Catherine Childress A, Otcheretko V, Warrington LE, et al.

Objectives: HLD200, a delayed-release and extended-release methylphenidate (DR/ER-MPH), is the first evening-dosed stimulant designed to provide an all-day treatment effect spanning into the evening from awakening. In 2 pivotal phase 3 trials, DR/ER-MPH was well tolerated in children (aged 6-12 years) with ADHD, with adverse events (AEs) collected weekly by questioning participants/parents in the usual unbiased manner, and AEs of special interest were directly queried. Here, we report postmarketing surveillance data from the first 25,000 patients exposed to DR/ER-MPH, with all AEs spontaneously reported.
Methods: A retrospective analysis of AEs spontaneously reported to Ironshore Pharmaceuticals Inc. was conducted. Information collected included, where available, age and gender, relevant medical history, dosing histories, time on drug when the AE occurred, and discontinuations. AE reports were categorized as listed (included in the package insert for DR/ER-MPH) or unlisted, and as serious or nonserious.
Results: A total of 125 children, adolescents, and adults reported 201 AEs, of which 157 (78.1%) were listed. The mean maximum dose reported among all patients was 42.4 mg, and the majority of patients were taking 20 or 40 mg when their AE occurred. Only 1 AE report was classified as serious (psychotic episode), and AEs preceded discontinuation in 75 patients. The majority of patients who discontinued did so after 1 to 7 days on DR/ER-MPH. The reported AEs were similar in type but were orders of magnitude lower in number compared to those reported in the open-label, treatment-optimization phase of a phase 3 trial of DR/ER-MPH (NCT02493777).
Conclusions: In postmarketing surveillance of the first 25,000 patients exposed to DR/ER-MPH, its safety profile was consistent with that observed in phase 3 trials of DR/ER-MPH and with those of other MPH formulations. Differences between the number of AEs reported here and in the package insert for DR/ER-MPH may be partially explained by spontaneous reporting with pharmacovigilance data vs weekly collection with direct query of AEs of special interest in clinical trials. ADHD, MAE, TREAT

……..

J Am Acad Child Adolesc Psychiatry. 2020;59:S299.

22.2 MEDICATION USE LONG-TERM ADULT ADHD OUTCOME FROM THE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD AND FOLLOW-UP.

Swanson JM.

Objectives: The objectives of this presentation are to measure adherence and persistence of medication use in participants across the long-term observational follow-up of the Multimodal Treatment Study of Children with ADHD (MTA) and to evaluate the effects of common patterns of treatment as usual on a simple categorical measure of good outcome in adulthood.

Methods: Previous analyses of patterns of long-term medication use during the 16-year long-term follow-up documented that 23.5% did not seek long-term treatment in the community, 69.1% were treated inconsistently, and only 7.4% were treated consistently from childhood to adulthood. These patterns were based on the outdated concept of compliance (passive acceptance of the recommended assumed optimal pattern of uninterrupted treatment). Because only a few cases complied, analyses were statistically underpowered. They did not reveal significant long-term benefit but did not discount it either (absence of evidence is not evidence of absence). Recognizing this limitation, we conducted additional exploratory analyses, adopting the modern concept of adherence (cooperative decisions by patients and prescribers) to specify operational definitions of adherence and persistence, which we applied to evaluate how cases were treated in the follow-up rather than whether they were treated optimally. Also, we used a simple categorical outcome measure of less than 1 (just a little) on ratings of symptom severity that previously detected subtle effects in the initial RCT.

Results: Self-selected initiation and cessation of medication revealed episodes of medication use during the long-term follow-up with high adherence (>85% days treated/year) over a variable duration of uninterrupted treatment persistence (4.11 years). At the end of the long-term follow-up, the average symptom severity rating on the standard 0-to-3 scale was 1.09 -¦ 0.07 for parent ratings and 0.75 + 0.6 for self-ratings, indicating that many cases would meet the cutoff of 1.0, indicating good outcome. We will report the association of these measures of adherence and persistence of medication use with: 1) baseline and postbaseline factors to identify treatment selection biases; and 2) the simple categorical measure of good outcome.

Conclusions: Our previous analyses of compliance had methodological limitations, which we addressed in additional secondary analyses of adherence and persistence of medication use in the MTA follow-up. This provided clinically relevant information about the impact of common patterns of long-term medication on long-term good outcome, and it sets the stage for additional analyses of ratings of impairment and observations of functional outcomes. ADHD, LONG, PPC

……

J Am Acad Child Adolesc Psychiatry. 2020;59:S340.

48.4 EFFECT OF TRANSCENDENTAL MEDITATION USING FMRI, MAGNETOENCEPHALOGRAPHY, AND QUANTITATIVE EEG IN CIRCUITS INVOLVED IN ADHD, PTSD, AND BEHAVIORAL REGULATION.

Travis F.

Objectives: The objective of this presentation is to present research on the effects of transcendental meditation (TM) on ADHD, PTSD, and behavior regulation.

Methods: Several studies on the effects of TM using quantitative EEG (qEEG), fMRI, and magnetoencephalography (MEG) will be presented as well as other relevant research.

Results: Research has shown that TM practice resulted in: increased cerebral blood flow in frontal areas and decreased blood flow in the brainstem in an fMRI study; greater activity in prefrontal executive circuits and anterior cingulate attention circuits in an MEG study; and activation in the posterior cingulate and precuneus and the ventrolateral and dorsolateral prefrontal cortices in qEEG studies. Many of these circuits are linked to ADHD. In addition, TM practice stimulates activity in the prefrontal cortex in subjects with PTSD on fMRI and decreases activation of the sympathetic nervous system. Preliminary research with a single group design with 10 children with ADHD, aged 11-14 years, reported that 3 months of TM practice resulted in significant reductions in anxiety and depression, and significant improvements in executive function and behavior regulation. A random-assignment delayed-start study with 18 students with ADHD, aged 11-14 years, found that 3 months of TM practice resulted in significant decreases in theta/beta ratios, a brain marker of severity of ADHD, increased theta coherence, and increased letter fluency. The effects of TM in Congolese

refugees were studied. The PTSD Checklist-Civilian (PCL-C) was administered to nonmatched waitlist controls. Eleven refugees were taught TM, and then retested 10 days and 30 days after instruction. Average PCL-C scores dropped 29.9 points from 77.9 to 48.0 in 10 days, then dropped another 12.7 points to 35.3 at 30 days. The effect size at 10 days was high (d = 4.05). Another study assessed the effects of a TM program that was instituted in a school in San Francisco. In the first year that the school implemented a short session of TM twice a day, the number of suspensions fell by 45%. Within 4 years, the suspension rate was among the lowest in the city. Daily attendance rates climbed to 98% and grade point averages improved markedly.
Conclusions: These findings bring out the value of interventions such as TM for treating ADHD, PTSD, and behavioral regulation adjunctively or alone. R, NM, CAM

……..

Journal of the Chinese Medical Association. 2020;83:803-04.
THE IMPORTANCE OF MEASURING PROBLEMATIC SMARTPHONE USE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Tsai SJ.

……..

Kuwait Medical Journal. 2020;52:250-55.
ASSESSMENT OF CARDIOVASCULAR FUNCTIONS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WHO ARE NEW USERS OF METHYLPHENIDATE.
Sargin F, Oflaz MB, Yar A, et al.
Objectives: It was aimed to evaluate cardiovascular functions via blood pressure and electrocardiogram (ECG) of patients with attention deficit and hyperactivity disorder (ADHD) who were treated with methylphenidate.
Design: This is a descriptive and prospective study.
Settings: Necmettin Erbakan University Meram Faculty of Medicine and Konya Training and Research Hospital, Turkey
Subjects: Thirty-five patients with ADHD who were selected to be treated with methylphenidate were evaluated using ECG, heart rate (beats/minute), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) recorded before treatment, and after 1 month and 3 month of st rd treatment.
Interventions: Heart rate, rhythm, QRS axis, P-R interval, P dispersion, QT dispersion, QTc interval and QTc dispersion were measured on ECG. Main outcome measures: ECG changes of patients with ADHD who were treated with methylphenidate
Results: There were no statistically significant differences in the heart rate, systolic blood pressure, diastolic blood pressure, P-R interval, P dispersion, QT dispersion and QTc dispersion between the measurements performed at baseline and at one and three months of treatment. Statistically significantly increased QRS axes were observed at baseline, and at one and three months of treatment, although this increase was not clinically significant. None of the patients had adverse cardiovascular events.
Conclusion: In conclusion, methylphenidate which is used commonly in the treatment of ADHD does not alter the heart rate, blood pressure and ECG recordings at one and three months of treatment compared to the baseline

……..

Medicine (United Kingdom). 2020.

ASSESSMENT OF PSYCHIATRIC DISORDERS IN CHILDREN.

Hoyos C.

The aim of this article is to draw attention to how the process of assessment, diagnosis and formulation of children with suspected psychiatric disorder differs from that of adults. Development and the importance of context are two key concepts. These influence each stage of assessment: gathering clinical information, identifying the symptoms, making a diagnosis and developing a formulation

……..

Molecular Autism. 2020;11.

WHITE MATTER ALTERATIONS IN AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN RELATION TO SENSORY PROFILE.

Ohta H, Aoki YY, Itahashi T, et al.

Background: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) have high rates of co-occurrence and share atypical behavioral characteristics, including sensory symptoms. The present diffusion tensor imaging (DTI) study was conducted to examine whether and how white matter alterations are observed in adult populations with developmental disorders (DD) and to determine how brain-sensory relationships are either shared between or distinct to ASD and ADHD.

Methods: We collected DTI data from adult population with DD (a primary diagnosis of ASD: n = 105, ADHD: n = 55) as well as age- and sex-matched typically developing (TD) participants (n = 58). Voxel-wise fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity (RD) were analyzed using tract-based spatial statistics. The severities of sensory symptoms were assessed using the Adolescent/Adult Sensory Profile (AASP).

Results: Categorical analyses identified voxel clusters showing significant effects of DD on FA and RD in the posterior portion of the corpus callosum and its extension in the right hemisphere. Furthermore, regression analyses using the AASP scores revealed that slopes in relationships of FA or RD with the degree of sensory symptoms were parallel between the two DDs in large parts of the affected corpus callosum regions. A small but significant cluster did exist showing difference in association between an AASP subscale score and RD across ASD and ADHD. Limitations: Wide age range of the participants may be oversimplified.

Conclusions: These results indicate that white matter alteration and their relationships to sensory symptoms are largely shared between ASD and ADHD, with localized abnormalities showing significant between-diagnosis differences within DD

……..

Mol Psychiatry. 2020 Sep;25:2047-57.

IDENTIFICATION OF ADHD RISK GENES IN EXTENDED PEDIGREES BY COMBINING LINKAGE ANALYSIS AND WHOLE-EXOME SEQUENCING.

Corominas J, Klein M, Zayats T, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a complex genetic background, hampering identification of underlying genetic risk factors. We hypothesized that combining linkage analysis and whole-exome sequencing (WES) in multi-generation pedigrees with multiple affected individuals can point toward novel ADHD genes. Three families with multiple ADHD-affected members (Ntotal = 70) and apparent dominant inheritance pattern were included in this study. Genotyping was performed in 37 family members, and WES was additionally carried out in 10 of those. Linkage analysis was performed using multi-point analysis in Superlink Online SNP 1.1. From prioritized linkage regions with a LOD score = 2, a total of 24 genes harboring rare variants were selected. Those genes were taken forward and were jointly analyzed in gene-set analyses of exome-chip data using the MAGMA software in an independent sample of patients with persistent ADHD and healthy controls (N = 9365). The gene-set including all 24 genes together, and particularly the gene-set from one of the three families (12 genes), were significantly associated with persistent ADHD in this sample. Among the latter, gene-wide analysis for the AAED1 gene reached significance. A rare variant (rs151326868) within AAED1 segregated with ADHD in

one of the families. The analytic strategy followed here is an effective approach for identifying novel ADHD risk genes. Additionally, this study suggests that both rare and more frequent variants in multiple genes act together in contributing to ADHD risk, even in individual multi-case families

……..

NeuroImage Clin. 2020;28.

PEDIATRIC ADHD SYMPTOM BURDEN RELATES TO DISTINCT NEURAL ACTIVITY ACROSS EXECUTIVE FUNCTION DOMAINS.

Nugiel T, Roe MA, Engelhardt LE, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent childhood disorder marked by inattention and/or hyperactivity symptoms. ADHD may also relate to impaired executive function (EF), but is often studied in a single EF task per sample. The current study addresses the question of unique vs. overlapping relations in brain activity across multiple EF tasks and ADHD symptom burden. Three in-scanner tasks drawn from distinct EF domains (cognitive flexibility, working memory, and inhibition) were collected from children with and without an ADHD diagnosis (N = 63). Whole-brain activity and 11 regions of interest were correlated with parent reports of inattention and hyperactivity symptoms. Across the three EF domains, brain activity related to ADHD symptom burden, but the direction and location of these associations differed across tasks. Overall, activity in sensory and default mode network regions related to ADHD, and these relations did not consistently overlap across EF domains. We observed both distinct and overlapping patterns for inattention and hyperactivity symptoms. By studying multiple EF tasks in the same sample, we identified a heterogenous neural profile related to attention symptom burden in children. Our results inform ADHD characterization and treatment and explain some of the variable brain results related to EF and ADHD reported in the literature

……..

Neurology. 2020;94.

CORRELATIONS OF POSSIBLE TMS BIOMARKERS OF COGNITIVE AND EMOTIONAL DYSFUNCTION IN ADHD.

Vera AZ, Horn P, Mostofsky S, et al.

Objective: To determine, in children with Attention Deficit/Hyperactivity Disorder (ADHD) and typically developing (TD) controls, if primary motor cortex (M1) short-interval cortical inhibition (SICI) and task-related up-modulation (TRUM) of motor evoked potentials (MEPs) correlate with each other, suggesting they capture commonly disrupted neurobiological circuits, or do not correlate, consistent with them reflecting distinct neurobiological circuits.

Background: ADHD is a heterogeneous, behaviorally-defined diagnosis. Physiological biomarkers, if valid, might identify distinct, clinically important subgroups relating to critical areas of cognitive or emotional dysfunction. Studies using transcranial magnetic stimulation (TMS) in children recently identified that SICI and TRUM are diminished in ADHD and correlate with clinical symptoms.

Design/Methods: A case-control study comparing TMS-evoked SICI and TRUM in 8-12 year old children with ADHD and Typically Developing (TD) controls during 1) a stop signal reaction time (SSRT) task testing cognitive control (n=43 ADHD; 40 TD) and 2) a reward cue task evaluating positive valence (n=33 ADHD; 31 TD). TRUM is ratio of the mean task (SSRT 80; Reward 105 pulses/trials) to the mean baseline (20 pulses, resting) MEP. The primary outcomes were the age-adjusted Spearman correlations between TRUM and SICI in the two tasks.

Results: Both SSRT and Reward tasks significantly reduced SICI and induced TRUM; and both were significantly reduced in ADHD. In the response inhibition task SICI correlated modestly with TRUM (r=-0.29; p=0.01) for the entire cohort but not within diagnostic groups. In the reward cue task, SICI correlated at trend level with TRUM (r =-0.21, p = 0.09) for the entire cohort but not within diagnostic groups.

Conclusions: In children with ADHD, SICI correlates only modestly with TRUM across two important domains of dysfunction. Further investigation could validate SICI and TRUM as distinct biomarkers for precise treatment selection

……..

Neuropediatrics. 2020;51:315-35.

ADHD: CURRENT CONCEPTS AND TREATMENTS IN CHILDREN AND ADOLESCENTS.

Drechsler R, Brem S, Brandeis D, et al.

Attention deficit hyperactivity disorder (ADHD) is among the most frequent disorders within child and adolescent psychiatry, with a prevalence of over 5%. Nosological systems, such as the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the International Classification of Diseases, editions 10 and 11 (ICD-10/11) continue to define ADHD according to behavioral criteria, based on observation and on informant reports. Despite an overwhelming body of research on ADHD over the last 10 to 20 years, valid neurobiological markers or other objective criteria that may lead to unequivocal diagnostic classification are still lacking. On the contrary, the concept of ADHD seems to have become broader and more heterogeneous. Thus, the diagnosis and treatment of ADHD are still challenging for clinicians, necessitating increased reliance on their expertise and experience. The first part of this review presents an overview of the current definitions of the disorder (DSM-5, ICD-10/11). Furthermore, it discusses more controversial aspects of the construct of ADHD, including the dimensional versus categorical approach, alternative ADHD constructs, and aspects pertaining to epidemiology and prevalence. The second part focuses on comorbidities, on the difficulty of distinguishing between primary and secondary ADHD for purposes of differential diagnosis, and on clinical diagnostic procedures. In the third and most prominent part, an overview of current neurobiological concepts of ADHD is given, including neuropsychological and neurophysiological researches and summaries of current neuroimaging and genetic studies. Finally, treatment options are reviewed, including a discussion of multimodal, pharmacological, and nonpharmacological interventions and their evidence base

……..

Neuropsychiatr Dis Treat. 2020;16:2025-43.

SPOTLIGHT ON COMPULSIVE SEXUAL BEHAVIOR DISORDER: A SYSTEMATIC REVIEW OF RESEARCH ON WOMEN.

Kowalewska E, Gola M, Kraus SW, et al.

Purpose of Review: World Health Organization recently included compulsive sexual behavior disorder (CSBD) to the upcoming 11th edition of International Classification of Diseases (6C72). Despite the potential benefits of this decision (eg, the acceleration of research in the field will allow the development of effective treatments), previous research focused mainly on men, and as a result, we do not have an accurate clinical picture of compulsive sexual behavior (CSB) among women. Therefore, in this systematic review, we aim to present available knowledge on this topical subject. Literature search was conducted in the guideline of PRISMA methodology. Studies were identified from multiple databases including Academic Search Ultimate, SocINDEX, PsycARTICLES, PsycINFO, PubMed, and MEDLINE. Out of a total of 10,531 articles identified and screened, 58 were included in this review. Included studies covered the following topics: prevalence and etiology of CSB, behavioral and cognitive processes involved, comorbidities, personality traits, psychosocial and interpersonal difficulties, traumatic experiences, and treatments.

Recent Findings: Available studies indicate that CSB symptom severity is lower in women than in men. Overall, women reported consuming pornography less often than men and exhibit lower rates of feeling urges to these materials. CSB symptoms (including problematic pornography use) have been found to be positively related to trait psychopathy, impulsivity, sensation seeking, attention-deficit/hyperactivity disorder symptoms, obsessive-compulsive disorder, pathological buying, sexual dysfunctions, general psychopathology, child sexual abuse, while negatively related to dispositional mindfulness.

Summary: Conclusions that can be drawn from prior studies are considerably limited. There are no accurate estimates of the CSB prevalence or severity among women, and studies have been mostly conducted on non-clinical populations, which has limited application for women diagnosed with CSBD

……..

Neuropsychopharmacologia Hungarica. 2020;22:112-20.

DEVELOPMENTAL PSYCHOPATHOLOGY PERSPECTIVE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Monika M, et al.

This review aims to give an insight into the developmental psychopathology perspective of attention-deficit/hyperactivity disorder (ADHD). According to evolutionary theories, phenotypes associated with ADHD might have been adaptive in the past but became dysfunctional in modern life (mismatch theory). Genome-wide association studies have supported this theory. Multiple developmental pathways lead to ADHD (equifinality), and risk factors associated with ADHD may lead to different outcomes (multifinality). Heritability of ADHD is high; however, its aetiology is heterogeneous and multifactorial, including genetic factors, gene-environment interactions and correlations, as well as epigenetic mechanism. Core symptoms of ADHD - inattention, hyperactivity, and impulsivity - are the same throughout the lifespan, but their presentation, as well as the comorbid profile, show typical age-specific differences. ADHD is characterized by strong homotypic continuity, ADHD in children persists in a large proportion into adolescence and adulthood - underlying the importance of lifespan perspective. Heterotypic continuity of ADHD has been described with externalizing and internalizing disorders; research on the different developmental pathways contribute to the recognition and prevention of maladaptive outcomes

……..

NeuroRehabilitation. 2020;47:121-31.

COMPARISON OF THE EFFECTS OF TREADMILL AND VIBRATION TRAINING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RANDOMIZED CONTROLLED TRIAL.

Durgut E, Orengul AC, Algun ZC.

OBJECTIVE: The aim of this study was to compare the effects of treadmill training (TT) and whole body vibration training (WBVT) on attention, severity of attention deficit hyperactivity disorder (ADHD) symptoms and impairment of executive function behaviors, and quality of life in children with ADHD.
METHODS: Thirty children (7-11 years of age) with ADHD were randomly assigned to either the 'TT' group or the 'WBVT in addition to TT' group (TT+WBVT). Both groups received TT for 8 weeks (3 days/week). The TT+WBWT group also received WBVT for 15 minutes. Stroop Test TBAG form, Behavior Rating Inventory of Executive Function (BRIEF), Conners' Rating Scale (CRS) and Pediatric Quality of Life Inventory (PedsQL) were applied at baseline and after 8 weeks of training.
RESULTS: All assessment results significantly improved in both groups at the end of the program compared to baseline values ($p<0,05$). There were significant differences between groups regarding improvements in CTRS-R/L and BRIEF-Teacher form in favor of the TT+WBVT group.
CONCLUSIONS: The findings suggest that exercise training including TT and WBVT might be used in the treatment of ADHD but further research is required to provide evidence of the effectiveness of the whole body vibration training in the management of ADHD

……..

Nord J Psychiatry. 2020.

CLASSIFYING ADHD SUBTYPES/PRESENTATIONS CONSIDERING THE JOINT EFFECT OF THREE LEVELS OF INVESTIGATION.

Rostami M, Khosrowabadi R, Albrecht B, et al.

Aim: Discriminant validity of the Attention Deficits/Hyperactive Disorders (ADHD) subtypes/presentations is not yet clear. The purpose of this study was to investigate joint contribution of the strongest factors of the

three dimensions, namely psychopathology, neuropsychology and electrophysiology for subtyping of presentations.
Method: A sample of 104 boys aged 7-12 years was subdivided into three groups with ADHD combined (n = 22), inattentive (n = 25) and hyperactive/impulsive subtype (n = 14), and 43 typically developing controls (TDC). Children were investigated regarding the Child Behavior Checklist (CBCL), the Integrated Visual and Auditory Test (IVA), and EEG spectral power during eyes closed resting state. Subsequently, statistical analysis included discriminant functional analysis and principle component analysis.
Results: Neuropsychological parameters had the highest contribution in classifying of the groups. EEG parameters had no effect on differentiation of the groups, and among the psychopathological parameters, only the oppositional behavioral disorder score contributed to correctly classify 74.3% of the groups. Furthermore, we found four factors with eigenvalues higher than 1 in the ADHD and typical groups, with one factor characterized by four CBCL scales, another one by auditory and visual vigilance, speed and beta band power, the third by auditory and visual prudence, and forth by theta band power.
Conclusions: Our results demonstrated that ADHD subtypes/presentations can be differentiated from each other at different levels of investigation despite some clinical symptoms overlap. The results suggested that not only psychopathology but also the impairment of sensory processing should be assessed in children with ADHD in order to use this additional information for a jointly multilevel clinical intervention, which may improve treatment success

……..

Padiatr Prax. 2019;92:576-86.
NEUROFEEDBACK FOR CHILDREN WITH ADHD - WHICH EFFECTS CAN BE EXPECTED? STATE OF RESEARCH AND SUGGESTIONS FOR PRACTICE.
Strehl U, Heinrich H, Rothenberger A, et al.
EEG neurofeedback is a possible complementary procedure for the treatment of ADHD. It is based on observations that children with ADHD exhibit physiologically hypoarousal of brain activity. Standard protocols in the frequency band (theta/beta, SMR) or event-related brain activity (Slow Coetical Potentials, SCP) have been investigated in a number of studies. They suggest that NF, using standard protocols and a neurobehavioral approach, is a specific, effective and evidence-based component for the treatment of children with ADHD. Open questions, which aim at a better understanding of the mechanisms of action and in particular at the optimisation and individualisation of training, must be pursued further

……..

Pediatr Integr. 2020;24:316-24.
ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDHOOD AND ADOLESCENCE.
Sanchez Mascaraque P, Cohen DS.
This article will review attention deficit hyperactivity disorder (ADHD) in childhood and adolescence, addressing epidemiology, aetiology, clinical symptoms, comorbidity, diagnosis, treatment, evolution and prognosis. ADHD is a heterogeneous neurodevelopmental disorder, which has a complex aetiology with evidence of influence of both genetic and environmental factors. Detection of the disorder and its diagnosis is done, in most cases, by the primary care paediatrician, who has to evaluate the severity of the nuclear symptoms: hyperactivity, inattention and impulsivity. To do a proper diagnosis, these symptoms must be excessive for the childΓÇÖs age or level of development. Treatment should be initiated with environmental modifications, while pharmacological therapy is reserved for cases where these symptoms cause severe impairment in the childΓÇÖs life in more than one environment

……..

Pediatr Ann. 2020;49:436-39.

DIAGNOSIS AND MANAGEMENT OF COMORBID ANXIETY AND ADHD IN PEDIATRIC PRIMARY CARE.

Janiczak D, Perez-Reisler M, Ballard R.

Attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders, which are the most common pediatric mental health problems, frequently co-occur. The overlap of symptoms and the varied presentations of both disorders can make diagnosis and treatment planning challenging. Picking an initial treatment target with reassessment of the diagnoses based on response may help clinicians successfully treat children with comor-bid ADHD/anxiety. Treating ADHD with stimulants can lead to improvement in ADHD-related anxiety symptoms. Treating anxiety can reduce anxiety-related attentional problems and executive functioning. Atomoxetine and alpha agonists treat ADHD and may have some benefit for anxiety symptoms. Behavioral treatment should be part of the plan for ADHD co-occurring with anxiety disorders

……..

Pediatric Obesity. 2020.

ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATIONS AND BMI TRAJECTORIES: THE ROLE OF MEDICATION TYPE, SEX AND AGE.

Gurka MJ, Siddiqi SU, Filipp SL, et al.

Objectives: Attention deficit hyperactivity disorder (ADHD) and the medications used to treat it are associated with obesity. Stimulants lead to weight loss, while antipsychotics and antidepressants lead to weight gain. Little is known, however, how alpha-2-agonists impact weight, or the independent effect on BMI of these four classes of medications, which are often prescribed concurrently. We aimed to estimate the proximal change in BMI associated with start of medication and to assess whether medication-specific departures in BMI varied by age and sex.

Study Design: We analysed longitudinal electronic health records from children (4-19 years) with an ADHD diagnosis seen at one healthcare system (2011-2018). Their BMI z-scores were fit as a cubic function of age via a mixed model, separately by sex and adjusting for race/ethnicity. From this model, we estimated annual changes in BMI-z after medication, allowing changes to vary by age and sex.

Results: Among the 22 714 children with ADHD (mean initial age = 10.0), 4335 (19.1%) were never prescribed ADHD medication. The others (80.9%) experienced departures in BMI-z after start of all four medication classes, which varied across age and sex (interaction P-values <.01). All medications had larger impacts at younger ages. As expected, decreased BMI-z was observed with stimulants, while antidepressants and antipsychotics led to BMI-z increases; alpha-agonists also were associated with BMI-z increases.

Conclusions: This longitudinal study revealed that ADHD medications are independently associated with proximal changes in BMI-z after initiation, significantly varying by sex and age. Future research should study further the interactions of these medications on long-term impacts on obesity

……..

Pediatrics. 2020 Oct;146.

KEEPING RELATIVE AGE EFFECTS AND ADHD CARE IN CONTEXT.

Butter EM.

……..

Pediatrics. 2020 Oct;146.

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

Vuori M, Martikainen JE, Koski-PirilÃ¤ A, et al.

OBJECTIVES: The youngest children in a classroom are at increased risk of being medicated for attention-deficit/hyperactivity disorder (ADHD). We examined the association between children's birth month and ADHD medication rates in Finland.

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

……..

Percept Mot Skills. 2020 Oct;127:858-73.
PHYSICAL FITNESS AND DYNAMIC BALANCE IN MEDICATION NAÏVE TURKISH CHILDREN WITH ADHD.
Buker N, Sengul YS, Ozbek A.
This study investigated physical fitness levels and dynamic balance in medication-naïve children with Attention-Deficit/Hyperactivity Disorder (ADHD). Participants were 24 medication-naïve Turkish children with ADHD (4 girls, 20 boys) and 19 typically developing (TD) Turkish children (4 girls, 15 boys). We measured physical fitness levels with the Eurofit Test Battery, body composition with the Inbody 720 Body Composition Analyzer, cognitive attention with the Stroop Test, and dynamic balance with the Y-Balance Test. We found significantly poorer dynamic balance and both upper extremity and running fitness problems among the medication-naïve Turkish children with ADHD compared to the TD group ($p = 0.002$; $p = 0.032$; $p = 0.002$). It may be important to adress dynamic balance and physical fitness when treating children with ADHD

……..

Pharm Times. 2020;2020.
Antipsychotics for Children with ADHD Should Be a Last Resort.
Wick JY.

……..

PLoS ONE. 2020;15.
GENDER DIFFERENCES IN ADULT ADHD: COGNITIVE FUNCTION ASSESSED BY THE TEST OF ATTENTIONAL PERFORMANCE.
Stibbe T, Huang J, Paucke M, et al.
Introduction The aim of this study was to assess cognitive differences between male and female adults with Attention Deficit Hyperactivity Disorder (ADHD).
Methods Patients with an ADHD diagnosis according to the DSM-IV guidelines were included in a cross-sectional study evaluating cognitive measures. 28 women and 41 men from ages 19 to 56 completed self-report questionnaires and performed a computer-based test of attentional performance (TAP). The TAP assesses cognitive functions highly affected in ADHD patients, including working memory, alertness and attention as well as behavioral control and response inhibition.
Results There were no measurable differences in self-report scales assessing current symptomology between the sexes, however men scored higher on the scale for childhood symptoms. Performance measures for general wakefulness were comparable between men and women, while working memory and behavioral control test results differed. Females reacted significantly slower and more unstable for both the TAP Go/NoGo paradigm and working memory subtest, while also making more errors in the latter.

Conclusions We found gender-specific effects regarding working memory and behavioral control in this sample of adult patients with ADHD. Further studies are warranted, examining whether these differences relate to differences in clinical presentation and comorbidity patterns between men and women

……..

PLoS ONE. 2020;15.

THE FEMALE SIDE OF PHARMACOTHERAPY FOR ADHD-A SYSTEMATIC LITERATURE REVIEW.

Kok FM, Groen Y, Fuermaier ABM, et al.

Objective This comprehensive review examined sex differences in prescription rates and efficacy or effectiveness of pharmacotherapy treatment in girls and women with attention deficit hyperactivity disorder (ADHD), while identifying gaps in the scientific knowledge on this topic.

Method A rigorous electronic database search was carried out in order to identify all published studies on female-specific effects of stimulants and non-stimulants in the treatment of ADHD. In total, 2672 studies were screened of which 21 studies (seven on prescription rates, 14 on effects of pharmacotherapy) met the inclusion criteria and were included for analysis.

Results In all seven studies on ADHD prescription rates, girls received significantly less prescriptions than boys, a difference however no longer seen in adults with the exception of one study. Each of the 14 studies on effectiveness / efficacy found at least one sex-difference in the effects of ADHD pharmacotherapy.

Conclusion Several sex-differences are demonstrated in the prescription, usage and efficacy /effectiveness of both stimulant and non-stimulant ADHD pharmacotherapy. A single daily use of MPH may possibly not be optimal for girls with ADHD and ATX may be a promising medication for girls and women with ADHD. The robustness of this result requires further investigation

……..

Prev Med. 2020.

CHILDHOOD EXERCISE AS MEDICINE: EXTRACURRICULAR SPORT DIMINISHES SUBSEQUENT ADHD SYMPTOMS.

Pagani LS, Harbec MJ, Fortin G, et al.

Extracurricular sport has been a valued educational investment to promote both physical and mental health in children and adolescents. Few longitudinal studies have tested whether extracurricular sport is associated with inattentive/hyperactive symptoms. Using a prospective-longitudinal birth cohort of 758 girls and 733 boys, we examined the prospective relationship between consistent middle childhood participation in extracurricular sport and subsequent ADHD symptoms. We hypothesized that engaging in extracurricular sport will promote reductions in symptoms. As a predictor, mothers reported on whether the child participated in sport or organized physical activities with a coach/instructor at ages 6, 7, 8, and 10 years. Developmental trajectories of the sport predictor, from ages 6 to 10 years, were generated using longitudinal latent class analysis. At age 12 years, sixth grade teachers reported on child ADHD symptom outcomes observed in the school setting over the last 6 months. ADHD symptoms were linearly regressed on trajectories of participation in organized sport in boys and girls, while controlling for pre-existing child and family characteristics. For girls, consistent participation in organized sport significantly predicted lower subsequent ADHD symptoms, compared with girls with low-inconsistent participation (unstandardized B = 0.07, p .05, 95% CI, 0.01-0.14). Early sustained middle childhood involvement in organized sport seems beneficial for the subsequent behavioral development of girls but no associations were found for boys. Middle childhood participation in structured venues that demand physical skill and effort with a coach or instructor may thus represent a valuable policy strategy to promote this aspect of behavioral development for girls

……..

Prog Neuro-Psychopharmacol Biol Psychiatry. 2021;105.

UNDERSTANDING MOTOR DIFFICULTIES IN CHILDREN WITH ADHD: A FIXEL-BASED ANALYSIS OF THE CORTICOSPINAL TRACT.

Hyde C, Fuelscher I, Sciberras E, et al.

Aims: Children with attention deficit hyperactivity disorder (ADHD) often present with deficits in fine motor control. The cortico-spinal tract (CST) is critical for voluntary motor control. Although neuroimaging work has identified anomalous microstructural properties in the CST in ADHD, no study to date has attempted to investigate the link between deficits in fine motor performance and microstructural properties of the CST in children with ADHD. This study aimed to address this gap using a novel fixel-based analysis (FBA).

Methods: Participants were 50 right-handed medication na+»ve children with a history of ADHD and 56 non-ADHD controls aged 9-11 years. Fine motor control was assessed using the Grooved Pegboard task. Children underwent high angular resolution diffusion MRI. Following pre-processing, FBA was performed and the semi-automated deep-learning TractSeg was used to delineate the CST bilaterally. Fibre density (FD), fibre cross-section (FC-log), and fibre density/cross-section (FDC) were extracted for each tract.

Results: Children with ADHD performed significantly worse than non-ADHD children on the Grooved Pegboard task when using their non-dominant hand. They also demonstrated widespread significantly lower diffusion metrics in both CSTs compared to non-ADHD controls. However, no correlations were observed between Grooved Pegboard performance and diffusion metrics for the CST in either hemisphere.

Conclusions: While we failed to detect a significant relationship between fine motor skill and FBA metrics in either group, this paper extends previous work by showing that children with ADHD and reduced fine motor competence demonstrate atypical microstructure within the CST relative to non-ADHD controls

……..

Psychiatr Danub. 2020;32:S33-S35.

AWAKE BRUXISM TREATED WITH PREGABALINE IN A PATIENT WITH GENERALIZED ANXIETY DISORDER.

Tecco JM, Tecco S.

Background: Bruxism is excessive teeth grinding or jaw clenching. Several symptoms are commonly associated with bruxism, including hypersensitive teeth, aching jaw muscles, headaches, tooth wear, and damage to dental restorations. There are two types of bruxism, awake bruxism and sleep bruxism. Awake bruxism is generally treated by dentists and maxilla-facial surgeons through several treatment modalities such as, counselling about triggers, relaxation, occlusal splints and botulinum toxin type A injections.

Methods: We will present the case of a 21-year-old woman presenting mood swings with a high level of anxiety and concentration difficulties since childhood. She also complained of awake bruxism. Intelligence was evaluated using The Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV). Attention-deficit hyperactivity disorder (ADHD) was investigated through a neuropsychology test.

Results: Intelligence evaluation showed normal intellectual function. Neuropsychology test showed a profile corresponding to ADHD. Bupropion XR 300 mg was initiated for ADHD. Pregabalin was prescribed for general anxiety syndrome. The patient reported a complete disappearance of awake bruxism at a daily dose of 375 mg, with no occlusal appliances. Following the improvement of the anxiety symptoms, the attempt to reduce the dose twice leading to the recurrence of bruxism

Conclusions: A 21 years old female treated with 375 mg daily doses of pregabalin for generalized anxiety disorder experienced a significant reduction of daytime bruxism. More studies are needed to determine whether pregabalin has a long term effect against awake bruxism

……..

Psychiatr Pol. 2020;54:317-32.

THE CHANGE IN THE INTENSITY OF SYMPTOMS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AFTER "WORKSHOPS FOR PARENTS OF HYPERACTIVE CHILDREN∀.

Pisula A, et al.

Aim. To evaluate changes in the intensity of ADHD symptoms and size effects after the completion of the twelve-week Workshops for Parents of Hyperactive Children.

Material. Intervention group included parents (N = 199) of children and adolescents diagnosed with ADHD, who completed the twelve-week parental training. The reference group included parents (N = 24) of children and adolescents diagnosed with ADHD, who received 1-2 standard psychiatric visits within twelve weeks (treatment-as-usual).
Method. The following questionnaires were completed by the participants at the beginning and at the end of the training: CBCL and Conners-IOWA-10 (parent's assessment of the child), TRF and Conners-RCTRS-28 (assessment of the child by the teacher/educator), and YSR (in children of 11 years and over). The same diagnostic regime was used in the reference group - the patients were assessed during the first visit and after twelve weeks.
Results. The majority of attendees were parents of boys diagnosed with: ADHD mixed type with or without ODD and ADHD predominantly inattentive type. The intervention resulted in significant reduction of inattentive-impulsive-hyperactive and oppositional-defiant symptoms in Conners-IOWA-10 and significant reduction of symptoms in the following CBCL scales: Social problems, Attention problems, Aggressive behavior, Externalizing behavior, as well as the overall score, as rated by mothers. The improvement was age, diagnosis and pharmacotherapy independent.
Conclusions. The therapeutic program used in our study resulted in small to moderate reduction of symptoms in children and adolescents with attention deficit hyperactivity disorder irrespective of subtype, comorbid disorders or pharmacotherapy (if implemented)

……..

Psychiatr Invest. 2020;17:925-33.

BRAIN NETWORK CONNECTIVITY AND ASSOCIATION WITH CATECHOL-O-METHYLTRANSFERASE GENE POLYMORPHISM IN KOREAN ATTENTION-DEFICIT HYPERACTIVITY DISORDER CHILDREN.

Park JH, Son YD, Kim Y, et al.

Objective We sought to determine if the links between and within the default mode network (DMN) and dorsal attention network (DAT) exhibited different conditions according to catechol-O-methyltransferase (COMT) gene polymorphism in relationship to atten-tion-deficit hyperactivity disorder (ADHD) symptoms.
Methods Fifty-seven children with ADHD and 48 healthy controls (HCs) were administered an intelligence test, the Children's Depression Inventory, the Korean ADHD rating scale, and continuous performance test. Resting-state brain functional MRI scans were obtained, and COMT genotyping was performed to distinguish valine carriers and methionine homozygotes.
Results Compared to controls, children with ADHD showed increased ADHD scale scores, increased visual commission errors, and increased functional connectivity (FC) within the DMN and DAT. Compared to all children with ADHD, children with the methionine homozygote and those who were valine carriers showed increased FC within the DMN and DAT and decreased FC between the DMN and DAT. FC within the DMN was also increased in HC valine carriers compared to HC children with the methionine homozygote, and in children with ADHD who were valine carriers compared to HC valine carriers.
Conclusion We observed increased brain connectivity within the DMN and DAT and altered brain connectivity within and between the DMN and DAT associated with COMT polymorphism in children with ADHD

……..

Psychol Neurosci. 2020 Oct.

A PILOT VISUAL-SPATIAL WORKING MEMORY TRAINING PROTOCOL IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Abou Sleiman L, Kechichian Khanji A.

Background: Executive function deficits give rise to attention-deficit hyperactivity disorder (ADHD) symptoms. Visual-spatial working memory (VSWM) is one of the main executive functions that plays a key role in learning at school as well as during everyday life. Rehabilitation of VSWM is needed for ADHD children because several studies have shown the importance of mnemonic training in improving this feature.
Objective: This pilot study provides and evaluates a training protocol targeting VSWM in ADHD children.

Method: We examined the impact of the protocol on 9 ADHD patients aged 8–9 years by using 2 tests: the Corsi block-tapping test and the Developmental NEuroPSYchological Assessment memory for faces task during the initial evaluation and after treatment. The protocol is based on 6 training sessions related to the different types of VSWM (sequential in forward and backward orders and simultaneous).
Results: Results showed greater scores on all variables from pretest to posttest, with statistically significant differences in each type of VSWM: Means changed from to 3.11 to 6.00 elements in forward order, from 2.55 to 5.55 elements in backward order, and from 14.00 to 24.44 points in the simultaneous working memory.
Conclusion: The studied performances improved from the pathological range to the normal range according to age. This protocol was shown to be effective in VSWM rehabilitation in ADHD children, potentially improving executive functioning.
Public Significance Statement: Visual-spatial working memory is one of the main executive functions, which is the ability to retain and manipulate visual information. This function plays a key role in learning at school as well as during everyday life. A treatment protocol based on six training sessions targeting visual-spatial working memory in attention-deficit hyperactivity disorder children aged 8–9 years enhanced their performances from the pathological range to the normal range, potentially improving executive functioning

……..

Psychoneuroendocrinology. 2020 Oct;120.

PRENATAL PREGNANCY-RELATED ANXIETY PREDICTS BOYS' ADHD SYMPTOMS VIA PLACENTAL C-REACTIVE PROTEIN.

Shao S, Wang J, Huang K, et al.

Many modes of stress (i.e. life events, catastrophic events) during pregnancy have been found to increase the risk of externalizing behaviors, and probably in a sex-specific way. Maternal immune activation may be the sex-difference mechanism, but direct evidence that assess three factors in conjunction—maternal stress, maternal immune activation, and offspring neurodevelopment -from human beings is lacking. This prospective study followed 2926 pregnant women from early pregnancy to 36 months after delivery. Pregnancy-related anxiety symptoms assessment was completed three times using the Pregnancy-Related Anxiety Questionnaire; child attention deficit hyperactivity disorder (ADHD) symptoms were assessed by the parent version of the Conners' Hyperactivity Index. More importantly, nine inflammatory cytokines were detected in placental tissues for the sex-difference mechanism investigation. Our results showed that after controlling for confounding factors, pregnancy-related anxiety during at least two trimesters of pregnancy increased the risk of ADHD for boys (adjusted odds ratio (aOR) = 3.37, 95 % confidence interval (95 % CI) = 1.78–6.38), but not for girls (aOR = 1.02, 95 %CI = 0.44–2.38), which confirmed previous findings. Besides, the structural equation models revealed that placental C-reactive protein (CRP) mRNA expression significantly mediated the association between pregnancy-related anxiety and ADHD for boys (indirect effect: ß = 0.025, P = 0.022), but not for girls (indirect effect: ß = 0.005, P = 0.589). This prospective study suggested that frequent pregnancy-related anxiety during pregnancy and its induced-placental inflammation partially contributed to the sex-bias of ADHD symptoms

……..

Res Autism Spectr Disord. 2020;79.

SLUGGISH COGNITIVE TEMPO IN AUTISM, ADHD, AND NEUROTYPICAL CHILD SAMPLES.

Mayes SD, Calhoun SL, Waschbusch DA.

Background: Sluggish cognitive tempo (SCT) recently experienced a resurgence of interest in children with ADHD, but only three small studies have investigated SCT in autism.
Method: Mothers rated 1,436 children with autism, 1,056 with ADHD without autism, and 186 typical controls, 2-17 years, on six SCT items from the Pediatric Behavior Scale.
Results: Almost half (49%) of children with autism scored 1.5 standard deviations or more above the typical SCT mean, as did 40% with ADHD-Inattentive and 31% with ADHD-Combined. The significantly greater prevalence in autism versus ADHD is largely explained by the high frequency of ADHD in autism and the increased risk of SCT when both disorders are present. However, the higher than normal prevalence of SCT

in autism is not accounted for by co-occurring ADHD because SCT scores were higher than the norm in children with autism who did not have ADHD and SCT scores did not differ significantly between children with autism without ADHD and children with ADHD without autism.
Conclusions: Previous research indicated SCT was associated with ADHD-Inattentive type, but our findings show that SCT is even more prevalent in autism. SCT is most common when autism and ADHD co-occur. Because autism without ADHD is rare (whereas ADHD without autism is not), it is important to assess both SCT and ADHD in children referred for autism evaluations and rule-out autism in children referred for ADHD. SCT may be another neurocognitive problem shared by children with autism and children with ADHD in need of assessment and intervention

……..

Res Dev Disabil. 2020;107.
ARITHMETIC IN DEVELOPMENTAL COGNITIVE DISABILITIES.
Dowker A.
This paper reviews and discusses research on arithmetical strengths and weaknesses in children with specific developmental cognitive disabilities. It focusses on children with dyslexia, developmental language disorder, attention deficit hyperactivity disorder and autism. In general, studies show that arithmetical weaknesses are commoner in children with any of these disorders than in controls. Autism is sometimes associated with specific strengths in arithmetic; but even in autism, it is commoner for arithmetic to be a relative weakness than a relative strength. There may be some genetic reasons why there is an overlap between mathematical difficulties and other developmental learning difficulties; but much of the reason seems to be that specific aspects of arithmetic are often influenced by other factors, including language comprehension, phonological awareness, verbal and spatial working memory and long-term memory, and executive functions. The findings discussed here will be discussed in relation to Pennington's (2006) Multiple Deficit Model

……..

Sleep Med. 2020;75:171-80.
HIGH PREVALENCE OF ADHD SYMPTOMS IN UNMEDICATED YOUTHS WITH POST-H1N1 NARCOLEPSY TYPE 1.
Hansen BH, Juvodden HT, Nordstrand SH, et al.
Objectives: To characterize attention deficit-hyperactivity disorder (ADHD) symptoms in unmedicated post-H1N1 narcolepsy type 1 (NT1) youths, and explore associations between ADHD symptoms and the narcolepsy phenotype.
Methods: A total of 50 consecutively enrolled post-H1N1 NT1 youths (7-20 years, 62% females, 98% HLA-DQB1 06:02-positive, 98% CSF hypocretin-1 deficient, 88% vaccinated) were assessed after two weeks off medication for ADHD (ADHD diagnosis pre/post-narcolepsy, parent-rated ADHD symptoms) and narcolepsy-phenotyped (semi-structured interview, Stanford Sleep Questionnaire, Epworth Sleepiness Scale, polysomnography (PSG), Multiple Sleep Latency Test (MSLT)).
Results: In sum, 26 (52%) and 15 (30%) of participants had ADHD symptoms above and below the clinical significant cut-off, respectively, while 9 (18%) had no ADHD symptoms. High values were found for ADHD total score (mean (SD), 17.9 (9.5)) and ADHD subscores (inattentive score, 11.0 (6.3); hyperactive/impulsivity score, 6.9 (4.7)). These were significantly higher than previously reported in a mainly medicated narcolepsy cohort ($p < 0.0001$). Age, gender and disease duration did not influence scores. Two participants (4%) had ADHD diagnosis prior to narcolepsy onset. ADHD symptoms were correlated with parent-rated, but not with patient rated ESS scores, objective sleepiness (mean sleep latency), sleep fragmentation (sleep stage shift index, awakening index), or CSF hypocretin-1 level.

Conclusion: Comorbid ADHD symptoms were more prevalent in unmedicated post-H1N1 NT1 youths than previously reported in mainly medicated pediatric narcolepsy cohorts. The high prevalence was not due to pre-existing ADHD and generally not correlated with core narcolepsy sleep/wake phenotype characteristics, indicating that the ADHD symptoms were not a direct consequence of disturbed sleep or daytime sleepiness

……..

Sleep Med. 2020;75:50-53.

THE EXPERIENCE-DEPENDENT INCREASE IN DEEP SLEEP ACTIVITY IS REDUCED IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Furrer M, Ringli M, Kurth S, et al.

Objective/Background: Learning of a visuomotor adaptation task during wakefulness leads to a local increase in slowΓÇôwave activity (SWA, EEG power between 1 and 4.5 Hz) during subsequent deep sleep. Here, we examined this relationship between learning and SWA in children with attention-deficit/hyperactivity disorder (ADHD).

Patients/Methods: Participants were 15 children with ADHD (9.7-14.8 y, one female) and 15 age-matched healthy controls (9.6ΓÇô15.7 y, three female). After the completion of a visuomotor adaptation task in the evening, participants underwent an all-night high-density (HD, 128 electrodes) sleep-EEG measurement.

Results: Healthy control children showed the expected right-parietal increase in sleep SWA after visuomotor learning. Despite no difference in visuomotor learning, the local up-regulation during sleep was significantly reduced in ADHD patients compared to healthy controls.

Conclusions: Our results indicate that the local, experience-dependent regulation of SWA is different in ADHD patients. Because the customarily observed heightened regulation in children was related to sensitive period maturation, ADHD patients may lack certain sensitive periods or show a developmental delay

……..

Sleep Med Rev. 2020 Oct;53.

IS THERE AN ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS AND THE OCCURRENCE OF BRUXISM? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Souto-Souza D, Mourão PS, Barroso HH, et al.

Aim of the present systematic review was to evaluate whether children and adolescents with attention-deficit/hyperactivity disorder (ADHD) are at greater chance of developing bruxism compared to individuals without this disorder. Observational studies that evaluated the occurrence of bruxism in children and adolescents with ADHD were included. The quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation criteria. Thirty-two studies involving a total of 2629 children/adolescents with ADHD and 1739 with bruxism (1629 with sleep bruxism and 110 with awake bruxism) were included. The prevalence of bruxism, irrespective of type, in the children/adolescents was 31% (95% CI: 0.22–0.41, I^2 = 93%). ADHD was associated with an increased chance of bruxism (OR: 2.94, 95% CI: 2.12–4.07, I^2 = 61%), independently of the type [sleep bruxism (OR: 2.77, 95% CI: 1.90–4.03, I^2 = 66%) or awake bruxism (OR: 10.64, 95% CI: 2.41–47.03, I^2 = 65%)]. The presence of signs of ADHD without a diagnostic confirmation was not associated with an increased chance of bruxism (OR: 3.26, 95% CI: 0.76–14.04, I^2 = 61%). Children and adolescents with a definitive diagnosis of ADHD are at greater chance of developing sleep and awake bruxism than those without this disorder

……..

Social Work with Groups. 2020 Oct;43:297-311.

THE ADHD TREASURE HUNT: A GROUP INTERVENTION USING A SOCIAL MODEL APPROACH TO DISABILITY.

Ankori G, Gutman C.

This article describes the ADHD Treasure Hunt - a groupwork model that integrates the spirit of a social model of disability into therapeutic practice with parents and children. Following a discussion on the discourse and controversy over the nature and treatment of ADHD in Western society, we evaluate our intervention in

terms of its usefulness in addressing a family's sense of helplessness and frustration in the face of social interactions. The model also focuses on helping the families recognize the value of their own experiential knowledge. We examine the contributions of the model to current practice as well as offer future directions for its development

……..

S Afr Fam Pract. 2020;62:1-8.

KNOWLEDGE AND MISCONCEPTIONS OF PARENTS OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER AT A HOSPITAL IN SOUTH AFRICA.

Rajcumar NR, Paruk S.

Background: Parents knowledge and misconception about attention-deficit hyperactivity disorder (ADHD) influences their children's access to care, its management and outcome. The study aimed to investigate parents knowledge and perceptions of ADHD.

Methods: The cross-sectional survey of 79 parents of children (aged 5-17 years) with ADHD at a specialist child psychiatry clinic in KwaZulu-Natal Province, South Africa, consisted of a socio-demographic and clinical questionnaire, and the Knowledge of Attention Disorders Scale questionnaire, was carried out.

Results: Twenty-six (32.9%) parents consulted a traditional healer, of whom 84.6% did so before consulting a medical doctor, with 61.5% reporting that the healer suggested psychiatric referral. Most parents had some knowledge of their child's ADHD diagnosis but held various misconceptions about its treatment and associated factors: 92.4% believed that reducing sugar or food additives were effective to reduce symptoms; 78.5% that treatments focussing on punishment reduced the symptoms; 67.1% that prolonged use of stimulant medications leads to increased addiction (i.e. drug, alcohol) in adulthood.

Conclusion: Many parents had misconceptions about ADHD's causes and treatment, some having consulted traditional healers, indicating the need to increase awareness among health practitioners to ensure timeous treatment access. A parent focussed psycho-education programme is required that provides information about causes, symptoms, treatment and prognosis

……..

Lancet Psychiatry. 2020;7:955-70.

ENVIRONMENTAL RISK FACTORS, PROTECTIVE FACTORS, AND PERIPHERAL BIOMARKERS FOR ADHD: AN UMBRELLA REVIEW.

Kim JH, Kim JY, Lee J, et al.

Background: Many potential environmental risk factors, environmental protective factors, and peripheral biomarkers for ADHD have been investigated, but the consistency and magnitude of their effects are unclear. We aimed to systematically appraise the published evidence of association between potential risk factors, protective factors, or peripheral biomarkers, and ADHD.

Methods: In this umbrella review of meta-analyses, we searched PubMed including MEDLINE, Embase, and the Cochrane Database of Systematic Reviews, from database inception to Oct 31, 2019, and screened the references of relevant articles. We included systematic reviews that provided meta-analyses of observational studies that examined associations of potential environmental risk factors, environmental protective factors, or peripheral biomarkers with diagnosis of ADHD. We included meta-analyses that used categorical ADHD diagnosis criteria according to DSM, hyperkinetic disorder according to ICD, or criteria that were less rigorous than DSM or ICD, such as self-report. We excluded articles that did not examine environmental risk factors, environmental protective factors, or peripheral biomarkers of ADHD; articles that did not include a meta-analysis; and articles that did not present enough data for re-analysis. We excluded non-human studies, primary studies, genetic studies, and conference abstracts. We calculated summary effect estimates (odds ratio [OR], relative risk [RR], weighted mean difference [WMD], Cohen's d, and Hedges' g), 95% CI, heterogeneity I2 statistic, 95% prediction interval, small study effects, and excess significance biases. We did analyses under credibility ceilings, and assessed the quality of the meta-analyses with AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2). This study is registered with PROSPERO, number CRD42019145032.

Findings: We identified 1839 articles, of which 35 were eligible for inclusion. These 35 articles yielded 63 meta-analyses encompassing 40 environmental risk factors and environmental protective factors (median cases 16 850, median population 91 954) and 23 peripheral biomarkers (median cases 175, median controls 187). Evidence of association was convincing (class I) for maternal pre-pregnancy obesity (OR 1-63, 95% CI 1-49 to 1-77), childhood eczema (1-31, 1-20 to 1-44), hypertensive disorders during pregnancy (1-29, 1-22 to 1-36), pre-eclampsia (1-28, 1-21 to 1-35), and maternal acetaminophen exposure during pregnancy (RR 1-25, 95% CI 1-17 to 1-34). Evidence of association was highly suggestive (class II) for maternal smoking during pregnancy (OR 1-6, 95% CI 1-45 to 1-76), childhood asthma (1-1, 1-4 to 1-63), maternal pre-pregnancy overweight (1-28, 1-21 to 1-35), and serum vitamin D (WMD 6-93, 95% CI 9-34 to 4-51).
Interpretation: Maternal pre-pregnancy obesity and overweight; pre-eclampsia, hypertension, acetaminophen exposure, and smoking during pregnancy; and childhood atopic diseases were strongly associated with ADHD. Previous familial studies suggest that maternal pre-pregnancy obesity, overweight, and smoking during pregnancy are confounded by familial or genetic factors, and further high-quality studies are therefore required to establish causality.
Funding: None

……..

Transl Psychiatry. 2020;10.

POLYGENIC RISK SCORE, PSYCHOSOCIAL ENVIRONMENT AND THE RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Ostergaard SD, Trabjerg BB, Als TD, et al.

The objective of the present study was to investigate whether the polygenic liability for attention-deficit/hyperactivity disorder (ADHD) and the psychosocial environment impact the risk of ADHD in interaction or independently of each other. We conducted a register- and biobank-based cohort study of 13,725 individuals with ADHD and 20,147 randomly drawn population-based controls. These 33,872 cohort members were genotyped on the Infinium PsychChip v1.0 array (Illumina). Subsequently, we calculated the polygenic risk score (PRS) for ADHD and extracted register data regarding the following risk factors pertaining to the psychosocial environment for each cohort member at the time of birth: maternal/paternal history of mental disorders, maternal/paternal education, maternal/paternal work status, and maternal/paternal income. We used logistic regression analyses to assess the main effects of the PRS for ADHD and the psychosocial environment on the risk of ADHD. Subsequently, we evaluated whether the effect of the PRS and the psychosocial environment act independently or in interaction upon the risk of ADHD. We found that ADHD was strongly associated with the PRS (odds ratio: 6.03, 95%CI: 4.74ΓÇô7.70 for highest vs. lowest 2% liability). All risk factors pertaining to the psychosocial environment were associated with an increased risk of ADHD. These associations were only slightly attenuated after mutual adjustments. We found no statistically significant interaction between the polygenic liability and the psychosocial environment upon the risk of ADHD. In conclusion, we found main effects of both polygenic liability and risk factors pertaining to the psychosocial environment on the risk of ADHD in the expected direction

……..

brain sciences

MDPI

Article

A Naturalistic Study of Youth Referred to a Tertiary Care Facility for Acute Hypomanic or Manic Episode

Gabriele Masi *, Stefano Berloffa, Pietro Muratori, Maria Mucci, Valentina Viglione, Arianna Villafranca, Emanuela Inguaggiato, Valentina Levantini, Francesca Placini, Chiara Pfanner, Giulia D'Acunto, Francesca Lenzi, Francesca Liboni and Annarita Milone

IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, 56028 Calambrone-Pisa, Italy; sberloffa@fsm.unipi.it (S.B.); pmuratori@fsm.unipi.it (P.M.); mmucci@fsm.unipi.it (M.M.); vviglione@fsm.unipi.it (V.V.); avillafranca@fsm.unipi.it (A.V.); einguaggiato@fsm.unipi.it (E.I.); valentina.levantini@unifi.it (V.L.); fplacini@fsm.unipi.it (F.P.); cpfanner@fsm.unipi.it (C.P.); gdacunto@fsm.unipi.it (G.D.); flenzi@fsm.unipi.it (F.L.); fliboni@fsm.unipi.it (F.L.); annarita.milone@fsm.unipi.it (A.M.)

* Correspondence: gabriele.masi@fsm.unipi.it; Tel.: +39-050-886-111; Fax: +39-050-886-301

Received: 12 August 2020; Accepted: 28 September 2020; Published: 29 September 2020

Abstract: Background: Bipolar Disorders (BD) in youth are a heterogeneous condition with different phenomenology, patterns of comorbidity and outcomes. Our aim was to explore the effects of gender; age at onset (prepubertal- vs. adolescent-onset) of BD; and elements associated with attention deficit hyperactivity disorder (ADHD) and Substance Use Disorder (SUD) comorbidities, severe suicidal ideation or attempts, and poorer response to pharmacological treatments. Method: 117 youth (69 males and 57 females, age range 7 to 18 years, mean age 14.5 ± 2.6 years) consecutively referred for (hypo)manic episodes according to the *Diagnostic and Statistical Manual of Mental Disorders*, 54th ed (DSM 5) were included. Results: Gender differences were not evident for any of the selected features. Prepubertal-onset BD was associated with higher rates of ADHD and externalizing disorders. SUD was higher in adolescent-onset BD and was associated with externalizing comorbidities and lower response to treatments. None of the selected measures differentiated patients with or without suicidality. At a 6-month follow up, 51.3% of the patients were responders to treatments, without difference between those receiving and not receiving a psychotherapy. Clinical severity at baseline and comorbidity with Conduct Disorder (CD) and SUD were associated with poorer response. Logistic regression indicated that baseline severity and number of externalizing disorders were associated with a poorer outcome. Conclusions: Disentangling broader clinical conditions in more specific phenotypes can help timely and focused preventative and therapeutic interventions.

