NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD AGOSTO 2017

Acta Medica Nagasakiensia. 2017;61:71-79.

CHARACTERISTICS OF INATTENTION AND HYPERACTIVITY, PERCEPTION OF GENERAL HEALTH, AND READING LITERACY OF JAPANESE ADOLESCENTS: RESULTS FROM A LARGE-SCALE COMMUNITY SAMPLE.

Yamada S, Imamura A, Honda S, et al.

Adolescents with reading literacy difficulty with comorbid attention deficit hyperactivity disorder are often at a greater risk for problems of communication, and behavioral and mental health challenges. We aimed to examine literacy weakness for the native Japanese language of KOKUGO and the foreign language of ENGLISH as perceived by Japanese adolescents. We also aimed to analyze the relationship between literacy weakness and inattention and hyperactivity characteristics. We conducted a largescale questionnaire survey of 2987 junior high school students. We used logistic regression analysis to examine the data from the self-report Strengths and Difficulties Questionnaire (SDQ), the General Health Questionnaire-12, and adolescents' perceptions of their command of KOKUGO and ENGLISH. We found a significant association between perceived literacy for both languages and SDQ inattention and hyperactivity characteristics. Reading difficulties in ENGLISH may be addressed by introducing ENGLISH at an earlier age supported by clinically enhanced pedagogy

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

ADHD Atten Deficit Hyperact Disord. 2017;9:S6-S7.

EARLY ANAESTHETIC EXPOSURE AND THE RISK OF ADHD.

Silva D, Tan J, Jois RS, et al.

Objectives: Although ADHD is predominantly a genetic condition approximately 40% variance may be due to environmental factors. Early environmental risk factors which may include exposure to general anaesthetic can impact on brain development. Our study investigates the risk of early exposure to one or more anaesthetics in children subsequently diagnosed and treated with stimulant medication for ADHD.

Methods: Population information was collected on 10,850 non-Aboriginal children<18 years (cases) who had been prescribed stimulant medication in WA for ADHD and were recorded on the monitoring of drugs dependency system (MODDS). A stratified random sample of birth records with no linkage to MODDS formed a comparison group (25,240). Case and comparison records were linked to the midwives notification system and the hospital morbidity database, which identified children who received an anaesthetic during their hospital admission. De-identified linked data files were provided for analysis.

Results: Twenty-three percent (23%) of non-Aboriginal children subsequently diagnosed with ADHD and 16% of their non-ADHD counterparts had received a general anaesthetic under four years of age. Children who received one anaesthetic under four years of age had an increased risk of being diagnosed with ADHD compared with their non-ADHD counterparts (OR 1.40; 95% CI 1.31-1.50). Having one or more general anaesthetics under four years of age increased this risk almost two-fold (OR 1.85; 95% CI 1.67-2.06) when adjusted for sex, maternal age, birth weight, marital status, socio-economic status and year of birth. Females appeared to have a higher risk compared to their male counterparts.

Conclusions: Although population studies are unable to show the causal direction of environmental exposures there is evidence that early exposure to anaesthetic and multiple exposures may increase the risk of being diagnosed with ADHD. Applying the developmental origins of health and disease (DoHAD) concepts to children with ADHD may assist in understanding environmental risks that may need to be explored further

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ADHD Atten Deficit Hyperact Disord. 2017;9:S37.

EFFECTS OF NEUROFEEDBACK TRAINING ON REDUCING EMOTIONAL AND BEHAVIOUR PROBLEMS IN CHILDREN WITH ADHD: A PILOT STUDY IN TAIWAN.

Shyu LY, Yeh CB, Fu A-T.

Objectives: Emotional problems in children with ADHD are considered an important issue for clinicians. Researchers had found that emotion dysregulation was linked to the symptoms and neurobiological deficiency. Objectives of the current study were to examine the effects of neurofeedback (NF) training on reducing emotional and behaviour problems in children with ADHD.

Methods: Participants were 18 children aged 7-12 years and their parents. NF training consisted of 40 sessions, were held 2-3 times per week. Each session lasted 60 min. NF comprised theta/beta training on the vertex (Cz). CBCL were rated by parents to evaluate children's emotional and behaviour problems. CPT-II and WISC-IV were used to assess children's cognitive function. Posttreatment evaluations were carried out after the last training session. Follow-up measurements were held six month after the last session.

Conclusions: NF training adjusted abnormal EEG and was effective in improving intelligence, symptoms and emotional/behaviour problems in children with ADHD. Children learned that they have to keep focus and calm in order to get high scores during NF programmes. Again and again, after 40 sessions, children try to control their behaviours and emotions. In the future, this study will add control groups for a more complete comparison

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ADHD Atten Deficit Hyperact Disord. 2017;9:S6.

AIRWAY ALLERGIC DISEASES INCREASE THE RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SCHOOLAGED CHILDREN INDEPENDENT OF SLEEPING PROBLEMS.

Shen C, Jiang X, Li K, et al.

Objectives: To explore the effects of airway allergic diseases on the risk of Attention-Deficit/Hyperactivity Disorder (ADHD) in schoolaged children.

Methods: The diagnosis history of ADHD and Airway allergic diseases, as well as general information on school-aged children from nine cities in China were collected from parental reports using clusterstratified methods. The Chinese version of children's sleep habits questionnaire (CSHQ) was used to measure sleeping problems. Subjects were divided into three groups based on airway allergic diseases, i.e. control group (neither allergic rhinitis nor bronchial asthma), single airway allergic disease group (either allergic rhinitis or bronchial asthma), mixed airway allergies group (both allergic rhinitis and bronchial asthma). Multiple logistic regression model was used for analysing the effect of airway allergic diseases and other related risk factors on ADHD in school-aged children.

Results: Airway allergic diseases significantly increase the risk of ADHD. The odds ratio of ADHD in children with a single airway allergic disease is 2.197 (95% confidence interval [CI] 1.823-2.648), and the odds ratio of ADHD in children with mixed airway disease is 3.150 (95% CI 2.082-4.76). Furthermore, the odds ratio of ADHD in children with single or mixed airway allergies changed little after adjusting sleeping problems.

Conclusions: Airway allergic diseases increase the risk of ADHD in Chinese school-aged children and the effect was independent of sleeping problems

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ADHD Atten Deficit Hyperact Disord. 2017;9:S42.

LONG-TERM SAFETY AND EFFICACY OF GUANFACINE EXTENDED RELEASE IN CHILDREN AND ADOLESCENTS WITH ADHD.

Newcorn J, Quiroga JAR, Dirks B, et al.

Objectives: To assess the long-term safety and efficacy of the nonstimulant treatment guanfacine extended release (GXR) at doses up to 7 mg/day in children and adolescents (aged 6-17 years) with Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: SPD503-318 was a phase 3, 2-year, open-label extension study for European participants of the GXR clinical trials SPD503-315 and SPD503-316. Participants received dose-optimised GXR (maximum permitted dose: children, 4 mg/day; adolescents, 4-7 mg/day depending on weight).

Results: Of 215 enrolled participants, 214 were included in the safety population and 133 completed the study. The mean age of participants was 11.7 years; 73.8% were male. Overall, treatment-emergent adverse events (TEAEs) were reported in 177 patients (82.7%). TEAEs reported in C10% participants were somnolence (77 [36.0%]), headache (61 [28.5%]), fatigue (43 [20.1%]) and nasopharyngitis (25 [11.7%]). No TEAEs of syncope were reported. Serious TEAEs and TEAEs leading to discontinuation were reported in 10 (4.7%) and 7 (3.3%) participants, respectively. There were no deaths. There were small changes from baseline to final assessment in mean (standard deviation) supine pulse (-5.5 [12.98] bpm) and blood pressure (systolic, 0.6 [9.32] mmHg; diastolic, 0.2 [9.17] mmHg). A decrease in ADHD-RS-IV total score was maintained throughout the 2-year study with a mean (standard error of mean) change from baseline of -19.8 (0.84; nominal $p < 0.0001$) at the final on-treatment assessment.

Conclusions: This 2-year European study confirms that GXR at doses up to 7 mg/day is well-tolerated during long-term use, with a safety profile similar to that previously observed. Improvements in ADHD symptoms were maintained throughout the study

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ADHD Atten Deficit Hyperact Disord. 2017;9:S34.

EFFECTS OF WHITE NOISE ON ACADEMIC PERFORMANCE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shih M-Y, Tsai P-L, Ma H-I, et al.

Objectives: Previous studies have suggested that white noise may adjust arousal of children with Attention-Deficit/Hyperactivity Disorder (ADHD) to an optimal level and enhance attention and memory performance. However, little is known about the benefit of white noise on academic performance in children with ADHD. The aim of the present study was to determine whether white noise could improve academic performance of elementary school children with ADHD.

Methods: Seventeen children with ADHD in grades two through four and 17 typically development (TD) children matched for age and gender performed four academic tasks (dictation test, copy test, reading test and mathematics test) under white noise and silence condition within two weeks. Two-way repeated ANOVAs were done to compare test scores of two auditory conditions in both groups.

Results: The ANOVAs showed that only the interaction effects of the dictation score ($p = .052$, $2p = .113$) and the reading accuracy score ($p = .060$, $2p = .106$) reached marginal significance, and the effect sizes were medium. Both scores in the silent condition were significantly lower in the ADHD group, but such disparity between the two groups disappeared under white noise conditions. Exposure to white noise led to significant improvements on dictation and reading performance for the ADHD group. Besides, the ADHD group had significantly lower scores than did the TD group on the copy and the mathematics tests under both conditions.

Conclusions: We first provide evidence of the positive effects of white noise on academic performance in elementary school children with ADHD. Our findings suggest that white noise enhances dictation and reading performance in children with ADHD. We speculate these findings can be attributed to the nature of both tasks, which require more memory function. Future research with a larger population or using different academic tasks is needed to validate the findings of this study

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ADHD Atten Deficit Hyperact Disord. 2017;9:S24.

INTRA-SUBJECT VARIABILITY OF BEHAVIOURAL AND ELECTRO-CORTICAL MEASURES OF PERFORMANCE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Salunkhe G, Feige B, Saville C, et al.

Objectives: Increased intra-subject variability (ISV) is a consistent finding in Attention-Deficit/Hyperactivity Disorder (ADHD) which may occur due to increased lapses in attention, represented as slow or absent reaction times (RTs). Attentional lapses have been linked with poor suppression of the default mode network (DMN), which is usually attenuated during goal-directed task performance. Furthermore, deficits in performance, like slow RTs and errors, may be associated with slow (< 0.1 Hz) quasi-periodic synchronisation of DMN structures.

Methods: ADHD patients (n = 18) and age and IQ-matched healthy controls (n = 18), 12-13 years old, participated in two EEG sessions using the Flanker Task. EEG was recorded from 64 channels of the 10-10 system with a DC amplifier (Brain Products, Germany). All participants completed 48 blocks containing 72 trials each. For each participant, scores of behavioural (RTs, accuracy) and electro-cortical variables (P300 amplitude and latency) were aggregated across the 24 blocks of a single EEG session, separately for congruent versus incongruent flankers.

Results: Preliminary behavioural and electro-cortical results for 12 patients and 12 controls show increased behavioural ISV and reduced P300 amplitudes in ADHD. During task-initiation, both groups have lower overall mean RTs and P300 amplitudes; higher accuracy in congruent trials and lower accuracy in incongruent trials. This is also followed by low frequency performance fluctuations in both patients and controls. Fast Fourier transform (FFT) on trial-wise averages of behavioural and EEG data will be employed in further analyses to identify the frequency spectrum of P300 amplitude and behavioural performance fluctuations.

Conclusions: The results of our study have replicated previous findings about increased ISV in ADHD. Our further analyses will shed light on the temporal characteristics of ISV at both the behavioural and electrophysiological levels and will be discussed in the context of concurrent theories of increased ISV in ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S50.

THE PURPLE HEX: PSYCHOSIS ASSOCIATED WITH ABUSE OF PROPYLHEXEDRINE NASAL INHALERS BY A YOUNG ADULT WITH HISTORY OF ADHD SEEKING REPLACEMENT FOR STIMULANT MEDICATION-WITH LITERATURE REVIEW AND HISTORICAL CONTEXT.

Cohen A, Perkel C.

Objectives: Propylhexedrine is a sympathomimetic drug structurally similar to methamphetamine. Currently it is widely available over the counter for under $10 as a Benzedrex brand nasal inhaler. We report the case of a young adult patient with a history of ADHD who developed psychosis after ingesting propylhexedrine in the form of the contents of nasal inhalers which he learned about through the Internet after seeking a replacement for stimulant ADHD medication. To our knowledge, the last case of psychosis associated with propylhexedrine use was published in 1972. This case highlights the potential for abuse of a widely available over the counter medication and the associated risk of psychosis. Physicians will learn to recognise and screen for the abuse of this “legal speed”. It also highlights one patient´s quest to find a replacement for stimulant ADHD medication he found helpful and the role of the Internet in connecting individuals seeking similar effects.

Methods: We present a case of a 26-year old patient with ADHD and marijuana/stimulant use disorder who presented with psychosis after daily ingestion of over the counter propylhexedrine - a sympathomimetic nasal decongestant available over the counter, as well as review of the literature on psychiatric symptoms associated with propylhexedrine use. A PubMed search using the words "propylhexedrine", "psychiatry" and "psychosis" was performed.

Results: This is a case of a 26-year old man with past psychiatric history of ADHD, stimulant/K2/cannabis use disorders, who was admitted after he presented with psychosis and suicidal ideation in the context of daily propylhexedrine ingestion. The patient stated he had prior diagnosis of ADHD treated as an adolescent with stimulant medication with good effect, but was lost to follow up in context of his mother´s substance abuse. The patient states he sought similar stimulant effects from methamphetamine purchased illegally but eventually found it cost prohibitive. He then turned to Internet message boards to find substances "like adderall" which could be obtained without seeing a physician. On learning about propylhexedrine, he began purchasing it from his local pharmacy, breaking open the inhalers and ingesting the contents. As his tolerance grew he moved on to stealing the inhalers to maintain his supply. On admission, the patient was disorganised and extremely aggressive and was treated with olanzapine. Over the course of hospitalisation, the patient showed improvement in psychosis and mood symptoms and was discharged to a inpatient rehab programme. Benzedrine amphetamine medication was a popular drug of abuse, immortalised in Jack Kerouac's "On the Road". In 1949, amphetamine sulphate-based benzedrine was replaced by propylhexedrine containing Benzedrex inhalers after of reports of psychosis, sudden death and wide spread abuse associated with benzedrine use. Benzedrex inhalers are widely available over the counter at pharmacies for $5 - 8 and at least in New York are not subject to the same sales restrictions as pseudoephedrine. Structurally similar to methamphetamine, propylhexedrine has a salicyclic cyclohexyl group in place of amphetamine´s aromatic phenyl group, and provides local vasoconstriction with reportedly 1/12 the central nervous system stimulant effects of amphetamine. Subsequently it was thought to have a lower potential for abuse, but reports emerged in the early 1970s of psychosis associated with propylhexedrine ingestion likely due to increasing abuse after amphetamine and methamphetamine were scheduled, restricting their availability.

Conclusions: Our patient, unable to obtain prescription stimulant medication which he had used for ADHD turned to a widely available over the counter medication and with chronic daily abuse he presented as floridly psychotic. While this drug is inexpensive and widely available, there is little information in the medical literature on the effects of its chronic use. Physicians need to be aware of its potential for abuse, particularly

among adolescents who are increasingly abusing over the counter medications for their euphoric effects, or in the case of our patient, in a self described effort to replace a previously prescribed psychiatric medication.

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ADHD Atten Deficit Hyperact Disord. 2017;9:S21.

DISSOCIATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM EVIDENCE FROM INTRA-SUBJECT VARIABILITY IN GAZE CONTROL.

Seernani DP, Ioannou C, Hill H, et al.

Objectives: Potential aetiological overlap between Attention-Deficit/Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD) is a current topic of research in neurodevelopmental disorders that requires systematic comparisons between these groups (Biscaldi et al. 2015; Rommelse et al. 2011). Among the most consistent findings in the ADHD literature is increased intra-subject variability (ISV), that is moment-to-moment fluctuation of performance, which has, so far, almost exclusively been studied with manual-motor responses. Here, we broaden the study of ISV from reaction time tasks with manual responses to the ISV of gaze control.

Methods: Children and adolescents with ADHD, ASD and healthy controls, aged 10-13 years (n = 90; all native German speakers) were invited for an ocular-motor testing session including a visual search and a gaze cueing task. In the visual search task, participants are required to find a Portuguese target word shown above a grid with multiple Portuguese German word pairs and to indicate its position by pressing response keys matching the search array. In the gaze cueing task, participants play the game 'I spy', and are required to follow the gaze of an on-screen face in order to correctly locate the target object. Fixation durations, saccadic latencies, saccadic amplitudes and initiation of search will be used to derive measures of ocular-motor ISV.