Keywords: bipolar disorders; children; adolescents: ADHD; substance use disorder; suicidality; anxiety disorders; externalizing disorders

1. Introduction

Even if bipolar disorder (BD) is a well-established clinical picture in adults, its presentation in children and early adolescents is frequently "atypical", compared to adult-onset presentation [1–3]. Formal systematic studies have led to a definition of clinical subtypes and early signs, but clinical phenotypes and boundaries of BD in youths are still debated, given the possible developmentally different presentations of the early-onset form [4,5] as well as the high rate of comorbidities [2,3]. A first clinical differentiation in manic children was between a "narrow" and a "broad" phenotype, according to the degree of fit to the full *Diagnostic and Statistical Manual of Mental Disorders*, 54th ed (DSM 5) diagnostic criteria for adult mania [4,6], but only the narrow phenotype (elated mood, euphoria and

grandiosity, as well as other typical manic symptoms) has been included in the DSM 5 while the broad phenotype has been prevalently included in the new DSM 5 category of "Disruptive Mood Dysregulation Disorder" [4,5,7].

Valuable clinical information can be derived from rigorous, controlled studies, with an experimental design, controlled variables, strict exclusion criteria (i.e, severe comorbidities, substance abuse and suicidal behavior), specific and focused outcome measures, and selected treatments, however limiting the generalizability of findings to broader clinical populations. Alternatively, observational studies in realistic, nonexperimental conditions, including larger samples of unselected, consecutively referred patients with all comorbidities assessed with global measures of outcome and treated as usual with adjunctive treatments, preclude solid conclusions and may be less innovative in terms of aims and findings but are more informative in terms of generalization of results to everyday clinical practice. An integration and a comparison of data from both sources can be more clinically informative. Consistent with the design and the aims of our study, we have included in this presentation only data from naturalistic settings, which may be descriptive in term of everyday clinical practice. However, evidence from these studies is partly inconsistent, suggesting that there is room for further studies.

Available information on possible developmental differences between prepubertal- or childhood-onset BD and adolescent-onset BD, in terms of presentation, comorbidities and treatment response, is still inconsistent. Some authors [2] did not find significant differences between bipolar children and adolescents, according to gender distribution, manic symptomatology and comorbidity. Perlis et al. [8] found that bipolar patients with prepubertal-onset are at risk of a particularly severe course, greater comorbidity, recurrence and chronicity and that patients with BD onset between 13 and 18 years of age are intermediate between the prepubertal-onset and the adult-onset BD. In Biederman et al.'s study [9], childhood-onset was characterized by greater comorbidity with attention deficit hyperactivity disorder (ADHD) and by prevalent chronic course, irritable mood, and comorbidity with disruptive behavior disorders and anxiety disorders, although these features were also largely represented in adolescent patients. Masi et al. [10] found that patients with childhood-onset were more frequently males, had a chronic course, and had more frequent comorbidity with ADHD and oppositional-defiant disorder (ODD). Severity, 6-month treatment outcome, prevalent mood (elated versus irritable) and comorbid anxiety did not differentiate the two groups.

Regarding comorbidity, two broad patterns have been described, the first with ADHD and disruptive behavior disorders, such as ODD and Conduct Disorder (CD), and the second with anxiety disorders, which may define specific subtypes and developmental pathways of BD [11]. The first pattern includes preexisting ADHD [12–14], with rates ranging from 30% to 90%, often associated with ODD and/or conduct disorder (CD) [15,16]. The second pattern of comorbidity includes anxiety disorders, often multiple [17,18], and obsessive compulsive disorder (OCD) [19]. Multiple anxiety disorders (MAD) have been more closely related to bipolarity [16,17,20,21]. The rates of ADHD comorbidity are particularly high in prepubertal children [12,22], and are confirmed when children are assessed after removing overlapping symptoms [23]. Bipolar patients with ADHD, compared to patients without ADHD, were predominantly males and younger and had an earlier onset of BD, presenting more frequently a chronic rather than an episodic course of BD, an irritable rather than elated mood and greater psychosocial impairment [22,24].

Adolescent BD markedly increases suicidal risk [25]. The comparison of BD adolescents with or without suicidality may help to highlight possible risk factors [26], including comorbidities with ADHD [27,28] and anxiety disorders [29,30]. Further research is needed to support these findings regarding possible vulnerability factors and putative targets of timely and preventative interventions.

Substance Use Disorder (SUD) is a common comorbidity arising during the early course of BD, even before the first activated episode [31,32], and it may have a devastatingly negative effect on the clinical course and prognosis. Swendsen et al. [33], based on the findings from the U.S. National Comorbidity Survey, highlighted that mood disorders are risk factors for the subsequent onset of SUD,

suggesting that early effective treatment of the primary illness is an important step in preventing the transition from use to abuse or dependence. Comorbid SUD has been associated with an earlier age of onset of BD, shortening of cycle length, delayed time to recovery, higher number of recurrences, more mixed and rapid cycling presentations, chronicity, disability, cognitive impairment and elevated mortality associated with medical decline as well as suicide; for review, see [34]. Further research in youth is needed to understand causative factors and to develop effective early intervention and prevention strategies [35].

Follow-up studies firstly supported the notion that BD in children and adolescents is associated with a more severe course and outcome [36,37]. However, predictors of treatment response in early-onset BD are not well defined. Some features, which in adult patients with BD are predictors of poor treatment response, such as baseline severity, mixed states, psychotic symptoms and comorbid SUD, are particularly frequent in youth. In the Werry and McClellan study [38], no clinical predictors of poor outcome were found, whereas the best predictors of future functioning were premorbid functioning, IQ < 80 and bipolar family history, suggesting a lower impact of the illness compared to factors external to the clinical picture. Some early studies [36] observed that comorbid psychopathology, mainly behavioral disorders, and, to a lesser degree, earlier age at onset and baseline clinical severity predicted a poorer outcome and, more specifically, that comorbid ADHD predicts lithium efficacy [39,40]. Other studies found that comorbidities, including ADHD, did not affect response to lithium treatment while the presence of psychotic symptoms was associated with poor lithium response [41]. In more recent studies, comorbidity with conduct disorder, anxiety disorder, psychotic symotoms ADHD, baseline clinical severity and higher number of lifetime systems-of-care for the child have been reported as possible negative predictors [42–45]. As regards psychotherapeutic interventions for youth with BD, studies found that family psychoeducational and cognitive-behavioral therapy are partially efficacious [46]. Greater results are reached when interventions that involve families, psychoeducation and skill-building are implemented in combination with pharmacotherapy [47].

The aim of the present naturalistic study, conducted in a sample of bipolar children and adolescents consecutively referred for (hypo)manic episodes in a 2-year period, was a systematic exploration on whether gender, age at onset, and ADHD and substance abuse comorbidity may influence phenomenology and outcome and to define possible elements associated to suicidality. This study also aimed to individuate possible clinical features associated to poorer response to pharmacological treatments.

2. Materials and Methods

2.1. Sample

This was a naturalistic study based on a clinical database of youth with BD consecutively referred during a 2-year period (2016–2018) for manic or hypomanic symptoms to our third-level Department of Child and Adolescent Psychiatry and Psychopharmacology, with nation-wide catchment, followed for at least 6 months and not included in previous studies. The inclusion criterion for participation was fulfillment of the DSM 5 criteria for BD, including the number of symptoms, duration and impairment, according to a Clinical Global Impression Scale (CGI-S) [48] score 4 or more (clinical severity), and Child Global Assessment Scale (C-GAS) [49] score 60 or less (functional impairment). All patients with intellectual disability were excluded. The sample consisted of 117 patients, 69 males (59.0%) and 48 females (41%), aged between 7 and 18 years, with a mean age at the time of admission of 14.5 ± 2.6 years. Thirty-nine patients (33.3%) presented a prepubertal onset of BD, before 12 years of age, while 78 (66.6%) had an adolescence onset, after 12 years.

All subjects were evaluated for current and lifetime Axis I psychiatric disorders at intake using historical information, a diagnostic interview, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (K-SADS-PL) [50], administered individually to the patients and to their parents by trained child psychiatrists.

Furthermore, behavioral and social-emotional skills were assessed during interactions with peers, parents and/or examiners by trained child psychiatrists throughout the diagnostic phase. The trained child psychiatrist was the same one who participated in the subsequent assessment procedures on the same subjects, along with other examiners, and thus, he was not blind to the nature of the diagnosis. To improve the reliability and validity of the structured interview, after each interview, clinical data from each patient–parent pair were reviewed, and when subject or parent interviews endorsed bipolar diagnosis and the other did not or when other questions arose, another consultation with both patient and parent was added for further clarification in order to obtain a definitive diagnosis. In 27 out of 117 cases (23.1%), subjects and parents differed in endorsing BD and needed further consultation. Good reliability using K-SADS-PL was found, with kappa coefficients of agreement higher than 0.75 (mean k = 0.85 for all diagnoses, k value for BD = 0.82).

All patients received a naturalistic pharmacological treatment, with the following rules regarding prescriptions. Bipolar patients were primarily treated in monotherapy with a mood stabilizer, lithium or valproic acid (VPA), then with an association of both lithium and VPA, while second-generation antipsychotics (SGAs) (risperidone, olanzapine, aripiprazole and quetiapine) were used in nonresponders or as a first option only when psychotic symptoms and/or severe aggression and hostility were associated. Other medications, particularly Methylphenidate (MPH) and antidepressant Selective Serotonin Reuptake Inhibitors (SSRIs) were used when needed.

After the 6-month follow-up, patients were reassessed with the CGI-S and C-GAS and with the CGI-Improvement score (CGI-I) and were considered responders when CGI-I was 1 or 2 (very much or much improved) and C-GAS improved at least 30%; the CGI-S score was below 3, and the C-GAS was higher than 60.

Patients and parents received detailed information on the characteristics of the assessment instruments and treatment options. All parents gave informed consent. The study was conducted in accordance with the Declaration of Helsinki. The methodology of the study was approved by the Ethics Committee of our Hospital (project identification code 153/2017).

2.2. Statistical Analyses

Descriptive analyses were used to describe demographic and clinical characteristics of the whole sample. Comparisons between groups were made using chi-square analyses on categorical variables and a *t*-test on continuous variables. Considering the large number of comparisons and the number of subjects in each group, our results are prone to both type I and type II errors, the false discovery rate (FDR) [51] correction of the *p*-values (implemented using the *p*.adjust function in R) [50] was applied for all these analyses. All these analyses were made using the Statistical Package for Social Science (SPSS) 25.0 for Windows.

We conducted a linear regression model with Children's Global Assessment Scale (CGAS) scores (6th month) as a dependent variable in order to individuate putative predictors of outcomes of the pharmacological treatment. The predictors tested were CGAS score at baseline, age, gender, psychotherapy add-on, total number of internalizing disorders diagnosis and total number of externalizing disorders diagnosis. We did a post hoc power analysis to determine the statistical power of this model; we set these input parametres: sample size, 117; predictors, 6; effect size, 0.20; and α err probability, 0.05. The results indicated that the sample of this study had a power of 0.96. All models were analyzed using the Statistical Package for Social Science (SPSS) 25.0 for Windows. The false discovery rate (FDR) [51] correction of the *p*-values (implemented using the *p*.adjust function in R) [52]) was applied in this model.

3. Results

3.1. Clinical Characteristics and Gender Differences in the Whole Sample

The characteristics of the sample are summarized in Table 1. Comorbidity was almost the rule (89.7%), and most of the patients presented multiple comorbidities (mean comorbid diagnoses 3.0 ± 1.3).

Anxiety disorders were reported in 62 patients (53.0%), and 29 patients (24.8%) had more than one anxiety disorder. Thirty-one patients (26.5%) had ADHD, and about 45% had ODD/CD. This was a sample of severely impaired patients, as evidenced not only by the baseline CGI-S and CGAS scores but also by the presence of severe suicidal ideation or suicidal attempts in 25 (21.4%) patients, whereas 32 patients (27.4%) presented a substance use disorder.

Table 1. Clinical characteristics of the sample.

	Total (*N* = 117)	**Gender**		**t or χ^2 (df)**
		Males (*N* = 69)	**Females (*N* = 48)**	
Age, mean (SD)	14.59 (2.51)	14.51 (2.76)	14.65 (2.13)	0.29 (115)
Age at onset, mean (SD)	12.55 (2.99)	12.41 (3.09)	12.82 (2.72)	0.74 (115)
Prepubertal-onset, *N* (%)	39 (33.30)	27 (39.10)	11 (22.90)	2.69 (1)
CGI Severity (baseline) mean (SD)	5.56 (.74)	5.59 (.73)	5.44 (.72)	1.10 (115)
CGI Severity (6th month) mean (SD)	3.27 (1.29)	3.34 (1.37)	3.17 (1.17)	0.79 (115)
CGAS Score (baseline), mean (SD)	37.89 (4.74)	38.32 (4.63)	37.53 (4.88)	0.89 (115)
CGAS Score (6th month), mean (SD)	52.72 (9.30)	52.36 (9.40)	54.11 (9.79)	0.97 (115)
CGI Improvement, mean (SD)	2.44 (.81)	2.46 (.79)	2.36 (.82)	0.66 (115)
Responders, *N* (%)	60 (51.30)	34 (49.30)	26 (54.17)	0.11 (1)
Suicidality *N* (%)	25 (21.40)	16 (23.20)	9 (18.70)	0.120 (1)
Lifetime comorbidity, *N* (%)				
GAD	32 (27.40)	21 (30.40)	11 (22.90)	0.47 (1)
Social phobia	17 (14.60)	12 (17.40)	5 (10.40)	1.28 (1)
Separation Anxiety	22 (18.80)	13 (18.80)	9 (18.70)	0.05 (1)
Panic Disorder-Agoraphobia	15 (12.80)	5 (7.50)	9 (18.70)	2.55 (1)
Simple Phobias	14 (12.00)	10 (14.50)	3 (6.20)	1.20 (1)
Anxiety Disorders	63 (53.80)	39 (56.50)	23 (47.90)	0.53 (1)
Multiple Anxiety Disorders	30 (25.60)	19 (27.50)	11 (22.90)	0.12 (1)
N * of Anxiety Disorders	0.95 (1.160)	0.96 (1.10)	0.96 (1.28)	0.00 (115)
OCD	21 (17.90)	17 (24.60)	4 (8.20)	4.06 (1)
Tic	4 (3.40)	4 (5.80)	0 (0.00)	1.39 (1)
ADHD	31 (26.50)	20 (29.00)	10 (20.40)	0.60 (1)
ODD	34 (29.10)	19 (27.50)	14 (28.60)	0.00 (1)
CD	25 (21.40)	11 (15.90)	13 (26.50)	1.53 (1)
ODD + CD	51 (43.60)	28 40.60)	21 (42.80)	0.02 (1)
Borderline Personality Disorder	16 (13.70)	4 (5.80)	10 (20.40)	4.73 (1)
Substance Use Disorder	33 (28.20)	14 (20.30)	8 (16.30)	0.09 (1)
Total Comorbidities	2.30 (1.44)	2.23 (1.48)	2.36 (1.43)	0.47 (115)
Total Internalizing Disorders	1.08 (1.23)	1.12 (1.32)	1.04 (1.40)	0.31 (115)
Total Externalizing Disorders	0.72 (0.71)	0.70 (0.71)	0.73 (0.69)	0.23 (115)
Pharmacological Treatment, *N* (%)				
SSRI	25 (21.40)	14 (20.30)	11 (22.90)	0.00 (1)
Mood stabilizers	95 (81.20)	58 (84.10)	34 (69.40)	2.21 (1)
Valproic Acid	57 (48.70)	35 (50.70)	20 (40.80)	0.60 (1)
Lithium	54 (46.20)	36 (59.20)	16 (32.60)	3.34 (1)
SGAs	72 (61.50)	41 (59.40)	29 (59.20)	0.01 (1)
Stimulants	23 (19.70)	16 (23.20)	7 (14.30)	0.84 (1)
MS only	45 (38.50)	28 (40.60)	16 (32.60)	0.36 (1)
Antipsychotic only	22 (18.80)	11 (15.90)	11 (22.90)	0.50 (1)
MS + Antipsychotics	50 (42.70)	30 (43.50)	18 (36.70)	0.21 (1)
Psychotherapy, *N* (%)	58 (49.60)	34 (49.30)	23 (46.90)	0.00 (1)

Note. CGI: Clinical Global Impression scale; CGAS: Children's Global Assessment Scale; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional-Defiant Disorder; CD: Conduct Disorder; SGAs: Second Generation Antipsychotics; MS: Mood Stabilizers. False discovery rate (FDR; [51]) correction of the *p*-values (implemented using the *p*.adjust function in R) was applied. * $p \leq 0.05$.

Regarding treatments, all patients received a pharmacological treatment, 81.2% with a mood stabilizer (with similar rates for lithium and valproic acid) and 61.5% with an SGA. Twenty-three patients, 19.7% of the total sample but 74.2% of the patients with comorbid ADHD, received MPH, while 25 (21.4%) received a SSRI. Of note, only 38.5% received monotherapy with mood stabilizers and 18.8% had SGA monotherapy, while a strong minority (42.7%) needed a combined mood stabilizer plus SGA pharmacotherapy. About half of the patients received additional psychotherapy.

It is noteworthy that a comparison between gender, after Benjamini–Hochberg correction, did not reveal significant differences in age at onset, severity, comorbidities (including ADHD, ODD, CD and substance use disorder) and rate of response to treatments, with pharmacotherapy and psychotherapy being similar in the two groups.

3.2. Comparison between Bipolar Disorders with Prepubertal and Postpubertal Onset

Thirty-nine patients (33.3%) had a BD onset before 12 years of age ("prepubertal onset"), while 78 (66.6%) had an onset after 12 years ("adolescent onset") (Table 2). Patients with prepubertal-onset presented a higher rate of ADHD (and consequently a higher use of MPH) and of ODD/CD and a higher number of externalizing comorbidities, while the difference in SUD (15.4% in prepubertal onset vs. 34.6% in adolescent-onset) did not survive the Benjamini–Hochberg correction. Patients with adolescent-onset BD more frequently received mood stabilizers, while the use of SGAs did not differ between groups. Of note, at the 6-month follow-up, rates of responders, CGI-S, CGAS and CGI-I did not differ between groups.

Table 2. Comparisons between prepubertal (*N* = 39) and adolescent-onset (*N* = 78).

	Prepub.-Onset (*N* = 39)	**Adolesc.-Onset (*N* = 78)**	**t or χ^2 (df)**
Gender, Males, *N* (%)	27 (69.20)	42 (53.80)	1.95 (1)
Age, mean (SD)	12.39 (2.65)	15.70 (1.53)	8.56 (115) ***
Age at onset, mean (SD)	8.98 (1.55)	14.33 (1.62)	17.08 (115) ***
CGI Severity (baseline) mean (SD)	5.61 (.63)	5.53 (.78)	0.56 (115)
CGI Severity (6th month) mean (SD)	3.43 (1.50)	3.19 (1.17)	0.95 (115)
CGAS Score (baseline), mean (SD)	37.69 (4.46)	37.99 (4.99)	0.32 (115)
CGAS Score (6th month), mean (SD)	52.23 (1.11)	52.96 (8.92)	0.51 (115)
CGI Improvement, mean (SD)	2.49 (0.85)	2.42 (.79)	0.44 (115)
Responders, *N* (%)	21 (53.80)	39 (50.00)	0.04 (1)
Suicidality, *N* (%)	10 (25.60)	15 (19.20)	0.31 (1)
Lifetime comorbidity, *N* (%)			
GAD	10 (25.60)	22 (28.20)	0.05 (1)
Social phobia	9 (23.10)	13 (16.70)	0.34 (1)
Separation Anxiety	9 (23.10)	13 (16.70)	0.34 (1)
Panic Disorder-Agoraphobia	4 (10.20)	11 (14.10)	0.09 (1)
Simple Phobias	8 (20.50)	6 (7.70)	2.93 (1)
Anxiety Disorders	23 (59.99)	40 (51.30)	0.35 (1)
Multiple Anxiety Disorders	23 (59.00)	40 (51.30)	0.35 (1)
N * of Anxiety Disorders	1.08 (1.26)	0.88 (1.10)	0.88 (115)
OCD	9 (23.10)	12 (15.40)	0.059 (1)
Tic	2 (5.10)	2 (2.60)	0.32 (1)
ADHD	25(12.80)	6 (7.70)	36.93 (1) ***
ODD	17 (43.60)	17 (21.80)	4.98 (1)
CD	5 (12.80)	13 (16.70)	0.07 (1)
ODD + CD	21 (53.80)	20 (25.60)	7.89 (1) *
Borderline Personality Disorder	3 (7.70)	13 (16.70)	0.10 (1)
Substance Use Disorder	6 (15.40)	27 (34.60)	3.85 (1)

Table 2. *Cont.*

	Prepub.-Onset (*N* = 39)	Adolesc.-Onset (*N* = 78)	t or χ^2 (df)
Total Comorbidities	2.67 (1.49)	2.11 (1.39)	2.00 (115)
Total Internalizing Disorders	1.23 (1.31)	1.00 (1.18)	0.96 (115)
Total Externalizing Disorders	1.13 (.80)	0.51 (.55)	4.91 (115) ***
Pharmacological Treatment, *N* (%)			
SSRI	9 (23.10)	16 (20.50)	0.01 (1)
Mood stabilizers	20 (51.30)	66 (84.60)	13.17 (1) ***
Valproic Acid	10 (25.60)	37 (47.40)	4.27 (1)
Lithium	14 (10.20)	40 (51.30)	5.98 (1)
SGAs	26 (66.60)	46 (59.00)	0.37 (1)
Stimulants	17 (43.60)	6 (7.70)	19.00 (1) ***
MS only	13 (33.30)	32 (41.00)	0.31 (1)
Antipsychotic only	10 (25.60)	12 (15.40)	1.18 (1)
MS + Antipsychotics	16 (41.00)	34 (43.60)	0.00 (1)
Psychotherapy, *N* (%)	24 (61.50)	34 (43.60)	2.87 (1)

Note. CGI: Clinical Global Impression scale; CGAS: Children's Global Assessment Scale; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional-Defiant Disorder; CD: Conduct Disorder; SGAs: Second Generation Antipsychotics; MS: Mood Stabilizers. False discovery rate (FDR; [51] correction of the *p*-values (implemented using the *p*.adjust function in R) was applied. * $p \leq 0.05$; *** $p \leq 0.001$.

3.3. Comparison between Bipolar Patients with or without ADHD

Thirty-one patients (26.6%) presented an associated ADHD (Table 3). Compared with the patients without ADHD, patients with ADHD presented an earlier age of onset of BD, and 76% had a prepubertal onset, compared to the 15% in BD patients without ADHD. They presented higher comorbidity with externalizing disorders, while baseline severity and response to treatments did not differ between groups.

Table 3. Comparison between patients with (*N* = 31) and without (*N* = 86) attention deficit hyperactivity disorder (ADHD).

	BD + ADHD (*N* = 31)	BD w/out ADHD (*N* = 86)	t or χ^2 (df)
Gender, Maled, *N* (%)	20 (64.50)	49 (56.90)	0.27 (1)
Age, mean (SD)	12.60 (2.84)	15.33 (1.92)	5.93 (115) ***
Age at onset, mean (SD)	9.91 (2.57)	13.50 (2.54)	6.73 (115) ***
Prepubertal onset, *N* (%)	25 (78.10)	14 (16.30)	39.63 (1) ***
CGI Severity (baseline) mean (SD)	5.52 (0.62)	5.53 (.78)	0.06 (115)
CGI Severity (6th month) mean (SD)	3.48 (1.41)	3.19 (1.17)	1.12 (115)
CGAS Score (baseline), mean (SD)	38.54 (4.95)	37.99 (4.99)	0.53 (115)
CGAS Score (6th month), mean (SD)	50.87 (10.02)	52.96 (8.92)	1.08 (115)
CGI Improvement, mean (SD)	2.61 (0.83)	2.42 (0.79)	1.13 (115)
Responders, *N* (%)	13 (41.90)	47 (54.60)	1.01 (1)
Suicidality, *N* (%)	8 (25.80)	17 (19.80)	0.20 (1)
Lifetime comorbidity, *N* (%)			
GAD	7 (22.60)	25 (29.10)	0.21 (1)
Social phobia	3 (9.70)	14 (16.30)	0.36 (1)
Separation Anxiety	5 (16.10)	17 (19.80)	0.03 (1)
Panic Disorder-Agoraphobia	4 (12.90)	11 (12.80)	0.09 (1)
Simple Phobias	6 (19.30)	8 (9.30)	1.34 (1)
Anxiety Disorders	17 (54.80)	46 (55.40)	0.01 (1)

Table 3. *Cont.*

	BD + ADHD (*N* = 31)	BD w/out ADHD (*N* = 86)	t or χ^2 (df)
Multiple Anxiety Disorders	6 (19.40)	24 (28.90)	0.43 (81)
N * of Anxiety Disorders	1.00 (1.27)	0.95 (1.14)	0.20 (115)
OCD	3 (9.70)	18 (21.70)	1.27 (1)
Tic	2 (6.40)	2 (2.30)	0.26 (1)
ODD	15 (48.40)	19 (22.1)	6.42 (1)
CD	4 (12.90)	21 (24.40)	1.18 (1)
ODD + CD	18 (58.10)	33 (38.40)	2.84 (10)
Borderline Personality Disorder	2 (6.40)	14 (16.30)	1.12 (1)
Substance Use Disorder	8 (25.80)	28 (32.60)	0.22 (1)
Total Comorbidities	2.77 (1.31)	2.13 (1.45)	2.16 (115)
Total Internalizing Disorders	1.03 (1.33)	1.09 (1.19)	0.23 (115)
Total Externalizing Disorders	1.48 (0.57)	0.44 (0.52)	9.31 (115) ***
Pharmacological Treatment, *N* (%)			
SSRI	5 (16.10)	20 (23.30)	0.33 (1)
Mood stabilizers	24 (77.40)	71 (82.60)	0.13 (1)
Valproic Acid	16 (51.60)	41 (47.70)	0.03 (1)
Lithium	12 (38.70)	42 (48.80)	0.58 (1)
SGAs	20 (64.50)	52 (60.40)	0.03 (1)
Stimulants	23 (74.20)	0 (0.00)	74.79 (1) ***
MS only	11 (35.50)	34 (39.50)	0.44 (1)
Antipsychotic only	7 (22.60)	15 (17.40)	0.13 (1)
MS + Antipsychotics	13 (41.90)	37 (43.00)	0.01 (1)
Psychotherapy, *N* (%)	17 (54.80)	41 (47.70)	0.22 (1)

Note. CGI: Clinical Global Impression scale; CGAS: Children's Global Assessment Scale; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional-Defiant Disorder; CD: Conduct Disorder; SGAs: Second Generation Antipsychotics; MS: Mood Stabilizers. False discovery rate (FDR; [51] correction of the *p*-values (implemented using the *p*.adjust function in R) was applied. * $p \leq 0.05$; *** $p \leq 0.001$.

3.4. Comparison between Bipolar Patients with or without Substance Use Disorders

Thirty-two patients (27.4%) fit the criteria for SUD (Table 4). Compared to patients without SUD, they were older and had a later onset of BD, while there was no significant difference between males and females. Externalizing comorbidities were more frequently associated with SUD. The severity and functional impairment at the 6-month follow-up as well as the rate of responders (21.2% vs. 63.1%) were negatively affected by SUD.

Table 4. Comparisons between patients with (*N* = 33) and without substance use disorder (*N* = 84).

	BD + SUD (*N* = 33)	BD w/o SUD (*N* = 84)	t or χ^2 (df)
Gender, Males, *N* (%)	14 (42.40)	55 (65.50)	4.29 (1)
Age, mean (SD)	15.60 (1.93)	14.20 (2.61)	2.79 (115) *
Age at onset, mean (SD)	13.76 (2.24)	12.07 (3.12)	2.83 (115) *
Prepubertal onset, *N* (%)	6 (18.20)	33 (39.30)	3.85 (1)
CGI Severity (baseline), mean (SD)	5.76 (0.79)	5.48 (0.70)	1.88 (115)
CGI Severity (6th month), mean (SD)	3.73 (0.91)	3.09 (1.38)	2.46 (115) ***
CGAS Score (baseline), mean (SD)	36.88 (4.13)	38.29 (4.92)	1.46 (115)
CGAS Score (6th month), mean (SD)	47.18 (7.89)	54.89 (8.94)	4.33 (115)
CGI Improvement, mean (SD)	2.85 (0.66)	2.28 (0.81)	3.60 (115) ***
Responders, *N* (%)	7 (21.20)	53 (63.10)	15.00 (1) ***
Suicidality, *N* (%)	10 (30.30)	15 (17.80)	1.51 (1)

Table 4. *Cont.*

	BD + SUD (*N* = 33)	BD w/o SUD (*N* = 84)	t or χ^2 (df)
Lifetime comorbidity, *N* (%)			
GAD	11 (33.30)	21 (25.00)	0.46 (1)
Social phobia	7 (21.20)	10 (11.90)	0.99 (1)
Separation Anxiety	9 (27.30)	13 (15.50)	1.46 (1)
Panic Disorder-Agoraphobia	8 (24.20)	7 (8.30)	4.04 (1)
Simple Phobias	4 (12.10)	10 (11.90)	0.08 (1)
Anxiety Disorders	21 (63.60)	42 (50.00)	1.69 (1)
Multiple Anxiety Disorders	11 (33.30)	19 (22.60)	0.92 (1)
N * of Anxiety Disorders	1.00 (1.27)	0.85 (1.09)	0.64 (115)
OCD	6 (18.20)	15 (17.80)	0.05 (1)
Tic	1 (3.00)	3 (3.60)	0.18 (1)
ADHD	5 (15.10)	26 (31.00)	1.83 (1)
ODD	3 (9.10)	19 (22.60)	2.02 (1)
CD	18 (54.50)	21 (25.00)	8.02 (1) *
ODD + CD	20 (60.60)	33 (39.30)	3.53 (1)
Borderline Personality Disorder	8 (24.20)	8 (9.50)	3.19 (1)
Total Comorbidities	2.77 (1.31)	1.93 (1.35)	0.28 (115)
Total Internalizing Disorders	1.03 (1.33)	0.99 (1.17)	0.16 (115)
Total Externalizing Disorders	1.48 (.57)	0.74 (0.75)	5.11 (115) ***
Pharmacological Treatment, *N* (%)			
SSRI	8 (24.20)	17 (20.20)	0.05 (1)
Mood stabilizers	24 (72.70)	71 (84.50)	1.46 (1)
Valproic Acid	15 (45.40)	42 (50.00)	0.06 (1)
Lithium	17 (51.50)	37 (44.00)	0.27 (1)
SGAs	25 (45.40)	47 (55.90)	3.13 (1)
Stimulants	4 (12.10)	19 (22.60)	1.05 (1)
MS only	8 (24.20)	37 (44.00)	3.13 (1)
Antipsychotic only	9 (27.30)	13 (15.50)	1.46 (1)
MS + Antipsychotics	16 (48.50)	34 (40.50)	0.34 (1)
Psychotherapy, *N* (%)	16 (48.50)	42 (50.00)	0.00 (1)

Note. CGI: Clinical Global Impression scale; CGAS: Children's Global Assessment Scale; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional-Defiant Disorder; CD: Conduct Disorder; SGAs: Second Generation Antipsychotics; MS: Mood Stabilizers. False discovery rate (FDR; [51] correction of the *p*-values (implemented using the *p*.adjust function in R) was applied. * $p \leq 0.05$; *** $p \leq 0.001$.

3.5. Comparison between Patients with or without Severe Suicidal Ideation or Behavior

Twenty-five patients (21.4%) presented severe suicidal ideation or behavior (Table 5). None of the selected measures differentiated patients with or without suicidality, including age at onset of BD; anxiety, ADHD or SUD comorbidities; and treatments.

Table 5. Comparisons between patients with (*N* = 25) and without suicidality (*N* = 92).

	BD + Suicidality (*N* = 25)	BD w/out Suicidality (*N* = 92)	t or χ^2 (df)
Gender, Maled, *N* (%)	16 (64.00)	53 (58.20)	0.12 (1)
Age, mean (SD)	15.24 (2.44)	14.42 (2.51)	1.46 (115)
Age at onset, mean (SD)	12.84 (3.27)	12.47 (2.92)	0.55 (115)
Prepubertal onset, *N* (%)	10 (40.00)	29 (31.90)	0.31 (1)
CGI Severity (baseline) mean (SD)	5.84 (0.75)	5.48 (0.72)	2.20 (115)
CGI Severity (6th month) mean (SD)	3.44 (1.42)	3.23 (1.26)	0.72 (115)
CGAS Score (baseline), mean (SD)	37.76 (3.62)	37.92 (5.02)	0.15 (115)

Table 5. *Cont.*

	BD + Suicidality (*N* = 25)	BD w/out Suicidality (*N* = 92)	t or χ^2 (df)
CGAS Score (6th month), mean (SD)	52.00 (9.77)	54.89 (8.94)	−1.40 (115)
CGI Improvement, mean (SD)	2.44 (0.85)	2.45 (0.80)	0.05 (115)
Responders, *N* (%)	12 (40.00)	48 (52.70)	0.02 (1)
Lifetime comorbidity, *N* (%)			
GAD	10 (40.00)	22 (23.90)	1.81 (1)
Social phobia	5 (20.00)	12 (13.00)	0.31 (1)
Separation Anxiety	9 (36.00)	13 (14.10)	4.81 (1)
Panic Disorder-Agoraphobia	6 (24.00)	9 (9.80)	2.40 (1)
Simple Phobias	3 (12.00)	11 (12.00)	0.12 (1)
Anxiety Disorders	18 (72.00)	45 (48.90)	3.34 (1)
Multiple Anxiety Disorders	12 (48.00)	18 (19.60)	6.91 (1)
N * of Anxiety Disorders	1.44 (1.19)	0.82 (1.12)	2.42 (115)
OCD	3 (12.00)	18 (19.60)	0.34 (1)
Tic	0 (0.00)	4 (4.30)	0.19 (1)
ADHD	8 (32.00)	23 (25.00)	0.47 (1)
ODD	8 (32.00)	26 (28.3)	0.01 (1)
CD	6 (24.00)	19 (20.60)	0.01 (1)
ODD + CD	11 (44.00)	40 (43.50)	0.03 (1)
Borderline Personality Disorder	5 (20.00)	11 (12.00)	0.50 (1)
Substance Abuse Disorder	10 (40.00)	23 (25.00)	1.51 (1)
Total Comorbidities	2.92 (1.41)	2.13 (1.41)	2.48 (115)
Total Internalizing Disorders	1.52 (1.19)	0.96 (1.21)	2.06 (115)
Total Externalizing Disorders	0.76 (0.72)	0.71 (0.70)	0.31 (115)
Pharmacological Treatment, *N* (%)			
SSRI	5 (20.00)	20 (21.70)	0.01 (1)
Mood stabilizers	19 (76.00)	76 (82.60)	0.21 (1)
Valproic Acid	8 (32.00)	41 (44.60)	0.81 (1)
Lithium	14 (56.00)	40 (43.50)	0.79 (1)
SGAs	14 (56.00)	58 (63.00)	2.21 (1)
Stimulants	7 (28.00)	16 (17.40)	0.81 (1)
MS only	11 (44.00)	34 (36.90)	0.17 (1)
Antipsychotic only	6 (24.00)	16 (17.40)	0.21 (1)
MS + Antipsychotics	8 (32.00)	42 (45.60)	0.99 (1)
Psychotherapy, *N* (%)	15 (60.00)	43 (46.70)	0.90 (1)

Note. CGI: Clinical Global Impression scale; CGAS: Children's Global Assessment Scale; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional-Defiant Disorder; CD: Conduct Disorder; SGAs: Second Generation Antipsychotics; MS: Mood Stabilizers. False discovery rate (FDR; [51] correction of the *p*-values (implemented using the *p*.adjust function in R) was applied. * $p \leq 0.05$.

Although baseline clinical severity, rate of multiple anxiety disorders (48% vs. 19.6%) and total number of comorbidities were higher in suicidal patients, differences did not survive the Benjamini–Hochberg correction.

3.6. Comparison between Bipolar Patients Responders and Nonresponders to Treatments

According to a double criterion of CGI-I scores 1 or 2 and an improvement of at least 30% of the CGAS, with a CGI-S score below 3 and C-GAS higher than 60 at the 6-month follow-up, 60 patients (51.3%) were considered responders (Table 6). The two groups received the same patterns of treatment (both pharmacotherapy and psychotherapy). Poorer response to treatments was associated with greater clinical severity (CGI-S) at baseline, and comorbidity was associated with CD and SUD. On the contrary, age at onset of BD and ADHD comorbidity did not affect the response to treatments.

Table 6. Comparison between patients responders (N = 60) and nonresponders (N = 57).

	Responders (N = 60)	**Nonresponders (N = 57)**	**t or χ^2 (df)**
Gender, Maled, *N* (%)	34 (56.70)	35 (61.40)	0.11 (1)
Age, mean (SD)	14.08 (2.72)	15.13 (2.16)	2.30 (115)
Age at onset, mean (SD)	12.43 (3.01)	12.67 (2.99)	0.43 (115)
Prepubertal onset, *N* (%)	21 (35.00)	18 (31.60)	0.04 (1)
CGI Severity (baseline) mean (SD)	5.37 (0.69)	5.75 (0.74)	2.87 (115) *
CGI Severity (6th month) mean (SD)	2.37 (0.64)	4.00 (1.00)	10.81 (115) ***
CGAS Score (baseline), mean (SD)	38.43 (4.73)	37.32 (4.72)	1.27 (115)
CGAS Score (6th month), mean (SD)	60.42 (1.67)	44.61 (6.78)	17.52 (115) ***
CGI Improvement, mean (SD)	1.83 (0.46)	3.09 (0.58)	13.82 (115) ***
Suicidality, *N* (%)	14 (23.30)	13 (22.80)	0.02 (1)
Lifetime comorbidity, *N* (%)			
GAD	18 (30.00)	14 (24.60)	0.20 (1)
Social phobia	14 (23.30)	14 (24.60)	0.00 (1)
Separation Anxiety	11 (18.30)	11 (19.30)	0.01 (1)
Panic Disorder-Agoraphobia	9 (15.00)	6 (10.50)	0.20 (1)
Simple Phobias	8 (13.30)	6 (10.50)	0.03 (1)
Anxiety Disorders	33 (55.00)	29 (50.90)	0.07 (1)
Multiple Anxiety Disorders	16 (26.70)	14 (24.60)	0.00 (1)
N * of Anxiety Disorders	1.00 (1.15)	0.89 (1.17)	0.51 (115)
OCD	12 (20.00)	9 (15.80)	0.12 (1)
Tic	1 (1.70)	3 (5.30)	0.31 (1)
ADHD	13 (21.70)	18 (31.60)	1.01 (1)
ODD	19 (31.70)	15 (26.30)	0.19 (1)
CD	5 (8.30)	20 (35.10)	10.91 (1) ***
ODD + CD	23 (38.30)	28 (49.10)	2.81 (1)
Borderline Personality Disorder	7 (11.70)	9 (15.80)	0.14 (1)
Substance Abuse Disorder	7 (11.70)	26 (45.69)	0.15 (1) ***
Total Comorbidities	2.08 (1.43)	2.53 (1.43)	1.70 (115)
Total Internalizing Disorders	1.15 (1.21)	1.00 (1.23)	0.66 (115)
Total Externalizing Disorders	0.58 (0.62)	0.86 (0.77)	−2.01 (115)
Pharmacological Treatment, *N* (%)			
SSRI	16 (26.70)	9 (15.80)	1.46 (1)
Mood stabilizers	47 (78.30)	48 (84.20)	0.33 (1)
Valproic Acid	27 (45.00)	30 (52.60)	0.41 (1)
Lithium	27 (45.00)	27 (47.40)	0.01 (1)
SGAs	33 (55.00)	39 (68.40)	1.69 (1)
Stimulants	8 (13.30)	15 (26.30)	2.35 (1)
MS only	27 (45.00)	18 (31.60)	1.69 (1)
Antipsychotic only	13 (21.70)	9 (15.80)	0.33 (1)
MS + Antipsychotics	20 (33.30)	30 (52.60)	3.69 (1)
Psychotherapy, *N* (%)	31 (51.70)	27 (47.40)	0.08 (1)

Note. CGI: Clinical Global Impression scale; CGAS: Children's Global Assessment Scale; GAD: Generalized Anxiety Disorder; OCD: Obsessive Compulsive Disorder; ODD: Oppositional-Defiant Disorder; CD: Conduct Disorder; SGAs: Second Generation Antipsychotics; MS: Mood Stabilizers. False discovery rate (FDR; [51]) correction of the *p*-values (implemented using the *p*.adjust function in R) was applied. * $p \leq 0.05$; *** $p \leq 0.001$.

Table 7 shows the results for the regression model testing putative predictors of response to treatment. The levels of the CGAS at baseline and the number of externalizing comorbidities predicted the levels of CGAS at follow-up: the more the number of externalizing comorbidities, the lower the levels of CGAS at the follow-up. This finding indicates that subjects with externalizing comorbidities are at risk for a worse outcome. Neither age, gender, psychotherapy add-on nor total number of internalizing comorbidities were significant predictors of change in CGAS scores. The regression model explained around 23% of the variance. Variance inflation (VIF) in this regression was 1.2.

Table 7. Linear regression model with CGAS scores (6th month) as the dependent variable.

	B	Std. Error	β	*p*
CGAS Score (baseline)	0.694	0.165	0.354	0.000
Age	−0.083	0.027	−0.269	0.004
Gender	−1.997	1.543	−0.106	0.252
Psychotherapy	1.946	1.542	0.105	0.252
Total Internalizing Disorders	−0.692	0.642	−0.091	0.284
Total Externalizing Disorders	−4.990	1.183	−0.378	0.000

Note. CGAS: Children's Global Assessment Scale. B: unstandardized beta. False discovery rate (FDR; [51]) correction of the *p*-values (implemented using the *p*.adjust function in R) was applied for all predictors. R = 0.523; R^2 = 0.273; and adjusted R^2 = 0.233.

4. Discussion

The aim of this naturalistic study, including a consecutive sample of children and adolescents referred with a manic or hypomanic episode, was to explore the effect of gender and age at onset (prepubertal and adolescent-onset) of BD, ADHD and SUD comorbidity on phenomenology, comorbidity and response to treatments. Furthermore, we explored possible elements associated with severe suicidal ideation or attempts and with poorer response to treatments. The sample consisted of patients referred for a pharmacological treatment and treated "as usual", allowing us to explore possible elements associated with the effectiveness of treatments in daily clinical practice. Given the type of referral, the sample included severely impaired patients and about 90% of the patients presented psychiatric comorbidities. More specifically, two main patterns of comorbidity are confirmed, those with ADHD, with associated externalizing behaviors (about 50% of the patients), and those with anxiety disorders (about 50%, about half of them with at least two anxiety disorders) and obsessive compulsive disorder. These conditions may represent possible pathways to early-onset bipolarity [11].

In our sample, 81.2% of the patients received a mood stabilizer, only 18.8% received a first SGA monotherapy and only 38.5% remained on a mood stabilizer monotherapy, while a strong minority (42.7%) received a polypharmacy with both a mood stabilizer and an SGA. This is the consequence of our therapeutic approach, which considered as a first choice lithium or VPA, given their safer profile compared to SGAs, namely in terms of weight gain and metabolic side effects. The rate of polypharmacy, even if high, was lower compared to other studies exploring pharmacological management of referred bipolar youths. A study on the use of medications in 111 bipolar children and adolescents treated in the community in the USA showed that these patients were receiving 3.40 ± 1.48 medications, that 18% of these children were taking five or more medications currently, and that 77% had a trial with an antipsychotic [53]. In Pavuluri et al.'s [54] study, only 17.5% of bipolar children and adolescents without psychotic symptoms were effectively controlled by a monotherapy with a mood stabilizer for at least 6 months while 66.3% of those receiving a combination treatment with a mood stabilizer and an atypical antipsychotic were considered responders [54]. In the present study, SSRIs and MPH were used only after a stabilization with mood stabilizers and/or atypical antipsychotics, without destabilizing effects. Scheffer et al. [55] showed that, in youth with BD and comorbid ADHD firstly stabilized with valproate, the outcome was significantly improved by adding a stimulant. It is noteworthy that, in this sample of severely impaired patients, comorbidities did not differ between males and females, including disorders with typical prevalence in males, such as ADHD, CD and SUD. A comparison between prepubertal-onset and adolescent-onset BD showed that the similarities of the clinical expression are more striking than the discrepancies, consistent with previous studies [2,9], supporting the notion that the manifestations of BD remain stable over time. The role of age at onset of BD was evident mainly in relation to ADHD and, to a lesser degree, with ODD/CD comorbidities. This finding suggests that a marker of very early onset BD is the association with ADHD and externalizing disorders [3,9,10,12,24]. A higher risk of SUD in adolescence-onset BD has been previously reported [31] and should be further explored with larger samples and perspective

studies. According to our data, an earlier onset as well as a lower chronological age do not influence the response to treatments, consistent with our previous findings [39,43].

These findings are consistent with those derived from the comparison between bipolar patients with or without ADHD. This association raised controversy, given the possibility of a chronic course and the overlap of symptoms, such as hyperactivity, impulsivity/aggressiveness, distractibility and emotional lability. In our study, comorbidity with ADHD is associated with an earlier onset and with a higher rate of externalizing disorders but it affects neither other comorbidities (including SUD) nor response to treatments. Differential diagnoses among early-onset mania, severe ADHD, ODD/CD with affective dysregulation and the cooccurrence of two or three of these disorders may be very difficult. The issue is not merely nosological, as a correct diagnosis has important implications for treatment options. The topic of comorbidity between ADHD, disruptive behavior disorders (particularly ODD) and bipolar spectrum disorders has been deeply explored, with the increasing impact of the concept of irritability and, more recently, of emotional dysregulation, that is an impaired regulation of emotional states, with excessive and inappropriate emotional expressions, high excitability and lability, temper outbursts, low tolerance to frustration and slow return to baseline [56]. This condition, firstly misconceived as a possible expression of BD comorbid to other clinical conditions, has been more recently and more adequately conceptualized as a neurodevelopmental condition of early severe dysregulation of emotions and behavior, not completely fitting any of the current clinical categories (i.e., ADHD, ODD and mood disorders), although they share features of all these domains. In a cross-sectional community study, mood lability, a concept closely related to emotional dysregulation, was strongly associated with comorbidity between internalizing and externalizing disorders, suggesting that it could be a shared risk factor for both disorders [57]. In a developmental perspective, children with ODD and emotional dysregulation at age 8 were found to be at higher risk of presenting mood disorders at age 14 [58].

Comorbidity with SUD is associate with greater severity and impairment, as expected, although it cannot be defined in the direction of this association (more severe patients are at higher risk of SUD, and/or SUD increases the severity of the affective and behavioral symptoms). The comorbidity of externalizing disorders (ADHD and ODD/CD) in BD youth with SUD has been previously reported [15,59] and probably represents the higher risk factor. These findings, including the higher rates of SUD in adolescent-onset BD, are comparable with those reported in Wilens et al.'s study [31], that found that both CD and BD are independent risk factors for adolescent-onset substance abuse. However, Wilens et al. [31] did not find a greater additive risk of substance abuse in youths with the combination of BD and CD. The lower response to treatments in patients with SUD may be related to the effects of substances on mood, to the greater severity of the clinical picture, or to the lower compliance to treatments.

The research of specific elements associated with suicidality in BD patients was disappointing, as none of the selected measures resulted in differentiating patients with or without suicidality, including age at onset of BD; anxiety, ADHD or SUD comorbidities; and pharmacological or psychological treatments. It may be possible that a larger sample may support the possible role of specific elements, including baseline clinical severity, rate of multiple anxiety disorders (48% vs. 19.6%) and the total number of comorbidities, which were no more significant after correction. More specifically, multiple anxiety disorders as a risk factor for suicidality in BD patients deserve a closer inspection [30].

Finally, both the comparison between responders and nonresponders and the logistic regressions underline the role of baseline severity and externalizing disorders as critical elements indicating the response to treatment. In previous studies [39,42,45], comorbidity with CD was the most important negative prredicitor of outcome and comorbid ADHD (odd ratio 2.30) and baseline CGI-S score were also significant.

Different mechanisms can be involved in treatment resistance of bipolar subjects with comorbid externalizing disorders. BD plus externalizing disorders may represent a specific subtype with earlier-onset and resistance to traditional anti-manic and mood stabilizing drugs [59]. Poorer treatment

response in BD with cooccurring externalizing disorders may be also accounted for by more problematic compliance to treatments. According to Carlson et al. [60], 61.5% of bipolar youths with comorbid externalizing disorder—compared to 22.2% in patients without externalizing disorder—discontinued the medication during follow-up and more than half of them had at least one recurrence. Their early course was negative; their global functioning at 24-month follow-up was low; and 50% of them, compared to 0% in the non-externalizing patients, were unable to interrupt the abuse of illicit drugs or alcohol during this period.

Our study presents several limitations. The main limitation is the lack of a control group and the use of mixed pharmacological treatments. Only patients referred to our third-level university hospital for severe symptomatology and pharmacological treatment were included, and they may represent a subgroup of more severely impaired subjects in terms of clinical presentation, pattern of comorbidity and response to treatments. The trained child psychiatrist was the same one who participated in the subsequent assessment procedures on the same subjects, and thus, he was not blind to the nature of the diagnosis. The age of onset of BD was assessed retrospectively, based on historical information and previous clinical reports. Only a selected number of features were considered relevant, and the diagnostic exploration did not include other potentially important elements. Environmental and personality trait variables may have been of interest [61], but they were not included in our study. Furthermore, the period of follow-up was limited to 6 months; a more extended observation would have been useful to better ascertain clinical characteristics and response to treatments. We have used as outcome measures CGI-S, C-GAS and CGI-I, not a specific measure of BD symptoms' severity and improvement. However, CGI-I is the criterion according to which usually clinicians decide treatment strategies, i.e., to continue or change a pharmacotherapy. In this situation, the clinical picture as a whole is more reliably captured by a global measure, considered to best fit the practical goals of our study.

Our findings describe an unselected sample of consecutive children and adolescents with BD treated in an "ordinary" clinical setting, which may actually be one of the strengths of our study. No exclusion criteria were applied (except for intellectual disability), and all comorbid conditions, which are often excluded in controlled trials but represent the rule in clinical settings, were included in the study. Furthermore, all the patients were treated as needed (mono- or polypharmacy) and followed-up in a routinary clinical setting. We submit that long-term naturalistic perspective studies might represent an important source of information regarding the effectiveness of treatment over extended periods of time under ordinary clinical conditions.

Author Contributions: Conceptualization: G.M., S.B. and A.M. Methodology: G.M., S.B., P.M. and V.L. Data collection: M.M., V.V., A.V., E.I., F.P., C.P., G.D., F.L. (Francesca Lenzi) and F.L. (Francesca Liboni). Statistical analyses: P.M. and V.L. Writing first draft: G.M. Discussion on the first draft and conclusions: S.B., A.M., M.M., V.V., A.V., E.I., F.P., C.P., G.D., F.L. (Francesca Lenzi) and F.L. (Francesca Liboni). All authors have read and agreed to the published version of the manuscript.

Funding: No funding was provided for this research.

Conflicts of Interest: G.M. received research grants from Lundbeck and Humana; was in an advisory board for Angelini; and was a speaker for Angelini, FB Health, Janssen, Lundbeck and Otsuka. C.P. received research grants from Eli Lilly and was a speaker for Eli Lilly. S.B., P.M., M.M., V.V., A.V., E.I., F.P., G.D., F.L. (Francesca Lenzi), F.L. (Francesca Liboni) and A.M. do not have conflict of interest to declare.

References

1. Wozniak, J.; Biederman, J.; Kiely, K.; Ablon, J.S.; Faraone, S.V.; Mundy, E.; Mennin, D. Mania-Like Symptoms Suggestive of Childhood-Onset Bipolar Disorder in Clinically Referred Children. *J. Am. Acad. Child Adolesc. Psychiatry* **1995**, *34*, 867–876. [CrossRef] [PubMed]
2. Findling, R.L.; Gracious, B.L.; McNamara, N.K.; Youngstrom, E.; A Demeter, C.; A Branicky, L.; Calabrese, J.R. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord.* **2001**, *3*, 202–210. [CrossRef] [PubMed]

3. Masi, G.; Perugi, G.; Millepiedi, S.; Mucci, M.; Pari, C.; Pfanner, C.; Berloffa, S.; Toni, C. Clinical Implications of DSM-IV Subtyping of Bipolar Disorders in Referred Children and Adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* **2007**, *46*, 1299–1306. [CrossRef]
4. Leibenluft, E.; Charney, D.S.; Towbin, K.; Bhangoo, R.; Pine, D.S. Defining Clinical Phenotypes of Juvenile Mania. *Am. J. Psychiatry* **2003**, *160*, 430–437. [CrossRef] [PubMed]
5. Leibenluft, E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am. J. Psychiatry* **2010**, *168*, 129–142. [CrossRef]
6. Nottelmann, E. National Institute of Mental Health Research Roundtable on Prepubertal Bipolar Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2001**, *40*, 871–878. [CrossRef]
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 54th ed.; American Psychiatric Association: Washington, DC, USA, 2013.
8. Perlis, R.H.; Miyahara, S.; Marangell, L.B.; Wisniewski, S.R.; Ostacher, M.; DelBello, M.P.; Bowden, C.L.; Sachs, G.S.; A Nierenberg, A. Long-Term implications of early onset in bipolar disorder: Data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol. Psychiatry* **2004**, *55*, 875–881. [CrossRef]
9. Biederman, J.; Faraone, S.V.; Wozniak, J.; Mick, E.; Kwon, A.; Cayton, G.A.; Clark, S.V. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J. Psychiatr. Res.* **2005**, *39*, 611–622. [CrossRef]
10. Masi, G.; Perugi, G.; Millepiedi, S.; Mucci, M.; Toni, C.; Bertini, N.; Pfanner, C.; Berloffa, S.; Pari, C. Developmental Differences According to Age at Onset in Juvenile Bipolar Disorder. *J. Child Adolesc. Psychopharmacol.* **2006**, *16*, 679–685. [CrossRef]
11. Masi, G.; Mucci, M.; Pfanner, C.; Berloffa, S.; Magazù, A.; Perugi, G. Developmental Pathways for Different Subtypes of Early-Onset Bipolarity in Youths. *J. Clin. Psychiatry* **2012**, *73*, 1335–1341. [CrossRef]
12. Faraone, S.V.; Biederman, J.; Wozniak, J.; Mundy, E.; Mennin, D.; O'Donnell, D. Is Comorbidity With ADHD a Marker for Juvenile-Onset Mania? *J. Am. Acad. Child Adolesc. Psychiatry* **1997**, *36*, 1046–1055. [CrossRef] [PubMed]
13. Galanter, C.A.; Leibenluft, E. Frontiers Between Attention Deficit Hyperactivity Disorder and Bipolar Disorder. *Child Adolesc. Psychiatr. Clin. N. Am.* **2008**, *17*, 325–346. [CrossRef]
14. Bernardi, S.; Cortese, S.; Solanto, M.V.; Hollander, E.; Pallanti, S. Bipolar disorder and comorbid attention deficit hyperactivity disorder. A distinct clinical phenotype? Clinical characteristics and temperamental traits1. *World J. Biol. Psychiatry* **2010**, *11*, 656–666. [CrossRef] [PubMed]
15. Masi, G.; Milone, A.; Manfredi, A.; Pari, C.; Paziente, A.; Millepiedi, S. Comorbidity of Conduct Disorder and Bipolar Disorder in Clinically Referred Children and Adolescents. *J. Child Adolesc. Psychopharmacol.* **2008**, *18*, 271–279. [CrossRef]
16. Wozniak, J.; Wilens, T.; Disalvo, M.; Farrell, A.; Wolenski, R.; Faraone, S.V.; Biederman, J. Comorbidity of bipolar I disorder and conduct disorder: A familial risk analysis. *Acta Psychiatr. Scand.* **2019**, *139*, 361–368. [CrossRef]
17. Masi, G.; Toni, C.; Perugi, G.; Mucci, M.; Millepiedi, S.; Akiskal, H.S. Anxiety disorders in children and adolescents with bipolar disorder: A neglected comorbidity. *Can. J. Psychiatry* **2001**, *46*, 797–802. [CrossRef]
18. Sala, R.; Axelson, D.A.; Castro-Fornieles, J.; Goldstein, T.R.; Ha, W.; Liao, F.; Gill, M.K.; Iyengar, S.; Strober, M.A.; Goldstein, B.I.; et al. Comorbid anxiety in children and adolescents with bipolar spectrum disorders: Prevalence and clinical correlates. *J. Clin. Psychiatry* **2010**, *71*, 1344–1350. [CrossRef]
19. Masi, G.; Berloffa, S.; Mucci, M.; Pfanner, C.; D'Acunto, G.; Lenzi, F.; Liboni, F.; Manfredi, A.; Milone, A. A naturalistic exploratory study of obsessive-compulsive bipolar comorbidity in youth. *J. Affect. Disord.* **2018**, *231*, 21–26. [CrossRef]
20. Wagner, K.D. Bipolar disorder and comorbid anxiety disorders in children and adolescents. *J. Clin. Psychiatry* **2006**, *67* (Suppl. 1), 16–20. [CrossRef]
21. Henin, A.; Biederman, J.; Mick, E.; Sachs, G.S.; Hirshfeld-Becker, D.R.; Siegel, R.S.; McMurrich, S.; Grandin, L.; Nierenberg, A.A. Psychopathology in the Offspring of Parents with Bipolar Disorder: A Controlled Study. *Biol. Psychiatry* **2005**, *58*, 554–561. [CrossRef]

22. Masi, G.; Perugi, G.; Toni, C.; Millepiedi, S.; Mucci, M.; Bertini, N.; Akiskal, H.S. The Clinical Phenotypes of Juvenile Bipolar Disorder: Toward a Validation of the Episodic-Chronic-Distinction. *Biol. Psychiatry* **2006**, *59*, 603–610. [CrossRef] [PubMed]
23. Biederman, J.; Faraone, S.; Mick, E.; Wozniak, J.; Chen, L.; Ouellette, C.; Marrs, A.; Moore, P.; Garcia, J.; Mennin, D.; et al. Attention-Deficit Hyperactivity Disorder and Juvenile Mania: An Overlooked Comorbidity? *J. Am. Acad. Child Adolesc. Psychiatry* **1996**, *35*, 997–1008. [CrossRef] [PubMed]
24. Masi, G.; Perugi, G.; Toni, C.; Millepiedi, S.; Mucci, M.; Bertini, N.; Pfanner, C. Attention-deficit hyperactivity disorder—Bipolar comorbidity in children and adolescents. *Bipolar Disord.* **2006**, *8*, 373–381. [CrossRef] [PubMed]
25. Plans, L.; Barrot, C.; Nieto, E.; Rios, J.; Schulze, T.; Papiol, S.; Mitjans, M.; Vieta, E.; Benabarre, A. Association between completed suicide and bipolar disorder: A systematic review of the literature. *J. Affect. Disord.* **2019**, *242*, 111–122. [CrossRef]
26. Klonsky, E.D.; Qiu, T.; Saffer, B.Y. Recent advances in differentiating suicide attempters from suicide ideators. *Curr. Opin. Psychiatry* **2017**, *30*, 15–20. [CrossRef]
27. Chronis-Tuscano, A.; Molina, B.S.G.; Pelham, W.E.; Applegate, B.; Dahlke, A.; Overmyer, M.; Lahey, B.B. Very Early Predictors of Adolescent Depression and Suicide Attempts in Children With Attention-Deficit/Hyperactivity Disorder. *Arch. Gen. Psychiatry* **2010**, *67*, 1044. [CrossRef]
28. Levy, T.; Kronenberg, S.; Crosbie, J.; Schachar, R.J. Attention-deficit/hyperactivity disorder (ADHD) symptoms and suicidality in children: The mediating role of depression, irritability and anxiety symptoms. *J. Affect. Disord.* **2020**, *265*, 200–206. [CrossRef]
29. Wang, X.; Liu, Z.; Li, Y.; Li, G.; Huang, Y. Association of comorbidity of mood and anxiety disorders with suicidal behaviors. *J. Affect. Disord.* **2018**, *227*, 810–816. [CrossRef]
30. Abreu, L.; Oquendo, M.A.; Galfavy, H.; Burke, A.; Grunebaum, M.F.; Sher, L.; Sullivan, G.M.; Sublette, M.E.; Mann, J.; Lafer, B.; et al. Are comorbid anxiety disorders a risk factor for suicide attempts in patients with mood disorders? A two-year prospective study. *Eur. Psychiatry* **2018**, *47*, 19–24. [CrossRef]
31. Wilens, T.E.; Biederman, J.; Kwon, A.; Ditterline, J.; Forkner, P.; Moore, H.; Swezey, A.; Snyder, L.; Henin, A.; Wozniak, J.; et al. Risk of Substance Use Disorders in Adolescents With Bipolar Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2004**, *43*, 1380–1386. [CrossRef]
32. Levin, F.R.; Hennessy, G. Bipolar disorder and substance abuse. *Biol. Psychiatry* **2004**, *56*, 738–748. [CrossRef] [PubMed]
33. Swendsen, J.; Conway, K.P.; Degenhardt, L.; Glantz, M.; Jin, R.; Merikangas, K.R.; Sampson, N.; Kessler, R.C. Mental disorders as risk factors for substance use, abuse and dependence: Results from the 10-year follow-up of the National Comorbidity Survey. *Addiction* **2010**, *105*, 1117–1128. [CrossRef] [PubMed]
34. Salloum, I.M.; E Thase, M. Impact of substance abuse on the course and treatment of bipolar disorder. *Bipolar Disord.* **2000**, *2*, 269–280. [CrossRef] [PubMed]
35. Duffy, A.; Horrocks, J.; Milin, R.; Doucette, S.; Persson, G.; Grof, P. Adolescent substance use disorder during the early stages of bipolar disorder: A prospective high-risk study. *J. Affect. Disord.* **2012**, *142*, 57–64. [CrossRef]
36. Carlson, G.A.; Bromet, E.J.; Driessens, C.; Mojtabai, R.; Schwartz, J.E. Age at Onset, Childhood Psychopathology, and 2-Year Outcome in Psychotic Bipolar Disorder. *Am. J. Psychiatry* **2002**, *159*, 307–309. [CrossRef]
37. Geller, B.; Craney, J.L.; Bolhofner, K.; Nickelsburg, M.J.; Williams, M.; Zimerman, B. Two-Year Prospective Follow-Up of Children With a Prepubertal and Early Adolescent Bipolar Disorder Phenotype. *Am. J. Psychiatry* **2002**, *159*, 927–933. [CrossRef]
38. Werry, J.S.; McClellan, J.M. Predicting Outcome in Child and Adolescent (Early Onset) Schizophrenia and Bipolar Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **1992**, *31*, 147–150. [CrossRef]
39. Masi, G.; Perugi, G.; Toni, C.; Millepiedi, S.; Mucci, M.; Bertini, N.; Akiskal, H.S. Predictors of treatment nonresponse in bipolar children and adolescents with manic or mixed episodes. *J. Child. Adolesc. Psychopharmacol.* **2004**, *14*, 395–404. [CrossRef]
40. Strober, M.; DeAntonio, M.; Schmidt-Lackner, S.; Freeman, R.; Lampert, C.; Diamond, J. Early childhood attention deficit hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. *J. Affect. Disord.* **1998**, *51*, 145–151. [CrossRef]

41. Kafantaris, V.; Coletti, D.J.; Dicker, R.; Padula, G.; Pollack, S. Are childhood psychiatric histories of bipolar adolescents associated with family history, psychosis, and response to lithium treatment? *J. Affect. Disord.* **1998**, *51*, 153–164. [CrossRef]
42. West, A.E.; Weinstein, S.M.; Celio, C.I.; Henry, D.; Pavuluri, M.N. Co-morbid Disruptive Behavior Disorder and Aggression Predict Functional Outcomes and Differential Response to Risperidone Versus Divalproex in Pharmacotherapy for Pediatric Bipolar Disorder. *J. Child Adolesc. Psychopharmacol.* **2011**, *21*, 545–553. [CrossRef] [PubMed]
43. Duffy, A.; Goodday, S.M.; Keown-Stoneman, C.; Grof, P. The Emergent Course of Bipolar Disorder: Observations Over Two Decades From the Canadian High-Risk Offspring Cohort. *Am. J. Psychiatry* **2019**, *176*, 720–729. [CrossRef] [PubMed]
44. Connor, D.F.; Ford, J.D.; Pearson, G.S.; Scranton, V.L.; Dusad, A. Early-Onset Bipolar Disorder: Characteristics and Outcomes in the Clinic. *J. Child Adolesc. Psychopharmacol.* **2017**, *27*, 875–883. [CrossRef]
45. Masi, G.; Perugi, G.; Millepiedi, S.; Mucci, M.; Pfanner, C.; Berloffa, S.; Pari, C.; Gagliano, A.; D'Amico, F.; Akiskal, H.S. Pharmacological response in juvenile bipolar disorder subtypes: A naturalistic retrospective examination. *Psychiatry Res.* **2010**, *177*, 192–198. [CrossRef] [PubMed]
46. Fristad, M.A.; MacPherson, H.A. Evidence-based psychosocial treatments for child and adolescent bipolar spectrum disorders. *J. Clin. Child Adolesc. Psychol.* **2013**, *43*, 339–355. [CrossRef]
47. Miklowitz, D.J.; Axelson, D.A.; Birmaher, B.; George, E.L.; Taylor, D.O.; Schneck, C.D.; Beresford, C.A.; Dickinson, L.M.; Craighead, W.E.; Brent, D.A. Family-Focused Treatment for Adolescents With Bipolar Disorder. *Arch. Gen. Psychiatry* **2008**, *65*, 1053–1061. [CrossRef]
48. Guy, W. *ECDEU Assessment Manual for Psychopharmacology*; US Department of Health, Education, and Welfare, Public Health Service: Rockville, MD, USA, 1976.
49. Shaffer, D.; Gould, M.S.; Brasic, J.; Ambrosini, P.; Fisher, P.; Bird, H.; Aluwahlia, S. A Children's Global Assessment Scale (CGAS). *Arch. Gen. Psychiatry* **1983**, *40*, 1228–1231. [CrossRef]
50. Kaufman, J.; Birmaher, B.; Brent, D.; Rao, U.; Flynn, C.; Moreci, P.; Williamson, D.; Ryan, N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *J. Am. Acad. Child Adolesc. Psychiatry* **1997**, *36*, 980–988. [CrossRef]
51. Benjamini, Y.; Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J. R. Stat. Soc. Ser. B* **1995**, *57*, 289–300. [CrossRef]
52. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Available online: https://www.R-project.org/ (accessed on 29 September 2020).
53. Bhangoo, R.; Lowe, C.H.; Myers, F.S.; Treland, J.; Curran, J.; Towbin, K.; Leibenluft, E. Medication Use in Children and Adolescents Treated in the Community for Bipolar Disorder. *J. Child Adolesc. Psychopharmacol.* **2003**, *13*, 515–522. [CrossRef]
54. Pavuluri, M.N.; Henry, D.B.; Devineni, B.; Carbray, J.A.; Naylor, M.W.; Janicak, P.G. A Pharmacotherapy Algorithm for Stabilization and Maintenance of Pediatric Bipolar Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2004**, *43*, 859–867. [CrossRef] [PubMed]
55. Scheffer, R.E.; Kowatch, R.A.; Carmody, T.J.; Rush, A.J. Randomized, Placebo-Controlled Trial of Mixed Amphetamine Salts for Symptoms of Comorbid ADHD in Pediatric Bipolar Disorder After Mood Stabilization With Divalproex Sodium. *Am. J. Psychiatry* **2005**, *162*, 58–64. [CrossRef] [PubMed]
56. Faraone, S.V.; Rostain, A.L.; Blader, J.; Busch, B.; Childress, A.C.; Connor, D.F.; Newcorn, J.H. Practitioner Review: Emotional dysregulation in attention-deficit/hyperactivity disorder—Implications for clinical recognition and intervention. *J. Child Psychol. Psychiatry* **2018**, *60*, 133–150. [CrossRef] [PubMed]
57. Stringaris, A.; Goodman, R. Longitudinal Outcome of Youth Oppositionality: Irritable, Headstrong, and Hurtful Behaviors Have Distinctive Predictions. *J. Am. Acad. Child Adolesc. Psychiatry* **2009**, *48*, 404–412. [CrossRef]
58. Masi, G.; Pisano, S.; Milone, A.; Muratori, P. Child behavior checklist dysregulation profile in children with disruptive behavior disorders: A longitudinal study. *J. Affect. Disord.* **2015**, *186*, 249–253. [CrossRef]
59. Biederman, J.; Mick, E.; Wozniak, J.; Monuteaux, M.C.; Galdo, M.; Faraone, S.V. Can a subtype of conduct disorder linked to bipolar disorder be identified? Integration of findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program. *Biol. Psychiatry* **2003**, *53*, 952–960. [CrossRef]

60. A Carlson, G.; Bromet, E.J.; Sievers, S. Phenomenology and Outcome of Subjects With Early- and Adult-Onset Psychotic Mania. *Am. J. Psychiatry* **2000**, *157*, 213–219. [CrossRef]
61. Muratori, P.; Milone, A.; Levantini, V.; Pisano, S.; Spensieri, V.; Valente, E.; Thomaes, S.; Masi, G. Narcissistic traits as predictors of emotional problems in children with oppositional defiant disorder: A longitudinal study. *J. Affect. Disord.* **2020**, *274*, 494–499. [CrossRef]

Clinical EEG and Neuroscience
1–12

DOI: 10.1177/1550059420962343
journals.sagepub.com/home/eeg
SAGE

Quantitative EEG in Childhood Attention Deficit Hyperactivity Disorder and Learning Disabilities

Giuseppe Augusto Chiarenza[1]

Abstract

The clinical use of the quantitative EEG (QEEG) from the pioneering work of John has received a new impetus thanks to new neuroimaging techniques and the possibility of using a number of normative databases both of normal subjects and of subjects with definite pathologies. In this direction, the term *personalized medicine* is becoming more and more common, a medical procedure that separates patients into different groups based on their predicted response to the quantitative EEG. This has allowed the study of single subjects and to customize health care, with decisions and treatments tailored to each individual patient, as well as improvement of knowledge of the pathophysiological mechanisms of specific diseases. This review article will present the most recent evidence in the field of developmental neuropsychiatric disorders obtained from the application of quantitative EEG both in clinical group studies (attention deficit hyperactivity disorder, developmental dyslexia, oppositional defiant disorder) and in individual case studies not yet published.

Keywords

quantitative EEG, QEEG, developmental dyslexia, oppositional defiant disorder, reading delay, atomoxetine, methylphenidate, micrography.

Received May 29, 2019; revised August 11, 2020; accepted September 4, 2020.

Introduction

Historically, conventional EEG has added little to the understanding of childhood psychiatric disorders, other than to rule out epilepsy or space occupying lesions. However, the advent of computerized, quantitative methods, from the pioneering work of John,[1] together with new neuroimaging techniques as brain sources localization and the availability of normative databases both of normal subjects and of subjects with definite pathologies has greatly enhanced the clinical application in neurodevelopmental disorders. Furthermore, in these past years, it has become more and more apparent that groups of patients with neuropsychiatric disorders, who meet symptom based diagnostic criteria for specific disorders (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [*DSM-IV*] or International Classification of Diseases, 10th Revision [ICD-10]) have varied responses to treatment, despite their relatively homogeneous clinical presentation. Using clinical diagnosis, the "treatment of choice" leads to a positive response approximately 60% of the time.[2] This poor response rate suggests heterogeneity within these relatively homogeneous clinical populations. In this direction, the term *personalized medicine* is becoming more and more common, a medical procedure that separates patients into different groups based on their electrophysiological profiles and predicted response to the quantitative EEG. This has allowed the study of single subjects and to customize health care, with decisions and treatments tailored to each individual patient, as well as improvement of knowledge of the pathophysiological mechanisms of specific diseases.

The Debate Around the Use of the Quantitative EEG in Clinical Practice

The use of quantitative EEG (QEEG) in clinical practice has always been hotly debated. The Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents of the American Academy of Pediatrics[3] states that to make a diagnosis of attention deficit hyperactivity disorder (ADHD), clinicians should conduct a clinical interview with parents, examine and observe the child, and obtain information from parents and teachers through *DSM*-based ADHD rating scales. One of the research questions developed by an ad hoc subcommittee was the following: "What is the comparative diagnostic accuracy of

[1]International Center for Learning, Attention and Hyperactivity Disorders (CIDAAI), Milan, Italy

Corresponding Author:
Giuseppe Augusto Chiarenza, International Center for Learning, Attention and Hyperactivity Disorders (CIDAAI), via Edolo 46, Milan, 20125, Italy.
Email: giuseppe.chiarenza@fastwebnet.it

EEG, imaging, or executive function approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 to their 18th birthday?" The only answer to this question is the following: "The use of neuropsychological testing has not been found to improve diagnostic accuracy in most cases, although it may have benefit in clarifying the child or adolescent's learning strengths and weaknesses."

The use of QEEG as a diagnostic tool has always been widely debated with numerous works in favor and others against. This uncertainty, in my opinion, stems from the fact that ADHD is not a disease but a syndrome. This primarily implies that the inclusion and exclusion criteria are not always homogeneous in the various studies, the diagnostic criteria are mainly based on clinical evaluations and scales that introduce further variability. This is to mention just a few factors without neglecting the more strictly technical ones related to the recording of the QEEG and to the physiological conditions of the subject examined, both normal and with ADHD. Quintana et al[4] in a recent study of comparison of a standard psychiatric evaluation to rating scales and EEG in the differential diagnosis of attention deficit hyperactivity disorder affirm that numerous studies have been conducted to establish the validity and reliability of ratings scales as an assessment tool for ADHD as covered in a recent 10-year review.[5] A broad review of the literature demonstrates that when taking statistical methods and experimental designs of these studies into consideration, the expected range of accuracy for rating scales is 55% to 79% in the identification of ADHD versus controls. In their study, Quintana et al[4] report that

> . . . rating scales were likely to classify attention, impulsivity, and/or hyperactivity symptoms as being due to ADHD, regardless of the actual underlying disorder, leading to a sensitivity of 81% and a specificity of 22% for the rating scales when applied to a clinical sample. The overall classification accuracy of the rating scales was 60%.

As far as the accuracy of the QEEG, Quintana et al[4] write that

> the age-matched EEG pattern for ADHD was observed to be present in 15 of 16 subjects diagnosed by the standard psychiatric evaluation as having ADHD (sensitivity = 94%). Regardless of the presence of ADHD-like symptoms, the EEG pattern for ADHD did not occur in any of these non-ADHD patients (specificity = 100%). The overall classification accuracy of the EEG test was 96%.

The authors conclude that QEEG may play a significant role in ADHD differential diagnosis. Similar classification accuracy results were obtained in other studies.[6-12]

On the contrary, recent review of meta-analysis failing to confirm the usefulness of theta-beta ratio in eyes open condition in the diagnosis of ADHD.[13] In addition, Ogrim et al[14] reported a significant elevated theta characteristic of a subgroup of ADHD patients that was correlated with inattention and executive problems with an accuracy of 62% at Cz.

However, it is a well-known fact that EEG activity shows a high variability with age. To assess what is normal or what deviates from normality, the subject's age has to be considered. To facilitate deviation from normality, assessment in the QEEG normative database have been recorded and regression equation against the age have been calculated. In this way, *z* scores are obtained using the raw spectra parameters and the means and standard deviations calculated from the normative data for the same parameter. This transformation accounts for the age variability in the EEG data.[15] Although EEG differences between eyes open and eyes closed are important to assess some pathological activities in the brain, the majority of databases used in the QEEG contain only information about eyes closed condition.

In this article, we focus on the study of EEG activity during resting state, which is the purpose of QEEG analysis. However, it has to be understood that EEG analysis is not appropriate when analyzing task-related brain activities. For that case, we suggest the technique of event-related potentials.

In order to provide a further contribution to the clinical utility of the quantitative EEG, the most recent evidences in the field of developmental neuropsychiatric disorders are presented in this review article obtained from the application of quantitative EEG both in clinical group studies, developmental dyslexia, reading retardation, ADHD with and without oppositional defiant disorder and in 2 case studies, not yet published and selected from the database of the International Center for Learning, Attention and Hyperactivity Disorders (CIDAAI).

The appendix describes the method of acquisition and processing of EEG signal used in studies whose results will be described here below.

Developmental Dyslexia and Reading Retardation

Boder and Jarrico[16] have developed a diagnostic screening procedure which identifies three main subtypes of dyslexia: dysphonetic dyslexia (DD), dyseidetic and mixed, besides a fourth group defined nonspecific reading delay (NSRD). These subgroups are identified by an algorithm that considers the reading quotient and the percentage of errors of the spelling test. The early identification of this NSRD subgroup, frequently overlooked or confounded with dysphonetic dyslexia, has evident clinical implications for diagnosis, therapy, and prognosis. While specific learning disabilities have been extensively studied with QEEG, reading retardation has not received the same attention instead. John[1] and Duffy et al[17] reported QEEG abnormalities in both hemispheres in dyslexic children at rest as well as during complex testing. John et al[18] found abnormal QEEGs present in 32.7% of the children with specific learning disorder (SLD) and 38.1% of the children with learning disorder (LD) groups, whereas only 5.5% of an independent sample of normal children had abnormal QEEGs. Children with learning disorders were shown to have different patterns of brain maturation than normal control subjects. Normal subjects, with increased age show an increase of posterior/vertex EEG

coherence and a decrease in coherence in frontal areas. Increased differentiation of frontal cortical regions, with age, leads to increased communication across basic sensory and association cortex. These systematic maturational changes are often not seen in children with learning disorders. Flynn and Deering[19] and Flynn et al,[20] using the Boder test classification,[21] investigated whether electrophysiological evidence among dyslexic subgroups, could be demonstrated by analysis of QEEG patterns during school-related tasks. The authors found increased left temporo-parietal theta activity in dyseidetic children assuming an overuse of the left-language system activation in patients with visuo-spatial problems recognition. Casarotto et al,[22] using reading-related potentials recorded during reading aloud self-paced single-letter, showed that children with DD had *abnormal activation* at short latencies in the left temporal polar area, at middle latencies in the temporal polar and inferior frontal regions bilaterally and at long latencies in fronto-temporal regions of the right hemisphere. This indicates an early involvement of frontal regions during reading and it may be related to a significantly higher activation of the right hemisphere. This would seem very likely to be related to compensatory mechanisms adopted by reading-impaired children to improve their performance. On the contrary, *impaired activation* of the dyslexic group was present in the left and medial parietal regions: at short and middle latencies, it was present in the angular and then in the supramarginal gyrus; at long latencies, it moved in the middle precuneus and occipital lobe. Therefore, behavioral signs of reading impairment can be related to reduced activation in the left dorsal parieto-occipital regions that have been shown to be specifically involved in reading processes and particularly in the storage and processing of the visual and auditory representations of alphabetic characters.[23] These results are consistent with previous findings of greater recruitment of cerebral regions in the right hemisphere in dyslexic children in comparison with controls.[24] Although all the cited studies identify the left temporo-parietal region as the region where the greatest differences between normal and dyslexic subjects are found, electrophysiological differences between subtypes of dyslexia according to Boder classification have not been further confirmed also due to different clinical classifications. Furthermore, we are not aware of studies that compare children with different subtypes of dyslexia with children with NSRD using electrophysiological methods. Recently, we have used QEEG to indicate which children with learning problems have a measurable underlying neurophysiological dysfunction and which do not.[25] The possibility of identifying early indicators of children with NSRD has obvious therapeutic and prognostic implications as well as clinical ones, above all to avoid that they are not identified, diagnosed, and treated belatedly, until the secondary school level or confounded with children with DD. In comparison with the children with reading delay, the children with DD showed significant excess in delta band in the middle line (Fz, Cz, and Pz), as well as Fp2 and the occipital leads bilaterally (O1 and O2). A significant excess in high theta (6-7.5 Hz) and low alpha (7.5-8.5 Hz) bands was also present in the Fz, Cz, and Fp2. Fz, Cz, and Pz also showed significant excess of activity in the DD group. However, a significant reduction of high alpha (11-12.5 Hz) activity was present in the DD group bilaterally in F3, C3, C4, and in P3. Additionally, significant reduction was also present in the left leads F7, F3, C3, P3, and T5. Figure 1 shows the significant differences of the *t* test at the source spectra of DD versus NSRD. The *t* tests at the sources showed a significant increase of activity of DD with regard to NSRD in delta, low (4.29 Hz) and high theta (7.5 Hz) bands, and a significant decrease of DD with regard to NSRD in beta band (18-19 Hz). In the delta band: bilaterally in the calcarine sulcus, cuneus, precuneus, lingual, occipital (superior, middle, and inferior lobes), fusiform and superior parietal gyrus; the right inferior parietal, the right angular gyrus and the right paracentral lobule. In the low theta band: the right superior parietal and the right inferior parietal gyrus. In the high theta band: bilaterally the frontal medial orbital and the right superior medial frontal gyri. In the beta band: bilaterally the calcarine sulcus, lingual and fusiform inferior gyri; the left occipital (superior, medial and inferior) gyrus, superior and inferior parietal gyrus, supramarginal gyrus, angular gyrus and middle and inferior temporal gyrus.

The observation of the differences of EEG source spectra between the 2 groups allows us to add further considerations. The first observation concerns the excess of delta and theta activity that is found in the dysphonetic subjects in a standard EEG recorded at rest, with eyes closed. This fact reinforces the hypothesis that dyslexia is not only a functional disorder, but the result of a structural disorder as reported by the studies of Galaburda,[26] which found in the brain of 5 severe dyslexics adults, the right temporal planum wider than the left in 100% of cases. In addition, a high frequency of microdysgenesis was also observed, particularly in the left frontal and temporal opercula. This report was subsequently confirmed by Shaywitz et al[27] who performed a series of language-based activation tasks with progressively increasing phonologic demands using functional magnetic resonance imaging (fMRI) in dyslexic adults. There was underactivation of the left posterior perysilvian and occipital regions (Wernicke's area, the angular gyrus, and striate cortex) and overactivation to even simple phonologic task in both left anterior (inferior frontal gyrus) and right posterior perisylvian regions. A certain dysregulation of the motor areas in dyslexic subjects has long been known.[28,29] Dyslexic patients have difficulty processing both rapid and visual stimuli as well as in generating rapid bimanual motor output. In 1982, Chiarenza et al[30] recorded the brain electrical activity, called "movement-related brain potentials," during a skilled motor task that to be performed adequately, required bimanual coordination, bimanual ballistic movements, adaptive programming and learning a proper timing. The dyslexic children presented a deficit of programming movements, a deficit of visual and kinesthetic sensory processes, and a reduced capacity to evaluate their performance and correct their errors. Chiarenza[31] advanced the hypothesis that dyslexia is not only a phonological or gestalt deficit but also a praxic disorder in which praxic abilities, such as motor programming, sequential and sensorial motor

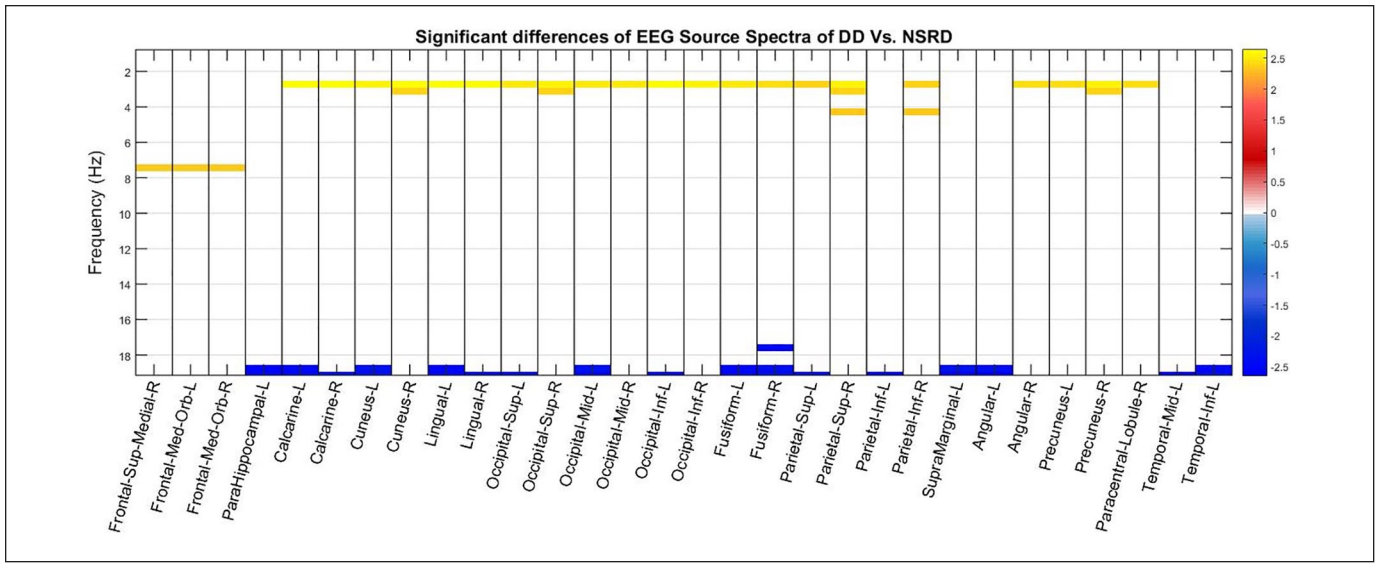


Figure 1. Significant differences of the *t* test at the source spectra of dysphonetic dyslexia (DD) versus nonspecific reading delay (NSRD). Red and yellow values indicate an excess of DD compared with NSRD; values in the blue scale indicate excess of NSRD compared with DD. Threshold corrected by multiple comparisons. Differences are concentrated in very narrow bands of frequencies. In general, DD have an excess of slow activity (delta and slightly theta) and a defect of fast activity (beta band). Age-dependent *z* score spectra of the EEG at the sources were used in this study. The *z* scores were calculated using the Cuban Normative Database and the QEEGT software developed by the Cuban Neuroscience Center.

integration and evaluation processes, are required and somehow defective in dyslexia. In addition, Chiarenza et al[30] have observed that dyslexic children showed a latency delay of movement-related potentials significantly different across the various cerebral areas during the same skilled motor task. Therefore, we have hypothesized that dyslexia could be the result of a timing defect that causes an integration defect and dysfunction of numerous processes hierarchically organized that occur at different levels and times. Also, Llinas[32] hypothesizes that at the base of the pathophysiology of dyslexia exists a more basic deficit of timing. This dynamic interplay of different frequencies in different brain areas confirms the idea of how the process of reading and writing occurs through a complex network in different brain areas and therefore it seems plausible that an alteration at one point in the network is inevitably reflected in other areas of the brain. A possible explanation of this temporal dysregulation could be a compensatory mechanism or, alternatively, the fact that in the dysphonetic subjects, the normal automatic interplay of gestalt and analytic-synthetic processes is interrupted. The DD subjects tend to persist in the gestalt approach preferring to guess at unfamiliar words rather than employ their word analysis skills. This apparently unusual reading mode of DD subjects is one of the reasons for early referral of teachers to child neuropsychiatrists. Subjects with NSRD, on the other hand, who made fewer misspellings both when reading and writing than DD subjects, but still present at the end of primary school, were referred late. Indeed, the comparison between the 2 groups of subjects revealed that the age of the Direct Test of Reading and Spelling (DTRS) testing was highly significant ($P = .0129$, $t = 12.51$). The children with NSRD were significantly older at the time of testing than those with DD and consequently had a significantly lower reading quotient than the subjects with DD.

ADHD and Oppositional Defiant Disorder

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.[33,34] 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.[35] The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context or it affects negatively on social, educational, or other important areas of functioning. One of the most frequent comorbidities associated to ODD is ADHD. The frequency with which ODD is associated with ADHD is 39% while that of anxiety disorders is 34% and 14% that of conduct disorders.[36] 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. Barkley[37-40] describes ADHD-C as a deficit in behavioral inhibition of 4 executive neuropsychological functions: working memory, self-regulation of affect–motivation–arousal, internalization of speech and reconstruction. Extensive neuroimaging studies (event-related potentials, positron emission tomography, fMRI) have

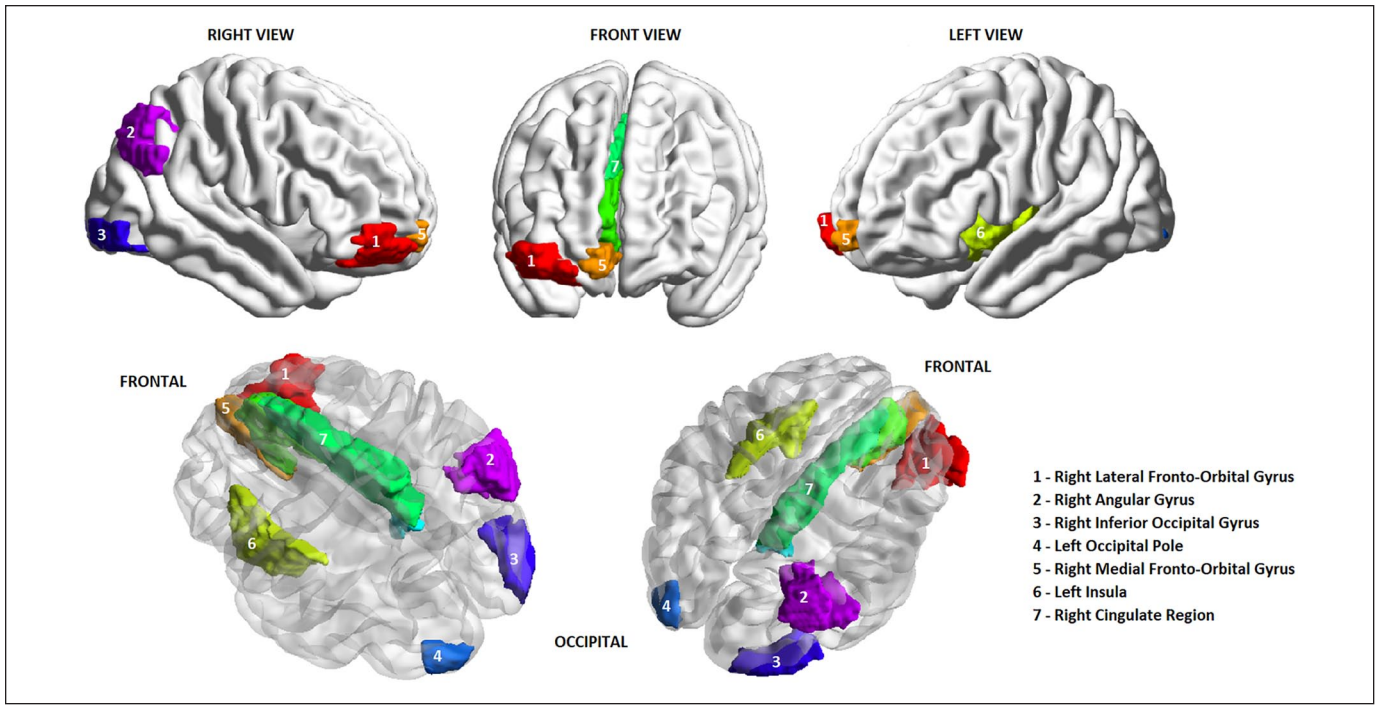


Figure 2. Brain regions selected by the classification procedure as biomarkers at the sources: left insula, right lateral orbito-frontal gyrus, right cingular region, right angular gyrus, right inferior occipital gyrus, left occipital pole, right medial orbito-frontal gyrus. The classification algorithm was applied to the age-dependent z score spectra of the EEG at the sources. The z scores were calculated using the Cuban Normative Database and the QEEGT software developed by the Cuban Neuroscience Center.

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.[41-48] 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.[6,49,50] Several studies have been conducted to associate these neurophysiological patterns with the diverse and multiform comorbidities present in ADHD subjects.[6,51,52,53] Although ADHD-C and ODD seem to share some similarities at neurofunctional level, Barry and Clarke[54] found little EEG difference between groups of children with ADHD, with and without ODD.

Chiarenza et al[55] compared the QEEG at the scalp and at the sources of subjects with ADHD-C with those of subjects with ADHD-C and ODD in order to identify possible electrophysiological biomarkers able to differentiate the 2 groups.

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 the 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.[56] 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,[57] inferential reasoning,[58] decision making.[59] These functions are impaired in children with ADHD_C.[37,38] These 2 groups of children that have ADHD-C in common, 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.

Figure 2 shows the brain regions selected as biomarkers by the classification procedure.[60] 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 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 significantly present. Many researches support that the main disorders associated with dysregulated OFC connectivity/circuitry are related with decision making, emotion regulation, and reward expectation.[61-63] 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.[64-66] 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.[67] 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.

ADHD and Pharmacotherapy

Recent evidence indicates that quantitative EEG is a powerful tool in pharmaco-EEG applications. The identification of treatment responsive QEEG subtypes has been described in depression,[68,69] obsessive-compulsive disorder,[70] and schizophrenia,[71] suggesting that understanding of the underlying neurophysiology of the patient can contribute significantly to treatment optimization. QEEG has been shown to distinguish between ADHD responders (R) and nonresponders (NR) to stimulant medication with sensitivity levels that fell between 68.7% and 81% with response to stimulants related to ADHD subtypes based on QEEG profile differences.[42,72] Another class of drugs used in ADHD is a selective inhibitor of norepinephrine transporters (SNRI), atomoxetine (ATX). Barry et al[54,73] investigated the effects of a single dose of ATX, on the EEG and performance of children with ADHD. After 1 hour, ATX produced significant global increases in absolute and relative beta, with several topographic changes in other bands. This was accompanied by a significant reduction in omission errors on a continuous performance task. The authors concluded that SNRIs can produce substantial normalization of the ADHD profile, together with behavioral performance improvements. Recently, Chiarenza et al[74] have reported the quantitative EEG characteristics of responders and nonresponders to long-term treatment with ATX in children with ADHDs. The subjects were classified as responders (R) and nonresponders (NR) based on an increase/decrease of SNAP (Swanson, Nolan, and Pelham–IV Questionnaire) *z* scores values between baseline and each of the time points (treatment). Subjects with a 30% increase or greater in SNAP scores were classified as responders. Subjects with a decrease of 30% or more in SNAP scores were called nonresponders. Figure 3 presents color coded head maps of *Z*-absolute power (compared with database of normal children) separately for the R and NR groups at baseline, 6 months, and 12 months following treatment. The effects of therapy are clearly visible at 6 months when R are compared with NR. Differences between R and NR were seen at baseline: The R show greater activity in the right prefrontal and frontal regions compared with the NR in the delta band. Theta activity is greater in the NR in the left temporal and parietal areas. The NR had greater alpha absolute power in central and left temporo-parietal and occipital regions bilaterally. Absolute power in the beta band especially in the posterior regions is higher in

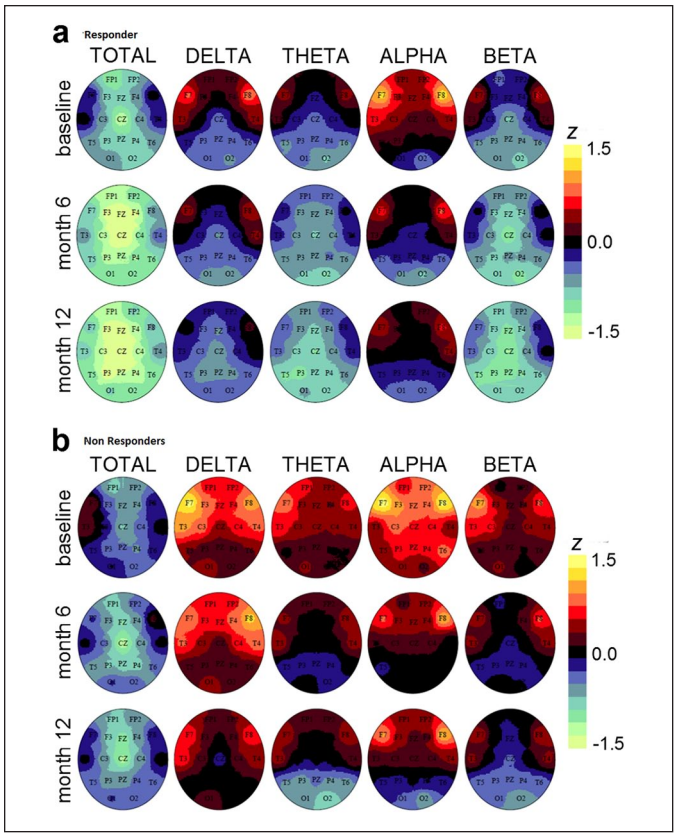


Figure 3. Average *Z*-score maps of absolute power for the delta, theta, alpha, and beta frequency bands of the responders (a) and nonresponders (b) at baseline, 6 months, and 12 months. *Z*-scores are relative to the normal population with statistical significance at the $P = .01$ level equal to a *Z*-score of $1.96/\sqrt{N}$. Age-dependent *z* score spectra of the EEG at the sources were used in this study. The *z* scores were calculated using the Nxlink data and software.

the NR. At 12 months of therapy, the R show a normalization of absolute power in all frequency bands while the NR maintain the excess of activity in all frequency bands except the alpha band. The differences between R and NR at 12 months were highly significant especially in the delta band posteriorly, the theta band centrally and the beta band anteriorly. Source localization proved also useful by indicating the cortical structures which show abnormal function in children with ADHD. ATX responders showed increased activation in right middle, superior, and inferior temporal gyrus, right insula, pre- and postcentral gyrus, supramarginal gyrus, middle frontal gyrus, posterior cingulate region, angular gyrus, medial frontal gyrus, and superior parietal lobe. This increased activation decreased after 6 and 12 months of ATX. Nonresponders to ATX showed increased activation in right medial, inferior, and superior temporal gyrus, pre- and postcentral gyrus, left inferior frontal gyrus, supramarginal gyrus, left medial frontal gyrus, the angular gyrus. This increased activation remained constant despite 12 months of treatment with ATX. The reduced activation remained the same in the occipito-temporal gyrus and the cerebellum. Similar findings have been reported with different

techniques supporting the evidence that these cerebral areas are involved in the pathophysiology of ADHD.[40] The analysis of sources localization shows that at baseline the brain regions that show an excess of beta activity are the same in R and in NR. This might suggest that subjects with ADHD-C both R and NR share the same structural organization. What distinguishes the R from NR is the functional organization as it appears by absolute power spectra. The NR continued to have an excess of beta activity and an excess of delta and theta activity.

Case Studies

QEEG is also a useful tool to validate medication efficacy on a case by case basis using prescriptive databases that enable to "predict" the likelihood of yielding a therapeutic effect (either positive or negative). A 9.6-year-old girl was diagnosed with a severe ADHD-C with moderate mental retardation of genetic nature. Her full IQ was 44 measured with WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence–III) when she was 7 years old. Before therapy, the *DSM-IV* Conners teacher rating scale,[75] for inattention and for hyperactivity and impulsivity were above 90. The z scores absolute power maps showed an excess of delta and theta activity, reduced alfa in the posterior regions, significant asymmetry (left > right) on the central and temporal areas in the delta, theta and alpha bands and a significant hypercoherence in the prefrontal and occipital regions. The discriminant scores were suggestive of ADHD ($P < .0025$). One of the EEG characteristics commonly present in ADHD include increased theta, particularly in frontal regions, and decreased or increased beta, particularly in posterior regions of the brain.[76-79] The majority of the literature suggests that acute administration of stimulants in patients with ADHD produce global EEG shifts toward normalization of EEG patterns characterized by increased beta and decreased slow waves.[80,81] Lubar et al[82] have also reported other acute positive effects following stimulant medication on other EEG measures, such as phase, coherence, and symmetry, suggesting improvement in cortical communication. Those who respond positively to stimulants treatment have also corresponding improvements in cognition.[83] Stimulants have been shown to reduce certain risk-prone behaviors,[84] enhance working memory in children[85] and adults,[86] and improve inhibitory control, performance accuracy and intellectual function.[87,88] Another important clinical sign of this subject was her mental retardation. EEG abnormalities in subjects with intellectual disability with a frequency ranging from 23% to 50% depending on the degree of severity of mental retardation is found quite frequently. These abnormalities have been found mainly in the frontal and left temporal cortex.[89] In subjects with fragile X syndrome (FXS), Van der Molen and Van der Molen[90] have reported significantly higher mean relative theta power and mean upper alpha power significantly lower in FXS than in controls. Therefore, based on the evidences reported in the literature,[91] despite the understandable initial resistance of parents and of the attending physician to accept and initiate drug therapy, the objective evidence reported by the QEEG and the Conners rating scales recommended the use of methylphenidate as a first-choice drug. After 3 months of treatment with methylphenidate hydrochloride (20 mg/d), the absolute power in the delta band was normalized and the excess of theta was restricted only to frontal areas. The asymmetry in the delta, theta, and alpha bands was not anymore present as well as the hypercoherence in the delta and theta band in the posterior regions (Figure 4). The patient's discriminant scores of the QEEG were not anymore indicative of ADHD but suggested the presence of abnormal features. The features making the largest contribution to this classification were: bipolar relative power for F7-T3 at combined frequencies and bipolar coherence for C3-Cz and C4-Cz at theta frequency. These features, as reported above, could be related to her mental retardation. After treatment, the Conners teacher rating scale showed that the oppositional behavior and perfectionism were within normal limits, her cognitive and attentional problems and hyperactivity were of borderline values (Table 1).

The 3-month follow-up of the QEEG and of the Conners rating scales confirmed the correctness of the pharmacological indication with stimulants and its continuation.

QEEG and Diagnostic Confirmation

The new techniques of EEG sources localization (sLORETA,[92] VARETA[15]) has given a new impulse to neuropsychological studies as it allows to associate clinical symptoms with possible dysregulation of brain rhythms. FL is a 14-year-old boy sent by teachers for a suspect of specific learning disabilities. All the clinical and neuropsychological tests were in the normal range except for the presence of micrography, which was orthographically correct but making the text almost illegible. The current source density analysis showed an hypoactivation at 3.5 Hz. The 3D sources localization (sLORETA) showed that the most probable sources with minimum value (z score = −3.9) were located at temporal lobe, fusiform gyrus, Brodmann area 37 bilaterally. In addition, an hyperactivation at 11.7 Hz was observed: the most probable sources with maximum value (z score = 4.8) were located at frontal lobe, paracentral lobule, Brodmann area 5 (Figure 5).

It is well known that BA37 is involved in associations of words with visual percepts. It is involved in some aspects of reading (eg, single letter processing and orthography-phonology link), because of visual-language associations. Disturbances in drawing (constructional apraxia or simply visuo-constructive disorder) are observed in cases of right hemisphere pathology, and according to fMRI studies, drawing activates right Brodmann area 37. The Brodmann area 5, the superior parietal lobe, is part of the sensory-motor associative cortex and is clearly involved in the visuo-spatial processing and spatial images. It could therefore be proposed that the dysregulation of these two areas could play a role for the micrography. Currently, the EEG source localization technique is being used not only as diagnostic tool but also as therapeutic one Recently the z score

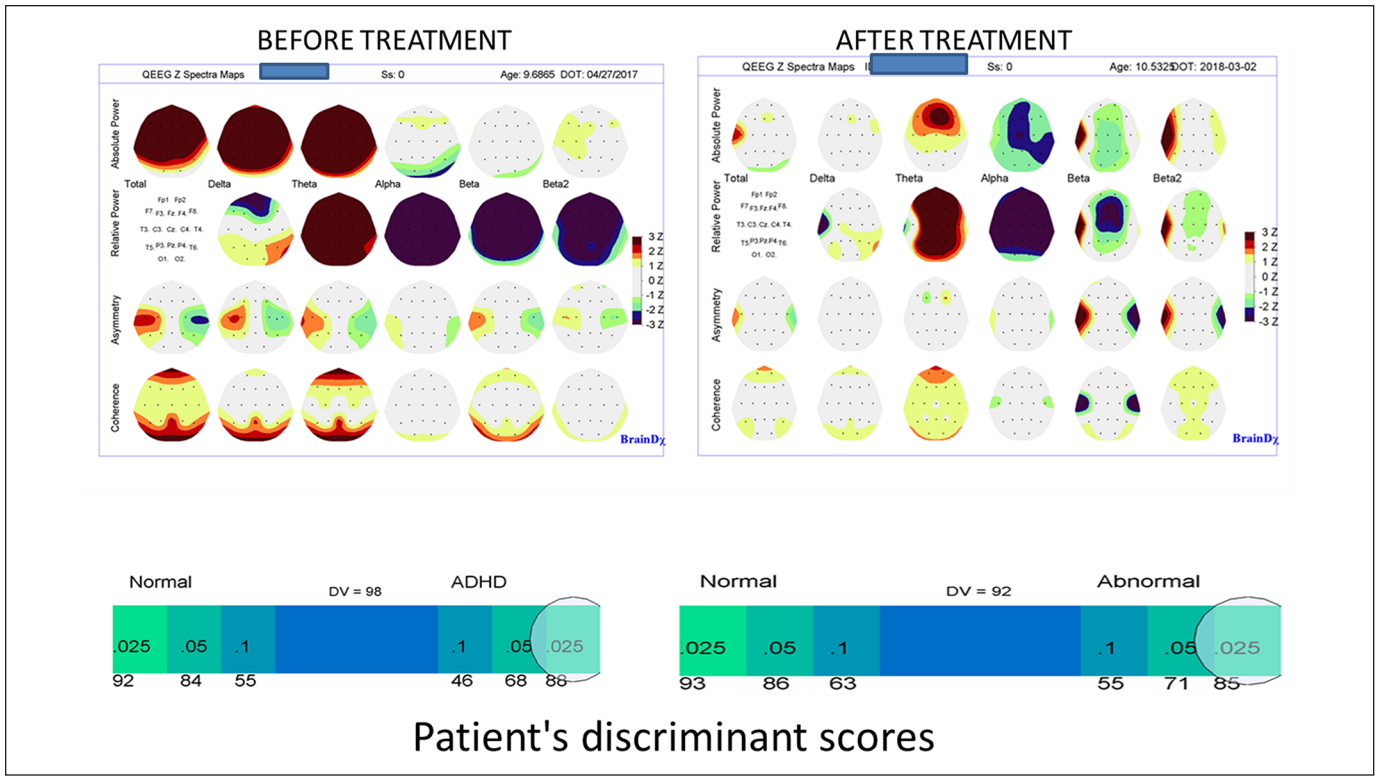


Figure 4. *Z*-score maps of absolute power, relative power, asymmetry and coherence for the delta, theta, alpha, and beta frequency bands and the discriminant score before and after treatment to methylphenidate hydrochloride 20 mg. Age-dependent z-score spectra of the EEG at the sources were used in this study. The z scores were calculated using the Nxlink data and software.

Table 1. Results of the Conners teachers' rating scale before and after treatment to methylphenidate hydrochloride 20 mg.

Conners teachers' scale scores	Before treatment (*T* values)[a]	After treatment (*T* values)[a]
Oppositional	74	46
Cognitive/attention problems	75	56
Hyperactivity	90	66
Anxious/shy	82	86
Perfectionism	58	43
Social problems	88	59
ADHD Conners Index	90	80
DSM-IV: Attention	90	77
DSM-IV: Hyperactivity/impulsivity	90	60
DSM-IV: Total	90	74

Abbreviations: ADHD, attention deficit hyperactivity disorder; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.
[a]*T* values: <55, not significant; 55-64, borderline; 65-69, significant; >70, highly significant.

sLORETA has been used to target the brain regions for neurofeedback training in depressed patients.[93]

In conclusion, using QEEG features, including age regression, clear abnormalities can be seen in all of the developmental disorders studied. Distinctive patterns of abnormalities can be seen in different diagnostic groups. The possibility to discriminate between different groups and normal with high sensitivity and specificity could help solve the problem of various comorbidities in a complex syndrome such as ADHD. The possibility to improve the neurophysiological typing of ADHD and the response to drugs could facilitate the identification of safer drugs and to monitor their therapeutic effects in the long term. Last but not least, QEEG may improve scientific knowledge of neurodevelopmental disorders.

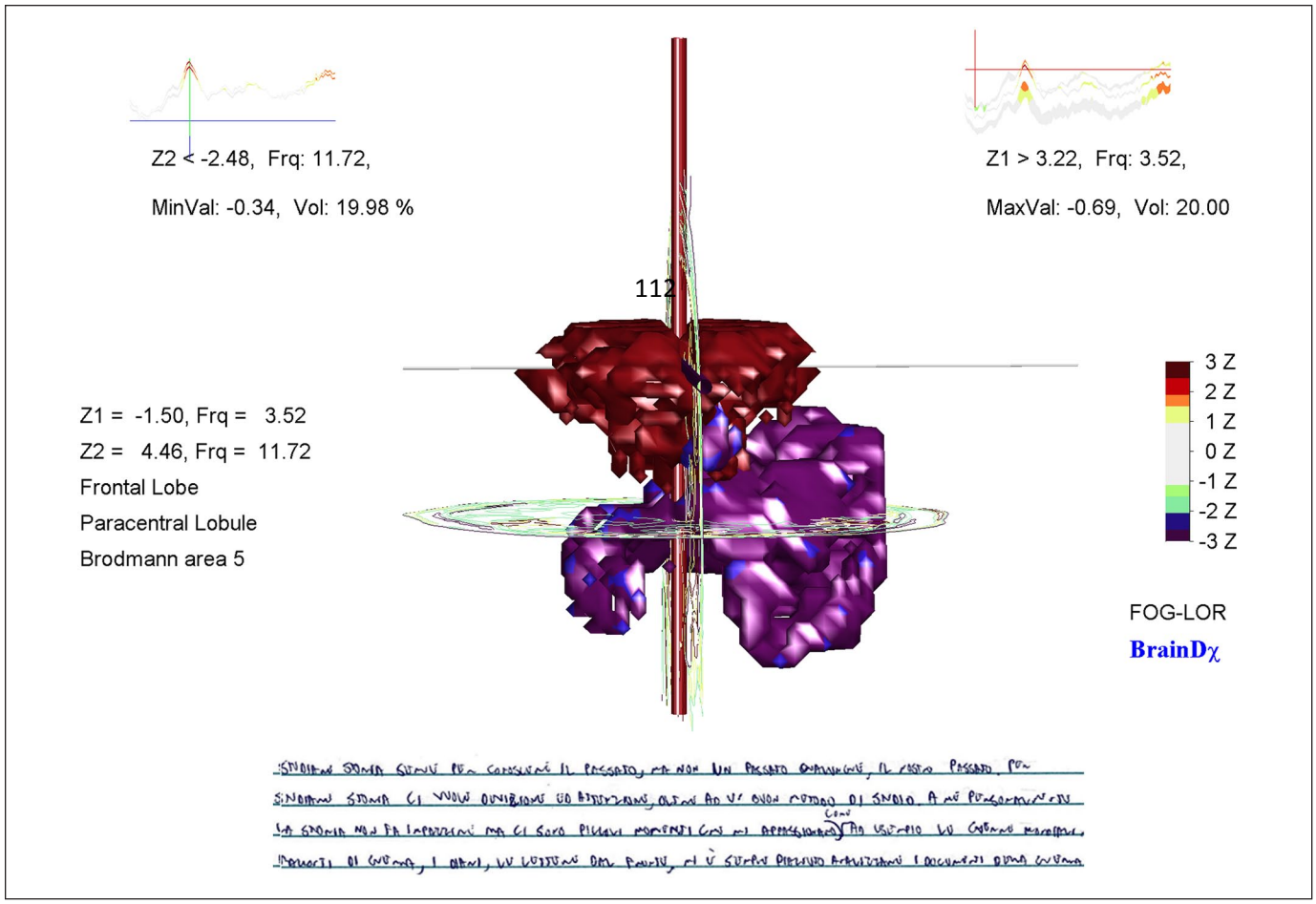


Figure 5. Volumetric 3-dimensional LORETA (standard low-resolution brain electrotomography) images and the writing of the subject. The current source density analysis showed an hypoactivation at 3.5 Hz. The 3D sources localization (sLORETA) showed that the most probable sources with minimum value (blue colors) (z score = −3.9) were located at temporal lobe, fusiform gyrus, Brodmann area 37 bilaterally. In addition, an hyperactivation at 11.7 Hz was observed: the most probable sources with maximum value (red color) (z score = 4.8) were located at frontal lobe, paracentral lobule, Brodmann area 5. Vol, volume; Frq, frequencies; Z1 and Z2, z scores. Age-dependent z-score spectra of the EEG at the sources were used in this study. The z scores were calculated using the Braindx data and software.

Appendix

EEG Data Acquisition and Analysis

The EEG was recorded at 19 leads of the 1020 International Positioning System (S10-20), using Electro-caps referenced to linked earlobes. Twenty minutes of eyes closed resting EEG were recorded. A differential eye channel (diagonally placed above and below the eye orbit) was used for detection of eye movements. All electrode impedances were <5000 ohm. The EEG amplifiers were set to a bandpass from 0.5 to 70 Hz (3 dB points). All EEG data were collected on the same digital system to achieve amplifier equivalence. Data were sampled at a rate of 256 Hz with 12-bit resolution. All the patients were recorded in the morning and instructed to keep their eyes closed and stay awake. This allowed to control for drowsiness during EEG recordings and to guarantee similar conditions throughout the different sessions. The technician was also aware of the subject's state to avoid drowsiness. Additionally, patients were monitored with a closed-circuit television system, during the recording.

The author visually edited the raw EEG data to select EEG epochs free of either biological (eg, muscle movement, EMG) as well as nonbiological (eg, electrical noise in the room) artifacts. This was augmented by a computerized artifact detection algorithm. A minimum of 30 epochs of 2.56 minutes (256 time points, since the sampling rate was 100 Hz) of artifact-free data were selected for each subject and submitted to frequency analysis. The EEG spectra were calculated using the high-resolution spectral (HRS) model[92,94] for all the channels by means of the fast Fourier transform (FFT), in a frequency range from 0.39 to 9.11 Hz, with a frequency resolution of 0.39 Hz. The selection of these frequency parameters was made on the basis that they match the available parameters from the Cuban Normative Database[95] to transform the raw EEG spectra into *Z*-probabilistic measurements, age corrected. The spectra were log-transformed, to approach them to Gaussianity[96,97] and the *Z*-transform was calculated against the Cuban Normative Database. Significant test-retest reliability for these measures has been demonstrated.[18,98,99]

To obtain the raw spectra at the EEG generators, the variable resolution electrical tomography (VARETA) method[15] was used for the source localization analysis. Same as with the spectra at the electrodes, the source density localization analysis was performed for frequencies between 0.39 and 19.11 Hz and for all the sources in the cerebral cortex for a grid of 3244 sources. VARETA is an already known technique for estimating the distribution of the primary current in the source generators of EEG data. VARETA is a discrete spline distributed solution, like LORETA.[92] This technique was used in all the studies reported above except for the 2 case reports where the LORETA technique was applied. For more details about these techniques, please read Bosch-Bayard et al[15,25] and Pascual-Marqui.[92]

Acknowledgments

I wish to acknowledge Dr Jorge Bosch- Bayard for his contribution in preparing some responses of the referees with regard to methodological questions and the referees for their comments for improving the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. John ER. Neurometric evaluation of brain function related to learning disorders. *Acta Neurol Scand*. 1981;64:87-100.
2. Prichep LS, Mas F, Hollander E, et al. Quantitative electroencephalographic subtyping of obsessive compulsive disorder. *Psychiatry Res*. 1993;50:25-32.
3. Wolraich ML, Hagan JF, Allan C, et al; Subcommittee on Children and Adolescents with Attention-Deficit/Hyperactive Disorder. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents of the American Academy of Pediatrics. *Pediatrics*. 2019;144:e20192528.
4. Quintana H, Snyder SM, Purnell W, Aponte C, Sita J. Comparison of a standard psychiatric evaluation to rating scales and EEG in the differential diagnosis of attention-deficit/hyperactivity disorder. *Psychiatry Res*. 2007;152:211-222.
5. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: scales assessing attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2003;42:1015-1037.
6. Chabot RJ, Merkin H, Wood LM, Davenport TL, Serfontein G. Sensitivity and specificity of qEEG in children with attention deficit or specific developmental learning disorders. *Clin Electroencephalogr*. 1996;27:26-34.
7. Chabot RJ, Serfontein G. Quantitative electroencephalographic profiles of children with attention deficit disorder. *Biol Psychiatry*. 1996;40:951-963.
8. Clarke AR, Barry RJ, McCarthy R, Selikowitz M, Brown CR. EEG evidence for a new conceptualisation of attention deficit hyperactivity disorder. *J Clin Neurophysiol*. 2002;113:1036-1044.
9. Kovatchev B, Cox D, Hill R, Reeve R, Robeva R, Loboschefski TA. psychophysiological marker of attention deficit/hyperactivity disorder (ADHD) defining the EEG consistency index. *Appl Psychophysiol Biofeedback*. 2001;26:127-140.
10. Mann CA, Lubar JF, Zimmerman AW, Miller CA, Muenchen RA. Quantitative analysis of EEG in boys with attention- deficit–hyperactivity disorder: controlled study with clinical implications. *Pediatr Neurol*. 1992;8:30-36.
11. Monastra VJ, Lubar JF, Linden M, et al. Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: an initial validation study. *Neuropsychology*. 1999;13:424-433.
12. Monastra VJ, Lubar JF, Linden M.The development of a quantitative electroencephalographic scanning process for attention deficit hyperactivity disorder: reliability and validity studies. *Neuropsychology*. 2001;15:136-144.
13. Arns M, Conners CK, Kraemer HC. A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *J Atten Disord*. 2013;(5):374-383. doi:10.1177/1087054712460087
14. Ogrim G, Kropotov J, Hestad K. The quantitative EEG theta/beta ratio in attention deficit/hyperactivity disorder and normal controls: sensitivity, specificity, and behavioral correlates. *Psychiatry Res*. 2012;198:482-488. doi:10.1016/j.psychres.2011.12.041
15. Bosch-Bayard J, Valdes-Sosa P, Virues-Alba T, et al. 3D statistical parametric mapping of EEG source spectra by means of variable resolution electromagnetic tomography (VARETA). *Clin Electroencephalogr*. 2001;32:47-61.
16. Boder E, Jarrico S. *The Boder Test of Reading-Spelling Patterns*. Grune & Stratton; 1982.
17. Duffy FH, Denckla MB, Bartels PH, Sandini G, Kiessling LS. Dyslexia: automated diagnosis by computerized classification of brain electrical activity. *Ann Neurol*. 1980;7:421-428.
18. John ER, Prichep LS, Ahn H, Easton P, Fridman J, Kaye H. Neurometric evaluation of cognitive dysfunctions and neurological disorders in children. *Prog Neurobiol*. 1983;21:239-290.
19. Flynn J, Deering W. Subtypes of dyslexia: Investigation of Boder's system using quantitative neurophysiology. *Dev Med Child Neurol*. 1989;31:215-223.
20. Flynn J, Deering W, Goldstein M, Rahbar MH. Electrophysiological correlates of dyslexic subtypes. *J Learn Disabil*. 1992;28:133-141.
21. Boder E. Developmental dyslexia: a diagnostic approach based on three typical reading-spelling patterns. *Dev Med Child Neurol*. 1973;15:663-687.
22. Casarotto S, Ricciardi E, Sani L, Guazzelli M, Pietrini P, Chiarenza GA. Single-letter reading elicits a different spatio-temporal modulation of brain activity in dyslexic children as compared to healthy controls. *Neuroimage*. 2007. https://www.semanticscholar.org/paper/Single-letter-reading-elicits-a-different-of-brain-Casarotto-Ricciardi/fa48c19ca52c660e82470e2ffea71cf03f738fba
23. Chiarenza GA. Normal and abnormal reading processes in children. *Neuropsychophysiol Stud*. 2017;10017:235-249.
24. Velikova S, Chiarenza GA. EEG correlates of clinical subtypes of developmental dyslexia: independent component analysis study. *Int J Psychophysiol*. 2012;3:322.
25. Bosch-Bayard J, Peluso V, Galan L, Valdes Sosa P, Chiarenza GA. Clinical and electrophysiological differences between subjects with dysphonetic dyslexia and non-specific reading delay. *Brain Sci*. 2018;8:172.