Results: Preliminary results suggest dissociation between ADHD and ASD, with only the ADHD group showing significantly higher ISV in ocular-motor parameters of the visual search as well as the gaze cueing task.

Conclusions: Our study will show to what extent increased ISV (a) can be found in the ocular-motor domain and (b) is specific to ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S3-S4.

ADVERSE FAMILY LIFE EVENTS DURING PREGNANCY AND ADHD SYMPTOMS IN 5-YEAR OLD OFFSPRING.

Rydell M, Sj+Âlander A, Larsson H, et al.

Objectives: To clarify if prenatal exposure to adverse life events in the family is associated with ADHD symptoms in 5-year old children, and to assess if such an association remains after controlling for shared familial factors.

Methods: This study is based on 37,147 children (including 6.423 siblings) whose mothers participated in the Norwegian mother and child cohort study during pregnancy and at the child's age of five. During pregnancy, mothers reported whether they had experienced the following events: Problems at work; financial problems; divorced/separated; conflicts with family/friends; seriously ill/injured; someone close seriously ill/injured; serious accident/fire/robbery; or lost loved ones. ADHD symptoms were reported by parents at the child's age of five using the Conners parent rating scale-revised: Short form. Linear regression models were used to compare mean ADHD scores (range 0-3) among children prenatally exposed to life events with those unexposed. Parental age at birth, marital status and child's year of birth were included in adjusted models. To adjust for unmeasured familial confounding, fixed-effect models were used to compare mean ADHD scores among exposure-discordant siblings. Sibling analyses were adjusted for parental age at birth, parity and child's year of birth.

Results: Children exposed to adverse life events had higher ADHD scores at age five. The strongest effect was observed for financial problems, and the weakest for having lost loved ones (mean differences 0.10 [95% CI 0.08-0.11] and 0.02 [95% CI 0.01-0.04] respectively in adjusted models). Comparing exposure-discordant siblings resulted in attenuated estimates that were no longer statistically significant (e.g. mean

difference for financial problems-0.02 [95% CI-0.07-0.02]). However, wide confidence intervals for specific life events hamper full interpretation of these results.
Conclusions: Prenatal exposure to adverse life events in the family is associated with ADHD symptoms in 5-year old children. Some associations seem to be explained by familial confounding

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ADHD Atten Deficit Hyperact Disord. 2017;9:S48.
ADHD AND SLPS: A SURVEY.
Roitsch J, Watson S.
Objectives: It is estimated that 30-50% of students with ADHD also have a specific learning disability. More specifically, as ADHD can negatively affect the language development of children, it is important to know how prepared Speech language pathologists (SLPs) feel about working with those students. Although self-assessments and perceptions of effectiveness are important to evaluation and treatment outcomes, few studies have queried how speech and language pathologists (SLPs) manage attention deficits within the clinical setting. Few researchers have interviewed school SLPs to determine their comfort levels in working with children with ADHD. The purpose of this research was to survey SLPs to determine the level of education and training that they received prior to working with children with ADHD and also to determine their comfort level when working with children with ADHD.
Methods: For this study, a total of 86 school SLPs whose clinical caseload included students diagnosed with ADHD participated in an online survey.
Results: Results revealed that only 27% (n = 22) of SLPs had received specific coursework in school prior to working with students with speech and language disorders who also have a diagnosis of ADHD. Nearly 61% (n = 51) of all SLPs surveyed had sought professional training regarding ADHD. Less than half (47%, n = 40) of the SLPs surveyed felt that they were adequately trained to work with children with ADHD. From the survey, 23% (n = 19) of SLPs reported that they rarely or never focused on executive functions during assessment and treatment sessions and 27% (n = 22) SLPs surveyed never assessed working memory capacity during initial evaluations.
Conclusions: These results suggest the need for increased training to better equip SLPs to work with students with ADHD prior to entering the school systems

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ADHD Atten Deficit Hyperact Disord. 2017;9:S18-S19.
ADHD DIAGNOSIS AND ADDICTIVE USE OF COMPUTER GAMING IN YOUNG CHILDREN FROM FRENCHSPEAKING AND GERMAN-SPEAKING COUNTRIES.
Paulus FW, Ohmann S, Saiag M-C, et al.
Objectives: Playing video games has become a common activity for children. As the association between computer game playing and ADHD has not yet been studied in young children, the aim of this study is to analyse and to compare addictive computer game playing and media use in French-speaking and German-speaking young children diagnosed with ADHD.
Methods: Parents of 463 children (73.9% boys; mean age 6.2 years, SD 1.2, range 4.0-8.0) with a diagnosis of ADHD (N = 323) or another ICD-10 diagnosis (control group, N = 140) filled out a standardised ADHD questionnaire (19 items), a media use questionnaire (9 items), and an 11-item addictive computer game playing questionnaire. The data were assessed in French-speaking (Paris, Strasbourg, Forbach, Monastir, Nice, Montpellier) and Germanspeaking (Homburg/Saar, Neuwied/Rhein, Dillingen, Mnster, Vienna) child psychiatric or neuropaediatric institutions.
Results: We found considerable differences between the ADHD group and the control group in access to computer or ownership of a stationary or portable game console. Young children with ADHD had significantly higher computer addiction scores (t = 3.96; p <.001) compared with children with other ICD-10-diagnoses. In the Frenchspeaking countries, the computer game addiction scores (t = 7.79; p <.001) and the ADHD symptom scores (t = 2.38; p =.02) for children diagnosed with ADHD were higher than in German-speaking countries.

Conclusions: When taking a historical approach or assessing young children with ADHD, the use of video games and addictive game playing should regularly be explored. We detected differences between French-speaking and German-speaking countries concerning the magnitude of addictive video game playing. We also discovered that diagnosis of ADHD in French-speaking countries implied a higher symptom intensity than in German-speaking countries

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ADHD Atten Deficit Hyperact Disord. 2017;9:S47.

COGNITIVE INSIGHTS INTO ADHD: EXPLORING THE RELATIONSHIP BETWEEN ADHD, THE KNOWLEDGE OF PARENTS/SCHOOLS, DYSFUNCTIONAL EXPECTATIONS, BELIEFS AND STIGMATIZATION IN PAKISTAN.

Vazir N.

Objectives: In Pakistan, there is an extreme dearth of awareness about the developmental needs of children, especially for those suffering from ADHD is sorely lacking. A comprehensive analysis of the published research literature of Pakistan demonstrates that so far no studies have been conducted on the significance of the knowledge of parents and teachers of ADHD. This study is an initial step to create awareness and tolerance for all those children who are different. The primary purpose of this study is to explore the existing knowledge and understanding (if any) of parents and teachers about ADHD. Moreover, to inquire how their cognition and belief towards mental health services for ADHD influences their decision to seek psychological assistance and medical help for their child's treatment.

Methods: Purposive sampling technique was used to select 150 (semi-literate) parents and teachers (untrained) of primary students (6-8 years) from lower middle class schools from three different towns of Karachi, Pakistan. Ten focus group interviews were conducted to collect data.

Results: The findings of the study show cognitive dysfunction of parents due to lack of awareness and acceptance of learning disabilities, stigmatisation, cultural taboos, societal pressure and rigid thinking (tunnel vision). Eighty percent (80%) of the mothers outlined the lack of decision-making (especially in case of children's disabilities) in a male dominant society. Moreover, mother's attributed lack of professional help/inclusive schools in Pakistan as compared to developed nations where ADHD treatment is much more common.

Conclusions: Our analysis shows that parents disregard the needs of their child over societal needs. This study is an investigation to identify and reach out to children, teachers and parents through awareness programmes and on-site psychological counselling

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ADHD Atten Deficit Hyperact Disord. 2017;9:S39.

EFFICACY AND SAFETY OF HLD200, A NOVEL DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE FORMULATION, IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RESULTS FROM A PIVOTAL PHASE 3 TRIAL.

Pliszka S, Arnold V, Marraffino A, et al.

Objectives: To determine whether evening-dosed HLD200 improves control of ADHD symptoms and at-home early morning and late afternoon/evening functional impairments versus placebo in children with Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: This was a pivotal, randomised, double-blind, placebocontrolled, phase 3 trial of HLD200 in children (6-12 years) with ADHD (NCT02520388). Subjects had current or prior response on methylphenidate. Following a screening/washout period, subjects were randomised (1:1) to HLD200 or placebo for three weeks. After one week, the initial 40 mg dose was titrated in 20 mg weekly increments to 60 and 80 mg, as tolerated, with a one-step down-titration permitted. The primary endpoint was the ADHD rating scale (ADHD-RS-IV) total score following three weeks of treatment. The key secondary endpoints were the before school functioning questionnaire (BSFQ) and parent rating of evening and morning behavior-revised, morning (PREMB-R AM) and evening (PREMB-R PM) following three weeks of treatment. Safety measures included treatment-emergent adverse events (TEAEs), with a focus on sleep and appetite.

Results: Of 163 children enrolled across 22 sites, 161 were included in the intent-to-treat population. After three weeks, children on HLD200 versus placebo achieved a significant improvement in ADHD symptoms (least squares [LS] mean ADHD-RS-IV: 24.1 vs. 31.2; P = 0.002), and at-home early morning (LS mean BSFQ: 18.7 vs. 28.4; P < 0.001; LS mean PREMB-R AM: 2.1 vs. 3.6; P < 0.001) and late afternoon/evening (LS mean PREMB-R PM: 9.4 vs. 12.2; P = 0.002) functioning. No serious TEAEs were reported; 1 HLD200 and 4 placebo subjects had TEAEs leading to early withdrawal. Most common TEAEs (C10%) on HLD200 were decreased appetite and insomnia. Sleep-related TEAEs were mild or moderate in severity and transient (96.6% resolved).
Conclusions: Evening-dosed HLD200 was well-tolerated and demonstrated significant improvements in ADHD symptoms and both at-home early morning and late afternoon/evening functional impairments versus placebo in children with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S34-S35.

TENTATIVE EFFECTIVENESS OF MULTI-SYSTEMIC FAMILY INTERVENTION ON IRRITABILITY AND DISRUPTIVE BEHAVIOR IN CHILDREN WITH ADHD.

Vuori M.

Objectives: Irritability and disruptiveness are the key features of oppositional defiant disorder (ODD) and frequently co-occur in clinically referred children with ADHD. The aim of the present study was to examine the effectiveness of multi-systemic family intervention on affective and behavioural difficulties in children with ADHD.
Methods: The prospective observational study was conducted in Finland. The time-limited intervention programme is designed to link the home and school settings to address the needs of children with neurodevelopmental conditions. Of the 124 children involved in the study, 94 children (mean age = 9.4 years, 17% female) fulfilled diagnostic criteria for ADHD (28 children had co-occurring conduct disorder). Repeated measures were analysed using linear mixedmodel design.
Results: By parent reports, irritability (t = -3.59, p =.001) and disruptive behaviour (t = -2.34, p =.021) in children decreased after one year of treatment regardless of gender and age of the child, and cooccurring conduct disorder. Significant main effect of gender of the child (t = 2.05, p =.043) indicated that boys showed higher levels of overt disruptive behaviour before and after the treatment relative to girls. Parental depression was related to higher levels of irritability (t = 3.36, p =.001) and disruptiveness (t = 2.24, p =.026) in children after controlling for other variables. By teacher report, children did not show improvements in irritability (t = -1.41, p =.165) or disruptive behaviour (t = -0.68, p =.501) in school settings.
Conclusions: Cognitive-behavioural family-based treatments are associated with improvements in ODD symptoms in children with ADHD. Despite improvements, children with ADHD are at risk for continued affective and behavioural difficulties across settings, even when treated with intensive psychosocial interventions. In particular, there is need to focus on strategies aimed at strengthening children's self-regulation skills and social adjustment in school settings

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ADHD Atten Deficit Hyperact Disord. 2017;9:S42.

TREATMENT PATTERNS, RESOURCE UTILISATION, AND HEALTHCARE COSTS ASSOCIATED WITH THE USE OF ATYPICAL ANTIPSYCHOTICS OR GUANFACINE EXTENDED RELEASE IN STIMULANT-TREATED CHILDREN AND ADOLESCENTS WITH ADHD IN QUEBEC.

van SJ, Lachaine J, Ben AL, et al.

Objectives: To assess treatment patterns, healthcare resource utilization (HRU) and healthcare costs in stimulant-treated children and adolescents with ADHD in Quebec who augmented with, or switched to, an atypical antipsychotic (AAP) or guanfacine extended release (GXR).
Methods: This study used healthcare claims data from 1 January 2007 to 31 March 2016 from Quebec's provincial health plan (r+®gie de l'assurance maladie du Quebec [RAMQ]) database. Individuals aged 6-17

years with ADHD were included if they had received C1 stimulant prescription and subsequently filled their first AAP or GXR prescription (index medication), without a diagnosis for which AAPs are indicated.
Results: Overall, 1.327 individuals were included (AAP, 1098; GXR, 229). At baseline, the mean age was approximately 10 years (AAP, 10.7; GXR, 10.1) and most participants were males (AAP, 77.1%; GXR, 76.4%). Twelve-month rates for discontinuing, augmenting or switching were 54.3, 22.5 and 11.7%, respectively, for AAPs, and 55.5, 17.0 and 17.5%, respectively, for GXR. With both AAPs and GXR, mean per patient total healthcare costs were significantly higher in the six months after than the six months before initiating the index medication. The mean number of all medical services used and mean all medical costs were significantly higher in the six months after initiating AAPs than the six months before, driven mainly by more psychiatric department visits and higher incurred costs. After initiating GXR, however, the mean number of all medical services used and mean all medical costs were unchanged or tended to be lower.
Conclusions: In stimulant-treated children and adolescents with ADHD, augmenting with, or switching to AAPs or GXR was associated with similar rates of subsequent treatment changes and higher total healthcare costs for both AAPs and GXR; AAPs and GXR were not compared directly, however, all medical costs increased significantly for AAP-users but not for GXR-users

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ADHD Atten Deficit Hyperact Disord. 2017;9:S11-S12.

ARE WE CONFUSING IMMATURITY WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN?

Ulberstad F, Bostrom H.

Objectives: Since ADHD decision-making can be impacted by relative age, we examined if objective measures of typical ADHD symptoms also differ between children of different relative age.
Methods: Anonymized records from a database containing objective tests of typical ADHD symptoms (Qb test) in consented individuals (6-12 years) were analysed. The tests had been performed in conjunction with assessment of ADHD in Sweden (n = 6066) and the UK (n = 5905) from April 2011 to April 2015. The total number of tests performed for each month of birth were calculated. In Sweden, the oldest children in a class are born in January and the youngest in December, whilst in the UK the oldest children in a class are born in September and the youngest in August. Therefore, relative age was set to one for Swedish children born in January and for UK children born in September.
Results: More tests were performed in the relatively younger children indicating that these children more often are assessed for ADHD. A Chi square test of children with relative age of 1 versus 12 showed a statistical significant effect of 38.5% in Sweden and 36.5% in the UK ($p < 0.001$). When the objective gender and aged matched performance scores for hyperactivity, inattention and impulsivity were analysed per relative age, no statistically significant difference could be observed for any of the objective symptoms.
Conclusions: This study confirms that relatively younger children more often are assessed for ADHD than their older peers. However, there was no difference in objective age and gender matched symptoms of ADHD between these children. Therefore, it seems as if the reason behind why more relatively immature children are assessed for and sometimes receive a diagnosis of ADHD is biased by subjective decisions influenced by relative age

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ADHD Atten Deficit Hyperact Disord. 2017;9:S10-S11.

PARENTAL AGE AND ADHD.

Mikkelsen SH, Olsen J, Bech BH, et al.