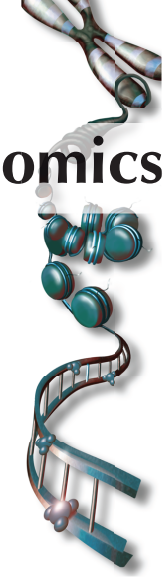
26. Galaburda AM. Neurology of developmental dyslexia. *Curr Opin Neurobiol*. 1993;3:237-242.
27. Shaywitz SE, Shaywitz BA, Pugh KR, et al. Functional disruption in the organization of the brain for reading in dyslexia. *Proc Natl Acad Sci USA*. 1998;95:2636-2641.
28. Wolff PH, Melngailis I, Kotwica K. Impaired motor timing control in specific reading retardation. *Neuropsychologia*. 1984;22: 587-600.
29. Wolff PH, Michel G, Ovrut M. The timing of syllables repetitions in developmental dyslexia. *J Speech Hear Res*. 1990;33:281-289.
30. Chiarenza GA, Papakostopoulos D, Guareschi-Cazzullo A, Giordana F, Giammari Aldè G. Movement related brain macropotentials during skilled performance task in children with learning disabilities. In: Chiarenza GA, Papakostopoulos D, eds. *Clinical Application of Cerebral Evoked Potentials in Pediatric Medicine*. Excerpta Medica; 1982:259-292.
31. Chiarenza GA. Motor-perceptual function in children with developmental reading disorders: neuropsychophysiological analysis. *J Learn Disabil*. 1990;23:375-385.
32. Llinas R. Is dyslexia a dyschronia? *Ann NY Acad Sci*. 1993;682: 48-56.
33. Hamilton SS, Armando J. Oppositional defiant disorder. *Am Fam Physician*. 2008;78:861-866.
34. Loeber R, Burke JD, Lahey BB, Winters A, Zera M. Oppositional defiant and conduct disorder: a review of the past 10 years. Part I. *J Am Acad Child Adolesc Psychiatry*. 2000;39:1468-1484.
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
36. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA cooperative group multimodal treatment study of children with ADHD. *Arch Gen Psychiatry*. 1999;56:1073-1086.
37. Barkley RA. *ADHD and the Nature of Self-Control*. The Guilford Press; 1997.
38. Barkley RA. Attention-deficit/hyperactivity disorder, self-regulation and time: toward a more comprehensive theory. *Dev Behav Pediatr*. 1997b;18:271-279.
39. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull*. 1997c;121:65-94.
40. Barkley RA. *Attention-Deficit/Hyperactivity Disorder. A Handbook for Diagnosis and Treatment*. The Guilford Press; 2006.
41. Cortese S, Kelly C, Chabernaud C, et al. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am J Psychiatry*. 2012;169:1038-1055.
42. di Michele F, Prichep LS, John ER, Chabot RJ. The neurophysiology of attention-deficit/hyperactivity disorder. *Int J Psychophysiol*. 2005;58:81-93.
43. Castellanos FX, Giedd JN, Marsh WL, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch of Gen Psych*. 1996;53:607-616.
44. Lou HC, Henriksen L, Bruhn P, Borner H, Nielsen JB. Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch Neurol*. 1989;46:48-52.
45. Rubia K, Halari R, Cubillo A, Mohammed AM, Brammer M, Taylor E. Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-nave boys with attention-deficit hyperactivity disorder. *Neuropsychopharmacology*. 2011;36:1575-1586.
46. Hastings J, Barkley RA. A review of psychophysiological research with hyperactive children. *J Abnorm Child Psychol*. 1978;7:413-337.
47. Klorman R. Cognitive event-related potentials in attention deficit disorder. In: Shaywitz SE, Shaywitz BA, eds. *Attention Deficit Disorder Comes of Age: Toward the Twenty-First Century*. PRO-ED; 1992:221-244.
48. Taylor EA. *The Overactive Child*. J P Lippincott; 1986.
49. Chabot RJ, di Michele F, Prichep LS, John ER. The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents. *J Neuropsychiatry Clin Neurosci*. 2001;13:171-186.
50. Clarke AR, Barry RJ, McCarthy R, Selikowitz M. Excess beta in children with attention-deficit/hyperactivity disorder: an atypical electrophysiological group. *Psychiatry Res*. 2001a;103:205-218.
51. Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electro- encephalography. *Clin Neurophysiol*. 2003;114:171-183.
52. Chabot RJ, di Michele F, Prichep LS, John ER. The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents. *J Neuropsychiatry Clin Neurosci*. 2001;13:171-186.
53. Chabot RJ, Coben R, Hirshberg L, Cantor DS. QEEG and VARETA based neurophysiological indices of brain dysfunction in attention deficit and autistic spectrum disorder. *Austin J Autism Relat Disabilities*. 2015;1:1007.
54. Barry RJ, Clarke AR. Spontaneous EEG oscillations in children, adolescents, and adults typical development, and pathological aspects in relation to AD/HD. *J Psychophysiol*. 2009;23:157-173.
55. Chiarenza GA, Villa S, Galan L, Valdes-Sosa P, Bosch-Bayard J. 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. *Int J Psychophysiol*. 2018;130:9-20.
56. Chabot RJ, Orgill AA, Crawford G, Harris MJ, Serfontein G. Behavioral and electrophysiologic predictors of treatment response to stimulants in children with attention disorders. *J Child Neurol*. 1999;14:343-351.
57. Kübler A, Dixon V, Garavan H. Automaticity and reestablishment of executive control-an fMRI study. *J Cogn Neurosci*. 2006;8:1331-1342.
58. Goel V, Gold B, Kapur S, Houle S. The seats of reason? An imaging study of deductive and inductive reasoning. *Neuroreport*. 1997;8:1305-1310.
59. Rogers RD, Owen AM, Middleton HC, et al. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *J Neurosci*. 1999;19:9029-9038.
60. Bosch-Bayard J, Galán-García L, Fernandez T, et al. Stable sparse classifiers identify qEEG signatures that predict learning disabilities (NOS) severity. *Front Neurosci*. 2018;11:749. doi:10.3389/fnins.2017.00749
61. Paulus MP, Hozack NE, Zauscher BE, et al. Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology*. 2002;26:53-63.
62. Toplak ME, Jain U, Tannock R. Executive and motivational processes in adolescents with attention-deficit-hyperactivity disorder (ADHD). *Behav Brain Funct*. 2005;1:8-20.

63. Verdejo-Garcia A, Bechara A, Recknor EC, Perez-Garcia M. Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *J Int Neuropsychol Soc*. 2006;12:405-415.
64. Ernst M, Nelson EE, McClure EB, et al. Choice selection and reward anticipation: an fMRI study. *Neuropsychologia*. 2004;42:1585-1597.
65. Kringelbach ML. The orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci*. 2005;6:691-702.
66. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbi-tofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol*. 2004;72:341-372.
67. Schoenbaum G, Takahashi Y, Liu T, McDannald M. Does the orbitofrontal cortex signal value? *Ann N Y Acad Sci*. 2011;1239:87-99.
68. Leuchter AF, Cook IA, Gilmer WS, et al. Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in major depressive disorder. *Psychiatry Res*. 2009a;169:132-138.
69. Leuchter AF, Cook I, Marangell L, et al. Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in major depressive disorder: results of the BRITE-MD study. *Psychiatry Res*. 2009b;169:124-131.
70. Prichep LS, Mas F, Hollander E, et al. Quantitative electroencephalographic subtyping of obsessive-compulsive disorder. *Psychiatry Res*. 1993;50:25-32. [TNJ: Repeated. Same as reference no. 2.]
71. John ER, Prichep LS, Wintere G, et al. Electrophysiological subtypes of psychotic states. *Acta Psychiatr Scand*. 2007;116:17-35.
72. Ogrim G, Kropotov J, Brunner JF, Candrian G, Sandvik L, Hestad KA. Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder: data from quantitative electroencephalography, event related potentials, and a go/no-go test. *Neuropsychiatr Dis Treat*. 2014;10:231-242.
73. Barry RJ, Clarke AR, Hajos M, McCarthy R, Selikowitz M, Bruggemann JM. Acute atomoxetine effects on the EEG of children with attention-deficit/hyperactivity disorder. *Neuropsychol Rev*. 2007;17:61-72.
74. Chiarenza GA, Chabot R, Isenhart R, et al. The quantitative EEG characteristics of responders and non-responders to long term treatment with atomoxetine in children with attention deficit hyperactive disorders. *Int J Psychophysiol*. 2016;104:44-52.
75. Conners CK. *Conners' Rating Scales-Revised, Technical Manual*. MultiHealth Systems Inc; 1997.
76. Arns M, Gunkleman J, Breteler M, Spronk D. EEG phenotypes predict treatment outcome to stimulants in children with ADHD. *J Integr Neurosci*. 2008;7:421-438.
77. Clarke A, Barry R, McCarthy R, Selikowitz M. EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. *Clin Neurophysiol*. 2001b;112:2098-2105.
78. Clarke A, Barry R, McCarthy R, Selikowitz M, Clarke D, Croft R. Effects of stimulant medications on children with attention-deficit/hyperactivity disorder and excessive beta activity in their EEG. *Clin Neurophysiol*. 2003;114:1729-1737.
79. Clarke A, Barry R, McCarthy R, Selikowitz M, Johnstone S. Effects of stimulant medications on the EEG of girls with attention-deficit/hyperactivity disorder. *Clin Neurophysiol*. 2007;118:2700-2708.
80. Goforth HW, Konopka LM, Primeau M, et al. Quantitative electroencephalography in frontotemporal dementia with methylphenidate response: a case study. *Clin EEG Neursci*. 2004;35:108-111.
81. Song DH, Shin DW, Jon DI, Ha EH. Effects of methylphenidate on quantitative EEG of boys with attention-deficit/hyperactivity disorder in continuous performance test. *Yonsei Med J*. 2005;46:34-41.
82. Lubar JF, White JN, Swartwood MO, Swartwood JN. Methylphenidate effects on global and complex measures of EEG. *Pediatr Neurol*. 1999;21:633-637.
83. Loo SK, Teale PD, Reite ML. EEG correlates of methylphenidate response among children with ADHD: a preliminary report. *Biol Psychiatry*. 1999;45:1657-1660.
84. De Vito EE, Blackwell AD, Kent L, et al. The effects of methylphenidate on decision making in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2008;64:636-639.
85. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbin TW. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. *J Neurosci*. 2000b;20:RC65.
86. Mehta MA, Calloway P, Sahakian BJ. Amelioration of specific working memory deficits by methylphenidate in a case of adult attention deficit/hyperactivity disorder. *J Psychopharmacol*. 2000a;14:299-302.
87. Berman T, Douglas VI, Barr RG. Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. *J Abnorm Psychol*. 1999;108:90-105.
88. Nazari MA, Querne L, De Broca A, Berquin P. Effectiveness of EEG biofeedback as compared with methylphenidate in the treatment of attention-deficit/hyperactivity disorder: a clinical outcome study. *Neurosci Med*. 2011;2:78-86.
89. Unal O, Ozcan O, Oner O, Akcakin M, Aysev A, Deda G. EEG and MRI findings and their relation with intellectual disability in pervasive developmental disorders. *World J Pediatr*. 2009;5:196-200.
90. Van der Molen MJW, Van der Molen MW. Reduced alpha and exaggerated theta power during the resting-state EEG in fragile X syndrome. *Biol Psychol*. 2013;92:216-219.
91. Konopka LMM, Zimmerman EM. Neurofeedback and psychopharmacology. designing effective treatment based on cognitive and EEG effects of medications. In: Cantor ED, Evans JR, eds. *Clinical Neurotherapy. Application of Techniques for Treatment*. Elsevier; 2014.
92. Pascual-Marqui RD, Valdes-Sosa PA, Alvarez-Amador A. A parametric model for multichannel EEG spectra. *Int J Neurosci*. 1998;40:89-99.
93. Kaur C, Singh P, Sahni S, Punia C. Advanced spatially specific neurofeedback for symptoms of depression and its electroencephalographic correlates. *Altern Ther Health Med*. 2019;25:54-63.
94. Valdes-Sosa P, Biscay-Lirio R, Galán-García L, Bosch-Bayard J, Szava S, Virues-Alba T. High resolution spectral EEG norms for topography. *Brain Topogr*. 1990;3:281-282.
95. Szava S, Valdes P, Biscay R, Galan L, Bosch J, Clark I, Jimenez JC. High resolution quantitative EEG analysis. *Brain Topogr*. 1993;6:211-219.
96. John ER, Ahn H, Prichep LS, Trepetin M, Brown D, Kaye H. Developmental equations for the electroencephalogram. *Science*. 1980;210:1255-1258.
97. Gasser T, Bacher P, Mochs J. Transformation towards the normal distribution of broadband spectral parameters of the EEG. *EEG Clin Neurophysiol*. 1982;53:119-124.
98. John ER, Prichep LS, Friedman J, Easton P. Neurometrics: computer-assisted differential diagnosis of brain dysfunctions. *Science*. 1988;293:162-169.
99. Kondacs A, Szabo M. Long-term intra-individual variability of the background EEG in normals. *Clin Neurophysiol*. 1999;110:1708-1716.

Short Communication

For reprint orders, please contact: reprints@futuremedicine.com

Epigenomics



Genetic and epigenetic *MTHFR* gene variants in the mothers of attention-deficit/hyperactivity disorder affected children as possible risk factors for neurodevelopmental disorders

Ignazio Stefano Piras[1], Anna Costa[2], Maria Cristina Tirindelli[3], Andrea Stoccoro[4], Matthew J Huentelman[1], Roberto Sacco[2], Fabio Coppedè[4] & Carla Lintas*[,2]

[1]Neurogenomics Division, Translational Genomics Research Institute, Phoenix, AZ 85004, USA

[2]Service for Neurodevelopmental Disorders, University Campus Bio-Medico, Rome, Italy

[3]Hematology Transfusion Medicine, University Campus Bio-Medico, Rome, Italy

[4]Medical Genetics Laboratory, Department of Translational Research & New Technologies in Medicine & Surgery, University of Pisa, Pisa, Italy

*Author for correspondence: Tel.: +39 06 2254 19174; c.lintas@unicampus.it

Aim: To assess promoter methylation levels, gene expression levels and 677C>T/1298A>C genotype and allele frequencies of the *MTHFR* gene in 45 mothers of attention-deficit/hyperactivity disorder affected child/children (ADHDM) and compare it with age matched healthy control mothers (HCM). **Materials & methods**: High resolution melting analysis, quantitative real time PCR and PCR-RFLP were performed to assess methylation, gene expression and genotyping, respectively. Significance between ADHDM and HCM was assessed by linear (methylation and gene expression) and logistic regression (genotypes). **Results:** *MTHFR* gene expression levels were significantly higher in the ADHDM compared with the HCM group (adj-p < 7.7E-04). No differences in *MTHFR* promoter methylation level and 677C>T/1298A>C genotype frequencies were detected between ADHDM and HCM. **Conclusion:** We observed increased *MTHFR* expression levels not resulting from promoter methylation changes in ADHDM respect to HMC, potentially contributing to the ADHD condition in their children and deserving further investigation.

First draft submitted: 22 November 2019; Accepted for publication: 4 March 2020; Published online: 2 June 2020

Keywords: 1298A>C polymorphism • 677C>T polymorphism • attention-deficit/hyperactivity disorder • folate deficiency during pregnancy • *MTHFR* gene promoter methylation • *MTHFR* mRNA expression • neurodevelopment • neurodevelopmental disorders

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in childhood with a mean worldwide prevalence of about 2.2% [1]. The disorder is characterized by inattentive, hyperactive and impulsive behavior [2] and is often in comorbidity with other neuropsychiatric conditions including specific learning disorder, motor disorder, intellectual disability, autism spectrum disorder, conduct disorder, anxiety disorder, oppositional defiant disorder and mood disorder [3].

Neurodevelopmental disorders are considered multifactorial diseases with both genetic and environmental component [4]. The genetic contribution is highly complex as it is based on the combination of hundreds of loci including both common and rare variants of copy number variants and single nucleotide variants [5,6].

Many environmental factors may contribute to neurodevelopmental disorders including, for example, smoking and alcohol consumption during pregnancy, delivery complications and viral injury during pregnancy and early postnatal life [7–9]. An additional well-studied environmental factor is folate supply especially during the periconceptional period and the first trimester of pregnancy [10,11]. Its deficiency has been associated with developmental anomalies as spina bifida and anencephaly [12,13] but also with less severe conditions including intellectual disabil-

Future Medicine

ity, ADHD [14] and autism spectrum disorder [15]. In adulthood, folate deficiency has been linked to dementia, schizophrenia and depression [16]. From a biological point of view folate is the main methyl donor for the conversion of homocysteine into methionine, which in turn is a precursor of *S*-adenosylmethionine, the universal methyl donor for DNA and histones, as well as for RNA, phospholipids and proteins [17,18]. Additionally, the folate cycle is also linked to other metabolic pathways relying on carbon source such as nucleic acid, neurotransmitter and aminoacid synthesis [17]. Folate and folate related pathways are regulated by many different enzymes encoded by genes whose polymorphisms have been associated with many different types of conditions and diseases [19,20]. Therefore, besides folate supply during pregnancy, also genetic and epigenetic variants in folate-pathway genes may be considered risk factors for neurodevelopmental disorders [20]. Indeed, dynamic changes in DNA methylation and biosynthesis occur following egg fertilization and continue during embryo development [21–23].

The most extensively studied gene of folate metabolism is the *MTHFR* gene encoding for methylenetetrahydrofolate reductase, an enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5′-methyltetrahydrofolate which is essential for homocysteine conversion to methionine. Both *MTHFR* 677C>T (rs1801133) and 1298A>C (rs1801131) polymorphisms have been demonstrated to reduce enzyme activity at various degrees [24,25]. The two SNPs are located in the coding region and cause the following amino acid changes: a substitution of an alanine to a valine at codon 222 for the 677C>T polymorphism and a substitution of glutamic acid to alanine at codon 429 for the 1298A>C one. The reduction in enzyme activity depends on the heterozygous/homozygous state of each SNP as well as on their combinations. The enzyme activity for the heterozygous and homozygous genotype is 67% and 25% of the wild-type and 83% and 61% of the wild-type for the 677C>T and 1298A>C, respectively. For the compound heterozygous state of both 677C>T and 1298A>C polymorphisms, enzyme activity is 48% of the wild-type genotype [24,25].

From a functional point of view, a reduction in *MTHFR* enzyme activity may adversely affect DNA methylation by causing a decrease in the synthesis of folate derivatives. Indeed, many studies have linked some *MTHFR* polymorphisms to an increased risk for many disease conditions including cardiovascular and neuronal disorders, cancer and several neuropsychiatric conditions [26–30]. Lately, other studies have also focused on *MTHFR* promoter methylation as a risk factor for several disease conditions [31–35]. Furthermore, recent evidence suggests that epigenetic dysregulation may contribute to the onset of some neurodevelopmental disorders such as autism spectrum disorder, ADHD and schizophrenia [36–39]. Since *MTHFR* is a key enzyme for methylation reactions, changes in its activity linked to the genotype and/or changes in its expression levels may influence DNA and histone methylation. These processes are crucial during fetal development when adequate maternal folate supply is mandatory for proper embryo development and subsequent offspring health. Hence maternal folate status and/or polymorphisms in folate-metabolizing genes may influence nutrient delivery to the fetus and subsequent neurodevelopment. Indeed, several studies have reported a positive association between maternal *MTHFR* polymorphisms (*MTHFR* 677 C>T and/or 1298 A>C) and adverse pregnancy outcomes (such as pre-eclampsia, placental abruption, spontaneous abortion and low birth weight), deficits in early cognitive development of their children [40] and an increased risk of autism spectrum disorder in their children [41]. These studies suggest a possible *MTHFR* maternal genetic contribution in the maternal-fetal metabolism of folate in pregnancy. Several studies have shown that the *MTHFR* 677 TT genotype is associated with reduced plasma and red cell folate concentration and with an increase in 5,10-methylenetetrahydrofolate and a decrease in 5′-methyltetrahydrofolate, the first required for nucleotide synthesis and the latter for methylation reactions [42]. The maternal to fetal transfer of folate is mediated by the placental folate receptor, which preferentially binds to 5′-methyltetrahydrofolate [43]. Hence variations in folate isoform concentration due to maternal *MTHFR* polymorphisms could affect DNA methylation and nucleotide synthesis downstream in the developing embryo.

In the light of these considerations, we hypothesize that mothers of child/children affected by ADHD (named ADHDM) may carry genetic and/or epigenetic alterations in the *MTHFR* gene compared with age matched mothers of healthy children (named HCM). Such alterations may increase the risk for ADHD in their child/children. In order to test our hypothesis, we assessed *MTHFR* promoter methylation, 677 C>T and 1298 A>C allele and genotype frequencies and gene expression levels, using DNA and RNA samples extracted from peripheral blood cells of 45 ADHDM and 45 age matched HCM.

Materials & methods

The clinical cohort

A total of 90 subjects were recruited at University Campus Bio-Medico of Rome (Italy). The subjects included 45 healthy ADHDM and 45 age matched HCM. HCM were included only if they had at least one full-term pregnancy and no child/children affected by neuropsychiatric/neurodevelopmental disorders or other disorders. Age at sampling ranged from 35–53 years and from 33–55 years in the ADHDM group and HCM group, respectively. ADHD diagnosis was assessed with standard psychodiagnostic tests including, Griffith Mental Developmental Scales [44], Child Behavior Check List [45] for parents and for teachers and Conner's Rating Scales [46]. All subjects had the same ethnicity and geographic origin. For all subjects, exclusion criteria included: smoking (they must have stopped smoking at least 6 months before blood collection to be enrolled), current use of drug knowing to interfere with DNA methylation and current use of folic acid or vitamin B supplements. The study was approved by the Ethical Committee of the University Campus Bio-Medico of Rome and patients signed the informed consent.

Blood collection & nucleic acid isolation

Peripheral blood was collected in two EDTA tubes, one for DNA and the other for RNA extraction. In order to preserve RNA integrity DNA/RNA Shield™ (Zymo Research, CA, USA) was immediately added to one blood tube. Genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, MD, USA) according to the manufacturer's protocol. RNA was extracted using the *Quick*-RNA Whole Blood Kit (Zymo Research, CA, USA) following manufacturer's instructions. ADHDM and HCM samples were treated simultaneously.

Bisulphite treatment & high resolution melting analysis

About 750 ng of genomic DNA was subjected to bisulfite conversion using the Epitect Bisulfite Kit (Qiagen, MD, USA) following manufacturer's instructions. Sodium bisulphite converts all unmethylated cytosines into uracil whereas methylated cytosines are left unchanged. PCR amplification was done in the region encompassing the 5′-UTR of the *MTHFR* gene, which contains seven CpG sites [47]. The Methylation-Sensitive High Resolution Melting method was used to quantify the mean level of methylation of each sample. Overall, 20 ng of converted DNA was used, in addition to 1× of EpiTect HRM PCR mix (Qiagen, MD, USA), ultrapure water and 1 picomole of each primer in a final volume of 20 µl. Primer sequences were the same used in previous studies [47]. PCR amplification was carried out using the 7900 HT Fast Real Time PCR System (Thermo Fisher Scientific, MA, USA) according to the following protocol: one step of denaturation at 95°C for 5 min, 40 cycles at 95°C for 30 s, 55°C for 30 s and 72°C for 30 s. The plate was immediately spinned and subjected to a high resolution melting step which consisted of a single step of 95°C for 15 s followed by temperature from 50 to 95°C using a ramp rate of 1% with holding steps of 60 and 15 s, respectively; a final step at 60°C for 15 s was done. Each assay included a negative control, unconverted genomic DNA and seven methylation standards (EpiTect PCR control DNA set, Qiagen, MD, USA) prepared by mixing fully methylated and unmethylated converted DNA in known proportions (0, 10, 20, 30, 40, 50 and 100% methylated DNA). Each sample was run in triplicate whereas methylation standards were run in duplicate. Temperature and fluorescence data relative to the melt curve of each sample and standard were exported from the SDS 2.4 software (Thermo Fisher Scientific, MA, USA) and used to derive interpolation curves. The interpolation method described elsewhere [47] was used to obtain a single mean methylation value for each sample, rather than a methylation range.

MTHFR 677C>T & 1298A>C genotyping

PCR and RFLP analysis were performed to genotype the 677C>T (rs1801133) and the 1298A>C (rs1801131) polymorphisms. For the 1298A>C position PCR conditions were: 95°C for 5 min, followed by 35 cycles 95°C for 30 s, 63°C for 30 s, 72°C for 30 s and a final step at 72°C for 7 min. PCR conditions were the same for the 677C>T position except for the annealing temperature which was set at 61°C. Both reactions were carried out in a final volume of 25 µl using 2 µl of 100 ng of genomic DNA, 2.5 µl of 10X PCR buffer, 2.5 µl of 10 mM deoxynucleotide triphosphates, 1 µl 10 µM of each primer, 1 unit of Taq polymerase (Thermo Fisher Scientific, MA, USA) and 15 µl of ultrapure water. Primer sequences were the same used in a previous study [48]. PCR products were 256 and 198 bp for position 1298 and 677, respectively. Enzymatic digestion of the PCR products was done with *Hinf*I (New England Biolab, MA, USA) for the 677C>T polymorphism and with *Mbo*II (New England Biolab, MA, USA) for the 1298A>C polymorphism. Products of digestion were analyzed by 3% agarose

10.2217/epi-2019-0356

gel. The digestion pattern for each genotype combination of 677C>T and 1298A>C polymorphisms is detailed elsewhere [48].

Gene expression analysis

RNA was retrotranscribed using the Sensiscript reverse transcription (RT) kit (Qiagen, MD, USA) according to manufacturer's instructions. All samples were reverse transcribed in duplicate and cDNA was run in triplicate to allow assessment of sample homogeneity and technical variability. ADHDM and age matched HCM samples were run in the same plate and subject simultaneously to quantify *MTHFR* and internal control *GAPDH* cDNAs. Quantification of *MTHFR* and *GAPDH* expression was performed with the Power Up SYBR Green Master Mix (Thermo Fisher Scientific, MA, USA) following manufacturer's protocol and using the 7900 HT Fast Real Time PCR System (Thermo Fisher Scientific, MA, USA). The amount of *MTHFR* mRNA was calculated using the 2-ΔΔCt method and expression value was normalized to the internal control gene *GAPDH*. We used two independent retrotranscribed cDNA reactions and two different primer pairs for *MTHFR* quantification. The first primer pair targeted the 3′UTR region and sequences were: 5′-CCTTTGCCCTGTGGATTGAG-3′ for the forward primer and 5′-TGTACTGGATGATGGTGCGG-3′ for the reverse primer. The second primer pair targeted the region between exon 18 and exon 19 and sequences were: 5′-TCCCGTCAGCTTCATGTTCT-3′ for the forward primer and 5′-TCATACAGCTTTCCCCACCG-3′ for the reverse primer. *GAPDH* primer sequences used to normalize were: 5′-ATGGAAATCCCATCACCA-3′ for the forward primer and 5′-CGCCCCACTTGATTTTGG-3′ for the reverse primer.

Statistical analysis

The relationship between expression and methylation level with status (ADHDM vs HCM) was evaluated separately using a linear model with the *lm* function as implemented in *R* [49]. The expression/methylation level was included as dependent variable and the status as the predictor. The model was adjusted for age and batch. All the analyses of the 677C>T and 1298A>C polymorphisms were instead conducted using PLINK v1.9 software [50]. We computed the Hardy–Weinberg equilibrium with an exact test, allele frequencies and linkage disequilibrium between the two polymorphisms using the r^2 metric. The association test between ADHDM and HCM and 677C>T and 1298A>C was conducted using a logistic regression adjusting for age.

After independent evaluation of expression level, methylation level and 677C>T/1298A>C polymorphisms, we used simple linear regression models adjusted for mothers' age and batch to assess the extent of the relationship between expression and methylation levels and expression and 677C>T and/or 1298A>C genotype (both single and additive models). p-values were adjusted using the Bonferroni methods, accounting for the seven tests conducted.

Results

MTHFR 677C>T & 1298A>C genotype frequencies are not associated with ADHD

We characterized 45 ADHDM and 45 age matched HCM. The average age of ADHDM was 44.4 ± 4.8 years (range: 35–53 years), whereas the average age of HCM was 44.8 ± 5.6 years (range: 33–55 years). The age between the two groups was not significantly different (t = -0.367; p = 0.715).

We first investigated the relationship between *MTHFR* polymorphisms and status (ADHDM vs HCM). Both SNPs were in Hardy–Weinberg equilibrium in the HCM group (677C>T: p = 1.000; 1298A>C: p = 0.283) and in the ADHDM group (677C>T: p = 0.765; 1298A>C: p = 0.132), and they did not show linkage disequilibrium (LD) (r^2 = 0.258). The genotype frequencies are reported in the barplot in Figure 1, and the allele frequencies are reported in Table 1A. The presence of association was computed using logistic regression adjusting for mothers' age, but the allele frequencies were not significantly different between ADHDM and HCM for both polymorphisms (Table 1B).

MTHFR methylation & expression in ADHD mothers versus HC mothers

Mean *MTHFR* gene methylation was 33.36 ± 5.00% and 32.70 ± 5.56% in ADHDM and HCM, respectively. The difference was not statistically significant, also after adjusting for confounding factors (β = 0.713; adj-p = 1.000) (Figure 2).

Then, we explored the relationship between mRNA levels between ADHDM and HCM by linear regression. We detected a significant increase of expression in ADHDM (lower Delta Ct value) (β = -1.073; adj-p = 0.035)

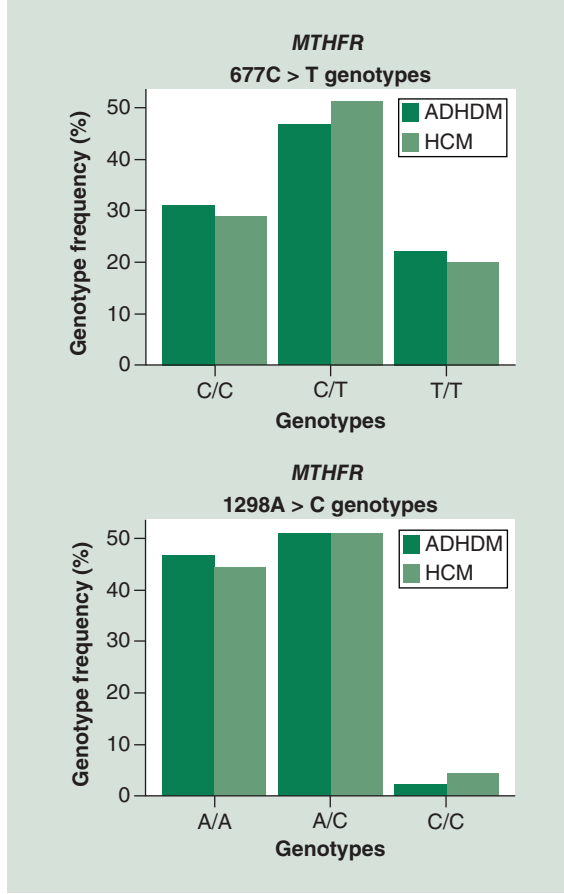


Figure 1. Genotype frequency in ADHD mothers and in HC mothers for (A) the 677C>T polymorphism and (B) the 1298A>C polymorphism.
ADHDM: Attention-deficit/hyperactivity disorder mothers; HCM: Healthy control mothers.

Table 1. *MTHFR* 677C>T and 1298A>C polymorphisms in attention-deficit/hyperactivity disorder and healthy control mothers.

A						
Polymorphisms	**Minor allele**	**Major allele**		**ADHD**	**HC**	
677C>T	T	C		45.6%	45.6%	
1298A>C	C	A		27.8%	30.0%	
B	**677C>T**			**1298A>C**		
Models	**OR**	**p-value**	**adj p-value**	**OR**	**p-value**	**adj p-value**
Additive	0.993	0.982	1.000	0.874	0.724	1.000

(A) Allele frequencies of the minor allele (lowest frequency allele across the total sample). **(B)** Results of the association analysis conducted using the additive genetic model adjusting for mothers' age.
ADHD: Attention-deficit/hyperactivity disorder; HC: Healthy control; OR: Odd ratio.

compared with HCM. The same result was obtained using two independent retrotranscribed cDNAs and two primer pairs targeting different regions of the *MTHFR* mRNA. The significance was confirmed when we adjusted for mothers' age (β = -1.056; adj-p = 0.035) and for mothers' age and batch (β = -1.066; adj-p = 0.00077) (Figure 3).

Correlations among *MTHFR* 677C>T/1298A>C polymorphisms & expression levels

We used different linear models to investigate the presence of the relationship between gene expression and methylation, and 677C>T/1298A>C polymorphisms and expression using the entire sample. All results were not statistically significant (Table 2).

Discussion

During the embryo-fetal life, maternal folate supply is essential for maintaining an adequate cell division rate and for the correct establishment of the epigenetic patterns that allow growth and differentiation. It is regulated by dietary

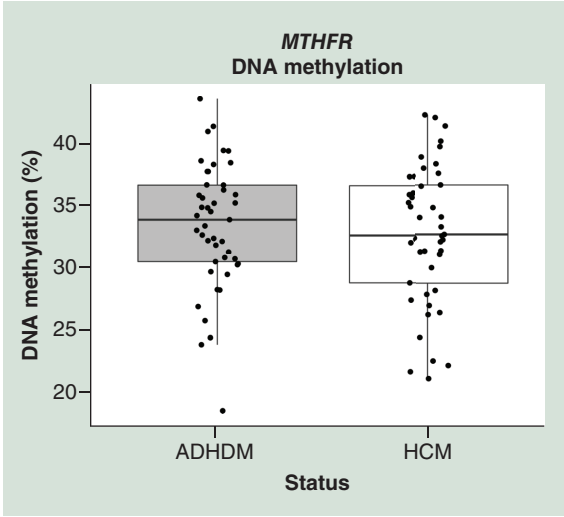


Figure 2. Percentage of *MTHFR* gene promoter methylation in attention-deficit/hyperactivity disorder mothers and in healthy control mothers.
ADHDM: Attention-deficit/hyperactivity disorder mothers; HCM: Healthy control mothers.

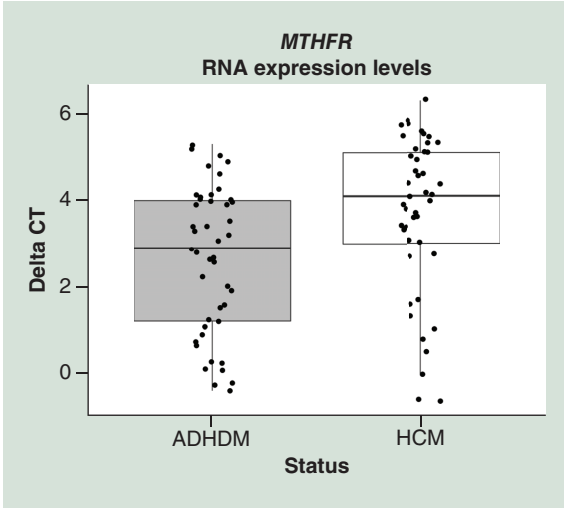


Figure 3. *MTHFR* mRNA expression levels expressed as delta_Ct in attention-deficit/hyperactivity disorder mothers and in healthy control mothers.
ADHDM: Attention-deficit/hyperactivity disorder mothers; Ct: Cycle threshold; HCM: Healthy control mothers.

Table 2. Results of the linear models applied aiming to identify relationship between 677C>T/1298A>C polymorphisms, expression and methylation levels. All models were adjusted for age and batch.

Model	CT			TT		
	β	p-value	adj p-value	β	p-value	adj p-value
Exp ~ 677C>T	0.125	0.714	1.000	0.261	0.536	1.000
Model	**AC**			**CC**		
	β	p-value	adj p-value	β	p-value	adj p-value
Exp ~ 1298A>C	−0.036	0.906	1.000	−0.052	0.951	1.000
Model	**β**	**p-value**	**adj p-value**			
Exp ~ Met	0.015	0.625	1.000			

and genetic factors during the pre- and periconceptional periods, which are increasingly considered as potential contributors to neurodevelopmental disorders [15], though further data are needed to verify this hypothesis. Indeed, DNA methylation reactions dramatically increase after egg fertilization and during embryo development when folate is delivered to the growing fetus through the maternal placenta. In the light of these considerations, we have chosen to screen common polymorphisms, as well as DNA methylation and expression levels of the *MTHFR* gene in the ADHDM and HCM as potential contributors to these conditions. The present study revealed no difference in the distribution of both *MTHFR* 677C>T or 1298A>C alleles or genotypes in ADHDM compared with

HCM. Similarly, *MTHFR* methylation levels were not statistically different between the two groups. However, we observed a significantly increased RNA expression of the *MTHFR* gene in the ADHDM group compared with the HCM, which could represent a maternal risk factor for having a child with ADHD. Such an increase in expression appears not to be a consequence of changes in gene DNA methylation levels in the characterized region, or in the two polymorphisms tested, though this preliminary data needs to be validated in a larger sample to reach a final conclusion.

Most studies on *MTHFR* 677C>T and 1298A>C polymorphisms have demonstrated an increased risk for many disease conditions such as cancers [29], cardiovascular disease [26], male infertility [51], pregnancy loss [52] as well as for several neuropsychiatric [28,53] and neurodegenerative [27,54] conditions. Among psychiatric diseases, the most consistent association was found for schizophrenia and the 677T allele for which many studies have been conducted [55,56]. Relatively limited studies on other neuropsychiatric/neurodevelopmental conditions including bipolar disorder, depression, autism spectrum disorder, intellectual disability and ADHD [57–59] have been performed to date. Most of these studies have considered the association between the own *MTHFR* polymorphisms and the risk of neurodevelopment disorders, but due to the importance that maternal folate supply plays during embryo development, some authors have also investigated the role of *MTHFR* common variants as maternal risk factors for neurodevelopmental disorders in their children. Liu *et al.* [41] found a preferential transmission of the 677T and 1298A alleles, as well as of the 677T-1298A haplotype, to the autism spectrum disorder affected offspring. Schmidt *et al.* [60] found a strong association between folic acid supplementation during pregnancy and reduced risk of autism spectrum disorder in the offspring of mothers with the *MTHFR* 677 T allele. A more recent study [40] shows that the maternal *MTHFR* 677T allele can predict deficits in early cognitive development of their offspring. Our data revealed that there are no differences in allele or genotype frequencies of the two studied polymorphisms between ADHDM and HCM, suggesting that they are unlikely to represent maternal risk factors for ADHD in their children. However, larger samples are needed to confirm our results.

More recently, also the contribution of maternal epigenetic variants of the *MTHFR* gene has been investigated as a potential contributor to aneuploidy or congenital disorders in the offspring. Particularly, *MTHFR* promoter hypermethylation has been observed in blood DNA from mothers of Down syndrome children with respect to matched control mothers and has been linked to chromosome damage [61] and to the risk of having Down syndrome children with congenital heart defects [31]. Furthermore, *MTHFR* hypermethylation has been recently observed in women with recurrent miscarriage [62]. Several investigators found correlations between *MTHFR* methylation levels and circulating folate or homocysteine levels [47,63,64]. Therefore, the *MTHFR* promoter hypermethylation observed in mothers of Down syndrome children with congenital heart defects, or in women with recurrent miscarriage, are considered indicators of impaired one-carbon metabolism in those women, likely contributing to an inadequate folate supply for the proper division of their oocytes and for the cellular divisions and methylation reactions required for the development of their embryos [31,61,62].

We found a mean *MTHFR* methylation percentage of 33.36 ± 5.00% and 32.70 ± 5.56% for ADHDM and HCM, respectively, which is similar to those previously reported for healthy women [61], and no statistical significant differences between the two groups were observed. Because both *MTHFR* 677C>T and 1298A>C polymorphisms can lead to changes in homocysteine levels, reducing its conversion to methionine [24,25,42], we also investigated if *MTHFR* methylation levels change according to the genotypes generated by these SNPs. However, we found no correlation between the *MTHFR* methylation levels and the two investigated, SNPs, which is consistent with a recent finding on a large cohort of healthy Italian subjects revealing that the two SNPs do not act as *cis*-acting elements to regulate their own promoter methylation levels [65]. Furthermore, we did not find a significant correlation between promoter methylation of the *MTHFR* gene and its expression as previously reported. In our study, *MTHFR* expression levels were significantly higher in ADHDM compared with HCM (Figure 3), though methylation levels were not significantly different between the two groups (Figure 2). Indeed, in addition to methylation, *MTHFR* mRNA levels can be modulated by other epigenetic processes including histone modifications and chromatin remodeling proteins as well as by miRNAs, small regulatory RNAs known to influence mRNA stability. Therefore, we could speculate that the increased *MTHFR* expression observed in ADHDM may be due to differences in other processes controlling mRNA level. In this regard, there is increasing evidence suggesting that miRNAs, such as miR-1203 or miR-2861, are able to regulate *MTHFR* expression levels in human cells [66,67]. Furthermore, a dysregulated expression of specific miRNAs has recently been reported in children and adolescents with ADHD [68].

10.2217/epi-2019-0356

One recent whole-blood gene expression case–control study [69] has identified specific ADHD transcriptome signature/alterations. Another genome wide methylation study [70] on salivary DNA in ADHD affected children and healthy children reported differential methylation in relevant genes. The higher *MTHFR* mRNA levels observed in ADHDM in this study could be correlated with the reported epigenetic and/or transcriptome alterations described in these studies. However, the biological significance of such an increase is not clear at the moment and should be firstly replicated in a larger sample.

In summary, our study has shown that both *MTHFR* 677C>T and 1298A>C polymorphisms and *MTHFR* promoter methylation in ADHDM are not risk factors for ADHD onset in their children. However, we observed a significantly higher *MTHFR* mRNA expression in ADHDM compared with HCM, whose mechanisms and potential contribution to the ADHD phenotype in their children deserve further scrutiny.

Future perspective

Future studies should be conducted aiming to replicate the *MTHFR* mRNA dysregulation detected in ADHDM in a larger sample in order to investigate whether it can be considered a maternal risk factor for the disease. The future studies should also investigate the biological basis of such dysregulation, and particularly whether it is due to transcriptional or post-transcriptional mechanisms, such as miRNAs. If *MTHFR* mRNA overexpression will be confirmed in larger samples of ADHDM, studies in animal models will be required to investigate if targeting the *MTHFR* mRNA could decrease the risk of neurodevelopmental disorders in the offspring.

Summary points

- Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorder with a worldwide prevalence of about 2.2% in children.
- We hypothesize that maternal genetic and epigenetic variants in the *MTHFR* gene could impair the folate supply to the embryo during pregnancy, thus representing maternal risk factors for neurodevelopmental disorders as ADHD.
- Our experimental sample consisted of 45 mothers who had at least one ADHD affected child (ADHDM) and 45 aged matched healthy control mothers (HCM).
- *MTHFR* gene promoter methylation levels were not significantly different in ADHDM compared with age matched HCM.
- The distribution of 677C>T and 1298A>C alleles and genotypes was not significantly different in the two groups.
- *MTHFR* mRNA expression levels were significantly higher in ADHDM compared with HCM.
- No significant correlation was found between methylation and expression, and 677C>T and/or 1298A>C genotypes and expression.
- Our study suggests that maternal *MTHFR* methylation levels and 677C>T and/or 1298A>C polymorphisms are not maternal risk factors for ADHD, but confirmation is required in further studies empowered in sample size.
- More studies are needed to clarify the significance of the higher *MTHFR* mRNA expression level detected in ADHDM compared with HCM in our study.

Author contributions

CL was responsible for study conception, design, acquisition of data, main drafting and revision of the manuscript; ISP and FC were responsible for data analysis, drafting and revision of the manuscript; CT for healthy control recruitment and RS and AC were responsible for patient recruitment and clinical assessment; AS and MJH for data analysis.

Acknowledgments

The authors gratefully acknowledge the patients, their family for their cooperation and Chiara Gregorj for helping in recruiting healthy controls.

Financial & competing interest disclosure

This study was funded by the Fund-Raising Office of University Campus Bio-Medico of Rome. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, informed consent has been obtained from the participants involved.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biol. Psychiatry* 57(11), 1215–1220 (2005).
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* American Psychiatric Publication, DC, USA (2013).
3. Spencer TJ. ADHD and comorbidity in childhood. *J. Clin. Psychiatry* 67(Suppl.8), S27–S31 (2006).
4. Hayman V, Fernandez TV. Genetic insights into ADHD biology. *Front. Psychiatry* 9, 251 (2018).
5. Faraone SV, Perlis RH, Doyle AE *et al.* Molecular genetics of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 57(11), 1313–1323 (2005).
6. Faraone SV, Mick E. Molecular genetics of attention-deficit/hyperactivity disorder. *Psychiatr. Clin. North Am.* 33(1), 159–180 (2010).
7. Georgieff MK, Tran PV, Carlson ES. Atypical fetal development: fetal alcohol syndrome, nutritional deprivation, teratogens and risk for neurodevelopmental disorders and psychopathology. *Dev. Psychopathol.* 30(3), 1063–1086 (2018).
8. Rice F, Langley K, Woodford C, Davey Smith G, Thapar A. Identifying the contribution of prenatal risk factors to offspring development and psychopathology: what designs to use and a critique of literature on maternal smoking and stress in pregnancy. *Dev. Psychopathol.* 30(3), 1107–1128 (2018).
9. Saez M, Barceló MA, Farrerons M, López-Casasnovas G. The association between exposure to environmental factors and the occurrence of attention-deficit/hyperactivity disorder (ADHD). A population-based retrospective cohort study. *Environ. Res.* 166, 205–214 (2018).
10. Blaise SA, Nédélec E, Schroeder H *et al.* Gestational vitamin B deficiency leads to homocysteine-associated brain apoptosis and alters neurobehavioral development in rats. *Am. J. Pathol.* 170(2), 667–679 (2007).
11. Craciunescu CN, Brown EC, Mar MH, Albright CD, Nadeau MR, Zeisel SH. Folic acid deficiency during late gestation decreases progenitor cell proliferation and increases apoptosis in fetal mouse brain. *J. Nutr.* 134(1), 162–166 (2004).
12. Pulikkunnel ST, Thomas SV. Neural tube defects: pathogenesis and folate metabolism. *J. Assoc. Physicians India* 53, 127–135 (2005).
13. Christensen B, Rosenblatt DS. Effects of folate deficiency on embryonic development. *Baillieres Clin. Haematol.* 8(3), 617–637 (1995).

•• **A summary of current evidences of how folate deficiency affects neurodevelopment.**

14. Schlotz W, Jones A, Phillips DI *et al.* Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. *J. Child Psychol. Psychiatry* 51(5), 594–602 (2010).
15. DeVilbiss EA, Gardner RM, Newschaffer CJ, Lee BK. Maternal folate status as a risk factor for autism spectrum disorders: a review of existing evidence. *Br. J. Nutr.* 114(5), 663–672 (2015).
16. Reynolds EH. The neurology of folic acid deficiency. *Handb. Clin. Neurol.* 120, 927–943 (2014).
17. Wagner C. Biochemical role of folate in cellular metabolism. In: *Folate in Health and Disease*. Bailey LB (Ed.). Marcel Dekker, NY, USA, 23–42 (1995).
18. Crider KS, Yang TP, Berry RJ, Bailey LB. Folate and DNA methylation: a review of molecular mechanisms and the evidence for folate's role. *Adv. Nutr.* 3(1), 21–38 (2012).
19. Stover PJ. Polymorphisms in 1-carbon metabolism, epigenetics and folate-related pathologies. *J. Nutrigenet. Nutrigenomics* 4(5), 293–305 (2011).
20. Lintas C. Linking genetics to epigenetics: the role of folate and folate-related pathways in neurodevelopmental disorders. *Clin. Genet.* 95(2), 241–252 (2019).
21. Hu WF, Chahrour MH, Walsh CA. The diverse genetic landscape of neurodevelopmental disorders. *Annu. Rev. Genomics Hum. Genet.* 15, 195–213 (2014).
22. Lister R, Mukamel EA, Nery JR *et al.* Global epigenomic reconfiguration during mammalian brain development. *Science* 341(6146), 1237905 (2013).

• **Report on the genome-wide composition, patterning, cell specificity and dynamics of DNA methylation at single-base resolution in human and mouse frontal cortex throughout their lifespan.**

23. Watanabe D, Suetake I, Tada T, Tajima S. Stage- and cell-specific expression of Dnmt3a and Dnmt3b during embryogenesis. *Mech. Dev.* 118(1–2), 187–190 (2002).
24. Liew SC, Gupta ED. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. *Eur. J. Med. Genet.* 58(1), 1–10 (2015).

• **An overview of the MTHFR C677T polymorphism and associated diseases.**

25. van der Put NM, Gabreëls F, Stevens EM *et al.* A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? *Am. J. Hum. Genet.* 62(5), 1044–1051 (1998).

- **Discovery of the association between MTHFR A1298C polymorphism and neural tube defects.**

26. Oztuzcu S, Ergun S, Ulaşlı M *et al.* Evaluation of Factor V G1691A, prothrombin G20210A, Factor XIII V34L, MTHFR A1298C, MTHFR C677T and PAI-1 4G/5G genotype frequencies of patients subjected to cardiovascular disease (CVD) panel in south-east region of Turkey. *Mol. Biol. Rep.* 41(6), 3671–3676 (2014).
27. Mansoori N, Tripathi M, Luthra K *et al.* MTHFR (677 and 1298) and IL-6-174 G/C genes in pathogenesis of Alzheimer's and vascular dementia and their epistatic interaction. *Neurobiol. Aging* 33(5), 1003 (2012).
28. An XK, Lu CX, Ma QL *et al.* Association of MTHFR C677T polymorphism with susceptibility to migraine in the Chinese population. *Neurosci. Lett.* 549, 78–81 (2013).
29. Ferrara M, Capozzi L, Russo R. Impact of the MTHFR C677T polymorphism on risk of Wilms tumor: case–control study. *J. Pediatr. Hematol. Oncol.* 31(4), 256–258 (2009).
30. Wan L, Li Y, Zhang Z, Sun Z, He Y, Li R. Methylenetetrahydrofolate reductase and psychiatric diseases. *Transl. Psychiatry* 8(1), 242 (2018).
31. Asim A, Agarwal S, Panigrahi I, Saiyed N, Bakshi S. MTHFR promoter hypermethylation may lead to congenital heart defects in Down syndrome. *Intractable Rare Dis. Res.* 6(4), 295–298 (2017).
32. Rotondo JC, Bosi S, Bazzan E *et al.* Methylenetetrahydrofolate reductase gene promoter hypermethylation in semen samples of infertile couples correlates with recurrent spontaneous abortion. *Hum. Reprod.* 27(12), 3632–3638 (2012).
33. Saraswathy KN, Kaur L, Talwar S *et al.* Methylenetetrahydrofolate reductase gene-specific methylation and recurrent miscarriages: a case-control study from North India. *J. Hum. Reprod. Sci.* 11(2), 142–147 (2018).
34. Jiménez KM, Pereira-Morales AJ, Forero DA. MTHFR gene methylation is associated with perceived stress in healthy young adults. *Psychiatr. Genet.* 28(3), 41–46 (2018).
35. Vaissière T, Hung RJ, Zaridze D *et al.* Quantitative analysis of DNA methylation profiles in lung cancer identifies aberrant DNA methylation of specific genes and its association with gender and cancer risk factors. *Cancer Res.* 69(1), 243–252 (2009).
36. Barker ED, Walton E, Cecil CAM *et al.* A methylome-wide association study of trajectories of oppositional defiant behaviors and biological overlap with attention deficit hyperactivity disorder. *Child Dev.* 89(5), 1839–1855 (2018).
37. Walton E, Pingault JB, Cecil CA *et al.* Epigenetic profiling of ADHD symptoms trajectories: a prospective, methylome-wide study. *Mol. Psychiatry* 22(2), 250–256 (2017).
38. Nardone S, Sams DS, Reuveni E *et al.* DNA methylation analysis of the autistic brain reveals multiple dysregulated biological pathways. *Transl. Psychiatry* 4, e433 (2014).
39. Wockner LF, Noble EP, Lawford BR *et al.* Genome-wide DNA methylation analysis of human brain tissue from schizophrenia patients. *Transl. Psychiatry.* 4, e339 (2014).
40. Pilsner JR, Hu H, Wright RO *et al.* Maternal MTHFR genotype and haplotype predict deficits in early cognitive development in a lead-exposed birth cohort in Mexico city. *Am. J. Clin. Nutr.* 92, 226–234 (2010).
41. Liu X, Solehdin F, Cohen IL *et al.* Population- and family-based studies associate the MTHFR gene with idiopathic autism in simplex families. *J. Autism Dev. Disord.* 41(7), 938–944 (2011).
42. Bagley PJ, Selhub J. A common mutation in the methylenetetrahydrofolate reductase gene is associated with an accumulation of formylated tetrahydrofolates in red blood cells. *Proc. Natl Acad. Sci. USA* 95, 13217–13220 (1998).
43. Antony AC. In utero physiology: role of folic acid in nutrient delivery and fetal development. *Am. J. Clin. Nutr.* 85, S598–S603 (2007).
44. Griffiths R. The Griffiths mental development scales from birth to 2 years, manual, the 1996 revision. *Henley: Association for Research in Infant and Child Development, Test Agency* (1996).
45. Achenbach TM. *Manual for Child Behavior Checklist/4-18 and 1991 Profile.* University of Vermont, Department of Psychiatry, VT, USA (1991).
46. Goyette CH, Conners CK, Ulrich RF. Normative data on revised Conners parent and teacher rating scales. *J. Abnorm. Child Psychol.* 6(2), 221–236 (1978).
47. Tannorella P, Stoccoro A, Tognoni G *et al.* Methylation analysis of multiple genes in blood DNA of Alzheimer's disease and healthy individuals. *Neurosci. Lett.* 600, 143–147 (2015).
48. Poorang S, Abdollahi S, Anvar Z *et al.* The impact of methylenetetrahydrofolate reductase (MTHFR) sperm methylation and variants on semen parameters and the chance of recurrent pregnancy loss in the couple. *Clin. Lab.* 64(7), 1121–1128 (2018).
49. R Core Team, R Development Core Team. R: a language and environment for statistical computing. (2016). www.r-project.org/
50. Purcell S, Neale B, Todd-Brown K *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* 81(3), 559–575 (2007).
51. Gupta N, Gupta S, Dama M *et al.* Strong association of 677 C>T substitution in the MTHFR gene with male infertility: a study on an Indian population and a meta-analysis. *PLoS ONE* 6(7), e22277 (2011).

52. Zhang Y, He X, Xiong X *et al.* The association between maternal methylenetetrahydrofolate reductase C677T and A1298C polymorphism and birth defects and adverse pregnancy outcomes. *Prenat. Diagn.* 39(1), 3–9 (2019).
53. Yoshimi A, Aleksic B, Kawamura Y *et al.* Gene-wide association study between the methylenetetrahydrofolate reductase gene (MTHFR) and schizophrenia in the Japanese population, with an updated meta-analysis on currently available data. *Schizophr. Res.* 124(1–3), 216–222 (2010).
54. Stoccoro A, Siciliano G, Migliore L, Coppedè F. Decreased methylation of the mitochondrial D-loop region in late-onset Alzheimer's disease. *J. Alzheimers Dis.* 59(2), 559–564 (2017).
55. Lewis SJ, Zammit S, Gunnell D, Smith GD. A meta-analysis of the MTHFR C677T polymorphism and schizophrenia risk. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 135B(1), 2–4 (2005).
56. Muntjewerff JW, Hoogendoorn ML, Kahn RS *et al.* Hyperhomocysteinemia, methylenetetrahydrofolate reductase 677TT genotype and the risk for schizophrenia: a Dutch population based case-control study. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 135B(1), 69–72 (2005).
57. Gokcen C, Kocak N, Pekgor A. Methylenetetrahydrofolate reductase gene polymorphisms in children with attention-deficit/hyperactivity disorder. *Int. J. Med. Sci.* 8(7), 523–528 (2011).

- **The only study reporting a significant association between A1298C SNP and attention-deficit/hyperactivity disorder (ADHD).**

58. Ergul E, Sazci A, Kara I. Methylenetetrahydrofolate reductase gene polymorphisms in Turkish children with attention-deficit/hyperactivity disorder. *Genet. Test Mol. Biomarkers* 16(1), 67–69 (2012).

- **Negative association study on A1298C and or C677T SNPs and ADHD.**

59. Saha T, Dutta S, Rajamma U, Sinha S, Mukhopadhyay K. A pilot study on the contribution of folate gene variants in the cognitive function of ADHD probands. *Neurochem. Res.* 39(11), 2058–2067 (2014).

- **Significant association between ADHD and the 677T allele in female probands but not in males.**

60. Schmidt RJ, Hansen RL, Hartiala J *et al.* Prenatal vitamins, one-carbon metabolism gene variants and risk for autism. *Epidemiology* 22(4), 476–485 (2011).
61. Coppedè F, Denaro M, Tannorella P, Migliore L. Increased MTHFR promoter methylation in mothers of Down syndrome individuals. *Mutat. Res.* 787, 1–6 (2016).
62. Saraswathy KN, Kaur L, Talwar S *et al.* Methylenetetrahydrofolate reductase gene-specific methylation and recurrent miscarriages: a case–control study from North India. *J. Hum. Reprod. Sci.* 11, 142–147 (2018).
63. Grossi E, Stoccoro A, Tannorella P, Migliore L, Coppedè F. Artificial neural networks link one-carbon metabolism to gene-promoter methylation in Alzheimer's disease. *J. Alzheimers Dis.* 53(4), 1517–1522 (2016).
64. Wei LK, Sutherland H, Au A *et al.* A potential epigenetic marker mediating serum folate and vitamin B12 levels contributes to the risk of ischemic stroke. *Biomed. Res. Int.* 2015, 167976 (2015).
65. Coppedè F, Stoccoro A, Tannorella P, Gallo R, Nicolì V, Migliore L. Association of polymorphisms in genes involved in one-carbon metabolism with MTHFR methylation levels. *Int. J. Mol. Sci.* 20(15), pii: E3754 (2019).
66. He W, Lu M, Li G, Sun Z, Liu D, Gu L. Methylene tetrahydrofolate reductase (MTHFR) rs868014 polymorphism regulated by miR-1203 associates with risk and short-term outcome of ischemic stroke. *Cell Physiol. Biochem.* 41, 701–710 (2017).
67. Liu X, Wang L, Chi H *et al.* The SNP rs915014 in MTHFR regulated by miRNA associates with atherosclerosis. *Cell Physiol. Biochem.* 45, 1149–1155 (2018).
68. Aydin SU, Kabukcu Basay B, Cetin GO, Gungor Aydin A, Tepeli E. Altered microRNA 5692b and microRNA let-7d expression levels in children and adolescents with attention deficit hyperactivity disorder. *J. Psychiatr. Res.* 115, 158–164 (2019).

- **Dysregulation of specific microRNAs in children and adolescents affected by ADHD.**

69. de Jong S, Newhouse SJ, Patel H *et al.* Immune signatures and disorder-specific patterns in across-disorder gene expression analysis. *Br. J. Psychiatry* 209(3), 202–208 (2016).
70. Wilmot B, Fry R, Smeester L, Musser ED, Mill J, Nigg JT. Methylomic analysis of salivary DNA in childhood ADHD identifies altered DNA methylation in VIPR2. *J. Child Psychol. Psychiatry* 57(2), 152–160 (2016).

- **Reports on genome-wide epigenetic dysregulation in ADHD children.**

EXPERT OPINION ON EMERGING DRUGS
https://doi.org/10.1080/14728214.2020.1820481

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Emerging drugs for the treatment of attention-deficit hyperactivity disorder (ADHD)

Marco Pozzi[a], Silvana Bertella[a], Erika Gatti[a], Gabriëlla G. A. M. Peeters[b], Carla Carnovale[b], Stefania Zambrano[a,c] and Maria Nobile[a]

[a]Child and Adolescent Psychiatry Unit, Scientific Institute IRCCS Eugenio Medea, Lecco, Italy; [b]Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università degli Studi di Milano, Milan, Italy; [c]Postgraduate Specialization School in Child and Adolescent Neuropsychiatry, Università degli Studi di Milano, Milan, Italy

ABSTRACT

Introduction: Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting up to 5.3% of children and 2.5% of adults depending on the country considered. Current pharmacological treatments for ADHD are based on stimulant or non-stimulant medications, targeting dopaminergic and noradrenergic systems in the frontal cortex and dopaminergic system in the basal ganglia. These drugs are effective and safe for the majority of patients, whereas about 20% of treated patients do not tolerate current therapies or experience insufficient efficacy. The adequate treatment of ADHD is necessary to allow a proper social placement and prevent the acquisition of additional, more severe, comorbidities.

Areas covered: We conducted a review of the scientific literature and of unpublished/ongoing clinical trials to summarize the advances made in the last 10 years (2010–2020) for the pharmacological treatment of ADHD. We found many pharmacological mechanisms beyond dopaminergic and noradrenergic ones have been investigated in patients.

Expert opinion: Some emerging drugs for ADHD may be promising as add-on treatment especially in children, amantadine to enhance cognitive functions and tipepidine for hyperactivity/impulsivity. Stand-alone emerging treatments for ADHD include viloxazine and dasotraline, which will soon have more clinical data available to support market access requests.