Objectives: Previous studies have suggested that young mothers more often have children with ADHD. We used sibling comparisons to examine the nature of this association and to investigate if this association is explained by early environment or genetic and socioeconomic factors.
Methods: A large population-based cohort including all singletons born in Denmark from 1 January 1991 through 31 December 2005 was followed from birth until 30 April 2011. Data were available for 94% (n = 943,785) of the population. Offspring ADHD was identified by an ICD-10 diagnosis of hyperkinetic disorder (HKD). We used sibling-matched Cox regression to control for genetic and socioeconomic factors. As an

important methodological strength, we controlled for time trends including the increase in ADHD diagnosis during the study period.
Results: In the population cohort we found that children born by parents 20 years or younger had more than twice the risk of being diagnosed with ADHD compared to children with parents between 26 and 30 years of age. When comparing full siblings, the associations were attenuated, but we found a trend of increased risk of ADHD with decreasing maternal age, which was not seen for paternal age.
Conclusions: Sibling comparisons suggested that the associations between both maternal and paternal age and ADHD are partly explained by common genetic and socio-economic factors. The trend of increased risk of ADHD with decreasing maternal age, but not with paternal age, may be linked to pregnancy or early life environmental factors. Even though only a smaller part of the association can be attributed to environmental factors, there is a public health interest to support young parents through their first years of parenthood

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ADHD Atten Deficit Hyperact Disord. 2017;9:S6.
NEONATAL UMBILICAL ARTERY CORD BLOOD PH VALUE AND ADHD, BY APGAR SCORE AND GESTATIONAL AGE.
Mikkelsen SH, Olsen J, Bech BH, et al.
AIM: Although birth asphyxia is a major risk factor for neonatal and childhood morbidity and mortality, it has not been investigated much in relation to attention deficit hyperactivity disorder (ADHD). We examined whether birth asphyxia measured by the pH of the blood in the umbilical artery cord was associated with childhood ADHD.
METHOD: A population-based cohort of 295 687 children born in Finland between 1991 and 2002 was followed until December 31, 2007. ADHD was identified by the International Classification of Diseases, 10th edition, as a diagnosis of hyperkinetic disorder. We examined the risk of ADHD with varying pH values using Cox regression, taking time trends into consideration.
RESULTS: When compared to the reference group, a pH value below 7.10 was significantly associated with an increased risk of ADHD. The strongest risks were observed among children with a pH value <7.15 and a gestational age of <32 weeks. The pH value did not contribute much to the risk among children with an Apgar score of 0-3.
CONCLUSION: Birth asphyxia, defined by low pH value, may predict an increased risk of ADHD in childhood. The association between the pH value and ADHD was homogenous when stratified by gestational age and the Apgar score

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ADHD Atten Deficit Hyperact Disord. 2017;9:S26.
NEUROPSYCHOLOGICAL COMPUTERISED SCREENING OF BRAZILIAN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Popi M, Riechi TI, Hamdam H.
Objectives: This research performed an analysis of the neuropsychological performance of children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) and controls properly enrolled in the public and private schools at Curitiba, Brazil.
Methods: Aclinical group of 38 participants (20 males and 18 females) with a diagnosis of ADHD without comorbidities and a control group of 170 subjects (67 males and 103 females) with no history of neurological impairment underwent neuropsychological computerised screening for children (NCSC). The work environment was in the Neuropediatric Ambulatory at Clinical Hospital (CENEP-HC), Laboratory of Neuropsychology of the Federal University of Paran-Brazil (UFPR).
Results: The analysis of results identify statistical differences between both groups. The ADHD group had poor results in the total score of NCSC and in eight of the ten analysed subtests (organisation acoustic-motor, tactile-kinesthetic ability, visual skills, oral expressive language, writing, reading, mathematical reasoning and immediate memory). Moreover, the results obtained by the ADHD group in temporal analysis also revealed poor results. The ADHD group also required more time to perform the test. There were significant statistical differences of neuropsychological performance between Brazilian children and

adolescents with and without ADHD. The neuropsychological computerised screening for children (NCSC) discriminated children and adolescents suspected of ADHD.
Conclusions: The NCSC demonstrated sensitivity in identifying patients with ADHD based on their cognitive performances in the total scores and in most subtests and times measured by the system. The final and practical objective of an appropriate evaluation instrument is to improve the preserved aspects of their cognitive functions, help them achieve quality of life in their own contexts and minimise academic failure. It is important to highlight that this population with ADHD can become productive, considering their limitations and cognitive deficits

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ADHD Atten Deficit Hyperact Disord. 2017;9:S42-S43.
INCREASE IN PRESCRIPTION RATES OF ADHD MEDICATION FROM PHARMACY DATA WITHIN AN URBAN CHILD AND ADOLESCENT SPECIALIST CLINIC IN LONDON: THERE WAS A DECLINE IN THE USE OF NEWER PREPARATIONS.
Perera D, Moghraby O, Akhunbay-Fudge M.
Objectives: The literature shows an increasing trend in the prescription of psychotropic drugs used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents between 1987 and 2016, especially in the United States. Few studies have addressed prescription rates in ADHD of both stimulant and nonstimulant medication. This study aims to investigate the prescription rates and trends of both stimulants and non-stimulants use for ADHD within an urban specialist child and adolescent clinic in London, United Kingdom (Lewisham).
Methods: Prescription data from April 2015 to February 2016 was obtained from prescriptions issued at local pharmacies and expenditure attributed to Lewisham clinic for all medication. These were divided into stimulants (methylphenidate and dexamphetamine; extended- and immediate-release preparations) and non-stimulants (atomoxetine and clonidine). We also investigated individual medication trends. Individual drug unit costs were calculated to determine total numbers of units sold, with one drug unit assumed to be equivalent to a single prescribed dose per patient.
Results: A total of 12,634 units were prescribed during the study period for an estimated 330 patients. Preliminary data demonstrated an absolute increase in medication prescribed (938-1688 units prescribed of all medication, per month). There was a trend towards the prescription of stimulants (83%) over non-stimulants (which declined), especially methylphenidate (93% of total stimulants). There was a decline in the use of a newer formulation (lisdexamfetamine) over the year (57%). Individual patient specific data was not available.
Conclusions: There was a modest increase in prescribing rates. Rates of stimulant use was in line with widely reported evidence on efficacy. There was a greater tendency towards extended-release preparations but a decline in use of newer available formulations (lisdexamfetamine). Future studies are required to investigate trends in clinics locally and to obtain data on individual patient data. This will better inform future prescribing behaviour to improve quality of care

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ADHD Atten Deficit Hyperact Disord. 2017;9:S40.
THE COMPARISON OF METHYLPHENIDATE AND ATOMOXETINE ON COGNITIVE FUNCTIONS IN CHILDREN AND ADOLESCENTS WITH ADHD: A META-ANALYSIS.
Ren J, Li Y, Yue S, et al.
Objectives: The stimulant methylphenidate (MPH) and the nonstimulant atomoxetine (ATX) are the commonly prescribed medications for ADHD. However, the comparation of their impacts on cognitive functions is less clearly understood. Our aim is to conduct a meta-analysis comparing the effects of MPH and ATX on cognitive functions in children and adolescents with ADHD.
Methods: A comprehensive search of the literature was undertaken until Sept 30, 2016 using search engines Ovid, PsycINFO, ISI Web of Science and PubMed/MEDLINE. Search terms used were 'methylphenidate', OR 'stimulants', AND 'non-stimulants', OR 'atomoxetine' AND specific neuropsychological names. Randomized controlled trial (RCTs) comparing efficacy of MPH with ATX on reaction time, reaction time

variability, response inhibition and working memory in children and adolescents (5-18 years) with formal diagnosis were included. Data from included studies were extracted by two reviewer and entered into Revman 5. Using a random effects model and meta-analytic regression, we assessed for heterogeneity and publication bias and adjusted for intrastudy clustering. Effect sizes were calculated as standardized mean differences (SMDs).
Results: Eight randomized controlled studies with a total number of 364 participants were included in the analysis. For these 8 studies, 36 data points were obtained. Meta-analysis did not find a statistically difference in efficacy between MPH and ATX on the four aspects of cognitive functions: reaction time, SMD = -0.12 [95% CI, -0.27 to 0.04], P = 0.14; I2 = 0%; reaction time variability, SMD = -0.30 [95% CI, -0.68 to 0.07], P = 0.11; I2 = 0%; response inhibition, SMD = -0.03, [95% CI-0.20 to 0.14], P = 0.71; I2 = 0%; working memory, SMD = -0.08 [95% CI-0.19 to 0.04], P = 0.20; I2 = 0%.
Conclusions: These data suggest that MPH and ATX have comparable effects on various aspects of cognitive functions in treatment of ADHD in children and adolescents

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ADHD Atten Deficit Hyperact Disord. 2017;9:S9.
TREATMENT FOR ADHD AMONG ADOLESCENTS WITH ADHD IN THE UNITED STATES, 2014.
Danielson M, Visser S, Holbrook J, et al.
Objectives: To characterize lifetime and current rates of ADHD treatments among a nationally-drawn sample of U.S. adolescents with ADHD, including differences by demographic and clinical factors.
Methods: This study's data source is the 2014 national survey of the diagnosis and treatment of ADHD and Tourette syndrome (NSDATA), a follow-back parent survey to the 2011-2012 national survey of children's health. Children reported to have ever received an ADHD diagnosis in the 2011-2012 survey were eligible to participate in the ADHD module of NS-DATA. These analyses focus on ADHD treatment, categorized into four types: Medication, school services, psychosocial interventions, and alternative treatments. The results presented here are for adolescents aged 12-17 years with current ADHD (n = 1725).
Results: Medication and school services were the most common treatments received by adolescents with current ADHD, with 62 and 61% currently receiving each treatment, respectively. Social skills training was the most common psychosocial treatment ever received (34%), followed by parent training (29%), peer intervention (28%), and cognitive-behavioural therapy (17%). Among alternative treatments, 8% of adolescents with ADHD were currently taking dietary supplements, and 11% had ever received neurofeedback. Prevalence of current medication usage was similar across most demographic and clinical subgroups, but there were significant differences in the receipt of school services and psychosocial treatments by current ADHD severity, ADHD symptom presentation, and presence of co-occurring conditions. Of treatment types recommended by clinical guidelines (current medication, current school services, lifetime psychosocial intervention), 60% were receiving treatment from at least two of the three categories, while 8% had received none of the three.
Conclusions: This study provides rates of various types of treatment received by adolescents with current ADHD. Future analyses will examine differences between treatments recommended by clinical guidelines and current clinical management to identify potential gaps in the treatment of adolescents with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S3.
A GENOME-WIDE ASSOCIATION STUDY OF A COGNITIVE ENDOPHENOTYPE OF ADHD IN A COMMUNITYBASED PAEDIATRIC SAMPLE.
Burton C, Crosbie J, Erdman L, et al.
Objectives: The power of genome-wide association studies (GWAS) of Attention-Deficit/Hyperactivity Disorder (ADHD) is reduced by clinical/genetic heterogeneity and insufficient clinical sample sizes. Using a cognitive endophenotype for ADHD, such as response inhibition, could decrease heterogeneity and increase power. Novel methods such as the hypothesis-driven GWAS (GWAS-HD) could also help to identify possible biological pathways involved in response inhibition (e.g., central nervous system [CNS] development). The

GWAS-HD conducts genome-wide hypothesis testing while prioritising single nucleotide polymorphisms (SNPs) within genes involved in the hypothesised pathway. We conducted a GWASHD to test the role of SNPs involved in CNS development on response inhibition measured in a large community paediatric sample.
Methods: Salivary DNA and performance on a measure of response inhibition (stop signal reaction time [SSRT] from the stop signal task) were collected on 17,263 youths (6-17 years old) visiting a science museum. We genotyped 5366 unrelated Caucasians using Illumina HumanCoreExome beadchips, and analysed 4.970 samples at 5,162,437 imputed and genotyped SNPs. For the GWAS-HD, individual SNPs in the CNS development set were tested using stratified false discovery rate (SFDR) while the whole gene set was tested using permutation tests for association with SSRT.
Results: Ninety-four percent (94%) of the sample passed QC (n = 4687). Several SNPs approached genome-wide significance (p = 1.3 +ù 10-7). The set of CNS development SNPs were significantly associated with SSRT.
Conclusions: SNPs that alter CNS development may be involved in response inhibition, and potentially ADHD (yet to be tested). Measurement of cognitive endophenotype such as response inhibition in a large community sample is a feasible and potentially powerful alternative strategy for psychiatric genetics

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ADHD Atten Deficit Hyperact Disord. 2017;9:S45.
RATIO OF TOPIC INITIATION TO TOPIC MAINTENANCE IN CHILDREN WITH ADHD.
Al-Dakroury W.
Objectives: This study investigated verbal pragmatic skills in children with attention deficit hyperactivity disorder (ADHD). It examined quantitatively the topic related skills which is represented by ratio of topic initiation to topic maintenance in the children with ADHD compared to age-matched typically developing (TD) children. The authors decided to compare ratio of topic initiation to topic maintenance, rather than compare the amount of topic initiations and topic maintenance as separate phenomena to avoid the possible difference in the amount of verbal output between participants with ADHD and TD participants. The following research question was investigated, is the ratio of topic initiation to topic maintenance in children with ADHD higher than in typically developing children matched in age and gender?
Methods: The participants were twenty 4-5 year old boys. Ten were typically developing and ten had a diagnosis of ADHD. A 30 min sample of speech during free play was collected from each child in conversation with an examiner. All sessions were recorded on DVD using two video cameras. Transcription and coding systems were used to analyze the data. Comparisons were made between the TD children and the children with ADHD using quantitative techniques.
Results: The study results showed that children with ADHD have a significantly higher topic initiation to topic maintenance ratio compared to TD participants in the sessions with the examiner.
Conclusions: The differences were interpreted as evidence of the negative effect of the core behavioural characteristics of ADHD on verbal pragmatic skills and the presence of weak discourse skills in children with ADHD compared to TD age-matched children. The clinical implications are that very careful attention is needed in assessing children with ADHD to determine the nature and the extent of their language-use difficulties. Language-use difficulties exhibited by children with ADHD may be associated with a lack of social competence, which will be reflected in their conversational skills

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ADHD Atten Deficit Hyperact Disord. 2017;9:S34.
RESTRICTED ELIMINATION DIET IN CHILDREN WITH ADHD/ACUTE AND LONG-TERM EFFECTS.
Clement H-W, Blazynski N, Overdick L, et al.
Objectives: The meta-analysis of Sonuga-Barke et al. from 2013 includes all non-pharmacological interventions for ADHD along very critical, including the restricted elimination diet. Among them are works of the group of Buitelaar fromThe Netherlands that stand out with effect sizes 3-5. The aim of the present study is to evaluate whether under a standardised restricted elimination diet in children with ADHD, the symptoms

can be reduced and whether the establishment of the diet in Freiburg according to the Dutch model is possible.
Methods: Of 30 interested patient's families, 18 patients diagnosed with ADHD according to ICD ten participated in this study. Age range was between 7.3 and 13.6 years, five girls and 13 boys. The length of the restricted elimination diet was four weeks. Primary endpoint was the change in ADHD rating scale score between baseline and the end of the diet phase. Secondary endpoints were parents and teachers abbreviated Connors rating scale. Group differences were calculated with ANOVA and subsequent student t-test.
Results: The adherence to the diet was good, 16 of the 18 completed the diet phase. 10 of the 16 were responders with more then 40% improvement according to the ADHD rating scale. The total ADHD rating scale scores dropped to less then 50% from 31.56 ± 9.16 to 15.86 ± 8.04 (n = 16, MW ± SD). Significance was $p < 0.001$, for inattention $p < 0.001$, for hyperactive/impulsivity $p < 0.01$, respectively. Parents Conners abbreviated rating scale data confirmed these findings. At one year follow-up about 50% of the responders still followed the dietary recommendations with persistent improvements.
Conclusions: Taken together these data indicate that the restricted elimination diet followed by the reintroduction phase is a valid treatment option for children with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S33.

GOOD NIGHT PROJECT: BEHAVIOURAL SLEEP INTERVENTIONS FOR CHILDREN WITH ADHD: A RANDOMISED CONTROLLED TRIAL.

Alammar H, Kellar I, Nash H, et al.

Objectives: To examine the efficacy of behavioural interventions in helping 60 primary caregivers from different cities in Saudi Arabia to manage sleep difficulties in school-aged children with ADHD.
Methods: The present study is a randomised controlled trial (RCT). Primary caregivers will be randomly divided into one of two groups (intervention or control 'usual care'). Those in the intervention group will receive training by psychologists in three sessions over 3 weeks, while those in the control group, 'usual care', will attend their usual appointments and no intervention will be used. Assessments will be completed at three time points, baseline, post intervention and at a follow-up of two months, using subjective and objective measures.
Results: Baseline and post intervention assessments will be available in March 2017.
Conclusions: Management of sleep difficulties could improve sleep and daily functions for these children and their families

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ADHD Atten Deficit Hyperact Disord. 2017;9:S29.

ALTERED RESTING PERFUSION AND FUNCTIONAL CONNECTIVITY OF DEFAULT MODE NETWORK IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Cao Q, Wang P, Zou Q, et al.

Objectives: The aim of this study is to explore the association between functional connectivity (FC) and local metabolic activity, measured by cerebral blood flow (CBF), in default mode network (DMN) in children with Attention-Deficit/Hyperactivity Disorder (ADHD) simultaneously using resting-state functional magnetic resonance imaging (fMRI) and arterial spin labelling (ASL) MRI techniques.
Methods: Resting-state fMRI and ASL MRI were carried out in 49 children with ADHD (M/F = 33/16, 9.09 ± 1.69 years) and 37 controls (M/F = 21/16, 9.66 ± 1.78 years). Independent component analysis (ICA) was implemented in resting-state fMRI to extract DMN (including anterior DMN and posterior DMN), and then a mask of DMN was generated from results of the one-sample t-tests of all the sample ($P_{FWE} < 0.001$). Then, the voxel value of FC and CBF were calculate in the DMN mask for individuals and two sample t test was used to compare the FC and CBF differences in DMN between ADHD and control groups, using gender, IQ, age and handedness as covariance.