ARTICLE HISTORY
Received 2 May 2020
Accepted 3 September 2020

KEYWORDS
ADHD; emerging drugs; innovative drugs; pharmacological therapy

1. Background

Attention-Deficit/Hyperactivity disorder (ADHD) is a 'lifespan' neurodevelopmental disorder, which typically manifest early in development, characterized by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity. These features are displayed in a persistent pattern that is pervasive across multiple settings and causes substantial functional impairment of personal, social, academic, or occupational functioning [1]. Population surveys [2,3] suggest that ADHD occurs in most cultures in about 5.3% of children and about 2.5% of adults aged 19–45 years [4]. Individuals with ADHD are at increased risk for a range of poor social outcomes throughout their lifetime, including substance abuse and addiction, criminality, academic and occupational underachievement, social rejection by peers and family conflicts. Patients with ADHD are also at increased risk for obesity, suicide and premature death compared with the general population. Accordingly, these functional impairments translate to reduced quality of life as measured by psychological, social and health indicators [5]. According to both DSM 5 and ICD-11 criteria [6], ADHD is now considered a chronic condition, with specific criteria for children and adults, and medical treatment is usually provided over several years.

2. Medical need

Based on the perspective that ADHD is now considered a life-long disorder, with a high prevalence and a high comorbidity especially in adulthood, the developing of better long-term treatments, not only for children but also for adults, is needed. The development of new treatments must take into account the long-term effectiveness and, at the same time, focus on other issues including low adherence, adverse effects and non-tolerability, especially when comorbid diagnoses are present.

3. Existing treatment

Pharmacological treatments for ADHD are classified into stimulants (methylphenidate and amphetamine) and non-stimulants (atomoxetine, guanfacine and clonidine) [7]. Both classes present with limitations and adverse effects with a non-adherence rate ranging between 15 and 87% [8]. Stimulant drugs are the first-line pharmacological treatment for ADHD and their effectiveness has been widely demonstrated, albeit most studies report data only on their short-term use [7,9]. The duration of action is an important limit for these types of drugs. Depending on the active agent and individual variability, stimulants provide coverage of ADHD symptoms for no more than 12–13 hours per dose,

CONTACT Maria Nobile maria.nobile@lanostrafamiglia.it Child and Adolescent Psychiatry Unit, Scientific Institute IRCCS Eugenio Medea , Bosisio Parini (LC) 23842, Italy

Article highlights

- ADHD is a neurodevelopmental disorder affecting up to 5.3% of children and 2.5% of adults.
- About 20% of treated patients do not tolerate current therapies or experience insufficient efficacy.
- Amantadine to enhance cognitive functions and tipepidine for hyperactivity/impulsivity may be promising as add-on treatment, especially in children.
- Stand-alone emerging treatments for ADHD include viloxazine and dasotraline, both in children and adults.

considering extended-release formulations. Adverse effects are similar for both methylphenidate and amphetamine, presenting more frequently with the use of amphetamine. They include decreased appetite, sleep disturbances, nausea, xerostomia, headache and irritability, seen at all ages but slightly more frequent in young children [8–10]. Moreover, some data suggest that these drugs can affect negatively growth trajectories and increase weight and body-mass index after long-term treatment [7,11]. It has also been speculated that these drugs increase the likelihood of cardiovascular events or induce dependence, but longitudinal research has not confirmed these hypotheses [7]. Finally, it is commonly assumed that children with certain comorbidities should not be prescribed stimulants as they might worsen symptoms, e.g. in children with aggressive behavior, insomnia or tics [7,12].

The efficacy of non-stimulants in the short-term has also been reported [13]. Unlike stimulants Atomoxetine may not exacerbate tics in Tourette's syndrome patients with ADHD [12]. The combination of psychotropic drugs (i.e. polypharmacy) is an increasingly applied strategy in ADHD, especially when comorbidity is present. Many reports suggest that drug–drug interactions are not uncommon in patients on multiple psychotropic treatments [14], raising further concerns.

4. Current research goals

The highlighted limitations of current medical treatments underline the importance of the continued search for new and improved drugs. Current research goals include the development of drugs with enhanced long-term effectiveness, higher tolerability and with less adverse effects, mainly when comorbidities are present. Especially in adults, one of the main research focuses is on treating comorbidities and using non-stimulants drugs to avoid risks of misuse.

5. Scientific rationale

ADHD core symptoms include inattention, hyperactivity and impulsivity. It is currently hypothesized that all these symptoms are linked to specific malfunctioning in Cortico-Striato-Thalamo-Cortical (CSTC) circuits [15]. Several studies suggest that a dysregulation in the dopaminergic (DA) and noradrenergic (NA) systems, with a minor and unclear role of serotoninergic system, may underlay the disruption of the normal 'tuning' of neurons in prefrontal cortex, while a dopamine system dysfunction may be at the root of cytoarchitecture alterations within one or more basal ganglia nuclei. These findings have been confirmed by Magnetic Resonance Imaging (MRI) studies [15].

Boosting dopamine and/or norepinephrine in the prefrontal cortex and in the basal ganglia nuclei can reduce ADHD symptoms of both inattention and hyperactivity. Inhibition of dopamine reuptake (methylphenidate, amphetamine), and secondarily of noradrenaline reuptake (atomoxetine) are among the most effective mechanisms exploited by the current clinical practice.

Several treatments have been proposed for ADHD in children and adults targeting the same mechanisms of approved drugs (see following section on monoaminergic reuptake inhibitors), while the majority tried to act on mechanisms that have not been addressed yet in the context of ADHD, but are involved with cognition and attention in other disorders (including schizophrenia and Alzheimer's dementia). Some drugs (i.e. N-pantoyl-GABA, a fusion analog of GABA and pantothenic acid) were tested with no underlying specific hypotheses on their involvement with attention or ADHD. Other drugs were tested as add-on therapies to improve efficacy on residual symptoms or to mitigate possible adverse effects.

For instance, the glutamatergic system has an unclear role in the mechanism of attention and hyperactivity [16], even though modulators of AMPA receptor (n-NMDA receptor for glutamate) could reduce hyperactivity in a hydroxydopamine-lesioned rat model, and mGluR5 inhibition promoted hyperactivity in rats [17], thus suggesting a potential therapeutic role for drugs targeting these systems.

The exact mechanisms underlying the effect of melatoninergic agents are currently not completely clarified. Melatonin is an endogenous metabolite of serotonin, produced starting from the amino-acid tryptophan. Melatonin binds to several receptors, currently known only in part, and it is involved with the regulation of circadian rhythms, hormone production. It is antihypertensive, antidepressant, anxiolytic and anti-inflammatory. In addition, melatonin has been shown to reduce manifestations of ADHD in murine models [18]. Aside from acting directly on manifestations of inattention and hyperactivity, melatoninergic agonists may be useful to maintain the sleep-wake cycle in patients using stimulants, known to disrupt the melatonin cycle compromising sleep quality and amount [19].

Dopamine receptors D4 are also tightly linked to glutamatergic signaling. They have been related to a functional regulation of AMPA receptors activity [20]; moreover, specific modulators of D4 receptors could alter the phenotype of hydroxydopamine-lesioned rats and D4 knockout hydroxydopamine-lesioned rats do not display the expected hyperactivity.

Lots of antipsychotic drugs are frequently used for the control of problem behavior that, even though not a core feature of ADHD, is often an element that disrupts the lives of patients and of their families. Their mechanism of action is

predominantly based on D2 dopaminergic and H1 histaminergic antagonism. New drugs were tested according to this hypothesis.

The involvement of the cannabinoid system in ADHD and attention has no clear explanation and the clinical efficacy of phytocannabinoids for ADHD treatment is based on anecdotal evidence and self-administration by patients. Data on the role of phytocannabinoids in enhancing dopaminergic transmission [21–23], which is thought to be the main therapeutic mechanism of ADHD therapies, are still controversial [21–25] but worthy for further study.

Boosting acetylcholine function and enhancing prefrontal cortex activity with histamine are two other precognitive approaches. Nicotinic cholinergic transmissions in the central nervous system are crucial for the regulation of arousal, attention and cognition [26,27]. Nicotinic receptors of the α4β2 subtype (nAChR α4β2) are found only in some regions of the central nervous system (cortex, hippocampus, striatum and thalamus) implicated with attention [28] and specific nAChR α4β2 agonists were demonstrated to improve attention and cognitive performance in healthy adults [29]. Histaminergic transmission is traditionally known to control wakefulness and has been implicated with arousal and attention in animal models, with particular regard to H3 receptors [30]. H3 antagonists have been demonstrated to increase arousal without the adverse impact of stimulants [30] in the cat. H1 receptors are instead responsible of maintaining wakefulness and H1 antagonists are powerful sedatives and hypnotics.

6. Competitive environment

We have conducted a systematic review of the literature using PubMed as a source database, including all drugs that have been tested in clinical trials published during the years 2010–2020. This led to the inclusion of novel emerging drugs (not yet fully tested), repurposed emerging drugs (drugs that have been repurposed and systematically tested in clinical trials for ADHD) and drugs with a suspended clinical development (drugs that had negative results at clinical testing and are now on hold). Details of the reviewed drugs are available in Table 1 for drugs that have published trials and in Table 2 for drugs without public results.

6.1. Monoamine reuptake inhibitors

6.1.1. Noradrenergic reuptake inhibitors (NRIs)

6.1.1.1. Viloxazine (novel emerging). Viloxazine (SPN-812) is a novel NRI that was tested [31] in a parallel arms randomized double blind trial on children. Viloxazine 100, 200, 300, 400 mg/d was compared with placebo over 8 weeks. Tolerability was lower for viloxazine (23–33% drop-outs) than for placebo (12.5%), not dose dependent, and it was not stressed by the Authors. The most frequent adverse events were somnolence, headache, decreased appetite, and the overall incidence of psychiatric adverse events was approximately 20%: irritability was the only psychiatric adverse event listed as it occurred in more than 5% of subjects. Viloxazine was superior to placebo starting from week 4, although at the endpoint only the 300 and 400 mg/d doses retained superiority.

6.1.1.2. BLI-1008 (novel emerging). BLI-1008 is an NRI extract derived from a Chinese herbal sedative, currently under phase 2 development by BioLite for the treatment of adult ADHD [32]. BioLite claims BLI-1008 does not reduce appetite, yet in the ongoing clinical trial it is administered after meals.

6.1.1.3. NRIs on hold. Reboxetine is a specific NRI [33] suggested as potentially useful for attention and executive functions [34]. Reboxetine was tested in adults [35] and children [36] with suggestions of partial efficacy and with adverse effects including headache, low appetite, sleep disturbances, anxiety and irritability. Edivoxetine is a specific NRI, which has been tested on pediatric patients [37–39]. Edivoxetine had an efficacy and tolerability similar to the ones of methylphenidate; adverse events occurring more frequently with edivoxetine than with methylphenidate were nausea, vomiting and somnolence, while several events occurred less than with methylphenidate, especially sleep disorders and reduced appetite/weight loss. No statistical comparison between edivoxetine and methylphenidate regarding efficacy was published. Ampreloxetine from Theravance was discontinued for the treatment of ADHD after phase 2 trials [40]; it is now being developed for neurogenic orthostatic hypotension. Arbor Pharmaceuticals tested AR08, a noradrenergic functional agonist with unknown mechanism of action, up to phase 2 [41], when it was discontinued.

6.1.2. Serotonin–norepinephrine reuptake inhibitors (SNRIs)

Duloxetine (repurposed emerging) was tested [42] in a single-arm trial on adolescents, lasting 6 weeks. Duloxetine dose was 60 mg/d. A reduction of ADHD symptoms was evident since week 4, with all sub-scores reduced at week 6. We find it worth mentioning that 24% patients dropped out of treatment (18% for adverse events), which was not highlighted in the paper, and the most frequent adverse events were decreased appetite, dry mouth and insomnia, headache, nausea, somnolence, anxiety, and nervousness.

A subsequent randomized double-blind trial [43] on adults, tested duloxetine 60 mg/d versus placebo for 6 weeks. 40% patients dropped out of the duloxetine arm in the first week of administration, due to adverse events including xerostomia, increased anxiety, nausea, and dizziness, while the placebo arm had no drop-outs. Duloxetine resulted superior to placebo on self-reported ADHD symptoms but not on investigator-reported symptoms, possibly due to underpowerment.

6.1.3. Norepinephrine-dopamine reuptake inhibitor (NDRIs)

Bupropion (repurposed emerging) was tested [44] in pediatric patients. This was a parallel arms randomized double-blind

Table 1. Experimental treatments in ADHD – drugs with published results.

Molecule	Action	Study	Dose range (mg/day)	No of patients (#)	Age (yrs)	Inclusion criteria	Exclusion criteria	Control	Duration (weeks)	Primary outcome	Efficacy opinion*	Safety opinion**
Viloxazine	NRI	Johnson, 2020 [31]	100–400	222	6–12	ADHD-RS-IV ≥ 26	comorbidity	placebo	8	ADHD-RS-IV	1	0
Reboxetine	NRI	Riahi, 2010 [35]	16	40	adult	-	comorbidity	placebo	6	CAARS	1	0
Reboxetine	NRI	Riahi, 2013 [36]	4	25	6–16	comorbid anxiety disorders	comorbidity	none	4	CPRS, HAM-A	+ (non-controlled)	N/A
Edivoxetine	NRI	Jin, 2013 [37]	0.05–0.3 mg/kg	53	6–17	-	comorbidity	none	22 (avg)	ADHD-RS-IV	+ (non-controlled)	N/A
Edivoxetine	NRI	Lin, 2014 [38]	0.1–0.3 mg/kg	340	6–17	-	comorbidity	LA-methylphenidate, placebo	8	ADHD-RS-IV	1	2
Edivoxetine	NRI	Nery, 2017 [39]	0.1–0.3 mg/kg	267	6–17	-	comorbidity	none	5 years	ADHD-RS-IV	- (non-controlled)	N/A
Duloxetine	SNRI	Mahmoudi-Gharaei, 2011 [42]	60	17	11–18	-	comorbidity	none	6	CPRS	+ (non-controlled)	N/A
Duloxetine	SNRI	Bilodeau, 2014 [43]	60	30	adult	CAARS ≥ 20	comorbidity	placebo	6	CAARS	1	0
Bupropion	NDRI	Jafarinia, 2012 [44]	100–150	44	6–17	ADHD-RS-IV 1.5 SD above the norm	comorbidity, substance abuse	methylphenidate	6	ADHD-RS-IV	2	2
Bupropion	NDRI	Hamedi, 2014 [45]	150	42	adult	-	comorbidity, substance abuse	placebo	6	CAARS	1	1
Dasotraline	SNDRI	Koblan, 2015 [46]	4–8	341	adult	ADHD-RS-IV ≥ 26 and previously treated, or 22 and currently treated	comorbidity	placebo	4	ADHD-RS-IV	1	0
Dasotraline	SNDRI	Findling, 2019 [47]	2–4	342	6–12	ADHD-RS-IV ≥ 28	comorbidity, use of psychoactive drugs other than hypnotics	placebo	6	ADHD-RS-IV	1	0
Dasotraline	SNDRI	Wigal, 2020 [48]	4–6	112	6–12	ADHD-RS-IV ≥ 26	comorbidity	placebo	2	SKAMP; PERMP	1	0
Venlafaxine	SNRI	Zarinara, 2010 [51]	50–75	37	6–13	-	comorbidity	methylphenidate	6	ADHD-RS-IV	2 (power issues)	3
Venlafaxine	SNRI	Amiri, 2012 [52]	225	44	adult	Past ADHD diagnosis or relatives of children with ADHD	comorbidity	placebo	6	ADHD-RS-IV	0	0
Tipepidine	GIRK inhibitor	Sasaki, 2014 [55]	30	10	9–11	-	comorbidity	none	4	ADHD-RS-IV	+ (non-controlled)	N/A
Tipepidine	GIRK inhibitor	Tomoda, 2015 [56]	N/A	12	9–11	-	comorbidity	none	4	ADHD-RS-IV	+ (non-controlled)	N/A
Tipepidine	GIRK inhibitor	Dehbozorghi, 2019 [57]	15–30 (add-on)	53	6–12	treatment with methylphenidate	comorbidity	placebo	8	ADHD-RS-IV	1	1
Vortioxetine	SSRI/NaSSA	Biederman, 2019 [58]	10–20	227	adult	AISRS ≥ 24	comorbidity	placebo	12	AISRS	0	0
N-pantoyl-GABA	GABA agonist	Zavadenko, 2017 [33]	30 mg/kg	89	6–12	ADHD-RS-IV ≥ 22 (girls) or 25 (boys)	comorbidity	placebo	16	ADHD-RS-IV	0	1
N-pantoyl-GABA	GABA agonist	Kupriyanova, 2017 [34]	500–1250 (add-on)	24	6–11	inefficacious treatment with atomoxetine	comorbidity	none	8	CHIP	+ (non-controlled)	N/A
Amantadine	NMDA noncompetitive antagonist	Mohammadi, 2010 [59]	100–150	40	6–14	ADHD-RS-IV 1.5 SD above the norm	comorbidity	methylphenidate	6	ADHD-RS-IV	2	3
Memantine	NMDA noncompetitive antagonist	Surman, 2013 [60]	5–20	34	adult	CGI-S ≥ 4	comorbidity	none	12	AISRS	+ (non-controlled)	N/A
Memantine	NMDA noncompetitive antagonist	Mohammadi, 2015 [61]	20	40	6–11	ADHD-RS-IV 1.5 SD above the norm	comorbidity	methylphenidate	6	ADHD-RS-IV	inferior to methylphenidate	0
Memantine	NMDA noncompetitive antagonist	Mohammadzadeh, 2019 [62]	20	40	adult	Past ADHD diagnosis or relatives of children with ADHD	comorbidity	placebo	6	CAARS	1	0
Memantine	NMDA noncompetitive antagonist	Biederman, 2017 [63]	5–20 (add-on)	26	adult	under stimulant treatment, 2 BRIEF-A subscores > 65 T	comorbidity	placebo	12	BRIEF-A	1	1

(*Continued*)

Table 1. (Continued).

Molecule	Action	Study	Dose range (mg/day)	No of patients (#)	Age (yrs)	Inclusion criteria	Exclusion criteria	Control	Duration (weeks)	Primary outcome	Efficacy opinion*	Safety opinion**
Fasoracetam	mGluR agonist	Elia, 2018 [64]	50–400	30	12–17	Vanderbilt ≥ 16, mutations in genes of glutamatergic signaling	comorbidity	placebo	5	CGI-S	1	1
Org26576	AMPA positive allosteric modulator	Adler, 2012 [65]	200–600	68	adult	CGI-S ≥ 4, AISRS ≥ 22	comorbidity	placebo	8	AISRS	0	0
Melatonin	MTR agonist	Mohammadi, 2012 [67]	3–6 (add-on)	60	7–12	treatment with methylphenidate	comorbidity	placebo	8	SDSC	0	1
Agomelatine	MTR agonist	Niederhofer, 2012 [68]	25 (add-on)	10	17–19	pharmacological treatment	comorbidity	placebo	4	Wender-Utah rating scale	1	1
Agomelatine	MTR agonist	Salardini, 2016 [69]	15–25	54	6–15	ADHD-RS-IV 1.5 SD above the norm	comorbidity	methylphenidate	6	ADHD-RS-IV	2	2
Molindone	D2/H1 antagonism	Stocks, 2012 [70]	10–40	78	6–12	severe problem behavior	comorbidity	none	12	NCBRF behavior subscale	+ (non-controlled)	N/A
MK-0929	D4 antagonist	Rivkin, 2012 [71]	15	35	adult	AISRS ≥ 20	comorbidity	placebo	9	AISRS	0	1
Sativex	THC+CBD	Cooper, 2017 [72]	10.8 + 10–11.6 + 20	30	adult	CAARS ≥ 24	comorbidity, substance abuse	placebo	6	QbTest	0	1
MK-0249	H3 inverse agonist	Herring, 2012 [73]	10	72	adult	CAARS ≥ 24	comorbidity	LA-methylphenidate, placebo	10	AISRS	0	2
Bavisant	H3 antagonist	Weisler, 2012 [74]	1–10	424	adult	CAARS age-dependent threshold	comorbidity	LA-methylphenidate, atomoxetine, placebo	6	ADHD-RS-IV	0	0
2-pyridylacetic acid	metabolite of betahistine (H3 antagonist, H1 weak antagonist)	Moorthy, 2015 [75]	50–200	16	adult	CAARS ≥ 20	comorbidity	placebo	acute	CPT, SSRT	1	1
Pozanicline	nAChR α4β2 partial agonist	Wilens, 2011 [77]	0.085–0.7 mg/kg	393	6–12	CGI-S ≥ 4	comorbidity, previous non-response to stimulants	atomoxetine, placebo	6	ADHD-RS-IV	0	1
Pozanicline	nAChR α4β2 partial agonist	Apostol, 2012 [78]	2–80	221	adult	CGI-S ≥ 4	comorbidity	placebo	12	CAARS	1	1
Pozanicline	nAChR α4β2 partial agonist	Bain, 2012 [79]	40–80	160	adult	CGI-S ≥ 4	comorbidity	none	8	CAARS	0	0
Sofiniclin	nAChR α4β2 agonist	Bain, 2013 [81]	1–8	243	adult	CGI-S ≥ 4	comorbidity	atomoxetine, placebo	10	CAARS	1	3
AZD1446	nAChR α2β2/α4β2 agonist	Jucaite, 2014 [82]	30–240	79	adult	CGI-S ≥ 4	comorbidity	placebo	12	CAARS	0	1
AZD3480	nAChR α4β2 agonist	Potter, 2014 [83]	5–50	30	adult	CGI-S ≥ 4	comorbidity, smokers	placebo	12	CAARS	1	1

*Efficacy opinion: 0, not different from placebo; 1, superior to placebo; 2, not different from active treatment; 3, superior to active treatment; +, positive opinion (non-controlled study); -, negative opinion (non-controlled study).
**Safety opinion: 0, worse than placebo; 1, not different from placebo; 2, not different from active treatment; 3, superior to active treatment.

Table 2. Experimental treatments for ADHD – drugs without public results.

Molecule	Group	Action	Status	Age	Sponsor
BLI-1008	noradrenergic	NRI	phase 2 ongoing	adults	BioLite
Centanafadine	serotoninergic/dopaminergic/noradrenergic	SNDRI	phase 3 ongoing	adults	Otsuka
OPC-64005	serotoninergic/dopaminergic/noradrenergic	SNDRI	phase 2 completed	adults	Otsuka
Oxytocin nasal spray	hormone	OTR agonist	phase 1 ongoing	adults	nonprofit
Oxytocin nasal spray	hormone	OTR agonist	phase 2 ongoing	children	nonprofit
CX717	glutamatergic	AMPA positive allosteric modulator	unclear-phase 2		
Ampreloxetine	noradrenergic	NRI	discontinued-phase 2		
AR08	noradrenergic	unknown, functional agonist	discontinued-phase 2		
Bradanicline	cholinergic	nAChR α7 partial agonist	discontinued-phase 2		
Brilaroxazine	serotoninergic/dopaminergic	D2, D3, D4, 5-HT1A, 5-HT2A partial agonist and 5-HT2A, 5-HT2B, 5-HT6, 5-HT7 antagonist	discontinued-phase 1		
Ciforadenant	purinergic	A2A antagonist	discontinued-phase 2		
GlyTI-M	glycinergic	Glycine transporter I inhibitor	discontinued-phase 2		
IRL-752	serotoninergic/noradrenergic	5-HT7 antagonist and NE α antagonist	discontinued-phase 1		
Opipramol+nicotine	cholinergic/opioid	σ agonist, nAChR agonist	discontinued-phase 2		
Vafidemstat	dopaminergic/noradrenergic/other	KDM1A and MAO-B inhibitor	discontinued-phase 2		

study lasting 6 weeks where 100–150 mg/d bupropion were compared with 20–30 mg/d methylphenidate (depending on weight). The Authors concluded that bupropion was not different from methylphenidate regarding efficacy; however, they stated that a vastly larger sample size would have been required to statistically support non-inferiority. Adverse events were similar in quality and frequency.

Bupropion was tested [45] in adults. This 6-weeks parallel arm placebo controlled randomized double-blind trial used bupropion at a fixed 150 mg/d dose. Bupropion was significantly more effective than placebo after 6 weeks of treatment, while it was statistically as safe as placebo. However, we stress that several important adverse events were nominally more frequent with bupropion, including agitation, palpitations and paresthesia. Moreover, the Authors mentioned a sizable number of drop-outs, without clarifying the numbers and prevalence per arm, a fact that would suggest, in our opinion, an unsatisfying tolerability with bupropion.

6.1.4. SNDRIs

6.1.4.1. Dasotraline (novel emerging). Dasotraline is a triple reuptake inhibitor with a preference for dopamine and norepinephrine and a five-fold weaker affinity for the serotonin transporter. In preclinical tests, dasotraline significantly reduced impulsive and immediate reward choices, similarly to methylphenidate. In humans, dasotraline may be optimal for a once-daily administration, due to slow absorption and long half-life.

Dasotraline was tested in a placebo controlled randomized double-blind trial [46] in adults. Dasotraline 4–8 mg/d was administered for 4. The use of hypnotic Z-drugs (Zaleplon, Zolpidem, Zopiclone) was allowed to manage adverse events. Tolerability was good with dasotraline 4 mg/d (11% drop-outs vs. 9% for placebo) but not 8 mg/d (49% drop-outs). However, only the 8 mg/d arm showed significant reductions of the ADHD symptoms. The adverse events reported most frequently were insomnia, decreased appetite, nausea and dry mouth.

Another placebo controlled randomized double-blind trial [47] was conducted in children. Dasotraline was used at 2 or 4 mg/d for 6 weeks. Drop-out rates were similar across treatment arms (from 20 to 24%); however, in the 4 mg/d arm half of the drop-outs were due to adverse events, as compared to a quarter in the 2 mg/d arm. Treatment with 4 mg/d dasotraline, but not 2 mg/d, was superior to placebo on ADHD symptoms starting with the first week of treatment. The adverse events most frequent were insomnia, decreased appetite and weight, irritability and non-serious psychotic symptoms. Dasotraline 4 mg/d was thus effective, with some safety concerns.

A similar pediatric trial [48] tested dasotraline 4 and 6 mg/d at bedtime against placebo in a randomized double-blind manner, using academic performance scales as primary outcomes. The 6 mg/d arm was discontinued during the trial due to a 15% drop-out rate for adverse events, while the 4 mg/d arm showed a 5% drop-out rate, all due to adverse events, which was better than that of placebo (11%). Dasotraline 4 mg/d resulted in significant improvements on academic performances, sustained throughout the day. Common adverse events occurring significantly more for dasotraline 4 mg/d were insomnia, headache and decreased

appetite. Five percent (three) patients reported hallucinations connected with dasotraline, which resolved in 2/3 cases without altering treatment. Weight reduction was reported without stating its significance. Dasotraline 6 mg/d showed a higher incidence of insomnia, hallucinations, affect lability and larger weight loss, suggesting in our opinion low tolerability at high dose.

6.1.4.2. Centanafadine (novel emerging). Centanafadine is a triple reuptake inhibitor, with preferential potency for NE and DA and a mild effect on 5-HT in a ratio of 1:6:14, respectively; its sustained-release form is currently being development by Neurovance (Otsuka) in phase 3 for adult ADHD [49].

6.1.4.3. OPC-64005 (novel emerging). OPC-64005 is a triple reuptake inhibitor by Otsuka, which recently completed a phase 2 trial. Results should be soon published [50].

6.1.4.4. Venlafaxine (repurposed emerging). Venlafaxine is an inhibitor of monoamines reuptake, with a dose-dependent specificity. At low dose (75 mg) venlafaxine is an SSRI; at higher doses (150–225 mg) it acts as SNRI, while also having a weak effect on dopamine reuptake.

A randomized double-blind trial of venlafaxine [51] was conducted in children. Low-dose venlafaxine (25 mg x2-3/d) was compared with methylphenidate 20–30 mg/d. The trials lasted 6 weeks. Drop-out rates were equal across arms, while headaches and insomnia were more common with methylphenidate. No efficacy difference emerged.

Venlafaxine was tested also in adults [52]. This randomized double-blind trial lasting 6 weeks used venlafaxine 75 mg x3/d versus placebo. Venlafaxine was nominally more effective than placebo, yet reaching no significantly larger effect. Tolerability was similar, as the only adverse effect ascribed to venlafaxine was sexual dysfunction.

6.2. Other monoamine-based mechanisms

6.2.1. Tipepidine (novel emerging)

Tipepidine is an inhibitor of G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. This activity has been associated with an increase in monoamine levels in the brain [53] and tipepidine can suppress experimentally induced hyperactivity in rats [54].

Tipepidine was studied [55] in children, in a single-arm trial lasting 4 weeks. Tipepidine was dosed 10 mg x3/d and 7 among 10 children used tipepidine in adjunct to other psychiatric drugs. ADHD symptoms were reduced and there were no drop-outs nor adverse effects. A similar single-arm trial [56] obtained the same results.

A randomized placebo controlled double-blind trial [57] was conducted in children. Tipepidine 5–10 mg x3/d was added to a preexisting methylphenidate therapy (0.3–1.5 mg/kg/d) over 8 weeks. Tolerability was equal and good across arms, adverse events were also reported indifferently; the most common were anorexia, malaise and headache. Tipepidine add-on resulted in a significant incremental improvement of ADHD symptoms, especially hyperactivity – impulsivity.

6.2.2. Vortioxetine (repurposed emerging)

Vortioxetine is a SSRI and selective serotonin-norepinephrine modulator. Since it demonstrated some positive effects on cognition, vortioxetine was tested in a parallel arms randomize controlled trial [58] in adults. Vortioxetine 10 or 20 g/d was confronted with placebo for 12 weeks. Tolerability was similar for all arms, with drop-out rates around 10–15%, while adverse events with vortioxetine were nausea and fatigue. Vortioxetine was not superior to placebo on the main outcome.

6.2.3. Brilaroxazine (on hold)

Brilaroxazine is a multifunctional drug with dopaminergic D2, D3, D4 partial agonism, serotoninergic 5-HT1A, 5-HT2A partial agonism and 5-HT2A, 5-HT2B, 5-HT6, 5-HT7 antagonism. Brilaroxazine underwent phase 1 trials for ADHD, but is now being developed by Reviva Pharmaceuticals for pulmonary hypertension and schizophrenia.

6.3. GABAergic transmission

N-pantoyl-GABA (NPG) (novel emerging) is a fusion analog of GABA and pantothenic acid, which possesses particular neuropharmacological characteristics. It can act as GABA agonist; moreover, it has a dopaminergic effect and stimulates acetylcholine production. Its involvement with attention or ADHD is not clearly based. NPG was studied [33] on 6 children with ADHD without comorbidity. In this double-blind randomized controlled trial against placebo, NPG was titrated over 4 months up to 30 mg/kg in two daily fractions. Efficacy of NPG was not different from placebo at any time point, on the main outcome. However, a significant improvement in the secondary outcomes from the Weiss Functional Impairment Rating Scale (WFIRS) and Toulouse-Pieron test (TPT) was noted after 4 and 1 months, respectively. There were no serious adverse events and NPG performed similarly to placebo regarding safety. NPG was tested also as add-on [34] at the maximum dose of 1250 mg/d, in a single-arm study lasting 2 months. The additional NPG was efficacious from the second week, on the CHIP subscales school performance and risk aversion. Adverse effects were not investigated.

6.4. Glutamatergic transmission

Metabotropic glutamate receptors are functionally different: mGluR1 and 5 have agonistic effects on NMDA receptors while the other mGluRs are antagonists.

6.4.1. Amantadine (repurposed emerging)

Amantadine is a noncompetitive antagonist of NMDA receptors, which increases dopamine release and inhibits dopamine reuptake. It has been used as an antiviral and for Parkinson's dementia. Amantadine was studied [59] in a double-blind randomized controlled trial in children. Amantadine 50 mg, or methylphenidate 10 mg were administered 2 or 3 times per day depending on weight, for 6 weeks. One patient per group dropped out of study and adverse effects were comparable, except for appetite decrease and restlessness, which were more common with methylphenidate. The efficacy of

both treatments was similar at every time-point, with a similar decreasing trend.

6.4.2. Memantine (repurposed emerging)

Memantine is a noncompetitive antagonist of NMDA receptors, licensed for use in dementia, tested for several other psychiatric applications as a stand-alone or adjunct therapy.

Memantine was tested in a single-arm trial [60] on ADHD adults. Memantine doses were individually adjusted up to 10 mg x2/d. The study lasted 12 weeks. A considerable (18%) number of participants did not tolerate memantine, while the others reached the largest dose. The therapeutic effect on ADHD symptoms and neuropsychological parameters was large, to the point that 56% participants were clinically negative at the endpoint. The most common adverse effects included confusion, sedation, dizziness and gastrointestinal and musculoskeletal disturbances.

Memantine was tested also in children [61]. This randomized double-blind parallel arms trial compared memantine 10 mg x2/d versus methylphenidate 10 mg x2 or 3/d depending on weight. The study lasted 6 weeks. A significantly higher proportion of patients dropped out of memantine treatment as compared with methylphenidate (35% vs. 5%), which was not stressed by the Authors. Among study completers, there was no difference between memantine and methylphenidate treatments regarding adverse events, nor ADHD symptoms at any time point. However, there was a significant difference in the change of scores over time, indicating a larger reduction with methylphenidate. Memantine seemed to be less effective than methylphenidate in this study and, in our opinion, also less tolerable.

Memantine was tested again in a double-blind randomized controlled trial versus placebo in adults [62]. Memantine was used at 10 mg x2/d for 6 weeks. A sizable number of patients dropped out of memantine treatment as compared with placebo (30% vs. none), which was again not stressed by the Authors. Among study completers, there was no difference in the occurrence of adverse events, while memantine resulted much superior to placebo in the reduction of ADHD symptoms. Memantine was effective in reducing ADHD symptoms but in our opinion the higher rate of drop-out suggested tolerability issues, not reported by the Authors.

A different group of investigators [63] tried memantine as an add-on treatment to improve executive functions in adults with ADHD. This 12-week double-blind randomized controlled trial used memantine up to 10 mg x2/d versus placebo. Patients treated with additional memantine showed no significant increases in adverse events and similar rates of discontinuation as compared to those who received additional placebo. Inhibition and self-monitoring problems were significantly improved by memantine addition, while organization problems were worsened. No effect of additional memantine treatment was found on core ADHD symptoms.

6.4.3. Glutamatergic drugs on hold

Fasoracetam is a nonselective agonist of all mGluRs, with a non-clarified dose specificity. Fasoracetam was tested [64] in adolescents with ADHD and mutations in genes connected with the glutamatergic signaling, resulting to be tolerated and efficacious in this selected population. Four other clinical trials have been conducted with fasoracetam in the pediatric age, lasting up to summer 2019, but no results have been published and the sponsor does not have fasoracetam anymore in its pipeline. **Org25676** is a positive allosteric modulator of AMPA receptors, tested [65] in adults. Org25676 demonstrated potential efficacy and safety at a low dose, not with higher and flexible doses. **GlyTI-M** is an inhibitor of the glycine transporter I, which should affect the NMDA glutamatergic functioning; it was tested up to phase 2 by a nonprofit sponsor in Taiwan [66]. Its status is unknown.

6.5. Melatoninergic transmission

6.5.1. Melatonin (repurposed emerging)

Melatonin has been tested [67] at the prescription dose of 3–6 mg versus placebo in a parallel arms randomized double-blind trial in add-on to methylphenidate, in children. Melatonin had non-significant effect in contrasting the sleep deteriorations due to methylphenidate. In addition to the conclusions of the Authors, we remark that melatonin was more tolerable than placebo, as shown by respective drop-out rates of 7% and 25%. However, in retainers, melatonin caused more sadness than placebo.

6.5.2. Agomelatine (repurposed emerging)

Agomelatine is a multifunctional drug that combines melatoninergic agonism with serotoninergic 5-HT2C antagonism, possibly gaining an advantage over melatonin. It is currently used for the treatment of major depression forms with important shifts in the circadian rhythm.

Agomelatine was tested [68] as an add-on. This 4-weeks open-label trial of agomelatine 25 mg/d against placebo lasted 4 months. The authors did not report safety results, claiming agomelatine was similar to placebo in tolerability. In spite of the minimal sample size, agomelatine was superior to placebo in all sub-scores of the main measure. Agomelatine add-on to methylphenidate resulted to be safe and efficacious in increasing the improvement of ADHD core symptoms.

Agomelatine was tested also as a separate treatment [69] in children, in a 6 weeks parallel arms randomized double-blind trial. Agomelatine was used at 15–25 mg/d versus methylphenidate 20–30 mg/d. The two treatments displayed similar results on ADHD symptoms and the trial was adequately powered to claim non-inferiority. The Authors concluded that the treatments were equally safe; however, we noted that agomelatine tended to be safer than methylphenidate: the drop-outs were not different, while methylphenidate caused non-significantly more insomnia (24% vs. 4%, $p = 0.09$) and headache reactions (28% vs. 8%, $p = 0.13$).

6.6. Dopaminergic transmission

6.6.1. D2 receptors and molindone (repurposed emerging)

The mechanism of action of antipsychotic is predominantly based on D2 dopaminergic and H1 histaminergic antagonism.

Molindone was tested [70] at 10–40 mg/d on pediatric patients in a parallel arms non-controlled trial lasting 12 weeks. Adverse events were dose dependent in frequency and intensity and were mainly somnolence, weight increase, akathisia, sedation and abdominal pain. ADHD symptoms were reduced around 30% with molindone 10–30 mg/d and around 50% with 40 mg/d. No further trials of molindone were published.

6.6.2. D4 receptors and MK-0929 (on hold)

The D4 antagonist MK-0929 was evaluated [71] in adults, where it showed no efficacy.

6.7. Cannabinoid transmission

Sativex (repurposed emerging) is an oromucosal spray composed of equal parts of delta-9-tetrahydrocannabinol and cannabidiol, which has been tested [72] in adults. This double-blind randomized controlled trial against placebo lasted 2 weeks of titration and 4 at fixed dose. Tolerability was good and similar across treatment arms, adverse effects were minimal and those typical of sativex were mainly lightheadedness and diarrhea. No significant effect was found for sativex with respect to placebo, although some distinct sub-scores showed signs of improvement. The Authors concluded that the good effect seen in some participants for some indices, but not all participants and indices, is in keeping with the self-administration pattern frequently seen with ADHD patients.

6.8. Histaminergic transmission (drugs on hold)

MK-0249, a H3 inverse agonist, was tested [73] in adults, resulting in no appreciable efficacy and in increased insomnia. Bavisant, a highly selective H3 antagonist was tested [74] in adults, in which it was considered not efficacious. Adverse events occurring more with bavisant were insomnia (dose-dependent), abnormal dreams, dysgeusia, nausea and dizziness. 2-pyridylacetic acid is the major metabolite of betahistine, which is an analogue of histamine known to be a potent antagonist of H3 and weak antagonist of H1 receptors. It was tested [75] in adults, producing promising phase 1–2 results on the acute administration; however, no further trials or publications were found.

6.9. Nicotinic cholinergic transmission (drugs on hold)

Several partial and full agonists, for nAChR α4β2, have been tried in patients with ADHD. Pozanicline (ABT-089) [76] is a specific α4β2 partial agonist tested in children and adults [77–79]. It never showed a convincing dose-dependent response over placebo. Sofiniclin (ABT-894) [80] is a nAChR α4β2 full agonist. For this reason, a better efficacy was expected, after the failure of pozanicline. It was tested against atomoxetine [81], finding a similar effect, with possibly less adverse effects; however, sofiniclin was not investigated further. AZD1446 is a full agonist of the nAChR α4β2 and α2β2 tested [82] on adults on which it demonstrated no different efficacy or safety as compared with placebo. AZD3480 is a nAChR α4β2 full agonist tested [83] in adults with good tolerability and significant reduction of inattentive symptoms and memory problems and of emotional lability/impulsivity. Response inhibition was improved greatly. No further publications are available for AZD3480, nor clinical trials, despite a plausible usefulness. Bradanicline is a partial agonist of nAChR α7 cholinergic receptors developed by Targacept; it was discontinued after reaching phase 2 due to a lack of efficacy [84].

6.10. Other mechanisms and drugs without published results

CX717 (unclear status) is a positive allosteric modulator of AMPA receptors. Cortex Pharmaceuticals developed it up to phase 2; however, results were not published [85]. RespireRX has acquired it and its development status for ADHD is not clear. Oxytocin (repurposed emerging) in the form of nasal spray is currently undergoing nonprofit trials. Oxytocin is in phase 1 for cognitive aspects of ADHD in adults [86] and phase 2 for social and affective aspects of ADHD in children [87]. ND-0801 (on hold) by Neuroderm is a patch containing a combination of opipramol, which is a σ receptor agonist, and nicotine; it was discontinued after reaching phase 2 [88]. Ciforadenant (on hold) is an antagonist of A2A purinergic receptors, which reached phase 2 for the treatment of ADHD, but was discontinued. It is currently being developed as an anticancer drug by Corvus Pharmaceuticals.

7. Conclusion

More than one of the revised studies reported promising results in both children and adults. Most of them require replication studies for the considered drug to be used in clinical practice. All the monoaminergic reuptake inhibitors have a great potential to improve ADHD symptoms as they are active on the same mechanisms exploited by the currently-used drugs. The first tested NRIs, reboxetine and edivoxetine, unfortunately did not show the expected efficacy and all the study reported high level of dropouts mainly for side effects. A novel NRI, viloxazine, emerged to be more effective and with less side effects of the first tested NRIS (i.e. reboxetine and edivoxetine). Although less tolerable than placebo, and with unclear psychiatric adverse effects, it may be a valid option for treating ADHD in children. Following promising phase 2 results, viloxazine phase 3 trials are currently ongoing on both children and adults. Data on SNRI duloxetine are not conclusive and might be investigated further, ideally in larger controlled trials that escalate dose slowly, to minimize the impact of adverse events on therapy retention. Overall, the NDRI bupropion, even though it has been used to treat ADHD symptoms off-label for almost two decades, was only moderately effective and possibly more tolerable than methylphenidate for the treatment of patients with ADHD devoid of addictions. However, adequately powered, actively controlled randomized studies are required to support its use.

Both SNDRIs venlafaxine and, dasotraline might be a useful treatment option for childhood ADHD. However the number, size and reliability of studies on Venlafaxine need to be

increased, despite the frequent off-label use to treat ADHD especially in the U.S.

Dasotraline appears as a potentially valid treatment for pediatric ADHD, mainly due to its slow pharmacokinetics that allow bedtime administration and guarantee sustained performance through the following day. Its safety profile seems to be heavily dose-dependent and the therapeutic index may be narrow. An application for dasotraline was evaluated by the FDA and provisionally denied authorization for ADHD [52], pending further studies on safety. Other SNDRIs are on phase 2 and on phase 3 in adults with initially promising results.

Of the other monoamine active drugs, the only with promising results emerged to be Tipepidine, an inhibitor of G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. This new drug showed promising results as add-on therapy to methylphenidate, with a good tolerability profile. More studies are required.

The SSRI/NaSSA Vortioxetine might be further investigated for adult ADHD as provisional results are not convincing.

Moderation of glutamatergic system using drugs that seems to improve problems in cognitive function in other disorders like Parkinson's Disorders brought to some interesting results also in ADHD patients. Both amantadine in children and memantine in adults showed to be effective especially as add-on therapy at lower dosage to improve residual problems in executive functions. At higher dosages memantine raised some safety concerns, its use was associated with sizable dropout rates (around 30%). Also fasoracetam showed some promising results in a genetic selected adolescent population, as well as Org25676 in adults, but no replication studies are currently available.

The only study on melatonin as add-on therapy on side effect of methylphenidate showed limited evidence for efficacy; theoretically, melatonin may not be a good add-on choice for patients who have a drug-induced sympathetic activation, due to the susceptibility of melatonin to degradation.

On the contrary agomelatine would not be subjected to the physiological destruction of melatonin, and it seems to be a safe and potentially efficacious treatment for ADHD core symptoms. Whether this depends on the regularization of circadian rhythms or on direct effects, is yet to be clarified. The role of add-on or stand-alone therapy should be clarified by further studies, as agomelatine seems a promising option.

Boosting acetylcholine function through nicotinic receptor modulators may be a promising strategy especially for selected patient populations, without nicotinic addition. Full agonists (sofiniclin and AZD3480) showed higher efficacy than partial agonists (pozanicline). Sofiniclin could be suitable especially for patients who are intolerant to atomoxetine side effects. However, more data are needed but at present no ongoing studies are available.

Compounds active on GABAergic and histaminergic systems showed inconclusive results. Similarly, compounds blocking dopaminergic transmission did not show any efficacy on the core symptoms of ADHD. The use of cannabinoids in ADHD has no clear rationale and the only study available reported unclear results. Future studies need to focus on the different ratios of THC and CBD.

Future clinical studies on treatments for ADHD should include, aside clinical scoring tools, outcomes involving brain imaging. The effectiveness of stimulant drugs has been associated with the attenuation of ADHD-related abnormalities in brain structure, connectivity and function, in particular in the prefrontal cortex, basal ganglia, right amygdala, corpus callosum and cerebellum [89,90]. The use of structural/functional-MRI and/or Magnetic Resonance Spectroscopy (MRS) in combination with pharmacological trials, can help to identify the neural targets and mechanisms of action of new treatments in order to develop targeted therapies and to meet the needs of individual patients (precision medicine). The functional Near Infrared Spectroscopy (fNIRS) is another promising technique for studying metabolic alterations in the cerebral cortex and the effects of pharmacotherapies [91,92]. For instance, this tool has highlighted a frontal-cortical hypo-metabolism in children with ADHD performing neuropsychological tasks and an increase in the concentration of oxygenated hemoglobin in the same brain areas of patients receiving methylphenidate/atomoxetine. Techniques such as these may be particularly helpful when investigating novel drugs and mechanisms of action.

8. Expert opinion

In children and adolescents, stimulants are very effective. Concern is about their safety and potential for abuse or misuse, especially for amphetamine. The commonest adverse effects of stimulants include decreased appetite, including increased risk of growth retardation in weight and height, insomnia, stomachache, and headache, tics, increases in blood pressure [8–10]. Atomoxetine is recommended as monotherapy for the treatment of ADHD for individuals with ADHD and comorbidities including tics, mania, and suicidal ideation [7,13] even though the effect of atomoxetine on mania and suicidal ideation has not yet been clarified [93,94].

According to this perspective, innovative drugs for pediatric ADHD should be as effective as stimulants but with less adverse effects, sparing appetite, growth and sleep. Only a few drugs seem to fulfil these requirements.

The most promising innovative drugs seem to be agomelatine, both as an add-on or standalone therapy, and the glutamatergic ones: especially Amantadine and Fasoracetam, which would deserve more studies.

Among drugs active on noradrenergic and dopaminergic systems dasotraline showed comparable efficacy and less adverse effects then methylphenidate, but more data are needed to identify the correct dose range to support market access request.

Also, the NRI edivoxetine showed quite good efficacy, but the safety profile was similar to that of atomoxetine (including nausea vomiting and somnolence), even though better than methylphenidate (including sleep disorder, reduced appetite-weight loss).

Tipepidine, a GIRK inhibitor, deserves special attention for its potential efficacy as add-on treatment on symptoms of hyperactivity and impulsivity not completely responding to methylphenidate.

In adults, innovative drugs should treat comorbidities and avoid risks of misuse.

None of the numerous studies revised seemed to address directly the problem of comorbidity, except for the comorbidity with nicotine abuse. Nevertheless, some studies could be interesting, especially those using drugs that have proven to be effective in depressive and anxiety disorders.

Memantine, both as add-on or stand-alone has good potential, especially for inattentive symptoms and memory problems, and may reduce significantly emotional lability and impulsivity, even though more studies are needed. Both SNDRIs venlafaxine and dasotraline showed good efficacy, but dasotraline has some safety concerns that require further verification.

Imaging techniques such as MRI, fMRI, MRS, fNIRS should be implemented in future clinical trials to be probed as markers of drug efficacy.

Funding

This work was supported by the Italian Ministry of Health (Ricerca Corrente, to MP and MN) grants that are gratefully acknowledged. The funding public institution had no role in any part of the work.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they have received research support, writing support, has participated in advisory boards, or been a consultant and/or speaker for Allergan, Emalex Biosciences, Takeda, Lundbeck, Pearson, Akili Interactive, Arbor Pharmaceuticals, Cingulate Therapeutics, Ironshore Pharmaceuticals, Forest Laboratories, Aevi Genomic Medicine, Neos Therapeutics, Neurovance, Otsuka, Pfizer, Purdue Pharma, Adlon Therapeutics, Rhodes Pharmaceuticals, Sunovion, Tris Pharma, KemPharm, Supernus Pharmaceuticals, NLS Pharma and Jazz Pharmaceuticals. They also are the recipient of a U.S. Food and Drug Administration Grant. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington [etc.]: American Psychiatric Publishing; 2013.
2. Polanczyk GV, Salum GA, Sugaya LS, et al. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015;56:345–365.

• **Provides a complete epidemiological description of ADHD among underage people.**

3. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164:942–948.
4. Simon V, Czobor P, Balint S, et al. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry. 2009;194:204–211.

• **Provides a complete epidemiological description of ADHD among adult people.**

5. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit /hyperactivity disorder. Nat Rev Dis Primers. 2015;1:15020.
6. World Health Organization. International statistical classification of diseases and related health problems. 11th revision. Geneva: World Health Organization; 2018.
7. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet. 2020;395:450–462.

•• **State of the art and advances in the understanding, diagnosis and treatment of ADHD.**

8. Ahmed R, Aslani P. Attention-deficit/hyperactivity disorder: an update on medication adherence and persistence in children, adolescents and adults. Expert Rev Pharmacoecon Outcomes Res. 2013;13:791.
9. Schachter HM, Pham B, King J, et al. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. Can Med Assoc J. 2001;165:1475–1488.
10. Feldman ME, Charach A, Bélanger SA. ADHD in children and youth: part 2-Treatment. Paediatr Child Health. 2018;23:462–472.

•• **Comprehensive review of current pharmacological treatments for ADHD.**

11. Klein RG, Landa B, Mattes JA, et al. Methylphenidate and growth in hyperactive children. A controlled withdrawal study. Arch Gen Psychiatry. 1988;45:1127.
12. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev. 2018;6:CD007990.
13. Cunill R, Castells X, Tobias A, et al. Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. Pharmacoepidemiol Drug Saf. 2013;22:961–969.
14. Wu B, Bruns EJ, Tai M, et al. Psychotropic polypharmacy among youths with serious emotional and behavioral disorders receiving coordinated care services. Psychiatric Serv. 2018;69:716–722.
15. Sobel LJ, Bansal R, Maia TV, et al. Basal ganglia surface morphology and the effects of stimulant medications in youth with attention deficit hyperactivity disorder. Am J Psychiatry. 2010;167:977–986.
16. Matosin N, Fernandez-Enright F, Fung SJ, et al. Alterations of mGluR5 and its endogenous regulators Norbin, Tamalin and Preso1 in schizophrenia: towards a model of mGluR5 dysregulation. Acta Neuropathol. 2015;130:119–129.
17. Olsen CM, Childs DS, Stanwood GD, et al. Operant sensation seeking requires metabotropic glutamate receptor 5 (mGluR5). PloS One. 2010;5:e15085.
18. Park G, Jung Y, Park M, et al. Melatonin inhibits attention-deficit/hyperactivity disorder caused by atopic dermatitis-induced psychological stress in an NC/Nga atopic-like mouse model. Sci Rep. 2018;8:1–13.
19. Molina-Carballo A, Naranjo-Gómez A, Uberos J, et al. Methylphenidate effects on blood serotonin and melatonin levels may help to synchronise biological rhythms in children with ADHD. J Psychiatr Res. 2013;47:377–383.
20. Yuen EY, Yan Z. Dopamine D4 receptors regulate AMPA receptor trafficking and glutamatergic transmission in GABAergic interneurons of prefrontal cortex. J Neurosci. 2009;29:550–562.
21. Bossong M, Mehta M, van Berckel B, et al. Further human evidence for striatal dopamine release induced by administration of Δ9-tetrahydrocannabinol (THC): selectivity to limbic striatum. Psychopharmacology (Berl). 2015;232:2723–2729.
22. Bossong MG, van Berckel BNM, Boellaard R, et al. Delta 9-Tetrahydrocannabinol induces dopamine release in the human striatum. Neuropsychopharmacology. 2009;34:759–766.
23. Voruganti LNP, Slomka P, Zabel P, et al. Cannabis induced dopamine release: an in-vivo SPECT study. Psychiatry Res. 2001;107:173–177.
24. Barkus E, Morrison PD, Vuletic D, et al. Does intravenous Δ9-tetrahydrocannabinol increase dopamine release? A SPET study. J Psychopharmacol. 2011;25:1462.
25. Stokes PRA, Mehta MA, Curran HV, et al. Can recreational doses of THC produce significant dopamine release in the human striatum? Neuroimage. 2009;48:186–190.

26. Potter AS, Newhouse PA, Bucci DJ. Central nicotinic cholinergic systems: a role in the cognitive dysfunction in attention-deficit/hyperactivity disorder? Behav Brain Res. 2006;175:201–211.
27. Potter AS, Newhouse PA. Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder. Pharmacol Biochem Behav. 2008;88:407–417.
28. Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol. 2004;74:363–396.
29. Levin ED, Rezvani AH. Nicotinic-antipsychotic drug interactions and cognitive function. EXS. 2006;98:185.
30. Lin JS, Sakai K, Vanni-Mercier G, et al. Involvement of histaminergic neurons in arousal mechanisms demonstrated with H3-receptor ligands in the cat. Brain Res. 1990;523:325.
31. Johnson JK, Liranso T, Saylor K, et al. A phase II double-blind, placebo-controlled, efficacy and safety study of SPN-812 (extended-release viloxazine) in children with ADHD. J Atten Disord. 2020;24:348–358.
32. McBurnett KR A study of PDC-1421 treatment in adult patients with attention-deficit hyperactivity disorder (ADHD). 2016 Mar 1 [last updated 2020 Jan 18; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT02699086 ClinicalTrials.gov Identifier: NCT02699086
33. Zavadenko NN, Suvorinova NY, Vakula IN, et al. Pharmacotherapy of attention deficit hyperactivity disorder in children: the results of a multicenter double-blind placebo-controlled study of hopantenic acid. Zh Nevrol psikhiatr im S.S. Korsakova. 2017;117:39.
34. Kupriyanova TA, Koren EV, Alabusheva NN. A strategy for increasing the efficiency of psychopharmacological treatment of hyperkinetic behavior disorder with pantogam. Zh Nevrol psikhiatr im S.S. Korsakova. 2017;117:75.
35. Riahi F, Tehrani-Doost M, Shahrivar Z, et al. Efficacy of reboxetine in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial. Hum Psychopharmacol. 2010;25:570–576.
36. Riahi F, Tashakori A, Izadi-Mazidi S, et al. Effectiveness of reboxetine in treatment of outpatient children and adolescents with attention deficit-hyperactivity disorder with comorbid anxiety disorders. Iran J Psychiatry. 2013;8:195–200.
37. Jin L, Xu W, Krefetz D, et al. Clinical outcomes from an open-label study of edivoxetine use in pediatric patients with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2013;23:200.
38. Lin DY, Kratochvil CJ, Xu W, et al. A randomized trial of edivoxetine in pediatric patients with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2014;24:190.
39. Nery ESM, Bangs M, Liu P, et al. Long-term, open-label, safety study of edivoxetine monotherapy in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2017;27:700.
40. Theravance Biopharma, Inc. A Study of TD-9855 in Adults With Attention-Deficit/Hyperactivity Disorder (ADHD). 2011 Oct 20 [last updated 2019 Dic 9; no results posted: certification/extension first submitted 2018 Sept 10; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01458340 ClinicalTrials.gov Identifier: NCT01458340.
41. Downey L AR08 for Treatment of ADHD in Children. 2013 June 11 [last updated 2015 Dic 9; no results posted: certification/extension first submitted 2015 Jun 5; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01876719 ClinicalTrials.gov Identifier: NCT01876719
42. Mahmoudi-Gharaei J, Dodangi N, Tehrani-Doost M, et al. Duloxetine in the treatment of adolescents with attention deficit/hyperactivity disorder: an open-label study. Hum Psychopharmacol. 2011;26:155–160.
43. Bilodeau M, Simon T, Beauchamp MH, et al. Duloxetine in adults with ADHD: a randomized, placebo-controlled pilot study. J Atten Disord. 2014;18:169.
44. Jafarinia M, Mohammadi M, Modabbernia A, et al. Bupropion versus methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder: randomized double-blind study. Hum Psychopharmacol. 2012;27:411–418.
45. Hamedi M, Mohammdi M, Ghaleiha A, et al. Bupropion in adults with attention-deficit/hyperactivity disorder: a randomized, double-blind study. Acta Med Iran. 2014;52:675–680.
46. Koblan KS, Hopkins SC, Sarma K, et al. Dasotraline for the treatment of attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled, proof-of-concept trial in adults. Neuropsychopharmacology. 2015;40:2745–2752.
47. Findling RL, Adler LA, Spencer TJ, et al. Dasotraline in children with attention-deficit/hyperactivity disorder: a six-week, placebo-controlled, fixed-dose trial. J Child Adolesc Psychopharmacol. 2019. DOI:10.1089/cap.2018.0083
48. Wigal SB, Hopkins SC, Koblan KS, et al. Efficacy and safety of dasotraline in children with ADHD: a laboratory classroom study. J Atten Disord. 2020;24:192.
49. Otsuka Pharmaceutical Development & Commercialization, Inc. A trial evaluating the long-term safety and tolerability of centanafadine sustained-release tablets in adults with attention-deficit/hyperactivity disorder. 2018 June 28 [last updated 2020 Jan 31; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT03605849 ClinicalTrials.gov Identifier: NCT03605849.
50. Otsuka Pharmaceutical Development & Commercialization, Inc. The Safety and Efficacy of OPC-64005 in the Treatment of Adult Attention-deficit/Hyperactivity Disorder. 2017 Oct 25 [last updated 2019 Oct 9; no results posted: certification/extension first submitted 2019 Oct 1; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT03324581 ClinicalTrials.gov Identifier: NCT03324581
51. Zarinara A, Mohammadi M, Hazrati N, et al. Venlafaxine versus methylphenidate in pediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Hum Psychopharmacol. 2010;25:530–535.
52. Amiri S, Farhang S, Ghoreishizadeh MA, et al. Double-blind controlled trial of venlafaxine for treatment of adults with attention deficit/hyperactivity disorder. Hum Psychopharmacol. 2012;27:76.
53. Takahama K. Multiple pharmacological actions of centrally acting antitussives — do they target g protein-coupled inwardly rectifying K+ (GIRK) channels? J Pharmacol Sci. 2012;120:146–151.
54. Soeda F, Fujieda Y, Kinoshita M, et al. Centrally acting non-narcotic antitussives prevent hyperactivity in mice: involvement of GIRK channels. Pharmacol Biochem Behav. 2016;144:26–32.
55. Sasaki T, Hashimoto K, Tachibana M, et al. Tipepidine in children with attention deficit/hyperactivity disorder: a 4-week, open-label, preliminary study. Neuropsychiatr Dis Treat. 2014;10:147–151.
56. Tomoda A, Takiguchi S, Fujisawa TX, et al. Effectiveness of oral tipepidine administration for children with attention deficit/hyperactivity disorder: a 4-week, open-label clinical study: effectiveness of tipepidine in ADHD. Psychiatry Clin Neurosci. 2015;69:658–659.
57. Dehbozorghi S, Bagheri S, Moradi K, et al. Efficacy and safety of tipepidine as adjunctive therapy in children with attention-deficit/hyperactivity disorder: randomized, double-blind, placebo-controlled clinical trial. Psychiatry Clin Neurosci. 2019;73:690–696.
58. Biederman J, Lindsten A, Sluth LB, et al. Vortioxetine for attention deficit hyperactivity disorder in adults: a randomized, double-blind, placebo-controlled, proof-of-concept study. J Psychopharmacol. 2019;33:511.
59. Mohammadi M, Kazemi M, Zia E, et al. Amantadine versus methylphenidate in children and adolescents with attention deficit/hyperactivity disorder: a randomized, double-blind trial. Hum Psychopharmacol. 2010;25:560–565.
60. Surman CBH, Hammerness PG, Petty C, et al. A pilot open label prospective study of memantine monotherapy in adults with ADHD. World J Biol Psychiatry. 2013;14:291.