Results: Compared with controls, children with ADHD showed decreased FC in left posterior cingulate cortex (x-6, y-39, z 24; peak T 3.396, voxel with P < 0.05, cluster size>84, P < 0.05 corrected by AlphaSim) and increased CBF in almost the same location (x-3, y - 27, z 42; peak T 3.412, voxel with P < 0.05, cluster size >569, P < 0.05 corrected by AlphaSim) in DMN. There were no other brain regions showed either FC or CBF differences between two groups.
Conclusions: The children with ADHD not only showed abnormal FC but also had aberrant CBF in DMN in resting-state. The jointly assess resting CBF and FC may highlight new avenues for identifying imaging markers for ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S15.

FIRST VALIDATION OF THE QBMINI TO MEASURE SYMPTOMS OF ADHD IN 5-YEAR OLD CHILDREN.

Günther T, Labarga SVNZ, Hoberg K.

Objectives: The diagnosis of ADHD in preschool age is difficult and only a few methods for this age group are available. However, an early detection of the disorder is important to minimise negative consequences of the disease in the future. The aim of this ongoing study is the validation of the „QbMini“.
Methods: The "QbMini" is an age appropriate adaptation of the "Qb test" (for details see www.qbtech.com). This computer-based test measures the attention and impulsivity by a continuous performance test and the hyperactivity by recording the movements with an infrared camera. Until now, the QbMini and ADHD behavioural scales were conducted with 56 healthy 5-year-old children, 16 children with ADHD and 28 children with other developmental disorders.
Results: Comparing the QbMini and the behaviour questionnaires, significant correlations (r> .439) were found between the parameters and scales which measure the same construct (hyperactivity and inattention). Even more interesting, the behavioural inattention ratings were strongly correlated with the hyperactivity scores of the QbMini (r= .482). This suggest that the inattention scores of the behavioural rating scales are influenced by the hyperactive behaviour of the children. In the classification analyses, the QbMini could differentiate between healthy (n=56) and diseased children (n=54) for the symptoms of hyperactivity (area under ROC curve .849; good) and inattention (.772; fair). The area under the ROC curve for impulsivity was only .684 (poor). In contrast, the QbMini could not distinguish between children with ADHD and children with other developmental disorders (all areas < .592).
Conclusions: The first results of this study suggest that the QbMini is a valid instrument to measure symptoms of hyperactivity and inattention at preschool age. However, for a valid diagnosis of ADHD at this age group more additional clinical information is necessary

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ADHD Atten Deficit Hyperact Disord. 2017;9:S40.

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE NOVEL THERAPEUTIC AEVI-001 IN ADOLESCENTS WITH ADHD AND GLUTAMATERGIC NETWORK GENE MUTATIONS.

Finding RL, Fitts D, Squires L.

Objectives: Loss-of-function mutations (copy number variations, CNVs) in metabotropic glutamate receptors (GRMs) and related genes have been identified in Γêù20% of children/adolescents with ADHD, representing a population in which glutamatergic dysfunction may play a key role in ADHD pathogenesis. Children/adolescents with mutation-positive ADHD (GRM + ADHD) may be candidates for glutamate-modulating therapy. We will report results of a Phase 2 study evaluating the efficacy and tolerability of the glutamate modulator AEVI-001 in adolescents with moderate severity GRM + ADHD.
Methods: Phase 2 randomized, double-blind, placebo-controlled, parallel-group study of 6-week duration in subjects 12-17 yrs of age with moderate severity ADHD (baseline ADHD-RS-5 score: >28 without conventional ADHD therapy) and GRM biomarker-positive genotype (GRM + ADHD). All ADHD medications were discontinued with appropriate washout period before randomization. 4-wk dose optimization period: 100-mg b.i.d. starting dose increased at weekly intervals based on clinical response to maximal dose of 400 mg b.i.d. Optimized dose (100 mg, 200 mg, or 400 mg b.i.d.) was maintained 2 wks.

Results: 101 subjects were randomized 1:1 to placebo or study drug. Baseline characteristics: male, 63%; median age, 14 yrs; median age at ADHD diagnosis, 6 years; median yrs since ADHD diagnosis, 7 years; ADHD presentation: inattentive, 29%; hyperactive/impulsive, 2%; combined, 69%. Median Baseline CGI-S score, 4. Mean Baseline ADHD-RS-5 score, 38 (range 12-54). Efficacy and tolerability/safety results to be presented, including primary endpoint (ADHD-RS-5 total score change from Baseline to end of treatment as LOCF analysis) and secondary endpoint (number and percent of subjects Improved vs. Not Improved). Analyses will also include % patients meeting responder criteria defined as >30% change from Baseline ADHD-RS-5 or CGI-I score of 1 or 2.
Conclusions: Subject characteristics were consistent with expectations. Efficacy and safety/tolerability results will be presented. Study sponsored by Aevi Genomics Medicine

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ADHD Atten Deficit Hyperact Disord. 2017;9.

6TH WORLD CONGRESS ON ADHD: FROM CHILD TO ADULT DISORDER.

The proceedings contain 155 papers. The topics discussed include: evidence of concurrent and prospective associations between early maltreatment and adhd through adolescence; DLGAP1 gene is associated with cognitive flexibility in children with attention-deficit/hyperactivity disorder; a meta-analysis on association between lead exposure and ADHD and its symptom domains in children; neonatal umbilical artery cord blood pH value and ADHD, by Apgar score and gestational age; interaction effect between rs3785143 of NET1 and rs1611115 of DBH on the aberrant resting-state functional connectivity in the prefrontal-amygdala circuit in boys with ADHD; the effect of ITGA1 on brain white matter and cognitive phenotype in attention-deficit/hyperactivity disorder; glutamatergic network gene mutations in children and adolescents with attention-deficit/hyperactivity disorder (ADHD); discordance between parent-reported child behaviour and ADHD diagnosis; parental body mass index and behavioural problems in offspring: a Danish national birth cohort study; the prevalence, distribution and comorbidity of ADHD in children and adolescents aged 6-16 in Hunan Province, China; can we resolve varying ADHD prevalence estimates in the U.S.? a closer look at NSCH 2007 and 2008 and 2011-2012; and structure of the French version of the adult ADHD symptoms rating scale and validation against the DIVA interview

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ADHD Atten Deficit Hyperact Disord. 2017;9:S27-S28.

BEHAVIOURAL SENSITIVITY TO CHANGING REWARD FREQUENCY AMONG BRAZILIAN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Furukawa E, Alsop B, Casella E, et al.

Objectives: Altered reinforcement sensitivity has been hypothesised to underlie the symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD). Here we evaluate the ability of children with and without ADHD to adapt their behaviour when reward availability changes.
Methods: Forty typically developing (TD) children and 32 diagnosed with ADHD completed a signal-detection task in which correct discriminations between two stimuli were associated with different frequencies of reinforcement. The response alternative associated with the higher rate of reinforcement switched without warning after children received 30 rewards. Children's preference for the more frequently reinforced alternative (bias) was calculated for each block of ten reinforcements, compared separately for the initial and reversed reward distribution.
Results: The ADHD and TD groups developed a bias towards the more frequently reinforced response alternative over the initial three blocks, albeit smaller for the ADHD group ($F(1, 70) = 4.62$, $p < .05$). When the reward distribution reversed, the children's response allocation followed suit with both groups; bias scores approaching zero during the first reversal block. The TD group bias remained stable for the remainder of the reversal phase. Conversely, the ADHD group developed a significant bias towards the now more frequently reinforced alternative (group x Block, $F(1.86, 125.03) = 3.23$, $p < .05$).
Conclusions: Both groups of children demonstrated behavioural sensitivity to the asymmetric reward distribution, developing a preference towards a more frequently reinforced alternative and shifting their

behaviour when the reinforcement ratio reversed. The bias of children with ADHD increased with time-on-task following the reversal, remaining stable for those without ADHD. We hypothesise the response allocation of children with ADHD is influenced more by recent response contingencies rather than by their history of reward on the task. Differences in the temporal influence of reinforcement contingencies should be considered in the management of ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S52.

PERSISTENCE AND PREVALENCE OF ADHD IN ELEMENTARY SCHOOL CHILDREN.

Gökçe S, Yazgan Y, Ayaz B, et al.

Objectives: The American Psychiatric Association reported that the estimated prevalence of ADHD is 5% in school age children. However, many studies indicate that the prevalence rate among schoolaged children ranges between 1 and 20%. In this study, we aimed to estimate the prevalence and persistence rate of Attention-Deficit/Hyperactivity Disorder (ADHD) in third and forth grades of elementary school in a representative school sample of children in Istanbul, Turkey, whose ADHD symptom data were reported from their teachers in previous grades.

Methods: In this study we used a sample from our previous communitybased study from Istanbul in which we investigated the association ADHD symptoms in 4.356 first and second grades with their school entry age. In that study 342 children estimated to have possible ADHD. Two years after that study we were able to reach 154 children and performed K-SADS.

Results: 40.9% of (n: 63) the 154 children were diagnosed with ADHD. 79.3% of the children who were diagnosed with ADHD were from the sample who were estimated to have possible ADHD in previous study. 20% of the children who were diagnosed with ADHD were from the control group who had not possible ADHD in the previous study. 61.7% of the children who were determined to have possible ADHD in the previous study were diagnosed with ADHD. 17.8% of the children who were determined not to have possible ADHD, were diagnosed with ADHD.

Conclusions: According to our results we can suggest that teacher reported positive ADHD symptoms in earlier classes might predict ADHD diagnosis sooner, but also that ADHD symptoms in earlier ages might remit with growing age

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ADHD Atten Deficit Hyperact Disord. 2017;9:S37.

EFFECT OF METHYLPHENIDATE ON ATTENTIONAL FLUCTUATIONS AND SLOWNESS IN ADHD CHILDREN WITH AND WITHOUT EPILEPSY.

Berquin P, Querne L, Bourel-Ponchel E, et al.

Objectives: Methylphenidate is an effective treatment for children with epilepsy with ADHD criteria (EPIL + ADHD). Methylphenidate also improves performance during cognitive tasks. However, effects on sensorimotor versus attentional processes have been poorly investigated in these children. In ADHD,methylphenidate improved very slow response times (RT) which are linked to attentional fluctuations, rather than sensorimotor speed, as showed by RT-distribution analyses. The aim of the study was to compare the effect of methylphenidate on attentional fluctuations and sensorimotor processes in ADHD children and in children with epilepsy and ADHD.

Methods: The study included 117 children equally divided in three groups (EPIL + ADHD; ADHD; Control) strictly appeared for age, sex and WISC-IV (diagnostic for EPIL + ADHD and ADHD referred to DSM-IV criteria assessed by a multidisciplinary evaluation). Children realised a visuomotor task with and without methylphenidate for EPIL + ADHD and ADHD groups. Parameters analysed were the errors, mu and tau:Mu estimating the sensorimotor speed and tau the skewness of very slow responses by ex-gaussian modelling of RT-distribution.

Results: Statistical analyses after Holm-Sidak correction ($k = 10$, p and $+¦ < 0.05$) showed that methylphenidate improved errors ($p < 0.0001$) and tau ($p < 0.0001$) and had a marginal effect on mu in EPIL + ADHD and ADHD groups. Independently of methylphenidate, mu was higher in the EPIL + ADHD group

than in the control group (p < 0.001) (no difference was found for ADHD versus control groups). Methylphenidate normalised errors and tau in the ADHD group, but only errors in the EPIL + ADHD group (EPIL + ADHD and control groups differences for tau: p < 0.005).
Conclusions: The effects of methylphenidate were quite similar in EPIL + ADHD and ADHD groups: Methylphenidate strongly reduced errors and attentional fluctuations in both groups but the effect on sensorimotor processes was mild. The slowness during the task was not improved with methylphenidate in the EPIL + ADHD group. Methylphenidate improves attention but not sensorimotor processes in epileptic children with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S13-S14.

NORMATIVE SURVEY DATA FOR THE PARENT RATING OF EVENING AND MORNING BEHAVIOUR SCALE, REVISED (PREMB-R) IN YOUTHS WITH AND WITHOUT A HISTORY OF ADHD.

Faraone S, Wilens T, Nullmeier R, et al.

Objectives: The validated parent rating of evening and morning behavior scale, revised assesses at-home early morning (PREMB-R AM) and late afternoon/evening (PREMB-R PM) functioning in children with Attention-Deficit/Hyperactivity Disorder (ADHD). The objectives were to: (1) obtain normative data for the PREMB-R AM and PM, and (2) determine whether parent ratings differentiate youths without and with a history of ADHD, and are affected by age, gender, or comorbidities.
Methods: A normative survey was conducted with 1,200 respondents derived from a representative U.S. sample of primary caregivers of youths (6-17 years; n=50 per age/gender category) using an online questionnaire. Caregivers were enrolled if their children/adolescent never had ADHD, had a past history of ADHD, or currently had untreated ADHD. Caregivers rated their child´s at-home functional impairments on the 3-item PREMB-R AM and 8-item PREMB-R PM, with each item rated on a 4-point scale (0=none; 3=a lot). Differences in total and individual item scores were determined by an ANOVA with post-hoc comparisons and Chi-squared test, respectively.
Results: Of the 700 children (6-12 years) and 500 adolescents (13-17 years) rated by a caregiver (mothers/step-mothers: 68.9%), 1,079 had no history of ADHD, 40 had a history of ADHD, and 81 had current untreated ADHD. PREMB-R AM/PM scores were significantly higher for children versus adolescents (P=0.042/P<0.001), and those with ≥1 comorbidity versus no comorbidities (both P<0.001); however, there were no gender differences. There were significant differences in the total score distributions between youths without ADHD, with a history of ADHD, and with current untreated ADHD in PREMB-R AM (mean±SD: 2.27±2.13, 4.07±2.69, and 4.19±2.39; P<0.001) and PREMB-R PM (mean±SD: 5.05±4.80, 10.27±6.70, and 12.53±5.77; P<0.001), and across all individual items (P<0.001).
Conclusions: PREMB-R AM and PREMB-R PM discriminate between youths without and with a history of ADHD. Age and comorbidities, but not gender, had significant effects

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ADHD Atten Deficit Hyperact Disord. 2017;9:S14.

PARENT RATINGS ON THE BEFORE SCHOOL FUNCTIONING QUESTIONNAIRE (BSFQ) IN YOUTHS WITH AND WITHOUT A HISTORY OF ADHD: RESULTS FROM A NORMATIVE SURVEY.

Faraone S, Wilens T, Nullmeier R, et al.

Objectives: The validated before school functioning questionnaire (BSFQ) assesses dysfunction in early morning, before school activities associated with Attention-Deficit/Hyperactivity Disorder (ADHD) in children/adolescents. The objectives were to: (1) obtain normative data, and (2) determine whether parent BSFQ ratings differentiate youth without and with a history of ADHD, and are affected by age, gender, or comorbidities.
Methods: A normative survey was conducted with 1200 respondents derived from a representative U.S. sample of primary caregivers of children/adolescents (6-17 years; n = 50 per age/gender category) using an online questionnaire. Caregivers were enrolled if their child: (1) never had ADHD, (2) had a past history of ADHD; or (3) currently had untreated ADHD (no treatment during past 3 months). Using a severity scale of

0-3 (0 = none; 3 = severe), caregivers rated their child's at-home early morning functional impairments on the 20-item BSFQ (maximum score = 60). Differences in total and individual item scores were determined by an ANOVA with post hoc comparisons and Chi squared test, respectively.
Results: Of the 1200 youths (children [6-12 years]: n = 700; adolescents [13-17 years]: n = 500) rated by a caregiver (mothers/stepmothers: 68.9%), 1.079 had no history of ADHD, 40 had a history of ADHD, and 81 had current untreated ADHD. There were no differences in the total score distributions between males and females (P = 0.554); however, scores were 23.7% higher for children versus adolescents, and 54.4% higher for youths with C1 comorbidity versus no comorbidities (both P < 0.001). There were significant differences in the total score distributions between youth without ADHD, those with a history of ADHD, and those with current untreated ADHD (mean ± SD: 12.70 ± 11.00 vs. 21.17 ± 14.58 vs. 29.60 ± 13.15, respectively; P < 0.001), and also across all 20 items (P < 0.001).
Conclusions: Normative data suggest that the BSFQ discriminates between youths without and with a history of ADHD. Age and comorbidities, but not gender, had significant effects

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ADHD Atten Deficit Hyperact Disord. 2017;9:S11.

ADHD PREVALENCE ACCORDING TO SCHOOLS OF A BRAZILIAN COUNTRY TOWN.

Darim NP, Da Silva FP.

Objectives: ADHD students need special care throughout their educational development, and it is essential that school professionals are aware of the diagnosis. However, in Brazil this knowledge is held mostly by health professionals. To find out the knowledge of schools regarding the student's diagnosis and treatment, a research was carried out in a Brazilian country town.
Methods: All the schools were invited to participate, the schools that agreed were visited and answered a questionnaire. From the 252 schools invited, 72% (181) agreed to participate, so this research reached 62,899 students.
Results: The prevalence of students with ADHD was 1.32% (833 students) and the ones medicated with methylphenidate were 1.2% (762); 25% of the medicated students didn't have a diagnosis known by the schools. Out of the 833 ADHD students, 77% were boys and the student's ages varied from 2 to 25 years. Among the medicated, 89 were less than 6 years old, and this goes against the indications of the leaflet of Ritalin (the medicine taken by the majority of those students) as its efficiency and safety at that age is not yet known.
Conclusions: As demonstrated, at this specific city, the prevalence level known by the schools is lower than the average; almost all the schools related difficulties to connect with the parents, so they think that there are more students medicated and diagnosed and that the parents do not inform; that can seriously harm the educational process of the student. This kind of research has never been conducted and is extremely necessary in Brazil, so that it is possible to help the ADHD students by diagnosing and treating, but also by conveying reality outside the doctors' offices

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ADHD Atten Deficit Hyperact Disord. 2017;9:S41.

COGNITIVE FUNCTION IN CHILDREN AND ADOLESCENTS WITH ADHD RECEIVING LISDEXAMFETAMINE DIMESYLATE IN A 2-YEAR SAFETY STUDY.

Coghill D, Banaschewski T, Bliss C, et al.

Objectives: To measure cognitive function in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) who received lisdexamfetamine dimesylate (LDX) for 2 years in study SPD489-404. Cognitive function was assessed using the Cambridge neuropsychological test automated battery (CANTAB).
Methods: Participants aged 6-17 years received dose-optimised, open-label LDX (30, 50 or 70 mg/day) for 104 weeks (dose optimisation 4 weeks; dose maintenance, 100 weeks). Cognition was assessed in the safety population using four selected tests from the CANTAB (delayed matching to sample (DMS), spatial

working memory (SWM), stop signal task (SST) and reaction time (RTI). A group-wise change of>5% from baseline was considered potentially clinically significant.
Results: Of 314 enrolled participants, 314 (100%) received LDX and were included in the safety population, and 191 (60.8%) completed the study. Potentially clinically significant improvements from baseline to last on-treatment assessment (LOTA) were observed for DMS Median reaction time (mean percent change, -6.5), SWM total between errors (-32.6) and SST reaction time (-25.7). Changes from baseline to LOTA did not reach potential clinical significance for DMS percent correct (mean percent change, -1.3), RTI simple median reaction time (-2.6) or RTI 5-choice median reaction time (-3.1).
Conclusions: LDX treatment over two years was not associated with deterioration in cognitive function in children and adolescents with ADHD. Although some improvements in cognition were observed, the lack of a control group makes these data difficult to interpret and additional studies are required

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ADHD Atten Deficit Hyperact Disord. 2017;9:S41.

GROWTH AND SEXUAL MATURATION IN A TWO-YEAR, OPEN-LABEL CLINICAL STUDY OF LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AND ADOLESCENTS WITH ADHD.

Coghill D, Otero IH, Johnson M, et al.

Objectives: Individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) may require long-term medication. Here we evaluate the impact of treatment with lisdexamfetamine dimesylate (LDX) on growth and sexual maturation in a 2-year trial in children and adolescents with ADHD (SPD489-404).
Methods: Participants aged 6-17 years received dose-optimised, open-label LDX (30, 50 and 70 mg/day) for 104 weeks (dose optimisation, 4 weeks; dose maintenance, 100 weeks). Weight, height and body mass index (BMI) z-scores were derived using the Conners for disease control and prevention (CDC) norms. Sexual maturation was assessed using the Tanner scale (participant rated as closest to their stage of development based on standardised drawings).
Results: Of 314 enrolled participants, 191 (60.8%) completed the study. Mean z-scores at baseline and last on-treatment assessment (LOTA) were 0.53 (standard deviation [SD], 0.963) and 0.02 (1.032) for weight, 0.61 (1.124) and 0.37 (1.131) for height, and 0.32 (0.935) and -0.27 (1.052) for BMI. In general, z-scores for weight, height and BMI shifted lower over the first 36 weeks and then stabilised. At both baseline and LOTA respectively, the majority of participants had z-scores within one SD of the CDC mean for weight (62.7 and 67.1%), height (53.8 and 59.8%) and BMI (61.5 and 60.4%). For weight and BMI, but not height, the proportion of participants below one SD of the CDC mean increased from baseline to LOTA. At LOTA, most participants remained at their baseline Tanner stage or shifted higher, based on development of hair (males, 95.5%; females, 92.1%) or genitalia/breasts (males, 94.7%; females, 98.4%).
Conclusions: Consistent with previous studies of stimulants used to treat ADHD, z-scores for weight, height and BMI decreased, mostly in the first year, then stabilised. No clinically concerning trends of LDX treatment on sexual maturation or the onset of puberty were observed

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ADHD Atten Deficit Hyperact Disord. 2017;9:S33-S34.

NIRS-BASED NEUROFEEDBACK TRAINING IN VIRTUAL REALITY/EFFECTS ON BEHAVIOUR AND QUALITY OF LIFE IN CHILDREN WITH ADHD.

Blume F, Hudak J, Dresler T, et al.

Objectives: We investigate effects of a near-infrared spectroscopy (NIRS)-based neurofeedback training (NFT) and an electromyogram (EMG)-based biofeedback training (BFT) in a virtual reality (VR) compared to a 2D classroom environment in children with ADHD. We hypothesise to observe improvements in ADHD behaviour and health-related quality of life (QoL) in all three groups, with superior effects in both NFTs compared to BFT and in ecologically valid VR compared to the less valid 2D environment.
Methods: Eighteen children with ADHD were randomly assigned to either NFT in VR (n = 7), NFT in 2D (n = 5), or BFT in VR (n = 6). Neurofeedback trainings teach self-regulation at the level of oxygenation in the dlPFC, whereas BFT teaches self-regulation of tension of both musculi supraspinatus. Each participant

received 15 training sessions and participated in comprehensive pre- and a post tests including assessment of ADHD symptoms via parent and teacher ratings (Conners-3) and of QoL (Kid-KINDLR self-report questionnaire). Changes in cortical oxygenation were assessed using NIRS during a go/no-go task.
Results: As data collection is still ongoing, we only provide preliminary results from the NFT conditions here. For NFT in VR, parents report improvement of inattention and hyperactivity-impulsivity. Teachers report improvement of hyperactivity-impulsivity only. For NFT in 2D, parents report improvement of hyperactivityimpulsivity whereas teachers report increasing inattention and hyperactivity-impulsivity. Children in the VR condition report an increase in self-esteem and wellness at school. Children from the 2D condition report an increase in wellness at school only.
Conclusions: First results suggest that NFT in VR is more effective than in 2D. However, more participants need to be included and data from the BFT condition and a follow-up test must be analysed in order to allow for valid conclusions. Further examinations will need to clarify the moderating roles of expectancies and parental commitment to treatment

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ADHD Atten Deficit Hyperact Disord. 2017;9:S16.

STANDARDIZED CROSS-CULTURAL ASSESSMENT OF ABILITY AND DISABILITY IN ADHD: THE NEW WHO ICFCY CORE SETS.

Bölte S, Mahdi S, Selb M.

Objectives: To report the results of the ICF core set consensus conference for ADHD. Preparatory studies had yielded 132 ICF candidate categories for ADHD. This evidence was used as a starting point to generate a comprehensive, a common brief, and three agespecific WHO ICF ADHD core sets.
Methods: Twenty ADHD experts, representing all six WHO-regions and various disciplines, were invited to participate in the 3-day consensus conference held in Stockholm in November 2016. The experts followed a three-stage decision-making and consensus process to decide on the ICF categories that should be included in the ICF core sets for ADHD. In the first stage, the experts prioritized and selected ICF categories to be included in the comprehensive ICF core set. The second stage consisted of defining the common brief core set for ADHD. The third stage involved developing age-specific brief core sets for ADHD: ages 0-5 years, 6-16 and 16+ years.
Results: Finally, 72 s level categories were included in the comprehensive ICF Core Set with 35 categories from the activities and participation component, 29 environmental factors, and 8 body functions. The common brief ICF core set included 38 categories; 14 activities and participation categories, 17 environmental factors and 7 body functions. The brief ICF core set for the ages 0-5 consisted of 47 categories, while the 6-16 age group had 55 categories and the adult group 52 categories. Detailed category-wise results will be made available at http://www.icf-core-sets.org/.
Conclusions: When defining the ICF core sets for ADHD, a large number of categories were selected across all of the ICF components (except body structures) supporting the notion that ADHD impacts wide ranges of functions and participation, and is associated with many contextual factors. From these core sets, assessment tools will be derived for future usage in clinical, research, educational setting as well as health care administration

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ADHD Atten Deficit Hyperact Disord. 2017;9:S36.

THE EFFECT OF COGNITIVE COMPUTER TRAINING ON COGNITION AND SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): RESULTS FROM A RANDOMIZED, CONTROLLED TRIAL.

Bikic A, Leckman JF, Christensen T+, et al.

Objectives: To date very few trials have examined the effect of cognitive training targeting multiple cognitive functions. Our multicenter randomized clinical superiority single blind trial investigated the effect of a computer-training program targeting multiple cognitive skills, mainly executive functions, on cognition, symptoms and functional outcome.

Methods: 70 children with ADHD, aged 6-13, were randomized to intervention or control group. The intervention group used ACTIVATEΓäó for 40 min a day, six times a week for eight weeks and both groups received treatment as usual (TAU) and were assessed in regard to cognitive functions and symptoms after 8 weeks of intervention and in a 12- and 24-week follow-up.
Results: There were no significant differences in the primary outcome, sustained attention or the secondary outcomes ADHD-RS and BRIEF. The intervention group showed a significant and sustained difference in an objective planning ability test (p = 0.006), that was sustained at the 12-(p = 0.035) and 24-week follow up (p = 0.017). An exploratory analysis showed that children with ADHD-Inattentive subtype presented significant improvements in planning ability, working memory, impulse inhibition and also on the parent-rated BRIEF metacognition index, while children with ADHD-combined subtype only showed planning ability improvements.
Conclusions: Training multiple cognitive functions does not significantly improve sustained attention or ADHD symptoms, but it might durably improve the ability to plan and the intervention might be most effective for the ADHD-Inattentive subtype. Before dismissing cognitive training as a possible treatment option, it would be important to test more complex cognitive interventions that allow individually tailored training. Considering that ADHD is a very heterogenic disorder at the individual level, future studies with larger samples should also investigate effects of broader cognitive interventions at subgroup levels

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ADHD Atten Deficit Hyperact Disord. 2017;9:S23-S24.

EVOKED ERP P300 AND THETA/BETA RATIO ANALYSIS BETWEEN PREDOMINANTLY INATTENTIVE AND COMBINED ADHD.

Delgado FM, Rodriguez PR, Sanchez PO, et al.

Objectives: Diagnosis of ADHD is based in clinical criteria but there is strong research over the identification of neurophysiological correlates that may help better defining presentations and endophenotypes of the disorder, specially referred to the analysis of evoked components. It has been shown that combined and inattentive subtypes could show some differences in EEG and the topography and development of cognitive evoked component P300. Nevertheless, there's still controversy about the existence of core differences in latency and amplitude between ADHD subtypes. Furthermore, from the Q-EEG and brain mapping, the American Food and Drug Administration (FDA) stated the ADHD classification by the theta/-beta ratio analysed from the spectral power, showing significant high correlation when clinical correspondence was found.
Objectives: To explore differences in theta/beta quotient, and in latency and amplitude of visual ERP P300, between children diagnosed as ADHD combined and inattentive presentation.
Methods: 55 patients diagnosed of ADHD aged 5-18 years (combined group = 28 and inattentive group = 27). Component P300 was registered and analysed in Cz by a visual oddball task, setting latency msecs and amplitude in ++V. Theta/beta ratio was calculated from EEG spectral absolute power.
Results: We neither found statistical meaningful differences between ADHD-C and ADHD-I groups in P300 latency, nor a P300 amplitude. The theta/beta ratio showed no difference between groups
Conclusions: Our results do not allow conclusion about a different profile of visual ERP P300 between ADHD combined and inattentive presentations. Findings over the theta/beta ratio suggest this quotient could not be able to discriminate between these clinical presentations, suggesting that an underlying neurophysiological common base could exist. Further evaluation is needed, with higher sample size and other clinical features

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ADHD Atten Deficit Hyperact Disord. 2017;9:S4.

DLGAP1 GENE IS ASSOCIATED WITH COGNITIVE FLEXIBILITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Fan Z, Qian Y, Wang Y, et al.

Objectives: Seven hundred eighty-eight (788) ADHD children and 136 healthy controls were enrolled. The difference of shifting time by trail making to explore the association of DLGAP1 gene with cognitive flexibility in Attention-Deficit/Hyperactivity Disorder (ADHD) children.

Methods: Seven hundred eighty-eight (788) ADHD children and 136 healthy controls were enrolled. The difference of shifting time by trail making test between ADHD and controls was analysed using the analysis of covariance (ANCOVA), with IQ, sex, age as covariates. Both the associations of SNPs with cognitive flexibility and three symptom traits of ADHD were conducted using an additive linear regression model by PLINK with the same covariates as ANCOVA.

Results: Compared with controls, children with ADHD showed longer shifting times in the trail making test, suggesting poorer cognitive flexibility function (P = 0.011). Twenty-four SNPs have been found to be associated with TMT in ADHD cases. Among them, two SNPs (rs2049161, P value = 5.08e-7, adjusted P value = 1.63e-4, rs16946051, P value = 5.18e-7, adjusted P value = 1.66e-4) survived multiple tests and were validated in another cognitive flexibility related trait. Eight SNPs showed nominal significance to associate with ADHD-related symptoms. Validation in other psychiatric disorders, regulatory function of the SNPs, and DLGAP1 related interaction network were presented to support the association of DLGAP1 with cognitive flexibility in ADHD.

Conclusions: Children with ADHD showed cognitive flexibility deficit in comparison with control groups. DLGAP1 gene is involved in the variation of cognitive flexibility in ADHD children. The relation between gene DLGAP1 and ADHD is worth further exploration

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ADHD Atten Deficit Hyperact Disord. 2017;9:S49.

A SURVEY OF PARENTS OF TEENAGERS WITH ADHD TO ASSESS THEIR BASELINE KNOWLEDGE, HOW DIFFERENT ADHD MEDICATIONS WORK AND TO ENHANCE THEIR UNDERSTANDING THROUGH AN ILLUSTRATED LEAFLET USING THE ANALOGY OF POSTMEN.

Yemula C, Chaudhry S, Khan A, et al.

Objectives: Parents often lack a full understanding of their child's ADHD and how medications work. We sought to: 1. Ascertain their baseline knowledge of ADHD and how medications work 2. Find out if their knowledge improves after reading an educational leaflet 3. Obtain feedback if the leaflet is user-friendly

Methods: We developed an innovative leaflet to explain how stimulants and non-stimulants work, using the analogy of postmen with illustrations. Mr Norda (Noradrenaline) and Mr Dopa (Dopamine), the postmen cross the bridge (synapse) to deliver letters (messages) from one nerve cell to another. In ADHD, several postmen go on strike (reuptake) but the medication helps them to get back to work, streamlining the transfer of messages and improving ADHD symptoms. At our ADHD clinics, parents completed questionnaires regarding their knowledge of ADHD and how the medication works before and after reading this leaflet.

Results: Twenty-five (25) parents completed the survey. At baseline, 12% (n = 3) were not aware of what ADHD stands for, 32% (n = 8) lacked knowledge of ADHD symptoms and over half, 52% (n = 13) did not know about chemical messengers in the brain. A majority 64% (n = 16) were unaware of stimulant and non-stimulant medication and could not provide a basic explanation of how the medication works. After reading the leaflet, all knew the ADHD abbreviation and 92% (n = 23) understood ADHD symptoms and the role of chemical messengers. Interestingly, 96% (n = 24) knew about stimulants and non-stimulants, whilst 72% (n = 18) had learned how ADHD medication works. 72% (n = 18) found the leaflet easy to understand and 68% (n = 17) found the postman analogy helpful for children as well. Many parents provided positive comments.

Conclusions: This small pilot study indicated that the leaflet could be a user-friendly resource to educate parents and improve their knowledge of ADHD, chemical messengers and how ADHD medication works

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ADHD Atten Deficit Hyperact Disord. 2017;9:S9.

DISCORDANCE BETWEEN PARENT-REPORTED CHILD BEHAVIOUR AND ADHD DIAGNOSIS.

Madsen KB, Ravn M, Arnfred J, et al.