61. Mohammadi MR, Mohammadzadeh S, Akhondzadeh S. Memantine versus methylphenidate in children and adolescents with attention deficit hyperactivity disorder: a double-blind, randomized clinical trial. Iran J Psychiatry. 2015;10:106–114.
62. Mohammadzadeh S, Ahangari TK, Yousefi F. The effect of memantine in adult patients with attention deficit hyperactivity disorder. Hum Psychopharmacol. 2019;34:e2687-n/a.
63. Biederman J, Fried R, Tarko L, et al. Memantine in the treatment of executive function deficits in adults with ADHD. J Atten Disord. 2017;21(4):343.
64. Elia J, Ungal G, Kao C, et al. Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. Nat Commun. 2018;9:4–9.
65. Adler LA, Kroon RA, Stein M, et al. A translational approach to evaluate the efficacy and safety of the novel AMPA receptor positive allosteric modulator org 26576 in adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012;72:971–977.
66. Tzang R-F Placebo-controlled trial with GlyTI-M among children with attention deficit hyperactivity disorder (ADHD). 2012 Nov 6 [last updated 2013 Jul 16; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT01725737 ClinicalTrials.gov Identifier: NCT01725737
67. Mohammadi MR, Mostafavi SA, Keshavarz SA, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. Iran J Psychiatry. 2012;7:87–92.
68. Niederhofer H. Agomelatine treatment with adolescents with ADHD. J Atten Disord. 2012;16:530.
69. Salardini E, Zeinoddini A, Kohi A, et al. Agomelatine as a treatment for attention-deficit/hyperactivity disorder in children and adolescents: a double-blind, randomized clinical trial. J Child Adolesc Psychopharmacol. 2016;26:513.
70. Stocks JD, Taneja BK, Baroldi P, et al. A phase 2a randomized, parallel group, dose-ranging study of molindone in children with attention-deficit/hyperactivity disorder and persistent, serious conduct problems. J Child Adolesc Psychopharmacol. 2012;22:102.
71. Rivkin A, Alexander RC, Knighton J, et al. A randomized, double-blind, crossover comparison of MK-0929 and placebo in the treatment of adults with ADHD. J Atten Disord. 2012;16:664.
72. Cooper RE, Williams E, Seegobin S, et al. Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. Eur Neuropsychopharmacol. 2017;27:795–808.
73. Herring WJ, Wilens TE, Adler LA, et al. Randomized controlled study of the histamine H3 inverse agonist MK-0249 in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012;73:e891–e898.
74. Weisler RH, Pandina GJ, Daly EJ, et al. Randomized clinical study of a histamine H3 receptor antagonist for the treatment of adults with attention-deficit hyperactivity disorder. CNS Drugs. 2012;26:421–434.
75. Moorthy G, Sallee F, Gabbita P, et al. Safety, tolerability and pharmacokinetics of 2-pyridylacetic acid, a major metabolite of betahistine, in a phase 1 dose escalation study in subjects with ADHD: pharmacokinetics of 2-pyridylacetic acid, a metabolite of betahistine. Biopharm Drug Dispos. 2015;36:429–439.
76. Wilens TE, Verlinden MH, Adler LA, et al. ABT-089, a neuronal nicotinic receptor partial agonist, for the treatment of attention-deficit/hyperactivity disorder in adults: results of a pilot study. Biol Psychiatry. 2006;59:1065–1070.
77. Wilens TE, Gault LM, Childress A, et al. Safety and efficacy of ABT-089 in pediatric attention-deficit/hyperactivity disorder: results from two randomized placebo-controlled clinical trials. J Am Acad Child Adolesc Psychiatry. 2011;2010;50:73.
78. Apostol G, Abi-Saab W, Kratochvil CJ, et al. Efficacy and safety of the novel α4β2 neuronal nicotinic receptor partial agonist ABT-089 in adults with attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled crossover study. Psychopharmacology (Berl). 2012;219:715–725.
79. Bain EE, Apostol G, Sangal RB, et al. A randomized pilot study of the efficacy and safety of ABT-089, a novel α4β2 neuronal nicotinic receptor agonist, in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012;73:783–789.
80. Ji J, Schrimpf MR, Sippy KB, et al. Synthesis and structure-activity relationship studies of 3,6-diazabicyclo[3.2.0]heptanes as novel alpha4beta2 nicotinic acetylcholine receptor selective agonists. J Med Chem. 2007;50:5493.
81. Bain EE, Robieson W, Pritchett Y, et al. A randomized, double-blind, placebo-controlled phase 2 study of α4β2 agonist ABT-894 in adults with ADHD. Neuropsychopharmacology. 2013;2012(38):405–413.
82. Jucaite A, Öhd J, Potter AS, et al. A randomized, double-blind, placebo-controlled crossover study of α4β 2 nicotinic acetylcholine receptor agonist AZD1446 (TC-6683) in adults with attention-deficit /hyperactivity disorder. Psychopharmacology (Berl). 2014;231:1251.
83. Potter AS, Dunbar G, Mazzulla E, et al. AZD3480, a novel nicotinic receptor agonist, for the treatment of attention-deficit/hyperactivity disorder in adults. Biol Psychiatry. 2014;75:207–214.
84. Wilens T Safety & efficacy of TC-5619 in adults with inattentive-predominant attention deficit/hyperactivity disorder (ADHD). 2011 Nov 14 [last updated 2013 Apr 30; no results posted: certification/extension first submitted 2013 Apr 22; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT01472991 ClinicalTrials.gov Identifier: NCT01472991
85. Adler L CX717 in the Treatment of Adult ADHD. 2017 Dec 7 [last updated 2017 Dec 15; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT03375021 ClinicalTrials.gov Identifier: NCT03375021
86. Plessow F. Oxytocin and Cognitive Control in Adult ADHD. 2017 Apr 26 [last updated 2020 Feb 19; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT03136263 ClinicalTrials.gov Identifier: NCT03136263
87. Hwang S Oxytocin on Irritability/Emotional Dysregulation of Disruptive Behavior and Mood Disorders. 2016 June 27 [last updated 2019 Mar 5; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT02824627 ClinicalTrials.gov Identifier: NCT02824627.6
88. NeuroDerm Ltd. A Study of ND0801 in Attention Deficit/Hyperactivity Disorder (ADHD). 2010 Aug 1 [last updated 2019 Dec 5; no results posted; cited 2020 Apr 21]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. 2000. Available from: https://clinicaltrials.gov/ct2/show/NCT01174355 ClinicalTrials.gov Identifier: NCT01174355
89. Spencer TJ, Brown A, Seidman LJ, et al. Effect of psychostimulants on brain structure and function in ADHD: a qualitative literature review of magnetic resonance imaging-based neuroimaging studies. J Clin Psychiatry. 2013;74:902–917.
90. Posner J, Nagel BJ, Maia TV, et al. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:828.
91. Mauri M, Nobile M, Bellina M, et al. Light up ADHD: I. cortical hemodynamic responses measured by functional near infrared spectroscopy (fNIRS). J Affect Disord. 2018;234:358–364.
92. Grazioli S, Mauri M, Crippa A, et al. Light up ADHD: II. Neuropharmacological effects measured by near infrared spectroscopy: is there a biomarker? J Affect Disord. 2019;244:100–106.
93. Pozzi M, Carnovale C, Peeters GGAM, et al. Adverse drug events related to mood and emotion in paediatric patients treated for ADHD: a meta-analysis. J Affect Disord. 2018;238:161–178.
94. Pozzi M, Carnovale C, Mazhar F, et al. Adverse drug reactions related to mood and emotion in pediatric patients treated for attention deficit/hyperactivity disorder: a comparative analysis of the us food and drug administration adverse event reporting system database. J Clin Psychopharmacol. 2019;39(4):386–392.

International Journal of
Environmental Research and Public Health

MDPI

Article

Clinical Application of Mindfulness-Oriented Meditation: A Preliminary Study in Children with ADHD

Ornella Santonastaso [1], Vittoria Zaccari [1], Cristiano Crescentini [2], Franco Fabbro [2], Viviana Capurso [2], Stefano Vicari [1,3] and Deny Menghini [1,*]

1 Child and Adolescent Neuropsychiatry Unit, Department of Neurological and Psychiatric Science, Bambino Gesù Children's Hospital, 00165 Rome, Italy; ornella.santonastaso@libero.it (O.S.); zaccarivittoria89@hotmail.it (V.Z.); stefano.vicari@opbg.net (S.V.)
2 Department of Languages and Literatures, Communication, Education and Society, University of Udine, 33100 Udine, Italy; cristiano.crescentini@uniud.it (C.C.); franco.fabbro@uniud.it (F.F.); viviana.capurso@uniud.it (V.C.)
3 Department of Life Science and Public Health, Università Cattolica del Sacro Cuore, 00168 Rome, Italy
* Correspondence: deny.menghini@opbg.net

Received: 19 August 2020; Accepted: 18 September 2020; Published: 22 September 2020

Abstract: Mindfulness-oriented meditation (MOM) is a self-regulatory training used for attentional and behavioral problems. With its focus on attention, MOM is a promising form of training that is gaining empirical support as a complementary or alternative intervention for attention deficit/hyperactivity disorder (ADHD). In this study, we tested the preliminary efficacy of MOM training in children with ADHD, by comparing its efficacy with an active control condition (Emotion Education Program, EEP). Twenty-five children with ADHD aged 7–11 years participated in MOM training (n = 15) or EEP (n = 10) 3 times per week for 8 weeks. Neuropsychological and academic measures and behavioral, emotional, and mindfulness ratings were collected before and after the two programs. On average, MOM training had positive effects on neuropsychological measures, as evidenced by a significant mean improvement in all outcome measures after training. Moreover, positive effects on ADHD symptoms were found only in the MOM group. Although they are preliminary, our results documented that MOM training promotes changes in neuropsychological measures and in certain behavioral symptoms, suggesting it as a promising tool for ameliorating cognitive and clinical manifestations of ADHD.

Keywords: mindfulness meditation; attention-deficit/hyperactivity disorder; neurodevelopmental disorders; neuropsychological measures

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is one of the most common developmental disorders, with high persistence into adulthood. The global prevalence of ADHD is 3–7% [1], and approximately 5% of children [2] and 4% of adults show ADHD [3]. The main clinical features of ADHD are hyperactivity, having difficulty sustaining attention, inhibiting a prepotent response, and difficulty in holding goals and plans [4]. Due to its pervasiveness, ADHD can interfere negatively with general well-being, social life, academic performance, and development of social skills [5].

Many studies have highlighted deficits in executive functions as one of the main characteristics of ADHD, especially with regard to response inhibition, attention, and working memory [4,6–15]. Children with ADHD continue to show significant symptoms of the disorder into adulthood and

are at greater risk for long-term negative outcomes, such as lower education and employment, substance abuse, and adult psychiatric disorders, than their non-ADHD peers [16].

Given the serious academic, social, familial, and accidental injury-related effects of ADHD, the need to develop and disseminate effective treatments is pressing [17].

In Europe, the guidelines that were produced by The National Institute for Health and Clinical Excellence [18,19] recommend group-based parent training/education programs or other group-based psychological treatments (e.g., cognitive-behavioral therapy, social skills training and drugs for school-aged children and young people with severe ADHD. US guidelines recommend the use of psychostimulants in all cases of moderate or severe ADHD [20,21]. However, although children with ADHD respond to medication in the short term, its long-term effectiveness is unknown [17] and the development of sustained, generalized, evidence-based interventions for ADHD is the major challenge to date.

With its focus on attention, mindfulness meditation is a promising form of training that is gaining empirical support as a complementary or alternative intervention for ADHD [22,23]. It is based on Buddhist traditions and Western knowledge of psychology, in which awareness and nonjudgmental observations of present-moment experiences are increased while automatic responding is reduced [24,25]. A fundamental action mechanism of mindfulness meditation is attention regulation [26–28], derived from training to sustain the focus of attention on present-moment experiences (thoughts, emotions, body sensations), attempting to gently shift the attention of participants back to themselves when they become aware that their minds have drifted from the meditation object. Mindfulness meditation has emerged as a new approach for reducing stress and an important innovative training modality in treating psychiatric and neurodevelopmental disorders.

Researching the efficacy of mindfulness training in children and adolescents is a relatively new domain (see the meta-analyses and systematic reviews [29–31]). Existing evidence has demonstrated that it has positive effects on psychological well-being [32–35], pain management [36], depressive symptoms and anxiety [32,37–40], negative behaviors [31] and cognitive/executive functions and attention [34,40–42] in children and adolescents.

Several studies have also determined the effects of mindfulness meditation training in ADHD [22,23,29]. A meta-analysis by Cairncross and Miller [22] found that mindfulness interventions significantly reduce inattention and hyperactivity/impulsivity in individuals with ADHD, irrespective of informant (self-rating and observer rating) and age. However, the effect size for the decrease in inattention was larger for adults than for children/adolescents with ADHD. The authors [22] interpreted these results with caution, based on the significant heterogeneity across studies due to the informant type (self-informant or other-informant reports) and the age of the participants.

Compared with the meta-analysis by Cairncross and Miller [22], a review by Evans et al. [29] examined the use of meditation-based interventions in a more homogenous population (participants were under 18 years old), but selected heterogeneous meditation-based interventions, and considered various outcomes. The strongest effect sizes were found for yoga and meditation and when parents and children were targeted in the intervention. Mixed evidence for self-esteem, social functioning, internalizing/externalizing symptoms, and academic performance was observed. The authors addressed several limitations in the studies that were included in the review, such as the absence of control groups, the lack of randomization of participants, the small sample sizes, limited information on the participants and selection criteria, and non-validated measures of intervention.

A more recent meta-analysis and review by Zhang et al. [23] assessed the efficacy of meditation-based interventions (mindfulness and yoga techniques) with regard to the core symptoms of ADHD and the neuropsychological deficits that are associated with it. When symptoms of ADHD were considered, meditation-based interventions were significantly more effective than the control conditions in children and adolescents. The significant effects on core symptoms of ADHD were interpreted as being the direct consequence of meditation-based interventions that typically increase attention process, self-control,

and emotional regulation. In contrast, no significant effect was found for neuropsychological measures of inhibition or inattention, with evidence of heterogeneity for both measures. Similarly to earlier studies [22,29], Zhang et al. [23] raised concerns over several methodologically and clinically relevant issues in the studies that were examined, such as blinding concerns, selection bias, the lack of protocol, inconsistency between control conditions, the heterogeneous nature of the neuropsychological measures that were considered, and the simultaneous use of medication in certain participants.

In summary, preliminary studies on mindfulness training in children and adolescents with ADHD have demonstrated a positive effect on ADHD symptoms. Data derived by combining objective neuropsychological measures with parent- and self-report questionnaires is scarce, and the results that exist are controversial.

Moreover, evidence is limited by the lack of an active control group or the heterogeneity of control conditions, which varied between studies, encompassing self-guided handouts on skills, nonviolent resistance training for parents, psychoeducation, and wait list. Selection bias, lack of protocol, and the simultaneous use of medication should also urge caution in the interpretation of the results.

In considering mindfulness training in children with ADHD, studies must comprise homogeneous groups (e.g., for age, diagnosis, and pharmacological therapy) and replicable procedures (e.g., the implementation of protocols, neuropsychological measures other than self-reports and parent reports).

The present study attempted to control for issues affecting previous results on mindfulness training such as by providing an active control condition designed to be comparable with and structurally equivalent to the mindfulness-oriented meditation (MOM) program, by the combination of objective neuropsychological measures with parent and self-report questionnaires, the selection of children with ADHD with a narrow age range and no concurrent treatment, and the random assignment of participants to the MOM group (MOM G) or to the active control group.

With this aim, 32 children with ADHD aged 7–11 years were randomly assigned to the MOM G, which underwent mindfulness training or to the active control group, the Emotion Education Program group (EEP G), which entered the emotion awareness and recognition program. Participants were assessed at baseline (T0) and post-training (T1) for neuropsychological measures that involved executive functions (i.e., working memory, inhibitory control, switching, and sustained performance), ADHD symptoms, behavioral and emotional aspects, mindfulness measures, depressive and anxious symptoms, parenting stress (by using self-ratings and parent ratings), and academic skills (i.e., mental calculation and reading). None of the children had received or was receiving any pharmacological, psychological, behavioral, or educational treatment.

The MOM program, as one form of mindfulness [43], was recently proposed by Fabbro and Muratori [44], in turn inspired by the Theravada schools of Buddhism [45] and western-based mindfulness programs, such as mindfulness-based stress reduction [25,46–48]. The current MOM approach has been used with children [49], consisting of 3 sessions per week for 8 weeks and, consistent with previous mindfulness-meditation programs for children [34], the duration of the sessions increased gradually over time.

The EEP was designed to be comparable with and structurally equivalent to the MOM program. It was organized into 3 sessions per week for 8 weeks and the duration of the sessions followed the same progression as the MOM training. The activities of the EEP G consisted of listening to and commenting on chapters of a book to discover and be aware of various emotions.

Because mindfulness meditation programs focus on attention regulation and on reducing automatic responding, we predicted that MOM would have positive effects on neuropsychological measures that involve executive functions. We also expected to observe better effects on mindfulness measures and symptoms of ADHD, as rated by parents, in the MOM G versus EEP G. Due to the short duration of the intervention, we predicted limited effectiveness on academic skills, perceived family stress, anxiety, and depressive symptoms.

2. Materials and Methods

2.1. Participants

The estimated sample size [50] for this preliminary study was 32 participants.

Thirty-five children with ADHD (age range: 7–11; M = 8.9, *SD* = 1.2; 9 females) were recruited from a waiting list for a multimodal intervention that was based on psychological, behavioral, and educational interventions at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital (Rome, Italy).

All participants underwent a child psychiatric and neuropsychological examination conducted by experienced developmental psychiatrists and neuropsychologists. The diagnosis of ADHD was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria [2] and was based on developmental history, an extensive clinical examination, and a semi-structured interview, Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version, K-SADS-PL [51], which diagnoses current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria [52].

According to DSM-5 [2], the children with ADHD were characterized as follows: 30 fulfilled the diagnostic criteria for ADHD Combined presentation, 2 had ADHD predominantly Hyperactive-Impulsive presentation, and 3 had ADHD predominantly Inattentive presentation.

Global functioning was assessed with the Children's Global Assessment Scale (C-GAS) [53]. The C-GAS estimates the overall severity of disturbance (range, 0–100). Scores over 90 indicate superior functioning, whereas scores under 70 suggest impaired global functioning.

IQ was measured by using the Wechsler Intelligence Scale for Children-IV (WISC-IV, Italian edition) [54] or Colored Progressive Matrices [55].

Children with ADHD who were included in the study met the following criteria: (a) a primary diagnosis of ADHD, according to the criteria of DSM-5 [2]; (b) age between 7 and 11 years; (c) IQ $\geq$ 85.

The exclusion criteria were as follows: (a) the presence of neurological and neurosensory deficits; (b) the presence of comorbid psychopathological disorders or autism spectrum disorder; (c) past or present drug treatment, cognitive behavioral therapy, training/education program, or any other group-based psychological treatment for parents.

All participants and their parents gave written informed consent after receiving a comprehensive description of the study. This study was performed in accordance with the Declaration of Helsinki and was approved by the local ethical committee of the Bambino Gesù Children's Hospital (Process Number 1162/2016).

2.2. Procedure

This randomized study comprised two arms (see Figure 1). The baseline assessment (T0) was conducted twice at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital by two child developmental psychologists who were blind to the interventions, with each evaluation lasting approximately 1.5 h. After completing the baseline assessment, three children declined to participate, and ultimately, 32 participants (23 males) were allocated to the two arms (MOM program or EEP), based on simple random allocation using a computer-generated random number sequence that was performed by clinical staff members who were not involved in the research. The MOM G was composed of 16 children (3 females) who underwent mindfulness meditation training, and the EEP G comprised 16 children (6 females) who participated in an EEP on listening to and commenting on a book on the importance of feeling positive and negative emotions.

Both of the training programs were provided at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital. Before the training began, one participant in the MOM-G and six in the EEP G dropped out.

At T0, the two groups did not differ in chronological age (CA MOM G: M = 8.9, *SD* = 1.3; CA EEP G: M = 9, *SD* = 1.2), IQ (IQ MOM G: M = 109.9, *SD* = 11.1; IQ EEP G: M = 104.4, *SD* = 8.2), or C-GAS score (C-GAS MOM G: M = 53.4, *SD* = 2.6; C-GAS EEP G: M = 53.5, *SD* = 1.8).

The post-training evaluations (T1) were conducted twice within two weeks after the end of the training by two child developmental psychologists who were blind to the interventions, with each session lasting approximately 1.5 h.

Int. J. Environ. Res. Public Health 2020, 17, x 5 of 16

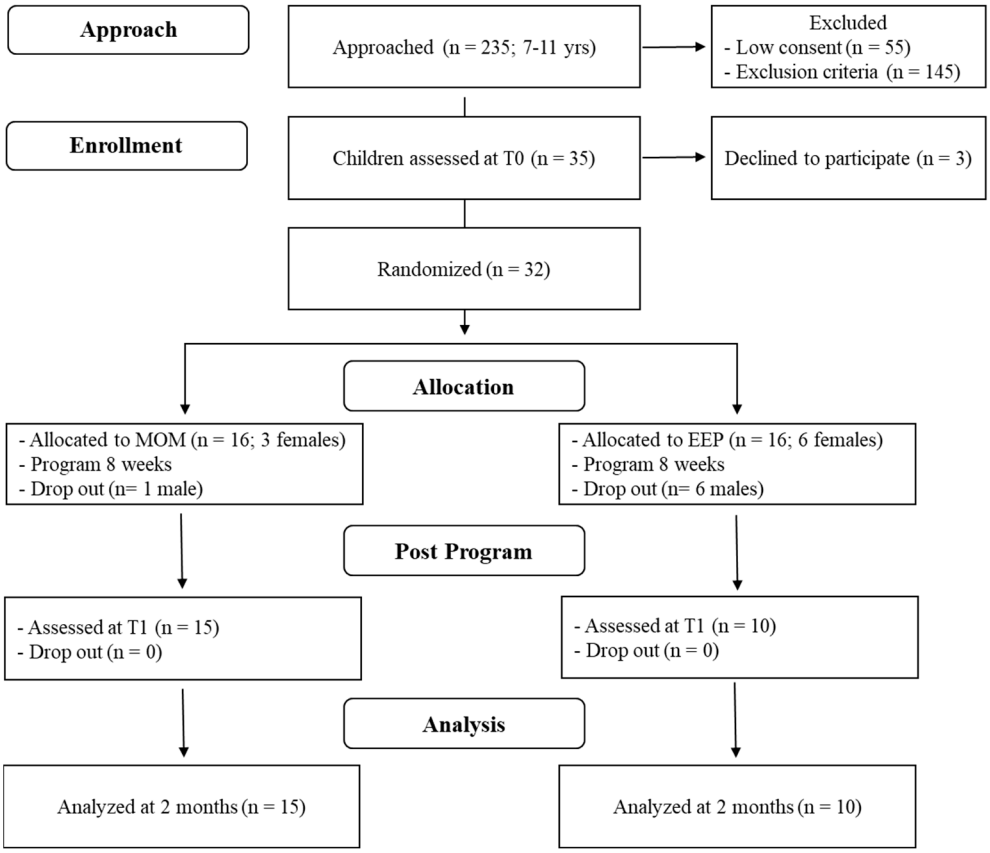


Figure 1. Study flow diagram.

2.3. Mindfulness-Oriented Meditation Training

Both of the training programs were provided at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Children's Hospital. Before the training began, one participant in the MOM-G and six in the EEP G dropped out.

The MOM program was conducted by two qualified mindfulness meditation instructors (VC and OS). A developmental psychologist (VZ) was also present to help children with ADHD to follow the sessions.

The training was inspired by previous MOM interventions for clinical and nonclinical adult and child populations [44,49,56–58], which were in turn based on the Mindfulness Based Stress Reduction protocol [23,47]. The MOM protocol consisted of three sessions per week for eight weeks [49]. Consistent with earlier mindfulness meditation programs for healthy children [34], the duration of the sessions increased gradually over the eight weeks, starting from 6 min and rising to 30 min. For the first two weeks, the MOM training lasted for less than 10 min at each meeting, rising to 30 min at the end of the course (Week 8). The reason for this adaptation was the lower attentional capacity of children with ADHD and their difficulty in engaging in a single activity for long periods.

2.3. Mindfulness-Oriented Meditation Training

The MOM program was conducted by two qualified mindfulness meditation instructors (VC and OS). A developmental psychologist (VZ) was also present to help children with ADHD to follow the sessions.

The training was inspired by previous MOM interventions for clinical and nonclinical adult and child populations [44,49,56–58], which were in turn based on the Mindfulness Based Stress Reduction protocol [23,47]. The MOM protocol consisted of three sessions per week for eight weeks [49]. Consistent with earlier mindfulness meditation programs for healthy children [34], the duration of the sessions increased gradually over the eight weeks, starting from 6 min and rising to 30 min. For the first two weeks, the MOM training lasted for less than 10 min at each meeting, rising to 30 min at the end of the course (Week 8). The reason for this adaptation was the lower attentional capacity of children with ADHD and their difficulty in engaging in a single activity for long periods.

Each session was divided into a series of three meditation exercises that focused on three types of activity: (i) mindfulness of breathing, (ii) mindfulness of body parts, and (iii) mindfulness of thoughts and emotions. After the meditation exercise, there was a brief debriefing phase that lasted approximately half of the time that was dedicated to the meditation exercises. It allowed the children to express their feelings and to answer questions about the exercise that had just been completed.

Specifically, the three meditation activities were proposed to the MOM G as "games" that were meant to promote awareness of breath, body parts, and thoughts. In each of the three weekly sessions, children with ADHD were first required to concentrate on breath. In the second meditation exercise, participants had to focus their attention on various body parts. In the last activity, children were encouraged to observe the stream of their thoughts and emotions. For a brief description of the structure of the sessions and activities included in the MOM training, see Supplementary Materials. At the end of each session, children were recommended to practice meditation wherever they were (several times per day) in order to generalize the gains that were made in training to daily life. During the eight weeks of training, children were given homework ("Meditation Diaries") and instructed to write about their meditation experiences in everyday life.

2.4. Emotion Education Program

The activities of the EEP G were designed to be comparable with and structurally equivalent to those of the MOM program (see MacCoon et al. [59] and Crescentini et al. [49]). Similar to the MOM training, the EEP was organized into three meetings per week for eight weeks.

The duration of the sessions followed the same progression as in the MOM training: for the first two weeks, the EEP lasted for less than 10 min at each session, rising to 30 min at the end of the course. The activities of the EEP G consisted of listening to and commenting on chapters of the book "Six Pixies in My Heart" ("Sei Folletti nel Mio Cuore") [60].

The program was led by the same trainers as in the MOM training. The book is about a shy and sensitive child who decides to avoid all of his emotions to avoid being defined as "sensitive" by his friends and schoolmates. However, at the end of the book, the child learns the importance of feeling positive and negative emotions in his heart and appreciates that he is sensitive.

During the sessions, the trainers asked the children to discuss the stories, the emotions that they felt, and the physical sensations that were associated with these emotions. The activities of listening to and commenting on the chapters allowed children to discover various emotions that can be experienced in many situations and to consider and be aware of their own emotions. At the end of each session, the children were recommended to pay attention to the emotions that were experienced in their everyday life in order to generalize the gains that were made in training to daily life.

During the eight weeks of the EEP, participants were given homework ("Diaries") and instructed to write down the situations in which they were aware of their emotions. For a brief description of the structure of the sessions and activities included in the EEP, see Supplementary Materials.

In summary, EEP was an active control condition for the MOM program because it shared several crucial elements with MOM, including timing and setting, requests for silence, group work, interaction between children and trainers, and the assignment of homework, but was designed not to be related to the practice of mindfulness [59].

3. Measures

Children from both groups were assessed at T0 and T1 with regard to the following.

3.1. Neuropsychological Measures

The Continuous Performance Test-II (CPT-II) 5th version [61] is a computerized measure of sustained performance. Children were required to press the spacebar when any letter except "X" appeared on the screen. Measures of CPT-II mean correct Hit Reaction Times (CPT-II HRT) and the standard deviation of correct CPT-II HRTs (CPT-II HRT-SD) were included in the analyses.

In the Stroop Color Word Test [62], children were instructed to read the words (cond1), name the colors (cond2), and, finally, name the color of the ink of the printed words when they were incongruous (cond3) as quickly and as accurately as possible. To calculate the cost of an incongruous response, the time for cond2 was subtracted from that of cond3 (cond3-cond2), to calculate the number of errors (cond3-cond2). To integrate time and the proportion of errors, an Inverse Efficiency Score (STROOP IES)

was calculated [63] as follows: time (cond3-cond2)/(1-proportion of errors cond3-cond2), where the proportion of errors was calculated, based on the number of stimuli (n = 100).

The stop task [64–67] consists of randomly intermixed Go and Stop Trials. In Go trials, children were instructed to press the spacebar as quickly as possible after the appearance of the go signal. In stop trials, after a variable delay (stop signal delay, SSD), a stop signal (red way stop) appeared after the Go signal, and children were instructed to refrain from responding. The Stop Signal Reaction Time (SSRT) was estimated (in msec) by subtracting the mean estimate of SSDs from the observed mean of the reaction times in no-stop trials.

In the N-Back task, children were presented with a single blue square at any location in a 3 × 3 grid on a computer screen and instructed to make a decision (yes/no) by pressing a button with regard to whether the current stimulus was in the same location as that presented N-positions earlier. Only when the accuracy was 80% was the next N-back level submitted. A N-Back Inefficiency Index (N-BACK II) was calculated, based on the percentage of errors in the last not-achieved n-back.

3.2. Parent and Self-Report Questionnaires

Conners' Parent Rating Scales Long Version Revised (CPRS-R:L) [68] is composed of behavior rating scales that are commonly used to assess behaviors that are related to ADHD and other disorders in children. It is completed by parents to obtain a measure of hyperactivity and inattention symptoms for ADHD. The CPRS-R:L comprises 7 subscales that have been derived by factor analysis: oppositional, cognitive problems/inattention, hyperactivity, anxious-shy, perfectionism, social problems, and psychosomatic problems. In addition, ADHD index, Conners' Global Index (CGI) Restless-Impulsive, CGI Emotional Lability, CGI Total, DSM-IV Inattentive, DSM-IV Hyperactive/Impulsive, and DSM-IV Total scores were calculated. The cutoff for T-scores for clinical significance was >70 (very elevated). T-scores from 60–70 were considered to be high average or elevated.

The Child Behavior Checklist for Ages 6–18 (CBCL 6-18) [69] is a paper-and-pencil-based questionnaire of child and adolescent behaviors and emotions that is completed by parents and comprises 8 syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), 3 broadband scores (internalizing and externalizing problems, and total problem), DSM-oriented scales (affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problem, oppositional defiant problems, conduct problems), and the 2007 Scales (sluggish cognitive tempo, obsessive-compulsive problems, post-traumatic stress problems). The CBCL 6-18 generates a T-score for each subscale. According to normative data, a T-score above 64 was considered to be significant for the 3 broadband scales, whereas for the syndrome scales, the cut-off for clinical significance was 70.

The Multidimensional Anxiety Scale for Children (MASC) [70] is a 39-item, paper-and-pencil-based self-reported measure that performs a multidimensional assessment of anxiety in children and adolescents. Total raw scores were converted to T-scores.

The Children's Depression Inventory (CDI) [71] is a 27-item self-reported inventory that measures depressive symptoms in children and adolescents. A score above 19 suggests the presence of clinically significant depressive symptoms.

The Child and Adolescent Mindfulness Measure (CAMM) [72] is an awareness scale for persons aged 6–18 years that detects their level of awareness. Higher total scores reflected a greater level of acceptance and mindfulness.

The Parenting Stress Index-Short Form (PSI-SF) [73–75] is a 36-item questionnaire that measures various aspects of perceived stress in the parenting role. A total stress score (PSI TOT) represents an index of the parent's overall perception of parenting stress. Raw scores were converted to percentiles.

3.3. Academic Skills

Text Reading (MT-2) [76]. Reading speed (the mean number of syllables per second) and accuracy (number of errors) were calculated. For both reading measures, scores were split into two categories (medium/high or low/poor) according to normative data.

Mental Calculation (Batteria per la Discalculia Evolutiva (BDE)) [77,78]. The ability to compute arithmetic facts was evaluated (sum and subtraction with numbers up to ten). Children were required to solve calculations that were posed by the clinician within 2 s. The number of errors was calculated and transformed into Z-scores, based on normative data on education level.

4. Results

Concerning Neuropsychological Measures (see Table 1), a repeated measures ANOVA was conducted on the five neuropsychological measures as the dependent variables (CPT-II HRT, CPT-II HRT-SD, STROOP IES, SSRT, and N-BACK II) with Group (MOM G, EEP G) and Time (T0, T1) as the independent variables. Significant effects for Group ($F_{1,23} = 4.8$, $p = 0.039$, $\eta p2 = 0.17$), Time ($F_{1,23} = 8.1$, $p = 0.009$, $\eta p2 = 0.26$), Task ($F_{4,92} = 234.4$, $p < 0.0001$, $\eta p2 = 0.91$), and Group × Time ($F_{1,23} = 5.98$, $p = 0.023$, $\eta p2 = 0.21$) were found. However, Group × Task ($F_{4,92} = 1.38$, $p = 0.25$, $\eta p2 = 0.06$), Task × Time ($F_{4,92} = 1.53$, $p = 0.2$, $\eta p2 = 0.06$), and Group × Task × Time interactions were not significant ($F_{4,92} = 1.3$, $p = 0.27$, $\eta p2 = 0.05$).

Table 1. Means and Standard Deviations of Neuropsychological Measures in the Mindfulness-Oriented Meditation Group and in the Emotion Education Program Group.

		MOM G	EEP G
Neuropsychological Measure	**Time**	**M (*SD*)**	**M (*SD*)**
CPT-II HRT (msec)	T0	505.39 (73.00)	445.37 (75.98)
	T1	431.33 (52.26)	428.21 (45.08)
CPT-II HRT-SD (msec)	T0	348.23 (89.39)	238.76 (94.94)
	T1	222.12 (93.04)	239.97 (65.26)
STROOP IES (msec/errors)	T0	115.48 (47.86)	110.76 (57.90)
	T1	96.62 (41.91)	107.26 (35.12)
SSRT (msec)	T0	347.24 (190.72)	279.62 (106.35)
	T1	319.74 (62.14)	271.39 (62.94)
N-BACK II (% of errors)	T0	55.67 (23.65)	36.40 (16.97)
	T1	48.93 (14.31)	45.50 (15.45)

Note. MOM G = Mindfulness-Oriented Meditation Group; EEP G = Emotion Education Program Group; CPT-II = Continuous Performance Test-II; HRT = Hit Reaction Times; HRT-SD = Hit Reaction Times-Standard Deviation; STROOP IES = Stroop Color Word Test Inverse Efficiency Score; SSRT = Stop Signal Reaction Time; N-BACK II = N-Back Inefficiency Index; T0 = baseline; T1 = post-training.

The post hoc analysis (Unequal N Tukey's Honestly Significant Difference test) of the effect of Group × Time showed that MOM G mean scores decreased from T0 to T1 ($p = 0.0028$), while EEP G mean scores did not change from T0 to T1 ($p = 0.99$). Moreover, the two groups differed at T0 ($p = 0.027$) but not at T1 ($p = 0.99$).

Concerning ADHD symptoms (see Table 2), a repeated measures ANOVA was conducted on CPRS-R:L, with T-scores of 14 subscales as the dependent variables, and Group (MOM G, EEP G) and Time (T0, T1) as the independent variables. Significant effects for Group ($F_{1,23} = 6.49$, $p = 0.018$, $\eta p^2 = 0.22$), Subscale ($F_{13,299} = 42.8$, $p < 0.0001$, $\eta p^2 = 0.65$), Group × Subscale ($F_{13,299} = 1.92$, $p = 0.028$, $\eta p^2 = 0.08$), and Group × Time × Subscale interactions ($F_{13,299} = 1.8$, $p = 0.04$, $\eta p^2 = 0.07$) were found. The main effect of Time ($F_{1,23} = 2.28$, $p = 0.14$, $\eta p^2 = 0.07$) and Group × Time interaction

($F_{1,23}$ = 2.17, p = 0.15, ηp^2 = 0.15) were not significant. As shown by the post hoc analysis of Group × Time × Subscale interaction (Unequal N Tukey's Honestly Significant Difference test), only scores in the MOM G decreased from T0 to T1 for the CGI Restless-Impulsive and CGI Total subscales (p = 0.04 and p = 0.023, respectively).

Table 2. Means and Standard Deviations of Conners' Parent Rating Scales Long Version Revised subscales in the Mindfulness-Oriented Meditation Group and in the Emotion Education Program Group.

		MOM G	EEP G
CPRS-R:L Subscale	**Time**	**T-Score M (*SD*)**	**T-Score M (*SD*)**
Oppositional	T0	64.13 (14.58)	67.90 (12.64)
	T1	56.47 (10.64) [b]	68.90 (14.16)
Cognitive Problems/Inattention	T0	76.80 (12.45)	86.20 (11.00)
	T1	75.00 (11.85)	84.00 (14.37)
Hyperactivity	T0	69.80 (14.51)	81.00 (12.02)
	T1	62.13 (10.98)	79.00 (13.22)
Anxious-Shy	T0	53.40 (13.89)	54.20 (13.07)
	T1	49.73 (11.50)	56.80 (12.85)
Perfectionism	T0	51.93 (9.25)	50.10 (8.37)
	T1	43.47 (7.08)	50.80 (7.54)
Social Problems	T0	63.40 (16.05)	64.80 (19.36)
	T1	65.80 (14.63)	61.50 (15.09)
Psychosomatic Problems	T0	55.93 (19.64)	60.80 (16.10)
	T1	48.93 (13.62)	64.90 (16.94)
ADHD Index	T0	78.80 (12.70)	83.80 (6.73)
	T1	71.47 (10.13)	80.50 (14.42)
CGI Restless-Impulsive	T0	73.47 (14.29)	76.90 (9.42)
	T1	63.93 (10.12) [a,b]	79.60 (11.17)
CGI Emotional Lability	T0	56.20 (14.66)	67.10 (12.74)
	T1	48.73 (8.94)	67.80 (17.67)
CGI Total	T0	70.40 (14.83)	76.70 (9.92)
	T1	60.53 (9.88) [a,b]	78.80 (13.20)
DSM-IV Inattentive	T0	78.66 (12.02)	84.60 (10.69)
	T1	74.80 (12.04)	84.20 (14.57)
DSM-IV Hyperactive/Impulsive	T0	70.00 (12.45)	77.10 (9.47)
	T1	63.13 (10.49) [b]	75.20 (14.77)
DSM-IV Total	T0	77.07 (12.65)	84.30 (9.94)
	T1	71.47 (10.53)	82.50 (14.76)

Note. CPRS-R:L = Conners' Parent Rating Scales Long Version Revised; MOM G = Mindfulness-Oriented Meditation Group; EEP G = Emotion Education Program Group; CGI = Children Global Index; T0 = baseline; T1 = post-training. [a] Statistical difference between T0 and T1 ($p \leq 0.05$). [b] Clinical change between T0 and T1.

Further, the change between T0 and T1 for the CGI Restless-Impulsive and CGI Total subscales had clinical significance only in the MOM G: the subscales scores decreased, on average, from a clinical level at T0 (mean T-scores higher than 70) to a borderline range at T1 (between 60 and 70). Although no effect of the training program was observed for the Oppositional subscale, the change between T0 and T1 had clinical significance only in the MOM G: Oppositional subscale scores decreased, on average, from a borderline range at T0 (mean T-scores between 60 and 70) to a typical level at T1 (lower than 60). Similarly, although training did not have any effect on it, DSM-IV Hyperactive/Impulsive subscale scores between T0 and T1 declined, on average, only in the MOM G, from a clinical level at T0 (mean T-scores above 70) to a borderline range at T1 (between 60 and 70).

For the CBCL 6-18, a repeated measures ANOVA was conducted on T-scores of the 24 subscales as the dependent variables, and Group (MOM G, EEP G) and Time (T0, T1) as the independent variables. Neither the Group ($F_{1,23}$ = 3.14, p = 0.09, ηp^2 = 0.12), Time ($F_{1,152}$ = 1.181, p = 0.29, ηp^2 = 0.05), Group × Time ($F_{1,23}$ = 1.72, p = 0.20, ηp^2 = 0.07) nor the Group × Time × Subscale interactions ($F_{23,529}$ = 1.00, p = 0.46, ηp^2 = 0.04) were significant. However, the main effect of Subscale ($F_{23,529}$ = 74.48, $p < 0.0001$, ηp^2 = 0.76) and the Group × Subscale interaction were significant ($F_{23,529}$ = 1.79, p = 0.01, ηp^2 = 0.07).

To determine the effects of MOM on parent and self-report questionnaires on anxiety, depressive symptoms, mindfulness, and parenting stress, a repeated measure ANOVA was performed, with MASC, CDI, CAMM, and PSI-SF scores as the dependent variables, and Group (MOM G, EEP G) and Time (T0, T1) as the independent variables. The main effects of Group ($F_{1,23}$ = 0.21, p = 0.65, ηp^2 = 0.01) and Time ($F_{1,23}$ = 0.04, p = 0.84, ηp^2 = 0.01) were not significant. The Group × Time ($F_{1,23}$ = 0.60, p = 0.44, ηp^2 = 0.02) and Group × Time × Task interactions ($F_{3,69}$ = 0.16, p = 0.92, ηp^2 = 0.01) were also not significant. However, the main effect of Task ($F_{3,69}$ = 96.15, $p < 0.0001$, ηp^2 = 0.8) was significant.

Concerning academic skills, a repeated measure ANOVA was performed on mental calculation Z-score as the dependent variable, and Group (MOM G, EEP G) and Time (T0, T1) as the independent variables. The main effect of Group ($F_{1,23}$ = 5.37, p = 0.03, ηp^2 = 0.2) was significant but Time effect ($F_{1,23}$ = 3.6, p = 0.07, ηp^2 = 0.1) and Group × Time interaction ($F_{1,23}$ = 0.23, p = 0.63, ηp^2 = 0.01) were not significant.

Chi-squared test was used to compare the number of participants in the two groups whose reading performance changed (medium/high or low/poor) from T0 to T1 with regard to reading speed or reading accuracy. For text reading also, the number of participants in the two groups whose reading performance changed from T0 to T1 with regard to speed (χ^2_3 = 0.27, p = 0.96) or accuracy (χ^2_3 = 3.49, p = 0.32) did not differ.

Discussion

The aim of this study was to evaluate the effects of an eight-week MOM program on neuropsychological measures, ADHD symptoms, behavioral and emotional aspects, depressive and anxious symptoms, a mindfulness measure, a parenting stress index, and academic skills in children with ADHD.

On average, MOM training had positive effects, with a large effect size, on neuropsychological measures (Group × Time effect), as evidenced by the average responses on neuropsychological measures improving significantly at T1 compared with T0 in the MOM G but not in the EEP G.

With regard to ADHD symptoms, only the MOM G had significantly lower T-scores at T1 than at T0 on the CGI Restless-Impulsive and CGI Total subscale scores (Group × Time × Subscale), with a small effect size. Moreover, the changes in ADHD symptoms after MOM training had clinical significance, based on parent rate T-scores declining on several CPRS-R:L subscales.

The significant mean improvement in all neuropsychological measures after training in the MOM G suggested that MOM training could appreciably reduce executive functions deficits in ADHD. Our tasks involved higher-order cognitive abilities, such as working memory, inhibitory control, switching, and sustained performance. However, there are few data on the association between mindfulness and executive functions [79–81] in typically developing children [42] and in children with neurodevelopmental disorders, having been studied primarily in adult populations and adolescents [82,83].

Concerning studies on typical populations, our results are in line with findings that showed an association between inhibition, working memory and mindfulness. Specifically, Riggs et al. [83] tested a model considering the association of different executive functions and mindfulness, ascertaining that only inhibition and working memory had unique associations with mindfulness in early adolescence.

The other two studies investigating working memory in relation to mindfulness in healthy adolescents [83,84] documented positive effects of mindfulness meditation interventions on working memory. It has been suggested [84] that individuals with greater working memory efficiency might be more able to remember their intention to maintain present moment awareness and, thus, be more mindful.

However, the review by Gallant [85] on the association between executive functions and mindfulness trainings showed that the effect of mindfulness interventions was more consistent for inhibition than other executive functions. It has been suggested that inhibition, in mindful awareness, does not consist of simply suppressing unwanted thoughts and behaviors, but, rather, of letting go of distractions and immersing oneself in the present moment [79].

A recent study [42] evaluated the relationship between mindfulness and executive functions in typically developing children by correlating child ratings on mindfulness and parent ratings on children's executive functions. Although the study was limited in that it used survey data, it reported a negative correlation between mindfulness and difficulties with inhibition, working memory, and shifting, confirming that children who were more mindful were less likely to experience such difficulties. Our results strengthened those correlational findings obtained indirectly by using child and parent ratings [42]. Indeed, by administering mindfulness training and analyzing its effects on neuropsychological measures that involve executive functions, we directly verified the relationship between mindfulness and executive functions.

To date, it is difficult to compare our results with other findings on ADHD because only few studies have focused on the association between mindfulness and executive functions in children/adolescents with ADHD. No significant effects of mindfulness interventions were found in a review [23] on neuropsychological measures of inhibition and working memory in children and adolescents with ADHD but we would urge caution in the interpretation of these results since the review was based on three studies only.

With regard to ADHD symptoms, our results were in line with a recent meta-analysis aimed at investigating the efficacy of mindfulness-based interventions on ADHD core symptoms in comparison with active control conditions [86]. The meta-analysis suggested that mindfulness-based interventions had large effects in reducing ADHD core symptoms. Authors interpreted these results as indicating that mindfulness-based exercise, which emphasized more the nonjudgmental attention of participants to occurring experience in the present moment, improves attentional regulation.

Looking at the effect sizes, our results also indicated that the effects of MOM training on neuropsychological measures were stronger than on parent ratings.

In general, the positive outcomes of MOM training on neuropsychological measures and ADHD symptoms that we found could be explained by considering that our program focused on three meditation exercises that allocated attentional resources to breath, various body parts, and thoughts. Thus, during MOM, our children with ADHD developed self-regulatory skills, especially attentional control, to maintain focus on present moment experiences and inhibit distractions [79].

Our results, although they are derived from a small group of children with ADHD, are strengthened by the inclusion of an active control group (the EEP group) that helps to control the alternative interpretation of the possible effects of the MOM intervention. As previously suggested ([86]), the inclusion of an active control group improves the internal validity of findings. Inactive conditions (i.e., treatment as usual and wait-list) have a significant impact on the heterogeneity of the results of mindfulness-based interventions on ADHD, and contributed to a smaller effect on ADHD core symptoms, when compared to active conditions.

Our study has some limitations. As a preliminary study, the number of participants was limited, but the results are encouraging and helpful in designing and executing a large-scale clinical trial on MOM. Recruiting more participants could remediate the possible bias of gender in our study, and children could be more equally distributed between the two conditions with regard to demographics such as gender.

Another limitation was the lack of multiple informants. Parents would/should be aware of the intervention condition to which their child was assigned, which would likely affect their ratings. Including several informants, such as teachers, would have helped with this problem.

Our study lacked also of a follow-up period, which should be included in future studies to verify the duration of changes in the MOM G.

Future studies should also understand why other measures, such as some behavioral and emotional aspects, depressive and anxiety symptoms, the mindfulness measure, parenting stress index, and academic skills, did not change after mindfulness practice, and should determine whether a longer duration of training would thus be more useful.

Our study is a preliminary step towards establishing the effectiveness of MOM intervention in ADHD and future studies are needed to confirm the benefits of MOM by including more participants, using longer training periods, combining neuropsychological measures with questionnaires from multiple respondents (child, parent, and teacher), and comparing results from groups of parents who do not participate in MOM interventions (as in our study) versus those who are asked to meditate with their children [87] or undergo mindful parent training in parallel [88].

5. Conclusions

When comparing our study with previous works on mindfulness training in children and adolescents with ADHD, it is one of the few that combined objective neuropsychological measures with parent- and self-report questionnaires. Moreover, our study included an active control condition (focused on emotion awareness and recognition) that was structurally equivalent to the mindfulness-meditation program, and we randomly assigned to the two conditions children with ADHD with a narrow age range and no concurrent treatment.

Overall, our results are encouraging and suggest that mindfulness meditation practices that are performed for a short period (eight weeks) promote changes in neuropsychological measures, especially those in which executive functions are involved, and behavioral symptoms in children with ADHD.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/18/6916/s1, Table S1: Overview of the activities included in the Mindfulness-Oriented Meditation training and in the Emotion Education Program.

Author Contributions: Conceptualization, C.C., F.F., S.V. and D.M.; Formal analysis, D.M. and C.C.; Methodology, C.C., D.M., O.S., V.Z., and V.C.; Supervision, S.V. and D.M.; Writing original draft, O.S., V.Z., C.C. and D.M.; Writing review & editing, D.M., C.C., F.F. and S.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: We are grateful to all the patients and their families.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Rowland, A.S.; Skipper, B.J.; Umbach, D.M.; Rabiner, D.L.; Campbell, R.A.; Naftel, A.J.; Sandler, D.P. The prevalence of ADHD in a population-based sample. *J. Atten. Disord.* **2015**, *19*, 741–754. [CrossRef] [PubMed]
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; (DSM-5); American Psychiatric Association: Washington, DC, USA, 2013.
3. Kessler, R.C.; Adler, L.; Barkley, R.; Biederman, J.; Conners, C.K.; Demler, O.; Faraone, S.V.; Greenhill, L.L.; Howes, M.J.; Secnik, K.; et al. The prevalence and correlates of adult ADHD in the United States: Results from the national comorbidity survey replication. *Am. J. Psychiatry* **2006**, *163*, 716–723. [CrossRef]
4. Willcutt, E.G.; Doyle, A.E.; Nigg, J.T.; Faraone, S.; Pennington, B.F. Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biol. Psychol.* **2005**, *57*, 1336–1346. [CrossRef]

5. Singh, A.; Yeh, C.J.; Verma, N.; Das, A.K. Overview of attention deficit/ hyperactivity disorder in young children. *Health Psychol. Res.* **2015**, *3*, 23–35. [CrossRef] [PubMed]
6. Pennington, B.F.; Ozonoff, S. Executive functions and developmentalpsychopathology. *J. Child Psychol. Psychiatry* **1996**, *37*, 51–87. [CrossRef]
7. Barkley, R.A. Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychol. Bull.* **1997**, *121*, 65–94. [CrossRef] [PubMed]
8. Rubia, K.; Taylor, E.; Smith, H.; Oksannen, H.; Overmeyer, S.; Newman, S. Neuropsychological analyses of impulsiveness in childhood hyperactivity. *Br. J. Psychiatry* **2001**, *179*, 138–143. [CrossRef]
9. Castellanos, F.X.; Tannock, R. Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nat. Rev. Neurosci.* **2002**, *3*, 617–628. [CrossRef]
10. Martinussen, R.; Hayden, J.; Hogg-Johnson, S.; Tannock, R. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2005**, *44*, 377–384. [CrossRef]
11. Nigg, J.T.; Stavro, G.; Ettenhofer, M.; Hambrick, D.Z.; Miller, T.; Henderson, J.M. Executive functions and ADHD in adults: Evidence for selective effects on ADHD symptom domains. *J. Abnorm. Psychol.* **2005**, *114*, 706–717. [CrossRef]
12. Doyle, A.E. Executive functions in attention-deficit/hyperactivity disorder. *J. Clin. Psychiatry* **2006**, *67*, 21–26. [PubMed]
13. Seidman, L.J.; Valera, E.M.; Makris, N.; Monuteaux, M.C.; Boriel, D.L.; Kelkar, K.; Kennedy, D.N.; Caviness, V.S.; Bush, G.; Aleardi, M.; et al. Dorsolateral prefrontal and anterior cingulated cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biol. Psychiatry* **2006**, *60*, 1071–1080. [CrossRef] [PubMed]
14. Barkley, R.A.; Murphy, K.R. Impairment in occupational functioning and adult ADHD: The predictive utility of executive function (EF) rating versus EF tests. *Arch. Clin. Neuropsychol.* **2010**, *25*, 157–173. [CrossRef] [PubMed]
15. Rubia, K.; Halari, R.; Cubillo, A.; Mohammad, A.M.; Scott, S.; Brammer, M. Disorder-specific inferior prefrontal hypofunction in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure conduct disorder during cognitive flexibility. *Hum. Brain Mapp.* **2010**, *31*, 1823–1833. [CrossRef] [PubMed]
16. Nigg, J.T. Attention-deficit/hyperactivity disorder and adverse health outcomes. *Clin. Psychol. Rev.* **2012**, *33*, 215–228. [CrossRef] [PubMed]
17. Hinshaw, S.P.; Arnold, L.E.; MTA Cooperative Group. Attention-deficit hyperactivity disorder, multimodal treatment, and longitudinal outcome: Evidence, paradox, and challenge. *Wiley Interdiscip. Rev. Cogn. Sci.* **2015**, *6*, 39–52. [CrossRef] [PubMed]
18. National Institute for Health and Care Excellence. *Clinical Guideline 72 [CG72]. Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults*; Scope NICE: London, UK, 2008.
19. National Institute for Health and Care Excellence. *NICE Guideline 87 [NG87]. Attention Deficit Hyperactivity Disorder: Diagnosis and Management*; Scope NICE: London, UK, 2018.
20. MTA Cooperative Group. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: The multimodal treatment study of children with attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry* **1999**, *56*, 1088–1096. [CrossRef] [PubMed]
21. American Academy Child and Adolescent Psychiatry. Practice parameters for the use of stimulant medication in children, adolescent and adults. *J. Am. Acad. Child. Adolesc. Psychiatry* **2002**, *41*, 26S–49S. [CrossRef]
22. Cairncross, M.; Miller, C.J. The effectiveness of mindfulness-based therapies for ADHD: A meta-analytic review. *J. Atten. Disord.* **2016**, *20*, 1–17. [CrossRef]
23. Zhang, J.; Díaz-Román, A.; Cortese, S. Meditation-based therapies for attention-deficit/hyperactivity disorder in children, adolescents, and adults: A systematic review and meta-analysis. *Evid. Based Ment. Health* **2018**, *21*, 87–94. [CrossRef]
24. Brown, K.W.; Ryan, R.M. The benefits of being present: Mindfulness and its role in psychological well-being. *J. Pers. Soc. Psychol.* **2003**, *84*, 822–848. [CrossRef] [PubMed]
25. Kabat-Zinn, J. Mindfulness-based interventions in context: Past, present, and future. *Clin. Psychol.* **2003**, *10*, 144–156. [CrossRef]

26. Bishop, S.R.; Lau, M.; Shapiro, S.; Carlson, L.; Anderson, N.; Carmody, J.; Segal, Z.; Abbey, S.; Speca, M.; Velting, D.; et al. Mindfulness: A proposed operational definition. *Clin. Psychol.* **2004**, *11*, 230–241. [CrossRef]
27. Hölzel, B.K.; Lazar, S.W.; Gard, T.; Schuman-Olivier, Z.; Vago, D.R.; Ott, U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. *Perspect. Psychol. Sci.* **2011**, *6*, 537–559. [CrossRef]
28. Malinowski, P. Neural mechanisms of attentional control in mindfulness meditation. *Neuroscience* **2013**, *7*, 8. [CrossRef]
29. Evans, S.; Ling, M.; Hill, B.; Rinehart, N.; Austin, D.; Sciberras, E. Systematic review of meditation-based interventions for children with ADHD. *Eur. Child Adolesc. Psychiatry* **2017**, *27*, 9–27. [CrossRef]
30. Carsley, D.; Khoury, B.; Heath, N.L. Effectiveness of mindfulness interventions for mental health in Schools: A comprehensive meta-analysis. *Mindfulness* **2018**, *9*, 693–707. [CrossRef]
31. Dunning, D.L.; Griffiths, K.; Kuyken, W.; Crane, C.; Foulkes, L.; Parker, J.; Dalgleish, T. Research review: The effects of mindfulness-based interventions on cognition and mental health in children and adolescents—A meta-analysis of randomized controlled trials. *J. Child Psychol. Psychiatry* **2019**, *60*, 244–258. [CrossRef]
32. Biegel, G.M.; Brown, K.W.; Shapiro, S.L.; Schubert, C.M. Mindfulness-based stress reduction for the treatment of adolescent psychiatric outpatients: A randomized clinical trial. *J. Consult. Clin. Psychol.* **2009**, *77*, 855–866. [CrossRef]
33. Burke, C.A. Mindfulness-based approaches with children and adolescents: A preliminary review of current research in an emergent field. *J. Child Fam. Stud.* **2010**, *19*, 133–144. [CrossRef]
34. Flook, L.; Smalley, S.L.; Kitil, M.J.; Galla, B.M.; Kaiser-Greenland, S.; Locke, J.; Ishijima, E.; Kasari, C. Effects of mindful awareness practices on executive functions in elementary school children. *J. Appl. Sch. Psychol.* **2010**, *26*, 70–95. [CrossRef]
35. Semple, R.J.; Lee, J.; Rosa, D.; Miller, L.F. A randomized trial of mindfulness-based cognitive therapy for children: Promoting mindful attention to enhance social-emotional resiliency in children. *J. Child Fam. Stud.* **2010**, *19*, 218–229. [CrossRef]
36. Thompson, M.; Gauntlett-Gilbert, J. Mindfulness with children and adolescents: Effective clinical application. *Clin. Child Psychol. Psychiatry* **2008**, *13*, 395–407. [CrossRef] [PubMed]
37. Allen, N.B.; Chambers, R.; Knight, W.; Melbourne Academic Mindfulness Interest Group. Mindfulness-based psychotherapies: A review of conceptual foundations, empirical evidence and practical considerations. *Aust. N. Z. J. Psychiatry* **2016**, *40*, 285–294.
38. Beauchemin, J.; Hutchins, T.L.; Patterson, F. Mindfulness meditation may lessen anxiety, promote social skills, and improve academic performance among adolescents with learning disabilities. *J. Evid. Based Integr. Med.* **2008**, *13*, 34–45. [CrossRef]
39. Broderick, P.C.; Metz, S. Learning to BREATHE: A pilot trial of a mindfulness curriculum for adolescents. *Adv. Sch. Ment. Health Promot.* **2009**, *2*, 35–46. [CrossRef]
40. Zoogman, S.; Goldberg, S.B.; Hoyt, W.T.; Miller, L. Mindfulness interventions with youth: A meta-analysis. *Mindfulness* **2014**, *6*, 290–302. [CrossRef]
41. Napoli, M.; Krech, P.R.; Holley, L.C. Mindfulness training for elementary school students: The attention academy. *J. Appl. Sch. Psychol.* **2005**, *21*, 99–125. [CrossRef]
42. Geronimi, E.M.; Arellano, B.; Woodruff-Borden, J. Relating mindfulness and executive function in children. *Clin. Child. Psychol. Psychiatry* **2020**, *25*, 1–11. [CrossRef]
43. Van Dam, N.T.; van Vugt, M.K.; Vago, D.R.; Schmalzl, L.; Saron, C.D.; Olendzki, A.; Meissner, T.; Lazar, S.W.; Kerr, C.E.; Gorchov, J.; et al. Mind the hype: A critical evaluation and prescriptive agenda for research on mindfulness and meditation. *Perspect. Psychol. Sci.* **2018**, *13*, 36–61. [CrossRef]
44. Fabbro, F.; Muratori, F. La mindfulness: Un nuovo approccio psicoterapeutico in età evolutiva. *G. Ital. Di Neuropsichiatr. Dell'età Evol.* **2012**, *32*, 248–259.
45. Gunaratana, H. *Mindfulness in Plain*; English Wisdom Publications: Somerville, MA, USA, 2002.
46. Kabat-Zinn, J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *Gen. Hosp. Psychiatry* **1982**, *4*, 33–47. [CrossRef]
47. Kabat-Zinn, J. *Full Catastrophe Living: The Program of the Stress Reduction Clinic at the University of Massachusetts Medical Center*; Dell: New York, NY, USA, 1990.