Objectives: A scientific and public debate is ongoing regarding whether Attention-Deficit/Hyperactivity Disorder (ADHD) is being systematically diagnosed in conformity with current diagnostic criteria. Misdiagnosis and under-identification have been reported, but this problem remains poorly researched. We estimate the extent of discordance between parent-reported child behaviour and ADHD diagnosis and report the socio-demographic characteristics of children where discordance exists.

Methods: Using the Danish national birth cohort (DNBC), a 7-year follow-up of parents of 51,526 children was conducted. Parents completed questionnaires including the strength and difficulties questionnaire (SDQ). ADHD diagnosis was identified through followup in Danish registers until child age 12-14 years and ADHD behaviour through the SDQ. The association between socio-demographic characteristics and children with discordant diagnosis and behaviour was examined using logistic regression analyses.

Results: Of the 1373 ADHD-diagnosed children, 39% did not exhibit ADHD behaviour. Conversely, of the 1.028 children with ADHD behaviour, 55% had no ADHD diagnosis. Children with ADHD behaviour and no diagnosis were more likely to be girls (OR: 1.90; 95% CI 1.53; 2.37) and to live in certain regions of the country (OR: Capital vs. Southern region: 1.88; 95% CI 1.42; 2.48) than children with an ADHD diagnosis. Children with a diagnosis and normal behaviour were more likely to have mothers with a high socio-occupational status (OR: low vs. high: 1.77; 95% CI 1.22; 2.56) and to be older at the time of diagnosis (OR: 6 vs. 11 years: 11.38; 95% CI 7.28; 17.79), and less likely to have mothers with hyperactivity problems (OR: 0.49; 95% CI 0.36; 0.68) than children with an ADHD diagnosis and concordant behaviour.

Conclusions: Our results corroborate previous studies suggesting the existence of under-identification and potential misdiagnosis of ADHD. Our results also underline the significance of socio-demographic factors as drivers in ADHD diagnosis

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ADHD Atten Deficit Hyperact Disord. 2017;9:S18.

METABOLIC CONTROL IN ADOLESCENTS WITH TYPE 1 DIABETES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Macek J, Battelino T, Bizjak M, et al.

Objectives: Diabetes mellitus type 1 (T1D) incidence is increasing in paediatric population. Beside a regulated diet, regular exercise and frequent daily self-monitoring of blood glucose., patients with T1D need lifelong insulin therapy. Risk for chronic complications is significantly reduced with good metabolic control, measured by glycated haemoglobin (HbA1c) level below 7.5% (58 mmol/mol). Due to poor metabolic control, some children were also referred to a child and adolescent psychiatrist to evaluate for psychiatric comorbidities as a potential cause; a significant proportion of patients exhibited several symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD). To the best of our knowledge, the prevalence of ADHD among adolescents with T1D has not been studied systematically yet. We aimed to identify adolescents with T1D and ADHD and assess the effect of ADHD on metabolic control.

Methods: This cross-sectional case-control study included 101 patients (11-17 years old) with T1D. development and well-being assessment (DAWBA) questionnaire and subsequent psychiatric clinical examination were used to identify a group with T1D and ADHD. Indicators of metabolic control were collected from available medical documentation for preceding 12 months and compared between cases (patients with T1D and ADHD) and controls (T1D patients without ADHD).

Results: ADHD was diagnosed in 12 out of 101 adolescents with T1D. We found a statistically significant difference ($p = 0.022$) in HbA1c between the two groups-higher in the group with T1D and ADHD (8.4% or 68.3 mmol/mol) than in the control group (7.8% or 61.7 mmol/mol).

Conclusions: We found that metabolic control was significantly poorer in adolescents with ADHD in comparison to those without. These results suggest that adolescents with T1D and ADHD should be

recognised early and offered appropriate treatment as well as an additional support in home and school environment to prevent the potential negative impact of ADHD on metabolic control and subsequent clinical outcome

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ADHD Atten Deficit Hyperact Disord. 2017;9:S5-S6.

EXECUTIVE FUNCTION MEDIATED THE ASSOCIATION BETWEEN NRXN1 GENE POLYMORPHISM AND ADHD.

Lu Q, Liu L, Li H, et al.

Objectives: Children with Attention-Deficit/Hyperactivity Disorder (ADHD) usually display executive function (EF) deficits, including set shifting, working memory, and response inhibition. NRXN1 gene was a candidate gene for many neuropsychiatric disorders including ADHD, which was essential for glutamatergic pathway and the function of prefrontal cortex (PFC) mediated by N-methyl-D-aspartate (NMDA) receptors. The aim of this study was to explore the association between NRXN1 single nucleotide polymorphism (SNP) and executive function of ADHD.

Methods: A total of 729 Han Chinese ADHD children and 121 Han Chinese unaffected children were involved in the analysis. Rey-Osterrieth complex figure test, Stroop color and word test, trail making test (TMT) were used to evaluate working memory, response inhibition and set shifting (including shifting time) respectively. Association between the genotype of SNP and EF was analysed with plink. Mediation analysis was used to evaluate the relationship of SNP, a diagnosis of ADHD and EFs.

Results: In ADHD cases, three SNPs existed nominal significance in association with shifting, including rs2602003 (P = 0.000061), rs1592728 (P = 0.010) and rs4971652 (P = 0.044), in which rs2602003 survived multiple test correction. rs2602003 was also associated with the scores of Rey complex figure test (for structure immediate, P = 0.024), for detail immediate, P = 0.015, for detail delayed, P = 0.046. rs4971652 also showed nominal significance in association with word interference time (IW) (P = 0.0094). Mediated analysis exhibited that set shifting was the only intermediary variable between rs2602003 and ADHD, the effect size was 0.085, while IW had a complete mediating effect between rs4971652 and ADHD, the effect size was 0.088.

Conclusions: The NRXN1 gene polymorphism rs2602003 is associated with set shifting of EF in ADHD children. Set shifting acts as a complete mediator in the relationship between rs2602003 and ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S46.

HEALTH AND ECONOMIC OUTCOMES IN CHILDREN OF MOTHERS WITH TREATED AND UNTREATED ADHD.

Merzon E, Merhasin I, Merzon T, et al.

Objectives: Data about health outcome in children born to mothers with Attention-Deficit/Hyperactivity Disorder (ADHD) is limited. The objective of our study was to investigate health and economic outcomes in children born to women, who had been diagnosed with ADHD.

Methods: Medical data from all children born in the period from 1/01/2014 to 1/12/2016 were collected and linked to their mothers' medical records using the electronic registry of a large Israeli health maintenance organization-Leumit Health Services. All women with the diagnosis of ADHD, as defined in International Classification of Diseases (ICD-10) were identified (n = 504), and divided into two groups: Those who purchased medications for at least 12 months, older than 18 years (n = 110) and those who did not (n = 394). A comparison group included children from other women, who had no ADHD diagnosis and had given birth during the same period (n = 4290). Main outcome measures were haemoglobin level, flu vaccinations; number of emergency room admissions; number of hospitalisations, length of hospital stays and total medical costs.

Results: Children born to mothers with diagnosed, but untreated, ADHD as compared to children born to mothers with treated ADHD or mothers without ADHD had a significantly lower haemoglobin level (10.5 vs.10.9 & 11.7, $p < 0.001$) and flu vaccination rate (21.4 vs. 22.6 & 35.4%, $p < 0.001$). They had higher rates of emergency room admissions (1.01 vs. 0.88 & 0.54, $p < 0.001$) and hospitalisations (0.65 vs. 0.25 & 0.22, $p < 0.001$). Their hospital stays were longer (2.87 vs. 0.88 & 0.63, $p < 0.001$) and medical costs higher

(13,364 NIS vs. 4992 NIS & 4971 NIS, p < 0.001). Risk ratio for hospitalisation of children of mothers with untreated ADHD was 3.22 (CI 95% 2.87; 3.63).
Conclusions: Children of mothers with untreated ADHD had worth health outcomes and significantly higher medical costs as compared to children born to motherswith treatedADHDor mothers without ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S10.
THE PREVALENCE, DISTRIBUTION AND COMORBIDITY OF ADHD IN CHILDREN AND ADOLESCENTS AGED 6-16 IN HUNAN PROVINCE, CHINA.
Luo X, Shen Y, Chan BSM.
Objectives: To understand the prevalence, distribution, and comorbidity of ADHD in children and adolescents aged 6-16 in Hunan Province in 2014.
Methods: 17,071 patients aged 6-16 were enrolled using stratified cluster sampling and two-stage epidemiological methods, screened using child behavior checklist (CBCL), and diagnosed using mini international neuropsychiatric interview for children and adolescents (MINI-Kid 5.0), with final verification using DSM-IV criteria.
Results: Prevalence of ADHD was 4.96%; boys, 7.10% and girls, 2.66%. The difference between genders was statistically significant (P < 0.001). Prevalence of group 6-11 years ranked highest (5.7%), followed by group 12-14 years (4.6%), and group 15-16 years (3.6%); the difference between age groups was statistically significant (P < 0.001). (2) There are three subtypes of ADHD: predominantly inattentive type (ADHD-I), hyperactive/impulsive type (ADHD-HI), and combined type (ADHD-C). Prevalence of ADHD-I ranked highest (1.86%), followed by ADHD-C (1.69%), and ADHD-HI (1.41%); the difference between subtypes was statistically significant (P = 0.004). Prevalence of ADHD-C and ADHD-HI decreased with age; this difference was statistically significant (P < 0.05). (3) 48.17% (408) of patients had comorbidities; 36.36% had one, 8.50% had two, and 3.31% had more than two. The most common comorbidities were oppositional defiant disorder (25.15%), conduct disorder (18.18%), and generalised anxiety disorder (6.38%). 20.55% of girls and 10.03% of boys had comorbid anxiety disorders; 9.13% of girls and 2.23% of boys had comorbid major depressive disorders.
Conclusions: (1) The prevalence of ADHD among children and adolescents in Hunan is 4.96%, is higher in boys, and occurs highest in younger children. (2) Prevalence of ADHD-I ranks highest. (3) Nearly 50% of patients have comorbidities; oppositional defiant disorder, conduct disorder, and anxiety disorder being most common. Females with ADHD are at greater risk of anxiety disorders and depressions

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ADHD Atten Deficit Hyperact Disord. 2017;9:S22.
ASSOCIATIONS BETWEEN P3 RESPONSES AND CONTINUOUS PERFORMANCE TEST IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Hung S-J, Hsieh M-H, Gawrilow C, et al.
Objectives: To investigate the associations between P3 responses induced by a go/no-go task (Paul et al. 2007) and behavioural performance on the continuous performance test (CPT) in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and typically developing (TD) children.
Methods: We assessed 21 children with ADHD (mean ± - SD = 9.84 ± 1.27 years) and 20 TD children (mean ± SD = 10.49 ± 1.12 years) with two neuropsychological tasks (i.e., go/no-go task and continuous performance test, CPT), which were randomly administered. Electrophysiological data were recorded while participants were performing the go/no-go task. Behavioural variables (i.e., omission errors, commission errors, reaction time [RT], and reaction time standard errors [RTSE]) measured by the CPT and event-related potentials (i.e., P3 latencies and amplitudes at electrode sites-Fz, Cz, and Pz) evoked by the go and no-go stimuli were collected. Correlations between behavioural variables and P3 responses were calculated.
Results: Regarding the correlations between the CPT performance and P3 responses, different patterns were observed between groups. For children with ADHD, significances were found between P3 latencies at Fz and RTs (r =.493, p <.05), P3 latencies at Cz and RTs (r =.566, p <.01), and P3 latencies at Cz and

RTSEs (r =.524, p <.05). In the control group, pronounced associations existed between P3 latencies at Fz and omission errors (r = -.584, p <.01), P3 latencies at Fz and RTSEs (r = -.601, p <.01), and no-go P3 latencies at Fz and omission errors (r =.482, p <.05).
Conclusions: The results provide evidence to support that some similar and some different mechanisms or strategies are involved when children with ADHD and TD children perform the neuropsychological tasks. Future studies with larger sample sizes are warranted to validate the current findings

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ADHD Atten Deficit Hyperact Disord. 2017;9:S4.

EVIDENCE OF CONCURRENT AND PROSPECTIVE ASSOCIATIONS BETWEEN EARLY MALTREATMENT AND ADHD THROUGH ADOLESCENCE.

Gonzalez R, Velez-Pastrana M, McCrory E, et al.

Objectives: An emerging body of work suggests a link between childhood maltreatment and Attention-Deficit/Hyperactivity Disorder (ADHD). However, there remains a lack of clarity regarding the role of early trauma in the early course of the disorder. We aimed to examine associations between maltreatment experiences and ADHD diagnosis, sex differences, and to estimate the risk between repetitive maltreatment exposure and ADHD through adolescence.
Methods: Data were obtained from the Boricua youth study, a longitudinal study of 2.491 children and adolescents of Puerto Rican background. Neglect, physical, emotional and sexual abuse, and foster placement were regressed on ADHD diagnosis measured at each wave using the diagnostic interview schedule for children-IV. Multilevel regressions estimated the effects of exposure on ADHD, adjusted by age, sex, income, household education, parental psychopathology, comorbidity and ADHD medication status.
Results: Emotional abuse and foster placement had robust associations with ADHD diagnosis. For girls, physical abuse had a three-fold increase in the odds of having ADHD diagnosis; for boys, associations were observed only for emotional abuse. Prospective models examining repetitive exposure suggested increased probability for ADHD persistence.
Conclusions: Associations between early maltreatment and ADHD were robust. Different categories of maltreatment increase the likelihood of ADHD for girls and for boys. Increased exposure to maltreatment may predict symptom persistence. Interventions addressing ADHD must consider the effects of both sex and family environment

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ADHD Atten Deficit Hyperact Disord. 2017;9:S28.

A DEVELOPMENTAL CHANGE FOR THE RELATIONSHIP BETWEEN NEUROPSYCHOLOGICAL FUNCTIONS AND THE SEVERITY OF ADHD AND ODD SYMPTOMS IN PRESCHOOLERS: A 3-YEAR FOLLOW-UP STUDY.

Hwang-Gu S-L, Chen Y-C, Gau SSF.

Objectives: The aim of this study was to investigate the developmental change for the relationship between neuropsychological functions-attention measured by Conners Kiddie continuous performance test (KCPT), inhibitory response measured by day/night Stroop, and delay aversion measured by delay choice task- and the severity of ADHD symptoms in preschoolers, both concurrently and longitudinally.
Methods: Fifty-eight preschoolers (4-5 years old), 1/2 who had been identified as being at risk for developing ADHD as clinical referral by the child psychiatrists, completed neuropsychological tasks designed to measure attention, inhibitory control, and delay aversion. Behavioral symptoms were measured through parental ratings of DSM-IV criteria for ADHD and ODD. The neuropsychological tasks and behavioural rating were completed two times (time one was 4-5 years, the second time was 6-7 years after the participants entered elementary school).
Results: Our results showed only attention and inhibitory control measured by the second time were associated with the severity of ADHD symptoms rated at time one and time two. There were no associations between neuropsychological functions and the ADHD symptoms in time one (age 4-5). Our results also did not show the association between delay aversion and ADHD symptoms, both concurrently and longitudinally.

The ODD symptoms were not associated with neuropsychological function, both concurrently and longitudinally.
Conclusions: The current study demonstrated that the neuropsychological functions might not be the important part to assess the ADHD symptoms in preschoolers, however, the performance of attention and inhibitory control might play a role to assess the ADHD symptoms in elementary school. The current study also demonstrated that neuropsychological functions might not relate to the ODD symptoms, no matter whether in preschoolers or school children

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ADHD Atten Deficit Hyperact Disord. 2017;9:S20.

WORKING MEMORY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Horovitz M, Penna R, Moscrip A, et al.

Objectives: Executive functioning (EF) impairments are a hallmark of Attention-Deficit/Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD). Historically, ASD and ADHD were thought of as mutually exclusive, and there was confusion with regard to apparently overlapping symptoms. Previous versions of the diagnostic and statistical manual (DSM) excluded the diagnosis of ADHD in children with ASD. However, current research and clinical practice recognises the need to conceptualise and treat both conditions, if present, and comorbid diagnosis is now recognised in DSM-V. While there are well established bodies of research analysing EF deficits in both groups, current research aims to analyse the EF profiles in individuals with comorbid diagnoses. This will promote better understanding of the interrelationship of these two conditions, as well as promote more targeted treatment efforts. The objective of the current research study was to analyse working memory profiles in groups of children diagnosed with ADHD, ASD, and dual diagnoses of comorbid ADHD and ASD.
Methods: A one-way, between groups ANOVA analysed working memory scores from standardised intelligence tests across three samples of children: ADHD only diagnosis (n = 65), ASD only diagnosis (n = 23), and ASD + ADHD diagnoses (n = 36). All participants received services at an outpatient interdisciplinary treatment clinic and had received previous comprehensive psychodiagnostic evaluation. The age range was 4-18 and children were excluded if FSIQ < 60.
Results: Analysis revealed group membership to significantly affect working memory scores, $F(2121) = 3.52$, $p < .05$, with similar scores in the ADHD only (M = 95.30) and ASD only (M = 97.00) groups, along with lower working memory scores in the ASD + ADHD group (M = 87.09).
Conclusions: While further research is needed with larger samples, current research results suggest a possible compounding effect of impairment in working memory when both ADHD and ASD are present

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ADHD Atten Deficit Hyperact Disord. 2017;9:S5.