48. Haydicky, J.; Wiener, C.; Badali, P.; Milligan, K.; Ducharme, J.M. Evaluation of a mindfulness-based intervention for adolescents with learning disability and co-occurring ADHD and anxiety. *Mindfulness* **2012**, *3*, 151–164. [CrossRef]
49. Crescentini, C.; Capurso, V.; Furlan, S.; Fabbro, F. Mindfulness-oriented meditation for primary school children: Effects on attention and psychological well-being. *Front Psychol.* **2016**, *7*, 805. [CrossRef] [PubMed]
50. Viechtbauer, W.; Smits, L.; Kotz, D.; Budé, L.; Spigt, M.; Serroyen, J.; Crutzen, R. A simple formula for the calculation of sample size in pilot studies. *J. Clin. Epidemiol.* **2015**, *68*, 1375–1379. [CrossRef]
51. Kaufman, J.; Birmaher, B.; Brent, D.; Rao, U. Schedule for affective disorders and schizophrenia for school-age children-present lifetime version (K-SADS-PL): Initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry* **1997**, *36*, 980–988. [CrossRef]
52. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; (DSM-IV-TR); American Psychiatric Association: Washington, DC, USA, 2000.
53. Shaffer, D.; Gould, M.S.; Brasic, J.; Ambrosini, P.; Fisher, P.; Bird, H.; Aluwahlia, S. A children's Global Assessment Scale (C-GAS). *Arch. Gen. Psychiatry* **1983**, *40*, 1228–1231. [CrossRef]
54. Orsini, A.; Pezzuti, L.; Picone, L. *WISC-IV: Contributo Alla Taratura Italiana*; (Italian Edition); Giunti, O.S., Ed.; Organizzazioni Speciali: Firenze, Italy, 2012.
55. Raven, J.C. *Coloured Progressive Matrices-CPM, Series A, AB, B*; (Italian Adaptation); Giunti, O.S., Ed.; Organizzazioni Speciali: Firenze, Italy, 2008.
56. Campanella, F.; Crescentini, C.; Urgesi, C.; Fabbro, F. Mindfulness-oriented meditation improves self-related character scales in healthy individuals. *Compr. Psychiatry* **2014**, *55*, 1269–1278. [CrossRef]
57. Crescentini, C.; Matiz, A.; Fabbro, F. Improving personality/character traits in individuals with alcohol dependence: The influence of mindfulness-oriented meditation. *J. Addict. Dis.* **2015**, *34*, 75–87. [CrossRef]
58. Crescentini, C.; Menghini, D. *La Mindfulness per l'ADHD e i Disturbi del Neurosviluppo. Applicazione Clinica Della Meditazione Orientata alla Mindfulness—MOM*; Centro Studi Erickson: Trento, Italy, 2019.
59. MacCoon, D.G.; Imel, Z.E.; Rosenkranz, M.A.; Sheftel, J.G.; Weng, H.Y.; Sullivan, J.C.; Lutz, A. The validation of an active control intervention for mindfulness based stress reduction (MBSR). *Behav. Res.* **2012**, *50*, 3–12. [CrossRef]
60. Corallo, R. *Sei Folletti Nel Mio Cuore (Six Pixies in My Heart)*; Centro Studi Erickson: Trento, Italy, 2011.
61. Conners, C.K.; MHS Staff. *Conners' Continuous Performance Test-II 5th Version (CPT-II V.5). Technical Guide and Software Manual*; Multi Health System: North Tonawanda, NY, USA, 2004.
62. Golden, C.J.; Freshwater, S.M. *The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*; Stoelting: Chicago, IL, USA, 2002.
63. Townsend, J.T.; Ashby, F.G. Methods of modeling capacity in simple processing systems. In *Cognitive Theory*; Castellan, J.N.J., Restle, F., Eds.; Lawrence Erlbaum Associates: New York, NY, USA, 1978; Volume 3, pp. 199–239.
64. Logan, G.D.; Cowan, W.B. On the ability to inhibit thought and action: A theory of an act of control. *Psychol. Rev.* **1984**, *91*, 295–327. [CrossRef]
65. Marcos, E.; Pani, P.; Brunamonti, E.; Deco, G.; Ferraina, S.; Verschure, P. Neural variability in premotor cortex is modulated by trial history and predicts behavioral performance. *Neuron* **2013**, *78*, 249–255. [CrossRef] [PubMed]
66. Pani, P.; Menghini, D.; Napolitano, C.; Calcagni, M.; Armando, M.; Sergeant, J.A.; Vicari, S. Proactive and reactive control of movement are differently affected in attention deficit hyperactivity disorder children. *Res. Dev. Disabil.* **2013**, *34*, 3104–3111. [CrossRef] [PubMed]
67. Menghini, D.; Armando, M.; Calcagni, M.; Napolitano, C.; Pasqualetti, P.; Sergeant, J.A.; Pani, P.; Vicari, S. The influence of generalized anxiety disorder on executive functions in children with ADHD. *Eur. Arch. Psychiatry Clin. Neurosci.* **2017**, *268*, 349–357. [CrossRef] [PubMed]
68. Conners, C.K. *Conners' Rating Scales–Revised*; (Italian adaptation); Giunti, O.S., Ed.; Organizzazioni Speciali: Firenze, Italy, 1997.
69. Achenbach, T.M.; Rescorla, L.A. *Manual for the ASEBA School-Age Forms and Profiles*; University of Vermont, Research Center for Children, Youth and Families: Burlington, VT, USA, 2001.
70. March, J.S.; Parker, J.D.A.; Sullivan, K.; Stallings, P.; Conners, C.K. The Multidimensional Anxiety Scale for Children (MASC): Factor structure, reliability, and validity. *J. Am. Acad. Child Adolesc. Psychiatry* **1997**, *36*, 554–565. [CrossRef]

71. Kovacs, M. *Children's Depression Inventory—CDI*; (Italian Adaptation); Giunti, O.S., Ed.; Organizzazioni Speciali: Firenze, Italy, 1982.
72. Greco, L.A.; Baer, R.A.; Smith, G.T. Assessing mindfulness in children and adolescents: Development and validation of the child and adolescent mindfulness measure (CAMM). *Psychol. Assess* **2011**, *23*, 606–614. [CrossRef]
73. Abidin, R.R. *The Parenting Stress Index-Short Form. Test Manual Pediatric*; Psychology Press: Charlottesville, VA, USA, 1990.
74. Abidin, R.R. *Parenting Stress Index: Professional Manual*, 3rd ed.; Psychological Assessment Resources: Odessa, FL, USA, 1995.
75. Guarino, A.; Di Blasio, P.; D'Alessio, M.; Camisasca, E.; Serantoni, G. *Parenting Stress Index—Short Form*; Giunti, O.S., Ed.; Organizzazioni Speciali: Firenze, Italy, 2008.
76. Cornoldi, C.; Colpo, G. *Prove di Lettura MT-2 per la Scuola Primaria*; Giunti, O.S., Ed.; Organizzazioni Speciali: Firenze, Italy, 2007.
77. Biancardi, A.; Nicoletti, C. *Batteria per la Discalculia Evolutiva (BDE)*; Edizioni Omega: Torino, Italy, 2004.
78. Cornoldi, C.; Lucangeli, D.; Bellina, M. *Test AC-MC 6-11. Test di Valutazione delle Abilità di Calcolo*; Centro Studi Erickson: Trento, Italy, 2012.
79. Holas, P.; Jankowski, T. A cognitive perspective on mindfulness. *Int. J. Psychol.* **2013**, *48*, 232–243. [CrossRef]
80. Chambers, R.; Lo, B.C.L.; Allen, N.B. The impact of intensive mindfulness training on attentional control, cognitive style, and affect. *Cogn. Res.* **2008**, *32*, 303–322. [CrossRef]
81. Lyvers, M.; Makin, C.; Toms, E.; Thorberg, F.A.; Samios, C. Trait mindfulness in relation to emotional self-regulation and executive function. *Mindfulness* **2014**, *5*, 619–625. [CrossRef]
82. Oberle, E.; Kimberly, A.S.C.; Molly, S.; Kimberly, C.T. Mindfulness and inhibitory control in early adolescence. *J. Early Adolesc.* **2012**, *32*, 565–588. [CrossRef]
83. Riggs, N.R.; Black, D.S.; Ritt-Olson, A. Associations between dispositional mindfulness and executive function in early adolescence. *J. Child Fam. Stud.* **2015**, *24*, 2745–2751. [CrossRef]
84. Quach, D.; Mano, K.E.J.; Alexander, K. A randomized controlled trial examining the effect of mindfulness meditation on working memory capacity in adolescents. *J. Adolesc. Health.* **2016**, *58*, 489–496. [CrossRef] [PubMed]
85. Gallant, S.N. Mindfulness meditation practice and executive functioning: Breaking down the benefit. *Conscious Cogn.* **2016**, *40*, 116–130. [CrossRef] [PubMed]
86. Xue, J.; Zhang, Y.; Huang, Y. A meta-analytic investigation of the impact of mindfulness-based interventions on ADHD symptoms. *Medicine* **2019**, *98*, e15957. [CrossRef]
87. Van de Weijer-Bergsma, E.; Formsma, A.R.; de Bruin, E.I.; Bogels, S.M. The effectiveness of mindfulness training on behavioral problems and attentional functioning in adolescents with ADHD. *J. Child Fam. Stud.* **2012**, *21*, 775–787. [CrossRef]
88. Van der Oord, S.; Bögels, S.M.; Peijnenburg, D. The effectiveness of mindfulness training for children with ADHD and mindful parenting for their parents. *J. Child Fam. Stud.* **2012**, *21*, 139–147. [CrossRef]

DIBABILITÀ, PATOLOGIE CRONICHE COMPLESSE E BISOGNI INEVASI: QUALI PROSPETTIVE?

Disabilità: un problema irrisolto e forse irrisolvibile

La percezione sociale del disabile sembra vivere un'eterna ambivalenza tra il rifiuto e l'accoglienza, l'amore e l'odio, la presa in carico e l'abbandono.

Nel mondo animale il malato è destinato a morire e così la selezione naturale protegge e migliora la specie. Ci sono esempi di cura e difesa dei malati o feriti, ma la regola generale è questa.

Noi uomini costituiamo un'anomalia. Tutta la medicina infatti è lo sforzo per combattere la naturale selezione della specie!

Nel corso dell'evoluzione l'uomo è riuscito a sopravvivere e prevalere perché è stato capace di essere gruppo, cooperazione, comunione delle esperienze e legami affettivi interpersonali solidi.

Tutto questo grazie a un cervello plastico che è riuscito ad adattarsi e specializzarsi nella capacità dell'incontro e della reciprocità. Nel cervello dell'uomo i meccanismi dell'empatia attivano la reazione di cura attraverso l'esperienza interiorizzata del dolore dell'altro. Il sistema dei neuroni specchio, quello della comunicazione emotiva non verbale, il bisogno della relazione, tipico della specie umana, sono fondati sulla reciproca capacità di sentire e vivere le emozioni dell'altro, belle o brutte. Emozioni che attivano comportamenti reattivi qualche volta anche estremi, fino al sacrificio della vita per la vita dell'altro!

Nel caso della disabilità cronica non sempre però il meccanismo di rispecchiamento ha il risultato della empatia o della presa in carico. I sistemi specchio possono non riconoscere l'immagine corporea che hanno davanti e avere difficoltà di ricostruirla nel proprio sé. Il vissuto della sofferenza poi, interiorizzata dopo l'incontro con una disabilità, può attivare una reazione di difesa attraverso il blocco dei meccanismi dell'empatia.

L'effetto è la distanza emotiva e il rifiuto. La difficoltà a percepire i bisogni e i problemi del disabile con il suo mondo emotivo. L'impulso immediato davanti a una deformità è la presa di distanza, la diffidenza, l'incapacità di sentirne la sofferenza. È necessaria l'elaborazione corticale che prenda il controllo delle emozioni perché realmente il primo impatto di rifiuto sia superato e si attivi un comportamento di soccorso e presa in carico. Tutto questo è alla base della cecità sociale che accompagna la disabilità tutta.

Il familiare, vicino affettivamente, ha un percorso diverso. Coinvolto emotivamente egli vive il dolore in prima persona. I meccanismi di evitamento e rifiuto diventano per lui complessi di colpa. L'inadeguatezza degli interventi, la percezione progressiva del fallimento delle speranze, accompagnata alla riduzione delle energie, costruiscono sindromi depressive e progetti di vita frantumati.

Un sistema sanitario che si rivolga alla cronicità e alla disabilità non può non considerare questi problemi.

La cecità sociale isola questi malati e non vede le problematiche complesse delle loro famiglie.

Il sistema di sostegno dovrebbe quindi conoscere i meccanismi che sottendono questi comportamenti sociali e porvi rimedio con interventi mirati al recupero della inclusione e alla rottura della solitudine.

Il primo passo è comprendere che il disabile è un *unicum* insieme a tutta la sua famiglia e che c'è una profonda differenza di bisogni alle varie età.

Un bambino è molto diverso da un anziano o un giovane! Ognuno dovrebbe avere un percorso di recupero differenziato. La gestione attuale è invece basata sull'offerta di contributi economici, presidi, facilitazioni e interventi riabilitativi, ma non tiene conto della peculiarità dei bisogni e non prevede nulla come sostegno umano familiare e di inclusione. In età pediatrica l'impegno è tutto mirato alla riabilitazione.

I bambini frequentano più o meno la scuola e i genitori, giovani, mantengono ancora viva la speranza di un futuro. Dopo i 18 anni però la scuola finisce, la riabilitazione lascia pochi margini alla speranza, i ragazzi rientrano in casa senza prospettive e i genitori, stanchi, si ritrovano a dover riprogettare un futuro di vita che questa volta non sembra offrire possibilità. Il risultato è la profonda solitudine, l'involuzione, la depressione familiare. Il carico di lavoro sui genitori diventa insopportabile con l'angoscia di un "dopo di noi" cui è impossibile trovare risposte.

La cecità sociale nelle età avanzate si acuisce. L'adattamento alla cronicità rende questi malati invisibili anche ai familiari (zii cugini ecc…) e non attiva più risposte emotive di sostegno. In questo contesto l'assegno di accompagnamento, unica risposta del sistema, resta un inutile risarcimento sociale, del tutto inadeguato ad affrontare le quotidiane problematiche complesse cui la famiglia, rimasta completamente sola, deve rispondere.

In che modo il sistema potrebbe migliorare un'offerta di cura in un contesto così difficile?

Il primo passo dovrebbe essere la presa in carico di tutta la famiglia. Serve un importante supporto psicologico ed emotivo per i genitori e uno mirato e particolare per i fratelli. Le famiglie hanno assoluto bisogno di non vivere ripiegate solo sui bisogni del disabile, ma di mantenere interessi e prospettive proprie!

Questo è possibile solo se non sono costrette a dover affrontare da sole le mille necessità logistiche quotidiane. Servono persone, presenze, relazioni, condivisioni! Percorsi di inclusione e soggiorno diurno o anche notturno in contesti propositivi dove ad attività riabilitative possano accompagnarsi attività ludiche e motorie tra abili e disabili!

Tutto questo comporta un impegno importante, ma assolutamente necessario.

Nella gestione della disabilità la patologia da curare non è il deficit intellettivo o l'atassia o la paresi… ma la cecità sociale, la depressione familiare, l'isolamento. E il paziente non è il singolo malato, ma la sua famiglia e il contesto sociale in cui è inserita. Il paziente è la città in cui vive. Un ambiente che dovrebbe essere accogliente, in grado di offrire luoghi accessibili e aggreganti. Un disabile chiuso in casa, davanti a un video, solo, è il quadro clinico comune a tutte le patologie croniche.

Nessun intervento fino a ora è mai riuscito a modificarlo.

Bibliografia di riferimento

- Rizzolatti G, Craighero L. The mirror-neuron system. Annu Rev Neurosci. 2004:27:169-92.
- Gallese V, Migone P, Eagle MN. La simulazione incarnata: i neuroni specchio, le basi neurofisiologiche dell'intersoggettività e alcune implicazioni per la psicoanalisi. Psicoterapia e Scienze Umane 2006;40(3):543-80.
- Gallese V. Dai neuroni specchio alla consonanza intenzionale, meccanismi neurofisiologici dell'intersoggettività. Rivista di Psicoanalisi 2007.
- Goleman D. Intelligenza emotiva. Ed. Bur 1999
- Goleman D. Intelligenza sociale. Ed. Bur 2007
- Selleri G. Handicap e famiglia.
- NOTIZIE CRH: newsletter a cura del Centro Risorse Handicap del Comune di Bologna. Invio del 9 luglio 2007.
- Aragona M, Puzella A. Come cambia l'empatia

per il dolore nelle neuroscienze. Una revisione critica della letteratura. Giorn Ital Psicopatol 2010; PDF researchgate.net
• Gazzetta Ufficiale. legge 5 Febbraio 1992, n° 104.

Tommaso Montini
Pediatra di famiglia, Napoli
Maria Elena Montini
Facoltà di Medicina e Chirurgia
(scuola di specializzazione???),
Università Federico II, Napoli
e-mail: *tom.montini@gmail.com*

Transitional healthcare per pazienti con patologia cronica complessa

Siamo pediatri da tempo coinvolti in un'Associazione di famiglie con figli affetti da una condizione rara: la sindrome cri du chat. L'Associazione, nata più di 20 anni fa, si chiama ABC (Associazione Bambini Cri du Chat), perché allora raccoglieva prevalentemente "nuove diagnosi", ma con l'andar degli anni i "bambini" sono diventati prevalentemente giovani e meno giovani adulti.

Abbiamo letto con interesse l'Aggiornamento su *Quaderni acp* sulla "Transitional Healthcare: il passaggio alla Medicina dell'adulto del paziente pediatrico affetto da patologia cronica e complessa", e vorremmo condividere con i lettori di *Medico e Bambino* alcune riflessioni.

I pazienti affetti da 5p- (delezione del braccio corto del cromosoma 5, altra definizione della sindrome) fanno parte, a nostro giudizio, dei pazienti "difficilmente transitabili", in quanto, come recita l'articolo: "il raggiungimento della maggiore età non comporta alcuna modifica nello status morale e sociale, né sortisce alcun effetto significativo in termini cognitivi, biologici o biografici. In termini giuridici, la loro condizione di minorità e la loro interdizione non può essere interrotta".

Però a 14 anni (o a 16, con deroga) anche loro perdono il diritto al pediatra di famiglia e afferiscono a un medico di Medicina generale che, per quanto volenteroso, il più delle volte delega al Centro di riferimento (o all'Associazione) i problemi di salute del suo assistito.

L'Associazione (la nostra, almeno) ha "un parco macchine" orientato all'età pediatrica (nel Comitato Scientifico dell'Associazione siamo rappresentati pediatri, NPI, genetisti, fisioterapisti, foniatri, medici nucleari) e crediamo che anche i Centri di riferimento abbiano una struttura analoga.

Abbiamo cercato di "rimpolpare le fila", ma i nostri *call for help* non sono andati a buon fine.

Personalmente non ci riconosciamo le competenze per problemi neurologici, ma anche della sfera sessuale, endocrina o cardiovascolare che i genitori ci sottopongono (oltretutto, spesso, "a distanza"…). E, per inciso, pensiamo di non essere neppure coperti da polizze assicurative, trattandosi spesso di pazienti che non conosciamo da quando erano bambini…

Qualche anno fa siamo stati ospitati sulle pagine di *Medico e Bambino* con una "presentazione della sindrome" a uso dei pediatri di famiglia, che è stata molto apprezzata dalle famiglie e dai loro curanti.

Abbiamo poi provato ad "allargarci" stilando delle "raccomandazioni" per l'assistenza, comprensive dell'età adulta. Inaspettatamente, questo lavoro è stato rifiutato da riviste scientifiche pediatriche anche italiane, proprio perché "sconfinava" nell'età adulta. Ma allora? Dove e come può formarsi un medico che desideri effettivamente farsi carico di questi pazienti? Come si può realizzare questa auspicata transizione? O cogestione?

Loro (i pazienti) starebbero molto meglio in Pediatria, ma sappiamo che per organizzare un *Day Hospital* bisogna chiedere il nulla osta in Direzione Sanitaria (e non tutte le Aziende lo concedono), il personale mal tollera il surplus di lavoro che un disabile adulto comporta, la commistione bambini-adulti è malvista dai genitori degli utenti pediatrici ecc. e sono pazienti "frustranti", come giustamente si ribadisce nell'articolo.

Già nella "Guida pratica intersocietaria Adolescenza e transizione" del 2017 sulle malattie rare ci si esprimeva così: "Per questi motivi le malattie rare pongono problemi assistenziali rilevanti proprio al momento della transizione in quanto, mentre per certe malattie croniche come ad esempio diabete, artrite idiopatica giovanile, malattie croniche intestinali, non è difficile trovare lo specialista dell'adulto che prenda in carico tali pazienti in età giovane-adulta, lo stesso non si può dire per le malattie rare, come la sindrome di Prader-Willi o di Turner, per le quali è difficile trovare medici dell'adulto con le necessarie competenze."

Forse i genetisti medici (che si occupano di bambini, ma anche di adulti) potrebbero essere il trait d'union. Ma quanti e dove sono? E all'estero come fanno?

Ci farebbe piacere aprire una discussione serena per sollevare il problema delle competenze culturali e assistenziali, per non assistere, nonostante le ottime intenzioni, all'"abbandono camuffato" dei malati. Una soluzione dobbiamo trovarla.

Maria Elena Liverani
Pediatra, Roma
Andrea Guala
Pediatra e Genetista, Verbania
e-mail: *meliverani@gmail.com*

Non è facile rispondere ai due compiuti e ben documentati contributi che ripropongono aspetti che, negli anni, sono stati a lungo discussi. Quando si parla di disabilità e di patologie croniche complesse quello di cui abbiamo bisogno, come riportato nelle lettere, è di un salto culturale in merito ai problemi che non hanno trovano ancora una prospettiva di compiuta risoluzione.

Ci sono alcuni semplici punti che vorrei sottolineare, con una visione che trae spunto dal vissuto quotidiano di una realtà ospedaliera (e come tale molto limitata), ma che sta cercando di andare "Oltre i Confini", in un tentativo di progetto di rete. Negli anni ho sempre sentito un profondo afflato assistenziale nei confronti della disabilità. Non so se è una questione di neuroni specchio, forse appartiene al semplice dovere motivato (inizialmente clinico) di rispondere a determinati bisogni incontrati strada facendo. Vivere l'assistenza partecipe alla disabilità (quella di gruppo, quella che si ritrova a discutere e a prevedere i Piani di Assistenza Individuali e a verificarli costantemente) è un valore professionale e umano aggiunto che nei successi, ma anche negli insuccessi e nelle emozioni, è impagabile. Hanno ragione Tommaso e Maria Elena Montini quando dicono che spesso esiste al contrario una distanza assistenziale, anche quando e soprattutto ci si limita alla prescrizione di presidi, alla richiesta di consulenze, a un esclusivo progetto riabilitativo. Quello che mi sento di dire è che il contesto di vita, di relazioni, di socialità (e anche di assistenza medica) della disabilità e delle patologie croniche complesse deve prevedere delle persone capaci, accoglienti e che vivono il loro ruolo professionale come un "normale" (e qualificato) modo di essere e di agire. Questo non si insegna nei corsi di laurea e nelle scuole di specialità. In questi luoghi non si consigliano le letture che appartengono a una pedagogia educativa della disabilità e di cui la letteratura specialistica o da libreria è piena. Mentre imparavo (o cercavo di farlo con un senso profondo di inadeguatezza) come sentirsi partecipe della vicinanza professionale ai "nostri" bambini speciali, leggevo i testi della Clara Sereni (Manicomio Primavera), di Giuseppe Pontiggia (Nati due volte) o di Gianluca Nicoletti (Una notte ho sognato che parlavi), per citarne solo alcuni. In quelle parole (così come in quelle di tanti genitori) mi sono sempre ritrovato per essere ancora più partecipe delle emozioni, del significato di un progetto, che non può limitarsi appunto a un intervento strettamente socio-sanitario.

Mi è capitato di parlare con insegnanti di sostegno e con educatori che fuggono dalle classi dove i bambini disabili sono relegati, che vanno in spazi aperti di libertà dentro le città o in periferia e sono partecipi di un progetto che vede coinvolti anche i bambini cosiddetti "normali" insieme a quelli con biso-

gni speciali. E mi è capitato di parlare con genitori che portano i loro figli in Centri diurni (alcuni molto e sempre di più qualificati) dove trovano i luoghi familiari di assistenza, dove il sorriso dei loro figli è percepibile dal primo minuto dell'accoglienza; altri dove invece si è in una condizione di continuo stress per "paure", per "difficoltà" organizzative e altro ancora. Pochi esempi positivi, pochi modelli rispetto a quanto andrebbe progettato nel modo più naturale e spontaneo possibile.

Devo dire che negli anni ho visto tanti progressi e non sarei pessimista nel pensare che tutto è o è rimasto irrisolvibile. Il vero dramma è quello dei nostri ragazzi che diventano adolescenti e poi adulti e delle loro famiglie. Non ci sono risposte, non ci sono modelli validi, non ci sono appunto progetti differenziati; sarebbe importante parlarne in modo molto concreto e non estemporaneo, anticipando le richieste e non inseguendole. Ci si chiede, ad esempio, rimanendo in un contesto strettamente medico (e come tale molto limitativo), se le famose Case della salute non possano essere un luogo aggregativo di professionisti in grado di condividere capacità, esperienze e prospettive di assistenza anche per i bambini (e futuri adulti) con patologie rare complesse. Ci si chiede se non sia arrivato il tempo di immaginare, per ogni ambito territoriale, dei "professionisti della transizione" per le patologie croniche complesse richiamate da Liverani e Guala. Forse bisognerebbe andare oltre il termine di transizione, ma semplicemente pensare che deve esistere e va programmata una assistenza che non ha un prima e un dopo, che non ha professionisti dedicati prima e da inventarsi dopo, ma che ha un "sempre", fatto di qualità e di mestiere.

Ma ci sarebbe ancora altro da immaginare e fare. Leggevo da esperti del design, che i luoghi fisici delle nostre piazze e delle nostre strade andrebbero previsti come spazi aggregativi e funzionali ai bisogni di vita sociale (parlarne di questi tempi suona male!). Gianluca Nicoletti questo, nel suo libro, lo ha già prefigurato, pensando al futuro del suo figlio autistico (quando lui come padre non ci sarà più): "Immaginavo di costruire la città felice che manca in ogni luogo, felice proprio perché chi la abita è disinteressato alla competizione, a schiacciare il prossimo, a sopraffare, scavalcare, insidiare. Felice perché ci vive chi è contento di fare le cose che a lui piacciono... chi è leggero di pensieri regala un sorriso a chiunque lo sfiori. Mi piacerebbe che pure chi, come i nostri ragazzi non ha più un posto e un ruolo, perché il mondo non sa che farsene di lui, ritrovasse in questa città qualcuno che dia un senso al suo esistere. Vigili in pensione, falegnami, decoratori, artigiani di ogni tipo trovassero a Insettopia formiche capaci di fare qualcosa o almeno che ci proverebbero. A Insettopia si ballerebbe, si farebbe musica, si mangerebbe e respirerebbe allegria, perché sarebbe come una fessura aperta sul mondo che non c'è. Ci andrebbero anche i ragazzi con il cervello tutto in regola, ma solo perché farlo diventerebbe più figo che passare le serate davanti a un locale...".

In queste parole non c'è buonismo o illusione. Forse c'è un cambio profondo di prospettiva che sarebbe in grado, da solo, di superare barriere fatte di accettazione, organizzazione, empatia e competenze. La normalità di contesto è diversa dalla ricerca spasmodica di inseguire ed evitare il minore danno.

Federico Marchetti

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 30, Number 8, 2020

Pp. 495–511
DOI: 10.1089/cap.2019.0165

Pediatric Acute-Onset Neuropsychiatric Syndrome: A Data Mining Approach to a Very Specific Constellation of Clinical Variables

Antonella Gagliano, MD, PhD,[1] Cecilia Galati, MD,[2] Massimo Ingrassia, BS,[3] Massimo Ciuffo, BS,[4] Maria Ausilia Alquino, BS,[2] Marcello G. Tanca, BS,[1] Sara Carucci, MD, PhD,[1] Alessandro Zuddas, MD,[1] and Enzo Grossi, MD[5]

Abstract

Objectives: Pediatric acute onset neuropsychiatric syndrome (PANS) is a clinically heterogeneous disorder presenting with: unusually abrupt onset of obsessive compulsive disorder (OCD) or severe eating restrictions, with at least two concomitant cognitive, behavioral, or affective symptoms such as anxiety, obsessive-compulsive behavior, and irritability/depression. This study describes the clinical and laboratory variables of 39 children (13 female and 26 male) with a mean age at recruitment of 8.6 years (standard deviation 3.1).

Methods: Using a mathematical approach based on Artificial Neural Networks, the putative associations between PANS working criteria, as defined at the NIH in July 2010 (Swedo et al. 2012), were explored by the Auto Contractive Map (Auto-CM) system, a mapping method able to compute the multidimensional association of strength of each variable with all other variables in predefined dataset.

Results: The PANS symptoms were strictly linked to one another on the semantic connectivity map, shaping a central ''diamond'' encompassing anxiety, irritability/oppositional defiant disorder symptoms, obsessive-compulsive symptoms, behavioral regression, sensory motor abnormalities, school performance deterioration, sleep disturbances, and emotional lability/depression. The semantic connectivity map also showed the aggregation between PANS symptoms and laboratory and clinical variables. In particular, the emotional lability/depression resulted as a highly connected hub linked to autoimmune disease in pregnancy, allergic and atopic disorders, and low Natural Killer percentage. Also anxiety symptoms were shown to be strongly related with recurrent infectious disease remarking the possible role of infections as a risk factor for PANS.

Conclusion: Our data mining approach shows a very specific constellation of symptoms having strong links to laboratory and clinical variables consistent with PANS feature.

Keywords: pediatric obsessive compulsive disorder, autoimmune-mediated inflammatory brain diseases, pediatric acute-onset neuropsychiatric syndrome, artificial neural network analysis

Introduction

Pediatric acute onset neuropsychiatric syndrome (PANS) is a clinically heterogeneous disorder presenting with: unusually abrupt onset of obsessive compulsive symptoms and/or severe eating restriction, with at least two concomitant cognitive, motor, behavioral, or affective symptoms such as anxiety and/or irritability/depression (Swedo et al. 2012).

The syndrome was described in 2012 as a result of the modification of the Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) criteria: an acute prepubertal onset of tics or Obsessive compulsive disorder (OCD) and specific neuropsychiatric symptoms triggered by infections with group A beta-hemolytic Streptococcus (GABHS) (Swedo et al. 1998). PANS can be associated with nonstreptococcal triggers, such as Mycoplasma pneumoniae, Epstein–Barr virus,

[1]Child & Adolescent Neuropsychiatry Unit, Department of Biomedical Sciences, University of Cagliari, & ''G. Brotzu'' Hospital Trust, Cagliari, Italy.
[2]Division of Child Neurology and Psychiatry, Department of Paediatrics, University of Messina, Messina, Italy.
[3]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.
[4]Department of Cognitive Psychological Pedagogical Sciences and Cultural Studies, University of Messina, Messina, Italy.
[5]Autism Research Unit, Villa Santa Maria Foundation, Tavernerio, Italy.
Funding: The authors received no specific funding.

influenza, or other common viruses, usually located in the upper respiratory tract (Chang et al. 2015).

Pediatric autoimmune-mediated inflammatory brain diseases, however, may also be triggered by different environmental agents (e.g., stress, substances, virus, or bacteria), in subjects with a brain susceptibility to autoimmunity (Van Mater 2014; Graus et al. 2016). In fact, neuroinflammation has been postulated to have a pathogenic role in many psychiatric illnesses (e.g., major depression, bipolar, schizophrenia, and OCDs) (Najjar et al. 2013; Pape et al. 2019).

According to the 2013 PANS Consensus Conference (Swedo et al. 2012; Chang et al. 2015), PANS is currently conceptualized as a complex syndrome with a number of etiologies and disease mechanisms, encompassing psychiatric symptoms, arising from immune abnormalities triggered by a variety of agents (Frankovich et al. 2015; Murphy et al. 2015). The PANS diagnostic construct was proposed as a clinical entity distinct from idiopathic or familial OCD, anxiety, or Tourette disorder on the basis of clinical observations. The validity and generalizability of epidemiologic studies about PANDAS and PANS have been criticized for highly biased participant sampling and nonvalidated causes, effects, and methods (Gilbert et al. 2018).

Nevertheless, PANS may be comparable to other persistent neuroinflammatory disorders such as multiple sclerosis, Sydenham chorea (SC), Behcet's disease, and asthma, underlining that infections and other environmental triggers play a role in provoking an inflammatory brain response, which evolves into a chronic or progressive neuroimmune disorder (Frankovich et al. 2015). Despite the fact that PANS is a clinical diagnosis of exclusion without a single defined etiology or specific clinical symptoms, it could be considered a useful construct for outlining the sudden onset of severe neuropsychiatric symptoms in children with a relapsing-remitting course.

Artificial Neural Networks (ANNs) are computational adaptive systems inspired by the functioning processes of the human brain: they are considered particularly useful to solve nonlinear problems and to discover subtle trends and associations among variables. Based on their learning through an adaptive way (i.e., extracting from the available data the information needed to achieve a specific aim and to generalize the acquired knowledge), the ANNs appear to be a powerful tool for data analysis in the presence of relatively small samples (Buscema et al. 2015).

In the last decade, a fourth generation ANN called Auto-Contractive Map has been increasingly used in medicine (Street et al. 2008; Gironi et al. 2013; Buscema et al. 2015; Narzisi et al. 2015; Toscano et al. 2017; Grossi et al. 2017, 2018). Overall, literature findings suggest that this method may be a strategic approach to grasp the core of the relationship between signs and symptoms of PANS.

This study aimed to explore the associations between the different PANS features and laboratory and clinical variables in a sample of 39 children diagnosed with PANS. We used the ANN approach to exploit putative subtle simultaneous connections among the full spectrum of clinical variables and different domains of impairment.

Methods

Participants

Consecutive patients referred for obsessive compulsive or anxiety symptoms and tic disorder, between December 2017 and December 2018 to the outpatient clinics of Child & Adolescent Neuropsychiatric Unit, ''G. Brotzu''Hospital Trust, Cagliari and the Child and Adolescent Psychiatry Unit, Policlinico ''G. Martino,'' Messina, were analyzed for possible PANS, according to PANS working criteria defined by experts convened at the National Institute of Mental Health (NIH) in July 2010 (Swedo et al. 2012), defined as follows:

(I) Abrupt dramatic onset of OCD or severely restricted food intake
(II) Concurrent presence of additional neuropsychiatric symptoms (with similarly severe and acute onset), from at least two of the following seven categories:
  (1) Anxiety
  (2) Emotional lability and/or depression
  (3) Irritability, aggression, and/or severely oppositional behaviors
  (4) Behavioral (developmental) regression
  (5) Deterioration in school performance (related to attention deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, and cognitive changes)
  (6) Sensory or motor abnormalities
  (7) Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency
(III) Symptoms are not better explained by a known neurologic or medical disorder, such as SC.

The diagnosis of PANS was confirmed by two child psychiatrists (A.G. and C.G.).

Exclusion criteria were the following: occurrence of immunologic diseases or cancer; presence of other medical or neurological/psychiatric diseases; active treatment with anti-inflammatory or corticosteroid agents; active treatment with psychoactive medications; and lack of consent form for participating in the study. Finally, patients with missing data on clinical records were excluded.

Variables

Patients were assessed according to the Consensus Statement clinical recommendations (Chang et al. 2015). An extensive physical, neurological, and psychiatric examination was performed. Parents were interviewed about family history and child medical history with a focus on the neurodevelopmental course, immune profile (autoimmune diseases, inflammatory diseases, immunodeficiency), and psychiatric conditions; family medical history included information about two generations (grandparents, parents, uncles, aunts, siblings, and cousins).

A blood sample was collected from each subject after the diagnosis and before starting any treatment. The battery of clinical laboratory test included: complete blood count, renal and liver function test, mineral panel, thyroid function indices, antithyroid antibodies (anti-thyroid peroxidase [anti-TPO], anti-thyroglobulin antibodies, TSH receptor antibodies [anti-TRAbs], and thyroid stimulating hormone receptor antibody [anti-TSH receptor]), and inflammatory blood markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and procalcitonin [PCT]). Serum level of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) Antibodies against Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae, Epstein–Barr virus, and Herpes Simplex Virus –HSV- Type 1 was also measured.

At enrollment all parents completed a checklist in Italian screening the symptoms and assessed their severity. The checklist was defined according to PANS criteria (Swedo et al. 2012).

It encompasses 10 items and systematically describes both main and additional PANS neuropsychiatric symptoms with multiple choice responses on a 4-point Likert scale (0 = absent; 1 = mild;

2 = severe; 3 = very severe). A narrative description of the meaning and implications of each item was provided to the parents (Tables 1) and a clinician helped the parents to fill out the checklist. In particular, parents were informed that the tool allows rating of how much the symptoms impact their child's life from 0 to 3, where 3 indicates the highest impact.

Ethical approval

The independent Ethics Committee of Cagliari University Hospital approved the study. All the parents were given a full explanation of the study methods and purposes and gave their written consent.

Data Analysis

All patients' clinical variables (family history, child symptom severity, medical history, and clinical laboratory test results) were collected on a specific database. The complete list of the variables is shown in Tables 1–3. The proportion of patients who had a specific symptom, a positive family history and maternal disease, and abnormal laboratory test results was calculated for each variable. Furthermore, the clinical variables were analyzed in three steps: linear correlation analysis, ANN analysis, and benchmarking analysis.

Linear correlation analysis

Spearman correlation analysis was performed on the 33 clinical and laboratory test variables expressed in binary format. A p-value <0.05 was considered to be statistically significant. Statistical analysis was performed with XLSTAT package 2018.

Benchmarking analysis

To handle a benchmarking analysis, the principal component analysis (PCA) and hierarchical agglomerative clustering (HAC) were carried out. Results of this benchmarking analysis allow to

Table 1. Mean Scores and SD at a 4-Point Likert Scale of the Main and Additional Pediatric Acute Onset Neuropsychiatric Syndrome Neuropsychiatric Symptoms and Number and Proportion of Patients Who Had Each Symptom

PANS neuropsychiatric symptoms	*Description*	*Mean score and standard deviation*	*Number of patients/39 and percentage*
Obsessive compulsive symptoms	Intrusive and repetitive thoughts (e.g., obsessional worries about contamination, order or symmetry, harm or danger, *etc.*) and/or compulsions (e.g., repeated checking, counting, tapping, arranging, repeating certain words/actions/questions, *etc.*; red ring around the mouth from excessive lip-licking, chapped hands from excessive washing, or irritation of the external genitalia from excessive wiping)	1.87 (0.95)	34/39 (87%)
Restricted food intake	Refusal to eat or marked decrease in food or fluid intake; worries about consequences of eating or avoidance based on the sensory characteristics of food; nausea or severe lack of interest in eating or food; secondary dehydration or emaciation	1.26 (1.14)	26/39 (66%)
Anxiety	Hyperalert, anxious, terrified, or in the ''fight or flight'' mode; separation anxiety (need to maintain proximity to familiar members or locations); irrational fears or phobias; general anxiety; panic episodes	1.97 (1.03)	35/39 (89%)
Emotional lability/depression	Emotional lability characterized by involuntary and uncontrollable episodes of crying or laughing that are mood incongruent; depression with a flat or depressed effect, auditory or visual hallucinations; self-injurious or aggressive behaviors	1.79 (1.23)	30/39 (76%)
Irritability/Oppositional defiant disorder	Severe impulsivity and agitation, oppositional behavior, irritability, aggression, and temper tantrum episodes, defiant/irrational demands; reactive aggressive behavior, rage attacks	2.15 (1.08)	35/39 (89%)
Behavioral regression	Developmental regression with ''baby talk'', paucity of speech or mutism, memory impairments; severe change in personality	1.36 (1.06)	30/39 (76%)
School performance deterioration	Meaningful changing in school achievement with a deterioration of school performance and behavior (difficulties in paying attention on cognitive tasks and in remaining seated). Deterioration of handwriting with mixtures of printing and cursive writing, irregular sizes, shapes, or slant of letters, and inconsistent position of letters on the page; difficulties in drawing even simple figures	1.59 (1.20)	29/39 (74%)
Sensory or motor abnormalities	Motor or phonic tics (grunting, squeaking, *etc.*); choreiform or ''piano playing fingers'' movements, mildly reduced proximal muscle weakness and slouched posture, adventitious movements, developmental motor regression. Heightened sensitivity to sounds, light, smell, or taste; shape or spatial distortion of object vision; visual or auditory hallucinations; dilated pupils –''terror stricken look''	1.59 (1.11)	32/39 (82%)
Sleep disturbances	Insomnia, inability to sleep, lengthy bedtime rituals, parasomnias (e.g., sleepwalking, night terrors), periodic limb movement, *etc.*	1.67 (1.13)	31/39 (79%)
Enuresis/urinary frequency	Increased urinary frequency or urge to urinate; urinary incontinence or inability to urinate.	0.95(1.07)	24/39 (61%)

(Likert scale from 0 = absence to 3 = extremely severe).
PANS, pediatric acute onset neuropsychiatric syndrome.

Table 2. Proportion of Patients Who Had a Family and Pregnancy-Related/Intrapartum History

Family history and maternal diseases	*N/39*	*%*
Family History of Autoimmune Diseases[a]	31	80
Family psychiatric history[b]	28	72
Maternal pregnancy-related/intrapartum complications[c]	25	64
Maternal infections in pregnancy[d]	6	15
Maternal autoimmune diseases in pregnancy[a]	23	59
Maternal Hashimoto's disease in pregnancy[e]	13	33

[a]Family History of Autoimmune Diseases in first-degree relatives: Sydenham chorea, Systemic lupus erythematosus (SLE), Sjögren syndrome, Kawasaki's disease, Myasthenia gravis, Asthma, Guillain–Barre' syndrome, Multiple sclerosis, Hughes syndrome, type 1 diabetes, Celiac disease, Crohn's disease, Vitiligo, Psoriasis, Scleroderma, Familial Mediterranean fever, and Behçet's Disease.

[b]Psychiatric history in first-degree relatives of OCD, eating disorders, emotional lability, mood disorders, ADHD, anxiety disorders, tic disorders, psychosis, disruptive disorders, autism spectrum disorder, language and communication disorders, intellectual disability, and specific learning disorders.

[c]Pregnancy/delivery complications: high blood pressure, gestational diabetes, preeclampsia, placenta previa, preterm labor, low birth weight, fetal distress, perinatal asphyxia.

[d]Infections in pregnancy: urinary tract infection, bacterial vaginosis, toxoplasmosis, cytomegalovirus, hepatitis B virus, influenza, Epstein–Barr virus infection. Group B Streptococcus infections.

[e]Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis in which the thyroid gland is gradually destroyed.

OCD, obsessive compulsive disorder; ADHD, attention-deficit/hyperactivity disorder.

Table 3. Proportion of Patients Who Had Diseases and Abnormal Laboratory Test Results

Children variables	*N/39*	*%*
Clinical variables		
Recurrent infections[a]	32	82
Allergic and atopic disease[b]	18	46
Atopic dermatitis[c]	23	59
EEG alterations[d]	22	56
Laboratory tests		
ASO test >250[e]	15	39
ASO test <250[e]	24	61
Positive other germ antibodies[f]	19	49
Positive antithyroid antibodies[g]	14	36
ANA >1:120[h]	13	33
ANA <1: 120[h]	26	67
Natural killer cells <3%[i]	28	72
Natural killer cells ≥3%[i]	11	28
Positive inflammatory markers[j]	7	18
Positive nasopharyngeal culture[k]	23	59
Brain MRI abnormalities[l]	8	21

[a]Recurrent child's infections: sinusitis, chronic otitis, pharyngitis or tonsillitis, pneumonia, skin infections (i.e., staph), and/or signs of GAS infection (i.e., pharyngitis, anal or vulvar redness, skin lesions); this variable has been estimated as a dichotomic condition; a cutoff has been established on three or more respiratory infections (e.g., sinusitis, otitis, and bronchitis) in 1 year or the need for antibiotics for 2 months/year (Ballow 2008).

[b]Frequent episodes of asthma, allergic rhinitis (AR), Immunoglobulin E (IgE)-mediated food allergies (FAs), and other immune-mediated food disorders requiring food avoidance.

[c]Common evidence for cracked and itching skin or red and brownish-gray patches on the hands, feet, knees, wrists, upper chest, face, scalp, *etc.*

[d]Standard and sleep EEG alterations.

[e]The antistreptolysin O (ASO) patient's values in the blood plasma have been pooled in two groups (antistreptolysin titer > or < of 250 IU), based on the upper reference limit.

[f]One or more IgG and IgM Antibodies against other germs (Anti-Mycoplasma pneumoniae, Chlamydia pneumoniae, Epstein–Barr virus, Borrelia Burgdorferi, and Herpes Simplex Virus –HSV- Type 1). Serological IgG/IgM at least fourfold rise in titer was considered positive.

[g]One or more antithyroid antibodies (Anti-thyroid peroxidase [anti-TPO], Thyroglobulin antibodies, TSH receptor antibodies [anti-TRAbs], Thyroid Stimulating Hormone Receptor Antibody [anti-TSH receptor]) above the upper reference limit

[h]The Antinuclear Antibody (ANA) patient's values in the blood plasma have been pooled in two groups (titers < or > of 1: 120), based on the upper reference limit.

[i]Among the Lymphocyte subset (T, B, natural killer [NK] cells) values we considered the NK cells ($CD3^+/CD56^+$) % value, and we pooled them in two groups (NK ≥3% or NK <3%), based on the lower reference limit of 3%.

[j]One or more inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) above the upper reference limit.

[k]Nasopharyngeal culture positive for Group A beta-hemolytic streptococcus (GABHS) or *Staphylococcus aureus* (MRSA), Streptococcus pneumoniae (pneumococcus), Haemophilus influenzae, or other upper respiratory tract pathogenic germs

[l]Evidences for changes in brain morphology at MRI with T-2 weighted images or contrast enhancement.

compare findings from the Auto-CM approach with findings from the traditional statistical approach.

Principal component analysis. PCA is mathematically defined as an orthogonal linear transformation of the data to a new coordinate system such that the highest variance by any projection of the data comes to lie on the first coordinate (called the first principal component), the second highest variance on the second coordinate, and so on. PCA is theoretically the optimum transform for given data in least square terms.

Hierarchical agglomerative clustering. HAC is one of the most popular clustering methods, which seeks to build a hierarchy of clusters with a ''bottom-up'' approach: each observation starts in its own cluster, and pairs of clusters are merged as one moves up the hierarchy. This method works from the dissimilarities between the objects to be grouped together, producing a so called ''dendrogram,'' which shows the progressive grouping of the data. It is then possible to gain an idea of a suitable number of classes into which the data can be grouped. PCA and AHC have been carried out with XLSTAT package 2018.

ANN analysis

General features. The Auto Contractive Map (Auto-CM) system is a fourth generation unsupervised ANNs, which has already been demonstrated to outperform several other unsupervised algorithms in a heterogeneous class of tasks (Buscema and Sacco 2017).

Auto-CM is a mapping method able to compute the multidimensional strength association of each variable with all other variables in a dataset, using a mathematical approach based on ANNs. Auto-CM is especially effective in highlighting any kind of consistent patterns, systematic relationships, hidden trends, and associations among variables. Indeed, this method is able to compute and graph a semantic connectivity map which:

(1) preserves nonlinear associations among variables,
(2) captures elusive connection schemes among clusters,
(3) highlights complex similarities among variables.

The 3-layer architecture and the mathematical models of Auto-CM have been described elsewhere (Buscema and Grossi 2008). In nontechnical terms, this model has both a training phase and a learning phase. After the former, Auto-CM determines the so-called ''weights'' of the vector matrix, which

(1) represent the warped landscape of the dataset and
(2) permit a direct interpretation.

Indeed, these weights are proportional to the strength of many-to-many associations across all variables and can be easily visualized by transforming them into physical distances: variables whose connection weights are higher get relatively nearer and vice versa. By applying a mathematical filter (i.e., minimum spanning tree, MST) (Kruskal 1956; Fredman and Willard 1990) to the matrix of distances, a graph named ''semantic connectivity map'' is generated. This representation allows a visual mapping of the complex web of connection schemes among variables, simplifying the detection of the variables that play a key role in the graph.

The adaptive learning algorithms of inference, based on the principle of a functional estimation like ANNs, overcome the problem of dimensionality. For this reason, we did not apply Bonferroni adjustment (applied in the case of significance tests carried out with dependent variables) preferring to use an exploratory analysis looking for important associations among many independent variables.

Minimum spanning tree. The MST (Figs. 3 and 4) shows among the full spectrum of possible ways to connect the variables in a tree, the shortest combination. Based on the MST theory, the Auto-CM reveals the connections among variables providing a graph in which the distances among variables reflect their bonding strength (weights) (Buscema and Grossi 2008, 2017; Buscema et al. 2008). In practical terms, MST shows the best way to connect the variables in a tree and the shortest possible combination allowing to present the data in a simplified graph.

In classical mechanics, Maupertuis's principle (Cheng 2012) states that the path followed by a physical system is the one of least length. It is a special case of the more generally stated principle of least action. Using the calculus of variations, it results in an integral equation formulation of the equations of motion for the system. The kinetic paths from least action principle quantify the transition processes among normal state and pathological state in biological systems. Also in case of variable interconnection, our assumption is that their system must naturally tend to minimum energy state, well described by the graph generated by MST.

This approach provides the map of relevant connections between and among variables and the principal hubs of the system. Hubs can be defined as variables with the maximum amount of connections in the map. The Auto-CM does not pose randomly the initial weights. Conversely, the Auto-CM starts with the same value. Thus, the resulting graph is reproducible along many runs. In other words, the Auto-CM visualizes in the space' the correlation among the variables (''closeness''), and the graph identifies only the relevant associations organizing them into a coherent picture. The ''central node'' is the inner node that remains after bottom-up recursively pruning away the ''leaves'' nodes.

The MST represents what could be called the 'nervous system' of any dataset. In fact, summing up all of the connection strengths among all the variables, it gets the total energy of the system. The MST selects only the connections that minimize this energy, that is, only the ones that are really necessary to keep the system coherent. Consequently, all the links included in the MST are fundamental, but, on the contrary, not every ''fundamental'' link of the dataset needs to be in the MST. Such limit is intrinsic to the nature of MST itself: every link that gives rise to a cycle into the graph (viz., that destroys the graph's ''treeness'') is eliminated, whatever its strength and meaningfulness. To fix this shortcoming and to better capture the intrinsic complexity of a dataset, it is necessary to add more links to the MST, according to two criteria:

(1) the new links have to be relevant from a quantitative point of view;
(2) the new links have to be able to generate new cyclic regular microstructures, from a qualitative point of view.

The additional links superimposed to MST graph generate a maximally regular graph (MRG).

Maximally regular graph. To understand how MRG works we must start remembering the nature of MST. MRG is the graph whose hubness function attains the highest value among all the graphs generated by adding back to the original MST, one by one, the connections previously skipped during the computation of the MST itself. Starting from the MST, the MRG presents the highest number of regular microstructures and highlights the most important connections of the dataset. In other words, to build the MRG the sorted list of the connections skipped during the derivation of the MST must be considered.

Each time we add a new connection to the MST basic structure, to monitor the variation of the complexity of the new graph at every step, with a specific parameter of complexity, called H Function. We call MRG the graph whose H Function attains the highest value among all the graphs generated by adding back to the original MST, one by one, the missing connections previously skipped during the computation of the MST itself. By this way, we draw a ''diamond'' expressing the complexity core of the system.

The frequency of a given symptom/variable influences the likelihood to become part of the central group of variables (core). Nevertheless, a high occurrence does not necessarily bring to the inclusion of a given variable in the core domain. In fact, even if the program is influenced by variable frequency, it picks up other kind of inherent information, independent from the simple frequency.

Results

Clinical variables

From a total of 312 consecutive outpatients referred for obsessive compulsive or anxiety symptoms and tic disorder, 42 were diagnosed with PANS. One child was excluded because parents refused to take part in research. Two children were excluded due to active treatment with anti-inflammatory agents.

Thus, in accordance with the inclusion and exclusion criteria of the study, 39 patients (13 females and 26 males) were enrolled into this study, corresponding to the 13% of the outpatients with obsessive compulsive or anxiety symptoms and tic disorder referred to the two units. Mean age at recruitment was 8.6 years (SD 3.1). For most of these patients (28/39 subjects; 72%), the symptom onset was close to the time of the first clinic assessment (between 1 and 12 weeks). In particular, 23/39 patients (59%) reported symptoms of infections (fever, coughing, ear pain, or diarrhea) within 4 weeks from the symptom onset. Instead, for the remaining 11/39 subjects (28%) the symptom onset lied between 3 months and 3 years before the first clinic visit, with relapsing/remitting course

or with a single previous episode (spontaneously recovered) before the first observation.

Independent from their onset, all patients showed acute psychiatric symptoms at the time of the enrollment. As reported in Table 1, ''anxiety'' and ''irritability/oppositional defiant disorder'' were the most frequent, interesting the 89% of subjects. The ''obsessive-compulsive symptoms'' have been reported in the 87% of the sample. The percentage of subjects showing the other symptoms was never below 60%. The less frequent symptoms were ''enuresis/urinary frequency'' and restricted food intake (respectively, 61% and 66%).

As reported in Table 2, a positive family history of Autoimmune Diseases was the most frequent condition associated to PANS (80%). Increased rates of psychiatric disorders (72%) in the family were also reported. The pregnancy-related/intrapartum complications were reported by 64% of the mothers of the enrolled patients, active infections in 15%, active preexisting or new onset autoimmune diseases during pregnancy in 59%, and Hashimoto's disease during pregnancy in 33%.

As shown in Table 3, recurrent maternal infections were frequent (32/39; 82%); allergy and atopic diseases were reported almost in half of the sample (18/39; 46%), atopic dermatitis being the most frequent atopic disease (23/39; 59%).

Laboratory variables

Only 15 patients (39%) showed a high antistreptolysin O antibody (ASO) level (i.e., >250 IU, laboratory upper reference limit). Nasopharyngeal culture was positive in 23/39 subjects (59%) and it revealed the presence of Group A beta-hemolytic streptococcus (GABHS) in 8 out of 23 patients; other bacteria isolated by the nasopharyngeal culture were *Staphylococcus aureus* (11/23), Streptococcus pneumoniae (pneumococcus) (1/23), Haemophilus influenzae (2/23), and Pseudomonas aeruginosa (1/23).

In a large portion of the sample (49%) a high antibody titer against different germs was observed: the most common were antibodies against Mycoplasma and Chlamydia. We found IgG and/or IgM, depending on the length of the interval between infection and neuropsychiatric symptom onset, since the IgM normally disappears after 2–3 weeks of their production. A serological diagnosis of Epstein–Barr virus infection (IgM antibodies) was made in one case. Lyme disease was suspected for a young girl with IgG antibodies against Borrelia burgdorferi, but further laboratory tests did not confirm the diagnosis.

Antithyroid antibodies were found above the upper reference limit in the 36% of our sample, although no patients with thyroid antibodies positivity showed reduced echogenicity on thyroid sonogram, nor clinical Hashimoto's thyroiditis features, nor overt hypothyroidism. They all showed normal levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4).

The antinuclear antibodies (ANAs) were also found above the upper reference limit (titers > of 1: 120) in 13/39 subjects (33%). The lupus workup was completed for all the children with elevated ANA title: none of them resulted positive for lupus-specific antibodies. Inflammatory markers like CRP, ESR, and PCT levels above the upper reference limit were observed in only 7/39 subjects (18%).

A reduction of the Natural Killer (NK) absolute cell counts in the peripheral blood lymphocyte was observed in almost all the enrolled children. Among the Lymphocyte subsets (T, B, NK cells), the NK cell ($CD3^+/CD56^+$) % value was considered to define two groups of patients (NK ≥3% or NK <3%), based on the lower reference limit (3%). In 72% of our children the percentage of NK cells was less for the lower reference limit (5 patients had 1% or 0% of NK cells).

In 22 patients (56% of the sample) the electroencephalography (EEG) overnight recording showed intermittent or persistent focal or generalized slowing (mainly localized in temporal-frontal regions). Some patients presented also a persistent and unvarying focal or generalized slow-wave activity in the vigilant state, but none of them have had epileptic seizures.

Minor structural brain magnetic resonance imaging (MRI) abnormalities (T-2 weighted images or contrast enhancement) were observed in 8/39 subjects of the sample (21%). These abnormalities were however considered ''incidental'': 2 slight ventricular asymmetries, 2 developmental venous anomalies, 1 isolated cerebellar vermis hypoplasia, 1 arachnoid cysts, 1 Arnold Chiari malformation, and 1 mild white matter hyperintensity in the periventricular area. No specific volumetric and/or inflammatory changes in the basal ganglia or cortical areas were found.

Linear correlation analysis

The Spearman linear correlation matrix of variables included in the study showed, as expected, a strong correlation between family history of autoimmune disease and maternal autoimmune disease in pregnancy and allergic and atopic disease ($R = 0.38$ and 0.40, respectively).

Remarkably, family history of autoimmune disease was correlated also to family psychiatric history ($R = 0.39$). Furthermore, family psychiatric history was related to EEG alteration and ASO positive test ($R = 0.38$ and 0.45, respectively).

Allergic and atopic diseases correlate to the increase of antibodies against other germs (Anti- Mycoplasma pneumoniae, Chlamydia pneumoniae, Epstein–Barr virus, Borrelia Burgdorferi, and Herpes Simplex Virus –HSV- Type 1) ($R = 0.33$) and against thyroid ($R = 0.38$).

High levels of ANA correlate with family history of autoimmune diseases ($R = 0.44$) and with positive other germ antibodies ($R = 0.51$). With regard to symptoms, ASO positive test is related to restricted food intake ($R = 0.40$), and the ANA positive test is related to enuresis/urinary frequency ($R = 0.37$). Emotional lability/depression correlates with the presence of positive other germ antibodies ($R = -0.32$) and with low NK cells ($R = 0.33$).

Benchmarking analysis

The PCA contains all possibly correlated variables distributed along vectors of different sizes (various numerical values), identifying the linearly uncorrelated variables (principal components) along which the variation in the data is maximal.

Here PCA map provided the identification of two clusters, shown in Figure 1. The first cluster is organized around the obsessive compulsive dimension and encompasses almost all PANS symptoms in the following hierarchy: enuresis/urinary frequency, school performance deterioration, sensory motor abnormalities, sleep disturbance, irritability/oppositional defiant disoder (ODD), behavioral regression, anxiety, and emotional lability/depression.

Among the variables of this cluster we also found the variables ASO test >150 and NK <3. The opposite variables (ASO test <150 and NK ≥3) in our PCA were uncorrelated variables.

The second cluster encompasses most of the familial and personal risk factors and conditions. Among them, autoimmune diseases during pregnancy, ANA >1:110, Antithyroid antibodies, familial autoimmunity, allergic atopic disorders, and

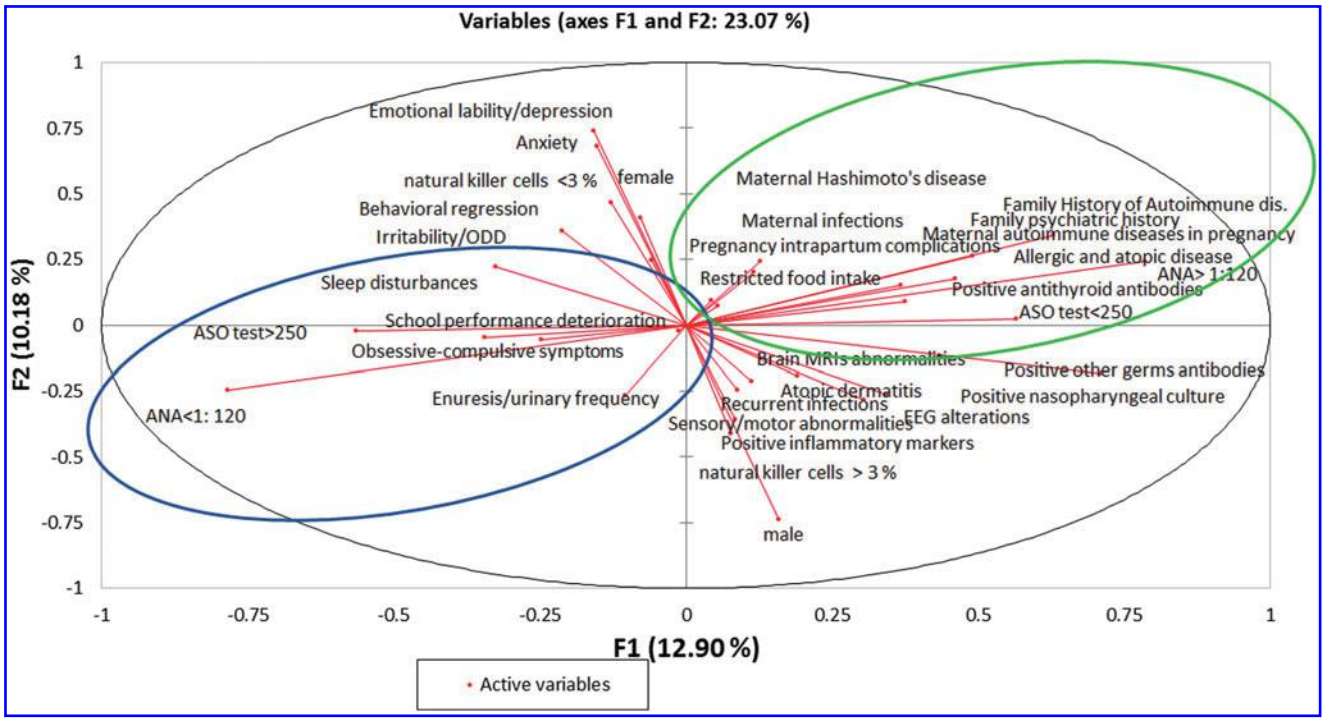


FIG. 1. PCA (FIRST Two Components): all possibly correlated variables distributed along vectors of different numerical values, identifying the linearly uncorrelated variables (principal components) along which the variation in the data is maximal. PCA, principal component analysis.

other germ (Anti-Mycoplasma pneumoniae, Chlamydia pneumoniae, Epstein–Barr virus, Borrelia Burgdorferi, and Herpes Simplex Virus –HSV- Type 1) antibodies are represented by vectors of largest size.