A META-ANALYSIS ON ASSOCIATION BETWEEN LEAD EXPOSURE AND ADHD AND ITS SYMPTOM DOMAINS IN CHILDREN.

Ha M, Oh S-E, Lee K-M .

Objectives: A well-known neurotoxicant for developing brain, lead, has been reported as having an association with ADHD in epidemiologic studies. We aimed to summarise current evidence of association between lead exposure and ADHD and its symptom domains.
Methods: A systemic review and meta-analysis was performed by searching databases of PubMed and Scopus, using several combinations of searching words including lead and ADHD without limitation of publication year in accordance to the guideline provided by the meta-analysis of observational studies in epidemiology. Among 548 searched, and after excluding papers that did not meet inclusion criteria, 39 original papers of 46 study populations were selected for the meta-analysis. The summary effect size (EF) was presented as standardised regression coefficient and Hedge's G after transformation of various types of effect estimates. The quality assessment on each paper was done by two independent reviewers using the modified short form of Research Triangle Institute.

Results: Lead exposure significantly associates with ADHD in overall (EF = 0.255, 95% CI 0.158-0.292), inattention (0.133, 0.076-0.190), and hyperactivity (0.284, 0.172-0.396) symptom domains in random models. The sensitivity analyses according to study design, types of biological samples the lead levels were measured, i.e., blood, teeth, and hair in children, showed consistent results except for lead level in cord blood. By analysing the level of children's blood lead, the highest ES did not show in the range between 5 and 10 ug/dL (0.338, 0.033-0.644), rather in the range < 5 or > 10 ++g/dL of blood lead levels.
Conclusions: Lead exposure can be significantly associated with ADHD in children and more strongly with the hyperactivity symptom domain

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ADHD Atten Deficit Hyperact Disord. 2017;9:S19.

ADHD AND IMPACT ON TYPE 1 DIABETES.

Midtlyng E, Skrivarhaug T, Naerland T.

Objectives: For individuals with ADHD the ADHD-related impairment often persists into adulthood (1). An increase in health-risk behaviour for adolescents with ADHD is reported, in particular in combination with other chronic conditions (2) and combined with conduct disorder (3). Type 1 diabetes (T1D) is a severe chronic condition where the glycemic regulation has stopped to work and it is a challenge for both the patients and their parents to substitute the child's glycemic regulation with a strict treatment regimen. Focus on attention and learning is therefore of great importance. How neurocognitive problems affect the outcome of T1D is an increasing body of knowledge (2). The recent German-Austrian Study with 56,000 T1D patients show that patients with comorbid ADHD (2.8%) suffered twice as often from diabetic ketoacidosis compared to the patients without ADHD, and they also have significant higher metabolic balance (HbA1c). There is a need for further research to better understand the impact of ADHD on diabetes control and complications and a closer collaboration between pediatric diabetologists and pediatric psychologists/psychiatrists (4). Objectives of the study. Describe how neurodevelopmental problems typical for ADHD affect the T1D treatment and the metabolic control for individuals with ADHD and T1D. Compare scores on Health-related quality of life between individuals with T1D and ADHD and individuals with T1D without ADHD. Investigate the effect of a strict treatment regimen forT1D on learning and self-regulation for individuals who also have ADHD. Evaluate the levels of HbA1c after onset of medical treatment for ADHD and the impact of ADHD on school performance for individuals with T1D.
Methods: Based on clinical examinations, neuropsychological tests and questionnaires our study will be linked to data from The Norwegian Childhood Diabetes Registry and Norwegian Prescription Database.
Results: Study under planning

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ADHD Atten Deficit Hyperact Disord. 2017;9:S28.

EXECUTIVE FUNCTION CHARACTERISTIC IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMORBID TIC DISORDERS.

Liao W, Jin J, Li H, et al.

Objectives: To answer the question whether executive function (EF) deficits are specific to Attention-Deficit/Hyperactivity Disorder (ADHD) or whether such deficits are also associated with tic disorder (TD).
Methods: A total of 112 ADHD comorbid tic disorder (ADHD +TD) children,112 pure ADHD children and 112 normal controls (criteria of diagnostic and statistical manual of mental disorders-fourth edition, DSM-IV) were collected as our samples. ADHD +TD group is comprised by 55 ADHD comorbid transient tic disorder (ADHD + TTD) children, 30 ADHD comorbid chronic tic disorder (ADHD + CTD) children, 11 ADHD comorbid Tourette syndrome (ADHD + TS) children and 16 ADHD comorbid unsubtyped tic disorder children. The former three groups (ADHD + TD, pure ADHD, and normal control) were matched by sex, age (less than 6 months) and IQ. The Rey-Osterrieth complex figure test, the trail making test, and the Stroop color word test were administered to assess working memory, shifting and inhibitory function respectively.
Results: Both pure ADHD group and ADHD + TD group performed worse (P < 0.05) in the aspects ofthe delay recalling structurescore, the immediate memory detail score, the delay recalling detail score of Rey

complex figure test, time of number-letter part and shifting time of trail making test, the time of Stroops 2, 4, the errors of Stroop 4 and word interference than normal controls. Pure ADHD group performed worse($P < 0.05$) in the aspects of the time of thestructureand detail forgetting scorethan normal controls, too; the pureADHDgroup also showed deficits in the aspects of the time of Stroops 2, and the errors of Stroop 4 compared with ADHD + TD group. The differences were significant ($P < 0.05$). ADHD + TS group performed worse ($P < 0.05$) in the aspects of the time of Stroops 2 than ADHD + TTD group and ADHD + CTD group. The other differences all were not significant ($P>0.05$).
Conclusions: The findings support the hypothesis that ADHD is related to executive function deficit, particularly in the tests assessing working memory, shifting and inhibitory function, whether or not comorbid tics disorder

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ADHD Atten Deficit Hyperact Disord. 2017;9:S17-S18.

CHILDHOOD BIPOLAR DISORDER MASQUERADING AS ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH EPISODIC OBSESSIVE COMPULSIVE DISORDER: A CASE REPORT WITH A REVIEW OF THE LITERATURE.

Kumar P, Tsheringla S, Naskar S, et al.

Objectives: Introduction: Contemporary literature suggests that among all the comorbidities of childhood bipolar disorder, Attention-Deficit/Hyperactivity Disorder ranks the highest with a prevalence of 60-90%. In pre-pubertal years of a child, the manifested symptoms of BPAD may often mimic that of ADHD (often called 'complex' ADHD), thus confusing the clinicians. BPAD in this age group usually has a non-episodic, ultra-rapid or ultradian cycling with a chronic course unlike episodic illness of adult BPAD that makes the diagnosis difficult. OCD comorbid with BPAD shows higher frequencies of depressive and panic episodes, higher rates of sexual obsessions and runs an episodic course.
Methods: Case: Six-years-old female child with a normal birth and developmental history and significant family history of mood disorders presented with low mood, school refusal, clinging behaviour and obsessional sexual thoughts. She has started on fluoxetine to which she responded well. Subsequent follow-up showed remission in her symptoms, but she was found to have hyperactivity with scores on ADHD rating scale significant enough to start her on atomoxetine. After four months, she presented with prominent hypersexual behaviour (speech and actions), over-talkativeness, excessive cheerfulness, decreased sleep and increased obsessions. On examination, she was restless with prolixity in speech, increased goal-directed activity as observed in her activities (drawings). Parent CMRS-P score was 26. She was diagnosed as a case of paediatric BPAD with a differential diagnosis of antidepressant and or atomoxetine induced manic switch with comorbid OCD. The patient was managed with a combination of rational pharmacotherapy and psychotherapy.
Conclusions: This case illustrates the complexity of comorbidities in children. There is a need to have caution while diagnosing and treating ADHD in cases of co-morbid OCD and depression in preadolescent children keeping in mind the masquerading presentation of Bipolar disorder in this age group. Furthermore, this case is an example of probable antidepressant and or atomoxetine induced manic switch at a very early age

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ADHD Atten Deficit Hyperact Disord. 2017;9:S7.

INTERACTION EFFECT BETWEEN RS3785143 OF NET1 AND RS1611115 OF DBH ON THE ABERRANT RESTING-STATE FUNCTIONAL CONNECTIVITY IN THE PREFRONTAL-AMYGDALA CIRCUIT IN BOYS WITH ADHD.

Liu L, Yu X, Sun L, et al.

Objectives: Our previous study found that the aberrant resting-state functional connectivity (RSFC) of prefrontal cortex (PFC) and amygdala may be associated with emotional lability (EL) in boys with ADHD (PMID: 27503948). In addition, genetic variants of noradrenergic genes (NET1) may influence the EL symptoms in children with ADHD (5th World Congress on ADHD). Our present study is to explore whether these genetic variants of the noradrenergic system and their interactions are associated with the aberrant imaging features.

Methods: Thirty-two boys with ADHD of Chinese Han descent were included. Twenty-two aberrant RSFCs of amygdala subregions with PFC in boys with ADHD observed in our previous imaging study were analysed as dependent variables. Genotyping was performed using a Taqman allelic genotyping assay for four SNPs including rs3785143(NET1), rs1611115 (DBH), rs4680 (COMT) and rs1137070 (MAOA). Genotypic effects of individual markers and interactions were analysed using analysis of covariance (ANCOVA) with age, IQ and head motion as covariance by SPSS17.0.
Results: Two SNPs, rs1611115 and rs3785143, showed genotypic effects on the RSFC between left superficial amygdala (SFA) and right dorsal-lateral PFC (DLPFC) (P = 0.001; 0.031 respectively). The SNP rs1611115 also showed association with the RSFC between right SFA and right DLPFC (P = 0.019). The SNP rs3785143 showed genotypic effect on the RSFC between right SFA and dorsal PFC bilaterally (P = 0.030). In addition, interaction between rs3785143 and rs1611115 showed strong effect on the RSFC of right SFA with dorsal PFC bilaterally (P = 5.52E-07). Specifically, among the subjects carrying the risk C allele of rs1611115, the rs3785143/T carriers showed reduced negative RSFC when compared to the rs3785143/CC carriers (P = 2.30E-04, +À2p = 0.501).
Conclusions: Combined with our previous findings, the genetic variants of the noradrenergic system may influence the EL in children with ADHD by medicating the RSFC in the PFC-Amygdala circuit. Replications in larger sample size are needed

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ADHD Atten Deficit Hyperact Disord. 2017;9:S51.

EARLY FOOD ALLERGY AND ALLERGIC SYMPTOMS ON THE RISK OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHINESE CHILDREN IN SCHOOL AGE.

Li F, Jiang X, Shen C.

Objectives: To explore the association between early food allergy and allergic symptoms and Attention-Deficit/Hyperactivity Disorder (ADHD) in Chinese school-aged children.
Methods: This is a cross-sectional survey. Cluster sampling was used for school-aged children selection from nine cities in China. Diagnosis of ADHD and allergic disease as well as demographic information of children were collected via a parent-administered questionnaire. Children were divided into non-food allergy (non-FA) group, single food allergy (FA) group, food allergy combined with one (FA + allergic rhinitis [AR]/bronchial asthma [BA]) and two allergic symptoms (FA + AR + BA) groups according to the previous diagnosis of food allergy and other allergic diseases. Difference in prevalence of food allergy in children with and without ADHD was analysed with univariate analysis, and multiple logistic regression model was used for analysing the effect of food allergy and allergic symptoms on ADHD in school-aged children.
Results: A total of 22,018 children were enrolled, among which there were 9921 (45.1%) boys and the mean age was 8.81 & plusmn; 1.79 years. 979 (44.5%) children were diagnosed of ADHD, and more children with food allergy was observed in ADHD children than non-ADHDones (10.3 vs. 5.4%, P < 0.001. Among 1223 children diagnosed with food allergy, there were 916 (74.9%), 226 (18.5%) and 81 (6.6%) children in FA, FA + AR/BA and FA + AR + BA groups, respectively. The prevalence of ADHD was 4.2, 6.7, 12.4 and 14.8% in non-FA, FA, FA + AR/BA and FA + AR + BA groups. Multivariate analysis data demonstrated that food allergy with or without allergic symptoms might be risk factors for ADHD (for FA, odds ratio [OR] = 1.589, 95% confidence interval [CI] 1.183-2.134, P = 0.002; for FA + AR/BA, OR 3.560, 95% CI 2.341-5.413, P < 0.001; for FA + AR + BA, OR 4.087, 95% CI 2.060-8.106, P < 0.001) in children.
Conclusions: Increased prevalence of ADHD was observed in school-aged children with food allergy, furthermore, early food allergy and allergic symptoms was associated with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S23.

RESTING-STATE EEG CORRELATES OF ECOLOGICAL EXECUTIVE FUNCTION IN ADULTS WITH ADHD.

Li H, Wang C-M, Zhao Q-H, et al.

Objectives: The purpose of the present study was to investigate the abnormalities in resting-state EEG in adults with ADHD, and the relationships between EEG characteristics and self-ratings of ecological executive function (EF), defined as indicators to reflect everyday life EF deficits.
Methods: Thirty-three adults diagnosed with ADHD in childhood according to DSM-IV and 30 carefully matched health control subjects were recruited and recorded with EEG signals during an eyeclosed resting state condition. The absolute and relative power in delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz) bands were analyzed. Meanwhile, the self-ratings of behavior rating inventory of executive function were used to measure the ecological EF and their correlation with EEG power.
Results: Compared to control adults, the ADHD group exhibited significantly higher global theta activity (F = 3.28, P = 0.041), higher central beta activity (F = 3.20, P = 0.003), and lower central alpha activity (F = 10.55, P = 0.002). There were different correlations between EEG and EF scores in two groups. In ADHD group, working memory scores positively related to the absolute theta power in left frontal brain (r = 0.43, P = 0.014), Emotional Control scores positively related to relative beta power in bilateral central brain(left: r = 0.55, P = 0.001; right: r = 0.37, P = 0.033), Shift scores positively related to relative theta power (r = 0.44, P = 0.011) and negatively related to relative alpha in left central brain (r = -0.39, P = 0.026). While in the control group, the correlation only existed in Emotional Control scores and central relative beta power (left: r = 0.62, P < 0.001; right: r = 0.54, P = 0.002).
Conclusions: This study demonstrated the resting-state EEG abnormalities remain in adults with ADHD. And their correlations with ecological EF imply the resting-state EEG might have the clinical value to assess the daily EF deficiencies in adults with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S31.

SEXUALLY DIMORPHIC FRONTAL LOBE DEVELOPMENT IN PRESCHOOLERS WITH ADHD: EARLIER ANOMALIES IN GIRLS.

Mahone M, Crocetti D, Dirlikov B, et al.

Objectives: By school age, children with ADHD have sexually dimorphic frontal morphology that underlies symptom presentation. To understand development of ADHD, biomarkers should be studied longitudinally in younger children, emphasising sex differences in trajectory.
Methods: High-resolution anatomical images, acquired at 3.0T, were analysed in 60 preschoolers (31 with ADHD;17 boys, 29 typically developing-TD-19 boys), each seen for three imaging visits, one year apart, beginning at age 4 or 5 years. The ADHD group was diagnosed using modified DSM-IV-TR criteria and screened for language disorders. Frontal lobe subregions were generated using an automated protocol, from which regional grey matter volumes for premotor and prefrontal cortex (PMC and PFC-summed across hemispheres) were derived. Linear mixed effects analyses were used to examine longitudinal effects of group, sex, and time on PFC, PMC, and total cerebral volume (TCV), and associations with ADHD symptomatology.
Results: At baseline, there were no group or sex differences in age or SES, and no sex differences in ADHD symptoms. Across visits, there were significant effects for sex (girls < boys), and group (ADHD < TD) for TCV, PMC, and PFC, but not for time. There was also a significant group-by-sex interaction for PFC. Examining within sex, ADHD-related reductions were observed for girls (but not boys), in TCV, PMC, and PFC. Within the ADHD group, reduced PMC volumes predicted hyperactive/impulsive ADHD symptoms in girls, but not boys. PFC volumes and TCV did not predict ADHD symptoms in either sex.
Conclusions: Anomalous prefrontal morphology among preschool girls with ADHD parallels findings observed in older female cohorts. Conversely, reduced premotor volumes among preschool girls (but not boys), and female-specific associations with ADHD symptoms, reflect the opposite pattern observed in school-aged children. These patterns in young girls with ADHD highlights earlier ΓÇ£normalisationΓÇØ of premotor anomalies that sets the stage for more rapid attenuation of hyperactive/impulsive symptoms

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ADHD Atten Deficit Hyperact Disord. 2017;9:S3.