The agglomerative hierarchical clustering (AHC) analysis resulted in a dendrogram, which shows the progressive grouping of the variables (Fig. 2). The dendrogram shows the clustering of the variables according to a particular kind of mathematics inherent to HAC technique. As stated in the figure legend there are different clusters marked with different colors. Our dendrogram shows three clusters identified by different colors. The green cluster encompasses almost all PANS symptoms, with some variables more closely related to each other, as obsessive compulsive symptoms and school performance deterioration, enuresis/urinary frequency and behavioral regression, sleep disturbance, and irritability/ODD. Furthermore, emotional lability/depression is linked to NK <3. The red cluster shows a predictable relationship between ''pregnancy/delivery complications'' and ''infection during pregnancy.'' Noteworthy, both these conditions appear linked with ''ASO test >150'' and are more frequent in female children. The blue cluster encompasses all other laboratory and clinical variables.

Semantic connectivity map

The semantic connectivity map (Auto-CM method)–MST graph (Fig. 3) shows the strength of association across the clinical and laboratory variables visualized by the concept of ''closeness'': the variables whose connection weights are higher get relatively nearer and vice versa. The links' strength values were all above 0.8. The connection strengths do not influence the solution of MST. They have a different meaning from the weights generated by Auto-CM and have only a descriptive function.

It is important to remember that the frequency of each variable influences the likelihood to become part of the central group of variables (*core*), but it does not necessarily bring to the inclusion of the variable in the core domain. For example, family history of autoimmune disease is the most frequent variable, but it is not included in the core domain.

As shown in the Figure 4, the ''Maximally Regular Graph'' superimposed to MST indicates the putative internal structure of the syndrome.

The map shows that PANS symptoms are strictly linked to each other in a central ''*diamond*,'' originated by the specific mathematical function called MRG (see Method section). It encompasses anxiety, irritability/ODD symptoms, obsessive compulsive symptoms, behavioral regression, sensory motor abnormalities, school performance deterioration, sleep disturbances, and emotional lability/depression. Two PANS symptoms (enuresis/urinary frequency and restricted food intake) are beyond the ''*diamond*,'' indicating a less frequent link with the other symptoms. Nevertheless, their high link strength value (≥0.8) with the other symptoms indicates a strong probability of co-occurrence with the other symptoms. In our opinion, the resulting ''diamond'' well expresses the complexity core of the PANS.

The robustness of Auto-CM system analyzing the stability of connections in the MST graph is described in Supplementary Data.

Discussion

Even though the data collected describe the already known characteristics of PANS, our study offers a statistic model for a

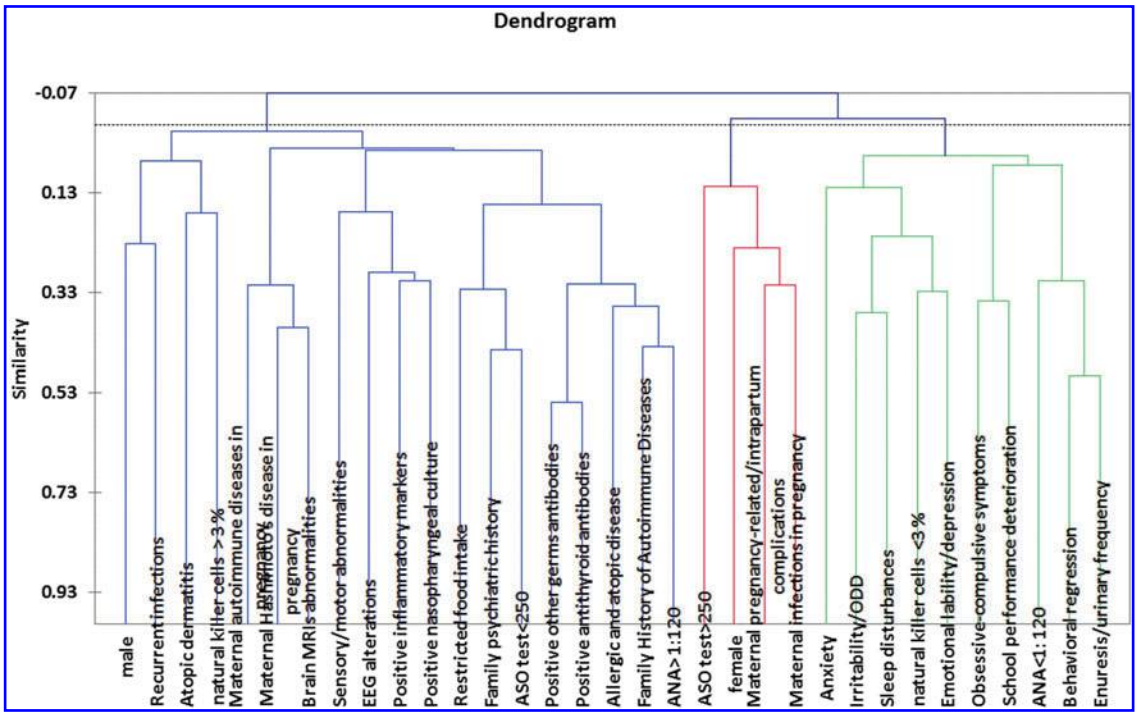


FIG. 2. AHC shows the progressive grouping of the variables resulting in a dendrogram with three clusters identified by different colors. AHC, agglomerative hierarchical clustering.

specific symptoms' constellation (syndrome) clinically distinct from other neurodevelopmental disorders.

PANS described by ANN analysis

Our study is the first one to have adopted Complex network mathematics approach like Auto-CM to face the complexity of PANS phenotype. The results of the study show that PANS symptoms, as defined by the PANS Collaborative Consortium (Swedo et al. 2012; Chang et al. 2015), are strictly connected one to another, shaping a central ''diamond'' encompassing anxiety, irritability/ODD symptoms, obsessive compulsive symptoms, behavioral regression, sensory motor abnormalities, school performance deterioration, sleep disturbances, emotional lability/depression, and laboratory measures.

The Auto-Contractive Map method also allowed to grasp the core of the relationship between symptomatology, history, and laboratory results of our subjects with PANS. Exploiting all not obvious connections among the full spectrum of clinical variables revealed the simultaneous connections among symptoms and clinical signs, highly consistent with the PANS Collaborative Consortium's description of the syndrome (Chang et al. 2015).

Noteworthy, the classical statistical analysis (Spearman linear correlation) resulted as far less explicative of the real relationships between the variables. It failed in showing the whole symptomatic dimensions even if it displayed the relationships among them. The traditional statistical analysis approach suffered from some criticisms. Indeed, due to the heterogeneity in clinical expression of the PANS syndrome (i.e., different degrees of symptom severity along with various pathogenesis), a traditional statistical analysis approach using a ''single symptom approach analysis'' may not provide comprehensive information on the putative nature of the PANS.

The semantic connectivity map (Figs. 3 and 4) describes the hidden internal construct of PANS and exemplifies the consistency of the PANS working criteria, as they were defined at the NIH in July 2010 (Swedo et al. 2012). In fact, the PANS symptoms are strictly linked to one another shaping a central ''diamond'' encompassing anxiety, irritability/ODD symptoms, obsessive compulsive symptoms, behavioral regression, sensory motor abnormalities, school performance deterioration, sleep disturbances, and emotional lability/depression.

In the present semantic connectivity map, the variable ''obsessive-compulsive symptoms'' node acts as a hub (variable with three or more links) receiving convergence from the other symptom nodes (anxiety, irritability/ODD symptoms, behavioral regression, and sensory and motor abnormalities) and from clinical variables (nasopharyngeal culture and pregnancy/delivery complications). Therefore, the obsessive compulsive dimension seems to represent the core symptom of the syndrome. At the same time, it is one of the most frequent symptoms, being reported in 87% of the sample.

Enuresis/urinary frequency is located beyond the ''diamond,'' even though it is strictly related to the other symptoms. This symptom, reported in the 61% of patients, could be underestimated because parents may not be aware of it at the early stage.

The only other symptom located outside the ''diamond'' is the restricted food intake, even though it is situated along one of the branches directly arising from the main hub (obsessive compulsive symptoms). Of note, even if this symptom was very common among the subjects of the present sample (66% of the subjects), most of the children had a relatively mild food intake restriction. It is possible that cultural reasons may explain this finding, since parents (mostly living in the south of Italy) are used to strongly encourage their children to eat even when they tend to refuse the food. This peculiar approach to feeding can also explain the

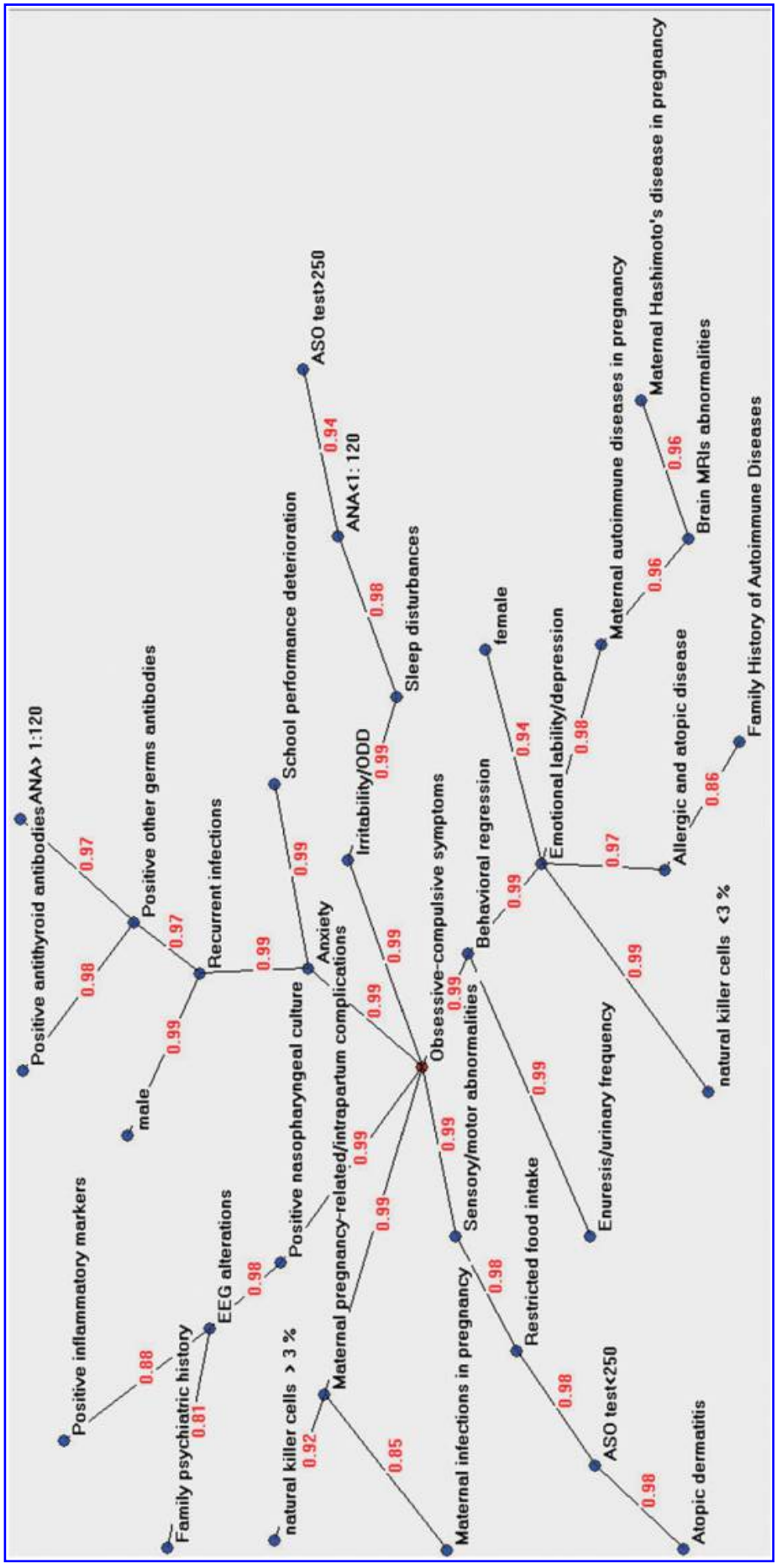


FIG. 3. Semantic connectivity map (Auto-CM method) Minimum spanning tree. Strength of association across the clinical and laboratory variables: as shorter is the distance in space as higher is the links' strength values between variables. Auto-CM, auto contractive map.

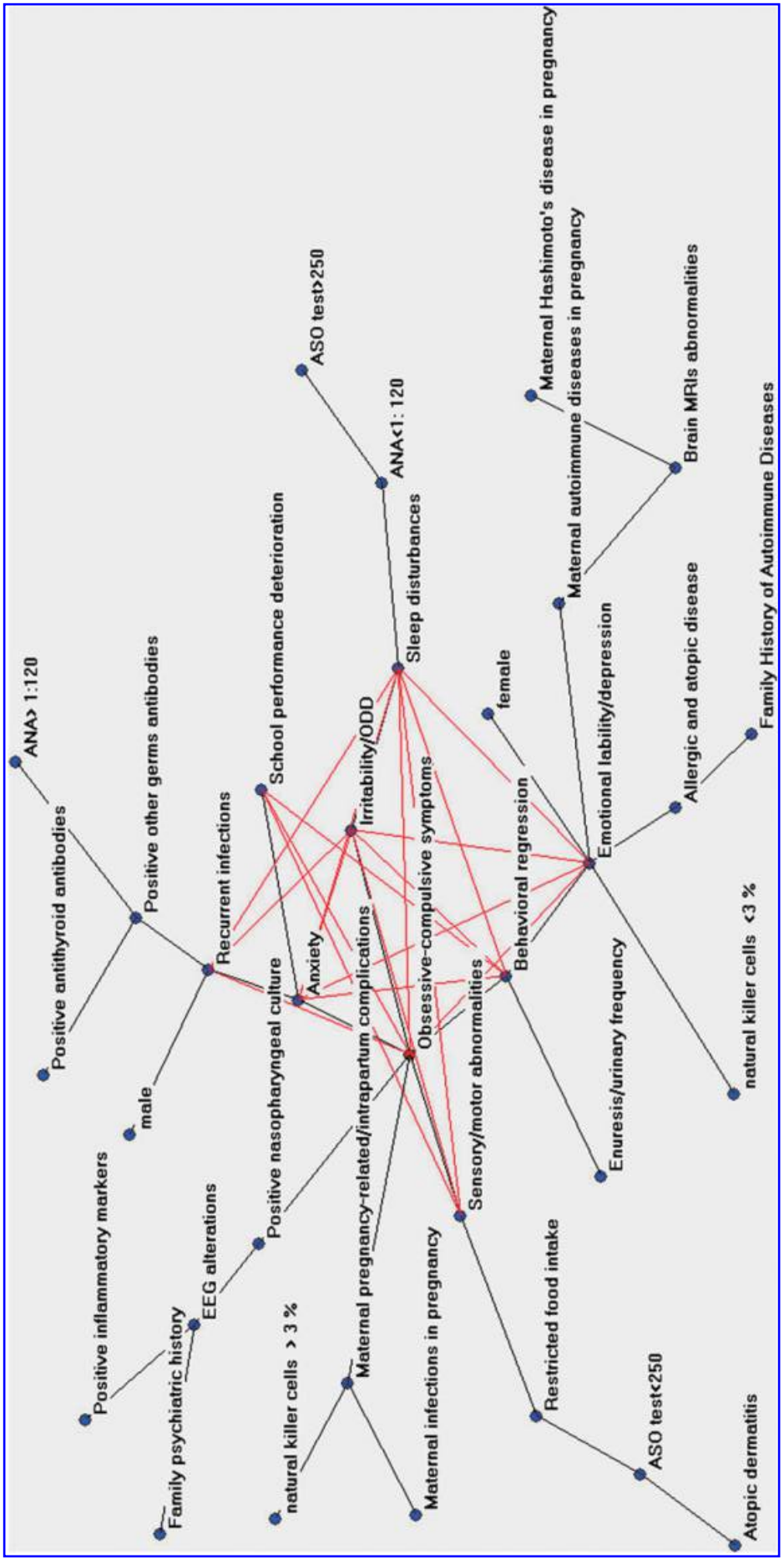


FIG. 4. Semantic connectivity map (Auto-CM method) Minimum spanning tree and Maximal Regular Graph. It indicates the most important connections of the dataset. The resulting "diamond" expresses the complexity core of the syndrome.

relatively lower frequency of food intake restriction compared to the other symptoms. However, in the semantic map, this symptom is allocated right beyond the sensory/motor abnormalities.

Interestingly, according to our clinical experience, some of the children with PANS that refused to eat also showed atypical sensory interests concerning the food (e.g., odor, consistency, or color of aliments) or compulsions and rituals related to the feeding act (e.g., crumbling the food, taking little bites, long chewing, moving the bite in the mouth, refusing to swallow, or swallowing only in specific positions, and so on). This suggests that, at least in part, the food intake restriction could be linked to the sensory and compulsive dimension of PANS clinical presentation rather than to simple loss of appetite.

The semantic map also describes the association between obsessive compulsive symptoms, school performance deterioration, and anxiety symptoms and between emotional lability/depression and behavioral regression, supporting the PANS phenotype description. Actually, the coherence of these symptoms was already evident in the benchmarking analysis. Both the PCA and the AHC provide clusters of symptoms closely and reciprocally linked.

From the PCA, the first cluster is organized around the obsessive compulsive dimension and encompasses almost all PANS symptoms in the following hierarchy: enuresis/urinary frequency, school performance deterioration, sensory motor abnormalities, sleep disturbance, irritability/ODD, behavioral regression, anxiety, and emotional lability/depression.

A second cluster encompasses the most of laboratory and clinical variables. This cluster underlines a meaningful relationship between most of the autoimmunity markers studied in our sample (''other germs antibodies,'' ''antithyroid antibodies,'' ''allergic and atopic disorder,'' ''familial autoimmunity,'' ''ANA >1:110,'' ''autoimmune diseases in pregnancy,'' and ''Hashimoto's disease in pregnancy''). It is known that most of the patients with PANS have both autoimmune/inflammatory diseases (e.g., autoimmune thyroiditis, post-infectious, enthesitis-related, psoriatic, or spondyloarthritis) and higher ANA and antithyroid antibodies than expected in the general population (Frankovich et al. 2015).

In particular, the AHC analysis resulted in a dendrogram, which shows the progressive grouping of the variables. It gains the idea of a suitable number of classes into which the variables can be grouped. One of the clusters of variables in our sample includes almost all PANS symptoms. Among them, it is possible to recognize variables closely related to each other, as obsessive compulsive symptoms and school performance deterioration, enuresis/urinary frequency and behavioral regression, sleep disturbance, and irritability/ODD.

The Auto-Contractive Map method also allowed to grasp the core of the relationship between symptomatology and family/children clinical history and laboratory results. The allocation of all the laboratory and clinical variables around the ''symptoms diamond'' suggests that we should consider potential biological markers of a disease with a multifactorial pathogenesis and different possible causative conditions. The semantic connectivity map shows that emotional lability/depression is a highly connected hub linked to autoimmune disease in pregnancy, allergic and atopic disorders, and low NK percentage. Also anxiety symptoms are strongly related, on our semantic connectivity map, with recurrent infectious disease remarking the possible role of infections as a risk factor for PANS. The aggregation between PANS symptoms and laboratory and clinical variables highlights the importance of testing some inflammatory markers and considering their role in the pathogenesis of PANS.

Furthermore, in our semantic map, both familial and maternal disease factors (familial autoimmunity, family history of psychiatric diseases, Hashimoto's disease in pregnancy, infections in pregnancy, and autoimmune diseases in pregnancy) and children clinical and laboratory variables (allergic and atopic disorders, atopic dermatitis, nasopharyngeal culture, EEG alterations, NK cells % value <3, inflammatory markers, ASO test, other germ antibodies, ANA, and antithyroid antibodies) are closely related to symptoms.

These suggest that it is important to take notice of the familial autoimmune/inflammatory profile and to consider the possible pathophysiologic role of immunological events during pregnancy. Even though factors having less than three links can be considered from a mathematical point of view, of relatively lower importance, they may represent the potential mechanisms, including direct influences of infections in the central nervous system (CNS), immune activation, and inflammatory mediators in PANS syndrome. Furthermore, emotional lability/depression is strongly related with NK cells % value <3.

PANS and familial, clinical, and laboratory variables

A second level of analysis with regard the familial, clinical, and laboratory data was described in our sample. As shown in Table 2, a high percentage of our patients had relatives affected by autoimmune disorders (80%) and psychiatric disorders (72%). Both conditions have been associated with PANS (Chang et al. 2015), even if most of the studies are focused on OCD and tic disorders among first-degree relatives of PANDAS probands (es. Lougee et al. 2000).

A recent survey, carried out by PANDAS network (Pohlman 2018) and based on parent's reports, described 47,34% of 1221 patients with PANS/PANDAS having autoimmune signals in the maternal and paternal lineage, 58,39% having anxiety disorders, and 27,52% having OCD in the maternal and paternal lineage. In our sample, both autoimmune and psychiatric diseases in the family members ranked higher than the survey data (around 70%). This difference may be attributed to the different method used to collect the information, because in the present study data were collected from a clinic interview by expert clinicians rather than a questionnaire. On the whole, a familiar probably genetic (Wang et al. 2015) susceptibility for both autoimmune and psychiatric disorders appears to play an important variable increasing the likelihood of developing PANS.

Results of the present study also showed a high prevalence rate of the pregnancy/delivery complications in general (64%) and active infections and autoimmune diseases during pregnancy in particular (15% and 59%, respectively) in our sample (Table 2). Prenatal exposure to infection is a risk factor for a wide range of neurodevelopmental and psychiatric disorders according to gene–environment interaction etiological model (Zhou 2012; Blomström et al. 2015). More recent studies have considered the interaction between maternal immune activation (MIA) and genetic risk factors for alterations in structural/functional neuronal network impairments leading to psychiatric conditions as autism spectrum disorder (ASD) and schizophrenia (Bergdolt and Dunaevsky 2018).

The link between maternal infection and neurodevelopmental disorders could also be regarded as a MIA potentially inducing prolonged immune alterations in the offspring's brain, independently from the infection itself (Boulanger-Bertolus et al. 2018). It is thought that the maternal activation of the innate and adaptive immune systems due to infection, stress, autoimmunity, asthma, allergies, or inflammation can lead to several neuropathologies in the progeny, particularly ASD and schizophrenia (Jiang et al.

2018). This is because MIA may influence the developing fetal CNS through the increased production of inflammatory cytokines acting as a disease primer or first ''hit'' and predisposing susceptible individuals for further exposures or ''hits'' later in life (Jiang et al. 2018; Bilbo et al. 2018). Furthermore, immune abnormalities seem to be more common in individuals and first degree relatives with ASD (e.g., Gładysz et al. 2018). For instance, fetal brain-specific antibodies have been identified in mothers of autistic children in several different studies (Keil et al. 2010; Nordahl et al. 2013; Fox-Edmiston and Van de Water 2015; Hughes et al. 2018).

In line with this hypothesis, we found that almost a third of the mothers of the enrolled patients suffered from Hashimoto's thyroiditis during pregnancy. This prevalence is almost thrice higher than the estimated prevalence (13%) of the disorder in the United States (Staii et al. 2010). Studies conducted in our geographic area found that between 5% and 20% of female and between 1% and 5% of male are affected by Hashimoto's thyroiditis in the general population (Chiovato et al. 1993). In the last decades, the disease has become even more common than it was until the early 1990s (Benvenga and Trimarchi 2008). It could be inferred that our children have been exposed to elevated levels of circulating antibodies during their intrauterine life. The association between autoimmune thyroiditis and psychiatric disorders in offspring has been poorly studied.

A family history of autoimmune disorders was described in children with ''regressive'' autism. Regression was significantly associated with a family history of autoimmune disorders (adjusted OR = 1.89) and particularly with autoimmune thyroid disease (adjusted OR = 2.09) (Molloy et al. 2006). A recent systematic review showed a significant association between maternal thyroid dysfunction during early pregnancy, including low and high thyroid hormone level and autoimmune thyroiditis, and several offspring behavioral and psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), autism, pervasive developmental problems, and externalizing behavior, in addition to epilepsy and seizures (Fetene et al. 2017). In particular, the odds of autism were increased by nearly 80% among offspring of mothers who were Thyroid peroxidase antibody (TPO-Ab) positive during pregnancy (OR = 1.78), compared to mothers negative for this autoantibody (Brown et al. 2015).

Gestational immune activation and the presence of maternal autoantibodies are thought to be directly contributing to abnormal brain development mechanisms and thus involved in the pathogenesis of ASD (Hughes et al. 2018). By the analogy with ASD and other neurodevelopmental disorders, we underline the strong presence of familial autoimmunity in our PANS sample arguing that maternal infective and immunological factors may play an important role also on the PANS phenotypic expression.

In parallel, it appears interesting that among the children of our sample, anti-TPO, Thyroglobulin antibodies, TSH receptor antibodies (anti-TRAbs), and Thyroid Stimulating Hormone Receptor Antibody (anti-TSH receptor) are above the upper reference limit in the 36% of our sample, even though none of our patients had overt hypothyroidism (Table 3). This rate is much higher than the prevalence of thyroid antibodies reported in other studies where TPO-Ab positive rates ranged between 11 and 13% in different areas of the world (Hollowell et al. 2002; Amouzegar al. 2017). Longitudinal studies on general population (e.g., Li et al. 2008) demonstrated that positive thyroid antibodies were associated with an increased risk of developing hypothyroidism later in life. In particular, thyroid peroxidase antibody (TPO-Ab) measurement has been considered appropriate to identify patients at risk of developing hypothyroidism (Zelaya et al. 2010). Nevertheless, according to our data, the positive antithyroid antibodies in euthyroid children with PANS are probably an expression of a condition arising from a more general abnormal immune response.

Recurrent infections are also frequently reported in the medical history of our patients. Recurrent infections are very common in children, mostly in healthy preschool children, who can experience up to six to eight respiratory tract infections per year (Gruber et al. 2008). However, the recent findings of a population-based cohort study using Danish nationwide registers provide evidence for the involvement of infections and the immune system in the etiology of a wide range of mental disorders in children and adolescents (Köhler-Forsberg et al. 2018). The role of infectious diseases and immune dysregulation has been recently studied also in specific populations, such as individuals with fragile X syndrome (Yu et al. 2020). In PANS/PANDAS, the infection history of children is of particular interest because most PANS are suspected to be post-infectious in origin, although no single microbe, other than GABHS, has yet been consistently associated with the onset of PANS (Chang et al. 2015).

Reliably, half of our sample had different germ antibodies (IgG and/or IgM Antibodies against Mycoplasma pneumoniae, Chlamydia pneumoniae, Epstein–Barr virus, Haemophilus influenzae, and Herpes Simplex Virus –HSV- Type 1) at the clinic presentation. The most common antibodies were IgG and/or IgM against Mycoplasma and Chlamydia that are considered important causative pathogens of community-acquired infections in school-age children and adolescents. Therefore, our results are consistent with the PANS Collaborative Consortium's hypothesis that other infectious agents, particularly those with characteristically prolonged colonization, have the potential to activate PANS (Chang et al. 2015).

In addition, the nasopharyngeal culture results were often positive for different germs such as *Staphylococcus aureus*, Streptococcus pneumoniae, and Haemophilus influenzae (see Description in Results section). Group A beta-hemolytic streptococcus (GABHS) was found in 21% of the subjects. Therefore, the percentage of patients with an active GABHS infection as a triggering agent in our sample appears lower than that reported in previous reports (Murphy et al. 2015; Calaprice et al. 2017), although the 39% of our study subjects were positive for the antistreptolysin O antibody (ASO). However, among our 15 children with ASO >250 IU, only in 9 of them (23% of whole sample) the value exceeded the laboratory's stated upper limit of normal by twofold.

In addition to recurrent infections, allergy and atopic diseases should be considered. Atopy causes chronic inflammation of the airways that facilitate the adherence of pathogens to the respiratory epithelium and the development of respiratory infections (Mucha and Baroody 2003). In our sample, allergic and atopic diseases were described almost in one in two children (46%). However, this rate of prevalence is not far from the prevalence of any atopic diseases (40%) in general pediatric population (Christiansen et al. 2016).

Notably this high atopy prevalence is mostly due to a high prevalence of rhinoconjunctivitis (33%), with lower prevalence of asthma (13%) and atopic dermatitis (8%) (Christiansen et al. 2016). Conversely, in our sample atopic dermatitis appears as the most frequent atopic disease (59%), largely more represented than in normal pediatric population. This finding is consistent with the accumulating evidence on the association between atopic dermatitis and several children mental health disorders (es. Kandelaki et al. 2015; Catal et al. 2016). In particular, attention-deficit/hyperactivity disorder and autism (Chen et al. 2014; Lee et al.

2016; Liao et al. 2016) and anxiety and depression (Cheng et al. 2015; Becker-Haimes et al. 2017) have been associated with atopic dermatitis. In a recent Japanese study, eczema and children mental health problems (emotional symptoms, conduct problems, hyperactivity/inattention, and peer problems) were found to be significantly related, and the mean Strengths and Difficulties Questionnaire total difficulties score was significantly increased with worsening eczema status (Kuniyoshi et al. 2018).

To the best of our knowledge, there are few reports on the putative association between PANS and atopic dermatitis. A recent study (Rosa et al. 2018) described a prevalence of allergic and immune-mediated food disorders similar to the general population in a group of 69 subjects with PANS, with the exception of a higher rate of allergic rhinitis and a lower rate of atopic dermatitis than the general population. However, studies showed that different allergic diseases, not limited to atopic dermatitis, have been associated with an increased hazard of psychiatric disorders both in adults (Perugi et al. 2015; Tzeng et al. 2018) and in children (Nanda et al. 2016; Miyazaki et al. 2017).

ESR and CRP are widely used laboratory markers of systemic inflammation. A very small portion of our patients (18%) had values above the upper reference limit. However, these tests have a low index of specificity and are influenced by numerous disease factors (Bray et al. 2016). Their utility in providing valuable information in PANS has not been established yet. These inflammatory markers could have low specificity for conditions characterized by brain inflammation. Also the ANA values resulted above the upper reference limit in a relatively small part of our subjects (33%), even though the rate exceeds the estimated prevalence of positive ANAs (12–13%) in healthy pediatric population (Satoh et al. 2012).

Likewise, our data coincide with the assumption of PANS Consortium (Chang et al. 2015) that the rate of positive ANAs in patients with PANDAS and PANS is higher than the baseline.

In the present sample, a low NK cell count appears strongly associated with PANS symptoms. The recommendations from the 2013 PANS Consensus Conference (Chang et al. 2015) suggest that immune evaluation should encompass the study of lymphocyte subsets. Seventy two percent of the sample showed a percentage of NK cells below the reference limit. NK cells are a component of the innate immune system and one of the first effectors on sites of inflammation. The regulatory function of NK cells is to limit and prevent autoimmunity by killing of autologous immune cells.

Their implication in neurotoxicity and neuroprotection following CNS pathology, as well as the cross talk between NK cells and brain-resident immune cells, has been recently linked to CNS and mental disorders (Poli et al. 2013). A deranged Th17/T regulator balance and a reduced NK cell number are considered to be associated intermediate biological factors in childhood trauma, psychosis liability, and social stress reactivity in psychotic patients (Counotte et al. 2018).

A few studies have documented a decreased regulatory T cell count among children with Tourette syndrome compared with healthy controls (e.g., Kawikova et al. 2007; Bos-Veneman et al. 2011). Some studies analyzed the NK cells and white blood cell counts and activity in OCD, although with contrasting results (Denys et al. 2004; Rodriguez et al. 2017). An altered number and function of NK and T cells have been shown also in patients with schizophrenia, psychotic disorders (Karpiński et al. 2016; Vasilyeva et al. 2016), and posttraumatic stress disorder (Bersani et al. 2016). Furthermore, a consistent decrease in cytotoxic activity of NK lymphocytes (NKCA) and in lymphocyte proliferation by mitogens has frequently been reported in patients with major depressive disorder (MDD) (Ravindran et al. 1999; Zorrilla et al. 2001). A more recent research (Jeon et al. 2018) found that the NKCA was more closely related to depressive and anxiety factor scores in their 49 patients with MDD. Furthermore, the CD8-positive cell number increased and CD4/CD8 ratio decreased after 4 weeks treatment with selective serotonin reuptake inhibitors. All these findings suggest that PANS is a complex syndrome encompassing many psychiatric symptoms (anxiety, obsessive compulsive behaviors, and irritability/depression) and potentially arising from immune abnormalities, where the reduced NK cell counts could be a potential biomarker.

Finally, a large portion of our sample (56%) had overnight EEG evaluation that showed intermittent or persistent focal or generalized slow wave activity both at rest (mainly localized in temporal–frontal regions) and in vigilant state, suggesting a focal or generalized cerebral dysfunction. Notably, none of these subjects had ever suffered from epilepsy. The Consensus guideline (Chang et al. 2015) suggests that EEGs, particularly overnight evaluations, may be helpful in demonstrating focal or generalized slowing and/or epileptiform activity.

Very few reports, however, have been published on EEG evaluations of subjects with PANS/PANDAS. One study describes the results of a polysomnographic investigation of 11 children with PANDAS showing periodic limb movements and abnormalities of rapid eye movement (REM) sleep, including REM behavior disorder and nonspecific REM motor disinhibition (Gaughan et al. 2016). One more polysomnographic study on 15 subjects meeting criteria for PANS revealed that 87% of them had evidence of various forms of REM sleep motor disinhibition (excessive movement, laughing, hand stereotypes, moaning, or the continuation of periodic limb movements during sleep into REM sleep) (Gaughan et al. 2016).

No further data are yet available for results of EEG evaluations in PANS. Accordingly, improving the awareness on EEG patterns and sleep characteristics associated with PANS could be helpful to obtain a comprehensive and multidisciplinary clinical management.

The whole familial, clinical, and laboratory variables, summarized in Table 4, appear very compound and describe the PANS as a complex syndrome supported by different clinical conditions. Genetic, metabolic, infective, and environmental risk factors seem to have important implications for the assessment of such children. The lines of evidence derived from the available studies suggest to be particularly comprehensive in searching for specific laboratory biomarkers of PANS taking into account the variety of factors potentially affecting not only the mental function but also the general health of the affected children.

Limitations

The present work presents an analysis of correlation between a limited laboratory dataset of pertinent PANS signs and relevant family history conditions: a semantic connectivity map analyzing a larger set of objective parameters could be more informative about PANS construct. Another limitation of the study is the lack of a control group, as only PANS patients were included. Nevertheless, the statistic model that we have used consent to analyze a single group dataset. Comparison with patients presenting a limited association of two or more PANS criteria, but not the complete disorder may help to verify the strength of the observed associations. Finally, an enlarged sample size will be useful to confirm the present results.

Table 4. Summary of Pediatric Acute Onset Neuropsychiatric Syndrome Familial, Clinical, and Laboratory Variables

A high prevalence rate of pregnancy/delivery complications, active infections, and autoimmune diseases during pregnancy is associated with PANS phenotype
Hashimoto's thyroiditis is very common among PANS children's mothers
A large part of PANS children has high titers of Anti-thyroid peroxidase (anti-TPO), Thyroglobulin antibodies, TSH receptor antibodies (anti-TRAbs), and Thyroid Stimulating Hormone Receptor Antibody (anti-TSH receptor), with no overt hypothyroidism
Recurrent infections are frequently reported in the medical history of PANS patients
Different germ antibodies (IgG and/or IgM against Mycoplasma pneumoniae, Chlamydia pneumoniae, Epstein–Barr virus, Haemophilus influenzae, and Herpes Simplex Virus –HSV-Type 1) are present in the serum of PANS patients
Nasopharyngeal culture is often positive for *Staphylococcus aureus*, Streptococcus pneumoniae, and Haemophilus influenza, Group A beta-hemolytic streptococcus (GABHS)
Atopic dermatitis is described in more than half of PANS children
ANA values are positive in around one-third of PANS patients
ESR and CRP are usually normal
Low Natural Killer (NK) cell count appears strongly associated with PANS
Almost 50% of patients with PANS shows EEG alterations both at rest and in vigilant

Forthcoming Issues

Further studies are needed to investigate the relationships and potential diagnostic values of autoimmune/inflammatory markers. It would be meaningful to check for possible relationship between maternal autoimmune activation and PANS in offspring. In particular, a possible association between maternal thyroid autoimmune disease and PANS in offspring would be detected. Furthermore, the existence of antithyroid antibodies in clinically euthyroid PANS children could represent an indicator of a larger abnormal immune response. In particular, TPO-Ab measurement may be appropriate to help identify patients at risk of developing true autoimmune hypothyroidism.

It could be also relevant to study the possible implication of human leukocyte antigen (HLA) genes in PANS because of the increasing data on the implication of HLA genes in psychiatric and neurodevelopmental disorders (Nudel et al. 2019). To the best of our knowledge, no specific studies on NK cell counting in children with PANS are still available. Our data suggest a putative role of the NK cell counting as biomarkers in the diagnosis of PANS. EEG features are understudied in relation to their importance in lending insight into the diagnosis of localized CNS or systemic immune-mediated inflammation. Finally, the large prevalence of sleep disorders in PANS children suggests to investigate the polysomnographic features to contribute in outlining the qualitative and quantitative aspects of the sleep in this population.

Conclusion

Our study could be considered a statistical validation of the existence of the still controversial clinical entity named PANS and describes it as a clinical complex constellation of psychiatric symptoms and adventitious movements, as well as the expression of different serological variables of an autoimmune/inflammatory disease. By a data mining approach, we describe the PANS as a very specific pattern of clinical variables, each of them having a low diagnostic meaning *per se*, but with significant predictive values as a whole. PANS, as well as the broad spectrum of autoimmune-mediated inflammatory brain diseases, represents a rapidly developing area of medical science.

Clinical Significance

This condition challenges clinicians to find reliable biomarkers facilitating the recognition of the brain susceptibility to autoimmunity and the accurate diagnosis and treatment of children presenting with new onset neuropsychiatric symptoms. The coherence among PANS symptoms may suggest to consider the syndrome as clinical entity *per se*, stimulating clinicians to search for a specific combination of symptoms and signs helpful in identifying this condition. Finally, PANS should represent for clinicians a stimulus to assume a new perspective looking to the brain as an organ strictly linked with the rest of the body and potentially influenced by some general pathological conditions such as inflammatory and autoimmune diseases.

Acknowledgments

The authors thank all the volunteers who participated in these clinical researches, as well as the physicians and study nurses who conducted the study. The authors also acknowledge the input from Dr. Jennifer Frankovich, Dr. Margo Thienemann, and Dr. Avis Chan from the Stanford PANS/Immune Behavioral Health Clinic and Research Program at Lucile Packard Children's Hospital and Stanford University School of Medicine, California, the United States, for reviewing the article.

Disclosures

Prof. Gagliano was in the advisory boards for Eli Lilly and Shire. She is/has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen, and Otsuka. She has been speaker for Novartis, Eli Lilly, and Shire. Dr. Sara Carucci has collaboration within projects from the European Union (7th Framework Program) and collaboration as subinvestigator in sponsored clinical trials by Lundbeck Otsuka and Janssen Cilag. Travel support from Fidia Farmaceutici. Prof. Alessandro Zuddas served in an advisory or consultancy role for Angelini, Lundbeck, Otsuka, and Edu-Pharma. He received conference support or speaker's fee from Angelini, Otzuka, and Takeda. He is/has been involved in clinical trials conducted by Angelini, Roche, Lundbeck, Janssen, Servier, and Otsuka. He received royalties from Oxford University Press and Giunti OS. The present work is unrelated to the above grants and relationships. Cecilia Galati, Massimo Ingrassia, Massimo Ciuffo, Maria Ausilia Alquino, Marcello G. Tanca, and Enzo Grossi have no institutional or corporate/commercial relationships to disclose.

Supplementary Material

Supplementary Data

References

Amouzegar A, Gharibzadeh S, Kazemian E, Mehran L, Tohidi M, Azizi F: The Prevalence, Incidence and Natural Course of Positive Antithyroperoxidase Antibodies in a Population-Based Study: TehranThyroid Study. PLoS One 12:e016928, 2017.

Ballow M: Approach to the patient with recurrent infections. Clin Rev Allergy Immunol 34:129–140, 2008.

Becker-Haimes EM, Diaz KI, Haimes BA, Ehrenreich-May J: Anxiety and Atopic Disease: Comorbidity in a Youth Mental Health Setting. Child Psychiatry Hum Dev 48:528–536, 2017.

Benvenga S, Trimarchi F: Changed presentation of Hashimoto's thyroiditis in North-Eastern Sicily and Calabria (Southern Italy) based on a 31-year experience. Thyroid 18:429–441, 2008.

Bergdolt L, Dunaevsky A: Brain changes in a maternal Immune activation model of neurodevelopmental brain disorders. Prog Neurobiol 175:1–19, 2018.

Bersani FS, Wolkowitz OM, Milush JM, Sinclair E, Eppling L, Aschbacher K, Lindqvist D, Yehuda R, Flory J, Bierer LM, Matokine I, Abu-Amara D, Reus VI, Coy M, Hough CM, Marmar CR, Mellon SH: A population of atypical CD56(−)CD16(+) natural killer cells is expanded in PTSD and is associated with symptom severity. Brain Behav Immun 56:264–270, 2016.

Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK: Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. Exp Neurol 299(Pt A):241–251, 2018.

Blomström A, Karlsson H, Gardner R, Jörgensen L, Magnusson C, Dalman C: Associations Between Maternal Infection During Pregnancy, Childhood Infections, and the Risk of Subsequent Psychotic Disorder—A Swedish Cohort Study of Nearly 2 Million Individuals. Schizophr Bull 42:125–133, 2015.

Bos-Veneman NG, Olieman R, Tobiasova Z, Hoekstra PJ, Katsovich L, Bothwell AL, Leckman JF, Kawikova I: Altered immunoglobulin profiles in children with Tourette syndrome. Brain Behav Immun 25:532–538, 2011.

Boulanger-Bertolus J, Pancaro C, Mashour GA: Increasing role of maternal immune activation in neurodevelopmental disorders. Front Behav Neurosci 12:230, 2018.

Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, Yale SH: Erythrocyte Sedimentation Rate and C-reactive protein measurements and their relevance in clinical medicine. WMJ 115:317–321, 2016.

Brown AS, Surcel HM, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Bao Y, Sourander A: Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. Prog Neuropsychopharmacol Biol Psychiatry 57:86–92, 2015.

Buscema M, Grossi E: The semantic connectivity map: An adapting self-organising knowledge discovery method in data bases. Experience in gastro-oesophageal reflux disease. Int J Data Min Bioinform 2:362–404, 2008.

Buscema M, Grossi E, Montanini L, Street ME: Data Mining of Determinants of Intrauterine Growth Retardation Revisited Using Novel Algorithms Generating Semantic Maps and Prototypical Discriminating Variable Profiles. PLoS One 10:e0126020, 2015.

Buscema M, Grossi E, Snowdon D, Antuono P: Auto-Contractive Maps: An artificial adaptive system for data mining. An application to Alzheimer disease. Curr Alzheimer Res 5:481–498, 2008.

Buscema M, Sacco PL: Digging deeper on ''deep'' learning: A computational ecology approach. Behav Brain Sci 40:e256, 2017.

Calaprice D, Tona J, Parker-Athill EC, Murphy TK: A survey of pediatric acute-onset neuropsychiatric syndrome characteristics and course. J Child Adolesc Psychopharmacol 27:607–618, 2017.

Catal F, Topal E, Soylu N, Ozel Ozcan O, Celiksoy MH, Babayiğit A, Karakoç HT, Erge D, Sancak R: Psychiatric disorders and symptoms severity in preschool children with atopic eczema. Allergol Immunopathol (Madr) 44:120–124, 2016.

Chang K, Frankovich J, Cooperstock M, Cunningham MW, Latimer ME, Murphy TK, Pasternack M, Thienemann M, Williams K, Walter J, Swedo SE: PANS Collaborative Consortium. Clinical evaluation of youth with pediatric acute-onset neuropsychiatric syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. J Child Adolesc Psychopharmacol 25:3–13, 2015.

Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, Chen TJ, Pan TL, Bai YM: Is atopy in early childhood a risk factor for ADHD and ASD? a longitudinal study. J Psychosom Res 77:316–321, 2014.

Cheng CM, Hsu JW, Huang KL, Bai YM, Su TP, Li CT, Yang AC, Chang WH, Chen TJ, Tsai SJ, Chen MH: Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: A nationwide longitudinal study. J Affect Disord 178:60–65, 2015.

Cheng W: Generalized Maupertuis' principle with applications. Acta Math Sin English Ser 28:2153–2160, 2012.

Chiovato L, Lapi P, Fiore E, Tonacchera M, Pinchera A: Thyroid autoimmunity and female gender. J Endocrinol Invest 16:384–391, 1993.

Christiansen ES, Kjaer HF, Eller E, Bindslev-Jensen C, Høst A, Mortz CG, Halken S: The prevalence of atopic diseases and the patterns of sensitization in adolescence. Pediatr Allergy Immunol 27:847–853, 2016.

Counotte J, Drexhage HA, Wijkhuijs JM, Pot-Kolder R, Bergink V, Hoek HW, Veling W: Th17/T regulator cell balance and NK cell numbers in relation to psychosis liability and social stress reactivity. Brain Behav Immun 69:408–417, 2018.

Denys D, Fluitman S, Kavelaars A, Heijnen C, Westenberg H: Decreased TNF-alpha and NK activity in obsessive-compulsive disorder. Psychoneuroendocrinology 29:945–952, 2004.

Fetene DM, Betts KS, Alati R: Mechanisms In Endocrinology: Maternal thyroid dysfunction during pregnancy and behavioural and psychiatric disorders of children: A systematic review. Eur J Endocrinol 177:R261–R273, 2017.

Fox-Edmiston E, Van de Water J: Maternal anti-fetal brain IgG autoantibodies and autism spectrum disorder: Current knowledge and its implications for potential therapeutics. CNS Drugs 29:715–724, 2015.

Frankovich J, Thienemann M, Pearlstein J, Crable A, Brown K, Chang K: Multidisciplinary clinic dedicated to treating youth with pediatric acute-onset neuropsychiatric syndrome: Presenting characteristics of the first 47 consecutive patients. J Child Adolesc Psychopharmacol 25:38–47, 2015.

Fredman ML, Willard DE: Trans-dichotomous algorithms for minimum spanning trees and shortest paths. In Proceedings 31st Annual Symposium on Foundations of Computer Science 2:719–725, 1990.

Gaughan T, Buckley A, Hommer R, Grant P, Williams K, Leckman JF, Swedo SE: Rapid Eye Movement Sleep Abnormalities in Children with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS). J Clin Sleep Med 12:1027–1032, 2016.

Gilbert DL, Mink J, Singer HS: A pediatric neurology perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome. J Pediatr 199:243–251, 2018.

Gironi M, Saresella M, Rovaris M, Vaghi M, Nemni R, Clerici M, Grossi E: A novel data mining system points out hidden relationships between immunological markers in multiple sclerosis. Immun Ageing 10:1, 2013.

Gładysz D, Krzywdzińska A, Hozyasz KK: Immune Abnormalities in Autism Spectrum Disorder—Could They Hold Promise for Causative Treatment? Mol Neurobiol 55:6387–6435, 2018.

Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Hoftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F,

Pruss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostasy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J: A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 15:391–404, 2016.

Grossi E, Migliore L, Muratori F: Pregnancy risk factors related to autism: An Italian case-control study in mothers of children with autism spectrum disorders (ASD), their siblings and of typically developing children. J Dev Orig Health Dis 9:442–449, 2018.

Grossi E, Olivieri C, Buscema M: Diagnosis of autism through EEG processed by advanced computational algorithms: A pilot study. Comput Methods Programs Biomed 142:73–79, 2017.

Gruber C, Keil T, Kulig M, Roll S, Wahn U, Wahn V: History of respiratory infections in the first 12 yr among children from a birth cohort. Pediatr Allergy Immunol 19:505–512, 2008.

Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CS, Braverman Le: Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87:489–499, 2002.

Hughes HK, Mills Ko E, Rose D, Ashwood P: Immune dysfunction and autoimmunity as pathological mechanisms in autism spectrum disorders. Front Cell Neurosci 12:405, 2018.

Jeon Y, Han S, Park EJ: The relation between immunologic variables and symptom factors in patients with major depressive disorder. Ann Gen Psychiatry 17:32, 2018.

Jiang NM, Cowan M, Moonah SN, Petri Jr WA: The impact of systemic inflammation on neurodevelopment. Trends Mol Med 24: 794–804, 2018.

Kandelaki E, Kavlashvili N, Kherkheulidze M, Chkhaidze I: Prevalence of atopic dermatitis symptom in children with developmental and behavioral problems. Georgian Med News 243:29–33, 2015.

Karpiński P, Frydecka D, Sąsiadek MM, Misiak B: Reduced number of peripheral natural killer cells in schizophrenia but not in bipolar disorder. Brain Behav Immun 54:194–200, 2016.

Kawikova I, Leckman JF, Kronig H, Katsovich L, Bessen DE, Ghebremichael M, Bothwell AL: Decreased numbers of regulatory T cells suggest impaired immune tolerance in children with Tourette syndrome: A preliminary study. Biol Psychiatry 61:273–278, 2007.

Keil A, Daniels JL, Forssen U, Hultman C, Cnattingius S, Söderberg KC, Feychting M, Sparen P: Parental autoimmune diseases associated with autism spectrum disorders in offspring. Epidemiology 21:805–808, 2010.

Köhler-Forsberg O, Petersen L, Gasse C, Mortensen PB, Dalsgaard S, Yolken RH, Mors O, Benros ME: A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and Adolescents. JAMA Psychiatry 76:271–279, 2018.

Kruskal JB: On the shortest spanning subtree of a graph and the traveling salesman problem. Proc Am Math Soc 7:48–50, 1956.

Kuniyoshi Y, Kikuya M, Miyashita M, Yamanaka C, Ishikuro M, Obara T, Metoki H, Nakaya N, Nagami F, Tomita H, Hozawa A, Tsuji I, Kure S, Yaegashi N, Yamamoto M, Kuriyama S: Severity of eczema and mental health problems in Japanese schoolchildren: The ToMMo Child Health Study. Allergol Int 67:481–486, 2018.

Lee CY, Chen MH, Jeng MJ, Hsu JW, Tsai SJ, Bai YM, Hung GY, Yen HJ, Chen TJ, Su TP: Longitudinal association between early atopic dermatitis and subsequent attention-deficit or autistic disorder: A population-based case-control study. Medicine (Baltimore) 95:e5005, 2016.

Li Y, Teng D, Shan Z, Teng X, Guan H, Yu X, Fan C, Chong W, Yang F, Dai H, Gu X, Yu Y, Mao J, Zhao D, Li J, Chen Y, Yang R, Li C, Teng W: Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. J Clin Endocrinol Metab 93:1751–1757, 2008.

Liao TC, Lien YT, Wang S, Huang SL, Chen CY: Comorbidity of atopic disorders with autism spectrum disorder and attention deficit/hyperactivity disorder. J Pediatr 171:248–255, 2016.

Lougee L, Perlmutter SJ, Nicolson R, Garvey MA, Swedo SE: Psychiatric disorders in first-degree relatives of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). J Am Acad Child Adolesc Psychiatry 39:1120–1126, 2000.

Miyazaki C, Koyama M, Ota E, Swa T, Mlunde LB, Amiya RM, Tachibana Y, Yamamoto-Hanada K, Mori R: Allergic diseases in children with attention deficit hyperactivity disorder: A systematic review and meta-analysis. BMC Psychiatry 17:120, 2017.

Molloy CA, Morrow AL, Meinzen-Derr J, Dawson G, Bernier R, Dunn M, Hyman SL, McMahon WM, Goudie-Nice J, Hepburn S, Minshew N, Rogers S, Sigman M, Spence MA, Tager-Flusberg H, Volkmar FR, Lord C: Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: A CPEA Study. J Autism Dev Disord 36:317–324, 2006.

Mucha SM, Baroody FM: Relationships between atopy and bacterial infections. Curr Allergy Asthma Rep 3:232–237, 2003.

Murphy TK, Goodman WK, Fudge MW, Williams RC Jr, Ayoub EM, Dalal M, Lewis MH, Zabriskie JB: B lymphocyte antigen D8/17: A peripheral marker for childhood-onset obsessive-compulsive disorder and tourette's syndrome? Am J Psychiatry 154:402–407, 1997.

Murphy TK, Patel PD, McGuire JF, Kennel A, Mutch PJ, Parker-Athill EC, Hanks CE, Lewin AB, Storch EA, Toufexis MD, Dadlani GH, Rodriguez CA: Characterization of the pediatric acute-onset neuropsychiatric syndrome phenotype. J Child Adolesc Psychopharmacol 25:14–25, 2015.

Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky OJ: Neuroinflammation and psychiatric illness. Neuroinflammation 10:43, 2013.

Nanda MK, LeMasters GK, Levin L, Rothenberg ME, Assa'ad AH, Newman N, Bernstein D, Khurana-Hershey G, Lockey JE, Ryan PH: Allergic diseases and internalizing behaviors in early childhood. Pediatrics 137:e20151922, 2016.

Narzisi A, Muratori F, Buscema M, Calderoni S, Grossi E: Outcome predictors in autism spectrum disorders preschoolers undergoing treatment as usual: Insights from an observational study using artificial neural networks. Neuropsychiatr Dis Treat 11:1587–1599, 2015.

Nordahl CW, Braunschweig D, Iosif AM, Lee A, Rogers S, Ashwood P, Amaral DG, Van deWater J: Maternal autoantibodies are associated with abnormal brain enlargement in a subgroup of children with autism spectrum disorder. Brain Behav Immun 30: 61–65, 2013.

Nudel R, Benros ME, Krebs MD, Allesøe RL, Lemvigh CK, Bybjerg-Grauholm J, Børglum AD, Daly MJ, Nordentoft M, Mors O, Hougaard DM: Immunity and mental illness: Findings from a Danish population-based immunogenetic study of seven psychiatric and neurodevelopmental disorders. Eur J Hum Genet 27:1445–1455, 2019.

Pape K, Tamouza R, Leboyer M, Zipp F: Immunoneuropsychiatry - novel perspectives on brain disorders. Nat Rev Neurol 15:317–328, 2019.

Perugi G, Quaranta G, Belletti S, Casalini F, Mosti N, Toni C, Dell'Osso L: General medical conditions in 347 bipolar disorder patients: Clinical correlates of metabolic and autoimmune-allergic diseases. J Affect Disord 170:95–103, 2015.

Pohlman D, PANDAS Network: PN 2018 State of Our Children SURVEY. 2018. Available at: http://pandasnetwork.org/wp-

content/uploads/2018/10/PN-SOOC-SURVEY_2018.pdf (Accessed September 16, 2019).

Poli A, Kmiecik J, Domingues O, Hentges F, Bléry M, Chekenya M, Boucraut J, Zimmer J: NK cells in central nervous system disorders. J Immunol 190:5355–5362, 2013.

Ravindran A, Griffith J, Merali Z, Anisman H: Circulating lymphocyte subsets in obsessive compulsive disorder, major depression and normal controls. J Affect Disord 52:1–10, 1999.

Rodriguez N, Morer A, Gonzalez-Navarro EA, Serra-Pages C, Boloc D, Torres T, Garcia-Cerro S, Mas S, Gasso P, Lazaro L: Inflammatory dysregulation of monocytes in pediatric patients with obsessive-compulsive disorder. J Neuroinflamm 14:261, 2017.

Rosa JS, Hernandez JD, Sherr JA, Smith BM, Brown KD, Farhadian B, Mahony T, McGhee SA, Lewis DB, Thienemann M, Frankovich JD: Allergic diseases and immune-mediated food disorders in pediatric acute-onset neuropsychiatric syndrome. Pediatr Allergy Immunol Pulmonol 31:158–165, 2018.

Satoh M, Chan EK, Ho LA, Rose KM, Parks CG, Cohn RD, Jusko TA, Walker NJ, Germolec DR, Whitt IZ, Crockett PW, Pauley BA, Chan JY, Ross SJ, Birnbaum LS, Zeldin DC, Miller FW: Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. Arthritis Rheum 64:2319–2327, 2012.

Staii A, Mirocha S, Todorova-Koteva K, Glinberg S, Jaume JC: Hashimoto thyroiditis is more frequent than expected when diagnosed by cytology which uncovers a preclinical state. Thyroid Res 3:11, 2010.

Street ME, Grossi E, Volta C, Faleschini E, Bernasconi S: Placental determinants of fetal growth: Identification of key factors in the insulin-like growth factor and cytokine systems using artificial neural networks. BMC Pediatr 8:24, 2008.

Swedo S, Leckman J, Rose N: From research subgroup to clinical syndrome: Modifying the PANDAS criteria to describe PANS (pediatric acute-onset neuropsychiatric syndrome). Pediatr Ther 2: 1–8, 2012.

Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. Am J Psychiatry 155:264–271, 1998.

Toscano M, De Grandi R, Peroni DG, Grossi E, Facchin V, Comberiati P, Drago L: Impact of delivery mode on the colostrum microbiota composition. BMC Microbiol 17:205, 2017.

Tzeng NS, Chang HA, Chung CH, Kao YC, Chang CC, Yeh HW, Chiang WS, Chou YC, Chang SY, Chien WC: Increased risk of psychiatric disorders in allergic diseases: A nationwide, population-based, cohort study. Front Psychiatry 9:133, 2018.

Van Mater H: Pediatric inflammatory brain diseases: A diagnostic approach. Curr Opin Rheumatol 26:553–561, 2014.

Vasilyeva EF, Kushner SG, Factor MI, Omelchenko MA, Bogdanova ED, Petrakova LN, Brusov OS: The cellular factors of innate immunity in nonpsychotic patients at high risk for schizophrenia. Zh Nevrol Psikhiatr Im S S Korsakova 116:60–65, 2016.

Wang Q, Yang C, Gelernter J, Zhao H: Pervasive pleiotropy between psychiatric disorders and immune disorders revealed by integrative analysis of multiple GWAS. Hum Genet 134:1195–1209, 2015.

Yu KH, Palmer N, Fox K, Prock L, Mandl KD, Kohane IS, Prilutsky D: The phenotypical implications of immune dysregulation in fragile X syndrome. European Journal of Neurology 27:590–593, 2020.

Zelaya AS, Stotts A, Nader S, Moreno CA: Antithyroid peroxidase antibodies in patients with high normal range thyroid stimulating hormone. Fam Med 42:111–115, 2010.

Zhou H: Maternal infection and neurodevelopmental disorders in the offspring. Am J Immunol 8:10–17, 2012.

Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, Mccorkle R, Selgman DA, Schmidt K: The relationship of depression and stressors to immunological assays: A meta- analytic review. Brain Behav Immun 15:199–226, 2001.

Address correspondence to:
Antonella Gagliano, MD, PhD
Child & Adolescent Neuropsychiatry Unit
Department of Biomedical Science
University of Cagliari
''G. Brotzu'' Hospital Trust
Via Jenner
Cagliari 09121
Italy

E-mail: antonellagagliano.npi@gmail.com

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

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

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

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