PARENTAL PSYCHIATRIC PROBLEMS INCREASE SEVERITY OF ADHD SYMPTOMS AND COMORBIDITY IN THEIR CHILDREN.

Madsen KB, +ÿvergaard KR, +ÿrbeck B, et al.

Objectives: Attention-Deficit/Hyperactivity Disorder (ADHD) is highly heritable, and studies have found parental ADHD symptoms to be strongly associated with severity and comorbidity of child ADHD symptoms. However, most studies have been cross-sectional. The aim was to examine whether parental reports of own childhood psychopathology influenced the risk of an ADHD diagnosis, severity of symptoms and comorbidity in their children in a longitudinal cohort study.

Methods: Our study was based on the Danish national birth cohort (DNBC) and included parents of 41,666 children. Parental reports on own childhood psychiatric symptoms were collected at age 6 months of their child. At 7-year follow-up parents completed the strength and difficulties questionnaire (SDQ) measuring severity of child ADHD symptoms and comorbidity with the SDQ subscales; hyperactivity/inattention (H/I), conduct, emotional, and impact. ADHD diagnosis was identified through follow-up in Danish registers until child age 12-14 years. Associations were analysed using Cox Proportional Hazards regression and linear regression models.

Results: Adjusting for child's gender, civil and socio-occupational status, children from families with reports of childhood hyperactivity in both mothers and fathers were in significant higher risk of an ADHD diagnosis [Hazard ratio (HR) 2.47; 95% CI 1.76; 3.45]. Maternal conduct and anxiety problems similarly increased the risk of offspring ADHD (HR 2.17; 95% CI 1.22; 3.84 and HR 1.81; 95% CI 1.51; 2.17, respectively), but not the severity of H/I symptoms. Children with an ADHD diagnosis had significantly higher symptom scores on the H/I scale ($p < 0.001$), the conduct scale ($p < 0.001$), and emotional scale ($p < 0.05$) if both parents had hyperactivity symptoms in childhood. Only paternal hyperactivity increased severity of impairment in children with ADHD ($p < 0.05$).

Conclusions: Parental psychopathology, in particular ADHD symptoms, increases risk of ADHD diagnosis in their children and affects severity of ADHD symptoms and comorbidity

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ADHD Atten Deficit Hyperact Disord. 2017;9:S28.

TEMPERAMENT AND CHARACTER PROFILES ASSOCIATED WITH INTERNALIZING AND EXTERNALIZING PROBLEMS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kwack YS, Kang NR.

Objectives: This study was to investigate how temperament and character profiles are related to internalising and externalising problems in children with ADHD.

Methods: The subjects were 74 ADHD children (mean age 8.51 ± 1.92 years) diagnosed in according to K-SADS-PL. To evaluate their comorbid problems we used the child behaviour checklist (CBCL) and also, their temperament and character profiles were examined by JTCI (junior temperament and character inventory), and we analysed the difference of TCI scale scores between children who had both internalising and externalising problems (N = 16, male 84.2%) and the rest of the children as comparison group (N = 55, male 76.8%).

Results: ADHD children who had both internalising and externalising problems showed a temperament profile significantly higher in novelty seeking ($p = 0.004$) and harm avoidance ($p = 0.002$), but scored significantly lower in self-directedness ($p = 0.012$), and cooperativeness ($p = 0.009$) than in the comparison group on JTCI.

Conclusions: The results of this study suggest that specific patterns of temperament and character traits such as high novelty seeking and harm avoidance but low self-directedness and cooperativeness could be related to more severe comorbid problems in children with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S39.

IS VIDEO-ASSISTED METHYLPHENIDATE DOSE FINDING FOR CHILDREN WITH ADHD A SUITABLE PROCEDURE FOR MEDICAL PRACTITIONERS? RESULTS AFTER 4-YEAR FOLLOWUP .

Kuehle H-J, Glaser T, Neuh+ñuser G.

Objectives: Video-assisted observation of facial expression changes and performance during math tests allows titration of optimal methylphenidate doses for children withADHD(Khle et al. JAttention Disorders 10, 2007). In this study-conducted in a community-based outpatient paediatric practice-patients were followed-up for four years in order to evaluate the long-term benefit of this diagnostic procedure.
Methods: All patients with an ADHD diagnosis, who underwent the video-assisted dose finding procedure in 2008, were invited for a 4-year follow-up study. 19/49 patients fulfilled all eligibility criteria for statistical analysis. DuPaul's parents rating scales, school reports and physical condition at beginning, in-between the first year and four years after video-assisted dose determination were analysed.
Results: Friedman's two-factor variance analysis and Wilcoxon's test for paired samples showed significant improvement of parent ratings of attention, impulsivity and hyperactivity during the first year of treatment, which remained stable during follow-up. School reports improved in the first year but returned to pre-therapy-levels after four years. All children grew on the same growth percentile of the time before therapy; blood pressure remained normal. Fifteen (15) patients maintained the dosage of the first determination; three patients lowered the single dose by 5, 7.5 and 10 mgs, two patients increased their single dose by 2.5 and 5 mgs.
Conclusions: Video-assisted observation of involuntary behaviours in children with ADHD supports clinical diagnostic procedures and offers sustainable long-term benefit. Moreover, the methodology is applicable in community-based clinical practice and (though not measured) improves interaction between patient and parents and the treating physician

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ADHD Atten Deficit Hyperact Disord. 2017;9:S19-S20.

SUBSTANCES USE AND FUNCTIONAL IMPAIRMENT AMONG COLLEGE STUDENTS WITH ADHD IN QUEBEC.

Leblanc JL, et al.

Objectives: This research project aims to develop knowledge about students with ADHD in post-secondary institutions in Quebec. More specifically, the study focuses on functional impairment in several spheres of life in this population. It also examines the prevalence of drug and psychoactive medication use, as well as the interaction of its variables with the functioning of the individual.
Methods: Participants in this study were students aged 17-55 years (M = 24.1, SD = 7.06) from seven colleges and two universities in the province of Quebec. The sample consisted of 243 students, 56.4% of whom were studying at a general and vocational college and 43.6% at university at the time of the study. The students were contacted by e-mail via the adapted services of their respective institutions, in order to answer the following questionnaires from an online computer platform: General information. Weiss Functional Impairment Rating Scale - Self-report (WFIR-S) (French version). Assessment and Screening of Assistance Needs – Alcohol (French version). Assessment and Screening of Assistance Needs – Drugs (French version) [assessment and screening of assistance needs-drugs]).
Results: Self-concept was the area with most functional impairments in students (M = 1.54, SD =.80) and work appeared to have the least number of impairments (M =.70, SD =.49). In addition, the MANOVA showed a significant effect, Wilks λ '= F(7,224) = 3,480,p< 0,001,n2= 0.098.): non-medicated students (M =.95, SD =.36) had higher scores on items compared to students taking medication for the disorder (M =.91, SD =.40). MANOVA results revealed significant difference according to the severity of alcohol consumption (F(14,446), 3.119, p <.001, +À2 =.089). Students with high-risk alcohol drinking (M =.10, SD =.37) reported more functional impairments than students with low-risk drinking (M =.89, SD =.38) or no risk (M =.89, SD =.45). MANOVA also revealed significant difference according to the severity of drug use (F(14,446), 4.441, p <.001, +À2 =.122). Students with high-risk drug use (M = 1.01, SD =.355) had higher scores on items, regardless of the functional area examined, than students with lowrisk drug use (M =.94, SD =.37) or no risk (M =.87, SD =.40).
Conclusions: ADHD-related functional impairment among college and university students was found to be generally low with the exception of self-concept which points to the importance of providing student support

in this area. In addition, absence of medication for the disorder would be linked to greater functional impairments associated with ADHD. Finally, students with ADHD reporting alcohol and/or drug use manifest generally more functional impairments in their lives than those with low or no risk drinking

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ADHD Atten Deficit Hyperact Disord. 2017;9:S36-S37.

MENTAL HEALTH INTEGRATION IN PRIMARY CARE: PRELIMINARY RESULTS FROM AN ADHD PROGRAMME IN A FAMILY HEALTH TEAM.

Gomaa W, Robaey P, Pajer K, et al.

Objectives: Although integrating mental health care into everyday primary care practice is easy to promote, the process is not evident, especially with children. Our model of Mental health integration (MHI) promotes three essential primary care practice changes: (1) it improves the detection, monitoring, stratification and management of mental health and physical problems, (2) it matches and adjusts treatment and intervention by tracking evidence of complexity and inadequate response, and (3) it reinforces the active role of the patient in ongoing interactions with the team to promote adherence and self-management.

Methods: We implemented the MHI model in the context of the family health teams (FHTs) in Ontario, focusing first on ADHD detection, treatment and monitoring. FHTs are primary health care organisations that include a team of family physicians, nurse practitioners (NP), registered nurses, social workers, dietitians, and other professionals who work together to provide primary health care for their communities. The NP collects standardised diagnostic and outcome information and includes the PCP or other members of the team at each turning point of the follow-up. Medication is adjusted following the Texas children's medication algorithm. She also defines the care management level, which involves a developmental paediatrician, or a child psychiatrist from a university affiliated outpatient clinic.

Results: Primary outcomes are externalising (especially ADHD) and internalising symptoms, as well as quality of life. Feasibility data will be presented with regard to the resources required for the programme, human and data management needs, and the outcome changes after the programme implementation.

Conclusions: This pilot study will allow proposing an ADHD integration programme that will be proposed to the 184 family health teams in Ontario, serving over three million Ontarians

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ADHD Atten Deficit Hyperact Disord. 2017;9:S25.

POOR QUALITY OF DECISION-MAKING IN ADULTS WITH ADHD IS LINKED TO DELAY AVERSION AND LONGER DELIBERATION TIME.

Sorensen L, Sonuga-Barke E, Brevik EB, et al.

Objectives: We have previously shown that children with ADHD's suboptimal decision-making (DM) in the face of risk is related to their delay aversion (the motivation to avoid delay), and not to a predominant tendency to be impulsive (short deliberation time) or risk prone (Sorensen et al. 2016). In the current study, we extended our study to adults by using the same task-the cambridge gambling task (CGT). On the basis of the previous results we predicted that adults with ADHD would also show suboptimal choice patterns linked to delay aversion.

Methods: A clinically recruited group of adults with ADHD (n = 29) and a group of healthy controls (HC) (n = 32) performed the CGT. The mean age of the sample was 34.49 years (SD = 8.28), with a female dominance (57.4%). The group differences in age and gender were non-significant. Univariate ANOVAs were conducted, with linear regression analyses as follow-up of significant between-group effects.

Results: Adults with ADHD showed lower quality of DM scores than the HCs (p = 0.005). None of the other CGT scores were different between the groups. Delay aversion and longer deliberation times predicted this poorer quality of DM score, whereas the scores of risk taking or risk adjustment did not.

Conclusions: Both adults and children with ADHD are less rational during DM. In both cases this is linked to delay aversion. It is possible that individuals with ADHD compensated for impulsive behaviour and slowed down their speed in DM. There is little evidence from our studies that ADHD is associated with risk proneness

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ADHD Atten Deficit Hyperact Disord. 2017;9:S11.

CAN WE RESOLVE VARYING ADHD PREVALENCE ESTIMATES IN THE U.S.? A CLOSER LOOK AT NSCH 2007 AND 2008 AND 2011-2012.

Song M, Dieckmann N, Nigg J.

Objectives: ADHD prevalence is widely discrepant among population surveys (11%) and epidemiological evaluations (2-6%). Estimates of changes in prevalence over time also vary, from a steady change (in surveys) to no change (epidemiological investigations). We aimed to clarify these discrepancies by re-examining a major U.S. survey of case identification rates, the national survey of children's health (NSCH).

Methods: Using NSCH 2007/2008 and 2011/2012 (n = 68,301 and 70,609) we stratified identification of ADHD by: Current status, severity, psychiatric comorbidity, and ADHD medication usage. Using those criteria, identifications were coded into four confidence levels: Definite, Probable, Doubtful, and No ADHD.

Results: In the 2011/2012 NSCH, 5.49% of children aged 5-17 had Definite ADHD; 7.83% were definite/probable. This was an increase from 4.04 and 6.06% (respectively) five years earlier. Definite rather than unlikely cases were the primary drivers of change over time.

Conclusions: This analysis enhances understanding of the discrepancy between epidemiological and case identification rates for ADHD in the U.S. When cases seen as low confidence identifications (e.g., mild, never treated) are considered false positives, case identification drops from around 11 to 5-8%, closer to, but still higher than, epidemiological estimates. Growth in case identification, however, was primarily within the definite category, suggesting the increase was not due to broadening DSM-V criteria or changes in clinician thresholds. Discussion will consider methodological issues

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ADHD Atten Deficit Hyperact Disord. 2017;9:S16.

NEUROBIOLOGICAL MARKER FOR CHILD AND ADULT ADHD DIAGNOSES.

Super H, et al.

Objectives: Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders affecting 3-7% of school-aged children worldwide. In the last decade it has become clear that ADHD is a chronic disease where about 50-60% of ADHD cases persist into adult life. ADHD is associated with a range of clinical and psychosocial impairments. In children hyperactivity, impulsivity and inattention are the core symptoms of ADHD. In adults these core symptoms are also present but inattention is more prominent. Correct diagnosis of ADHD remains challenging, especially as several other psychiatric and medical disorders show the similar symptomology. The diagnosis of ADHD is clinic-based upon a cluster of symptoms and criteria established by guidelines such as the DSM-V. However, objective markers are needed to support the clinical ADHD diagnosis in children and adults. Recent studies suggest that a neurobiological marker (eye vergence, i.e. where the eyes move in opposite directions) can detect ADHD in children and adults. The eyes converge during orienting attention (Sol Puig et al. PLoS One, 2013), as evidenced by visual event-related potentials at parietal locations (Sol Puig et al. PLoS One, 2016). This attention related vergence is impaired in ADHD patients (Sol Puig et al. PLoS One, 2015).

Methods: We review the neurobiology and current findings of eye vergence and the relevance of these measurements for the clinical diagnosis of ADHD.

Results: Neural circuits underlying eye vergence and attention largely overlap. Using machine learning, eye vergence measurements can classify ADHD in children and adults with high (>90%) accuracy.

Conclusions: Eye vergence is a promising candidate for an objective clinical diagnosis of ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S24.

A CAUSAL LINK BETWEEN ATTENTIONAL SELECTION AND READING ABILITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sun L, Wang E, Luo X, et al.

Objectives: Children with Attention-Deficit/Hyperactivity Disorder (ADHD) have been reported at significantly higher risk of showing reading disorder or difficulties. However, the neural substrate underlying this phenomenon has yet to be characterized. Here, we report a first attempt to identify the relationship between electroencephalographic (EEG) markers of spatial attention and reading ability in children with ADHD.
Methods: EEG data of 915-year-old children with ADHD (n = 38) and typically developing (TD) controls (n = 36) were collected while they searched for a shape circle target among diamonds. Additionally, rapid automatized naming task were conducted to evaluate the reading ability of children.
Results: Children with ADHD showed slower response times than TD children on rapid automatized naming task. For event-related potentials (ERPs), the shape target elicited smaller N2pc in children with ADHD compared with typically developing children. The smaller N2pc amplitude predicted lower levels of reading ability in children with ADHD but not in the TD children. Moreover, the early occipital P1 component did not show significant difference between the two groups. However, the P1amplitude was negatively correlated with the reading ability in TD children but not in the children with ADHD.
Conclusions: The correlation between the N2pc decrement and poor reading ability in ADHD suggests that their reading problems might in part be due to the impaired attentional selection. On the other hand, the early visual P1 component might play important roles in the development of reading for the TD children. Our findings provide a neurophysiological basis for the subjective reports of reading difficulty in children with ADHD and highlight the importance of visual spatial attention in higher neurocognitive functions

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ADHD Atten Deficit Hyperact Disord. 2017;9:S35-S36.

EARLY IDENTIFICATION OF AND FACILITATION FOR CHILDREN WITH SYMPTOMS OF ADHD IN PRESCHOOL.

Tangen R, Larsen K, Haugland Y.

Objectives: Children with ADHD spend most of their day in kindergarten or preschool. To ensure positive development it is essential that preschool staff have good knowledge on facilitation and teaching of preschool children with ADHD. This study sought to increase knowledge on early identification of ADHD symptoms in preschool-aged children, and education and facilitation for those children for preschool staff, educational advisors and parents. The study investigated whether a teaching and supervision programme for professionals and parents would increase the knowledge of early symptoms associated with ADHD, and on facilitation and education for those children.
Methods: The educational team and parents of 15 preschool children with symptoms associated with ADHD was included in the study. Pre-programme focus group interviews assessed participants' expectations, current knowledge and attitudes. In addition to serve as a baseline measure the information from these interviews influenced the content of the teaching and supervision programme (TSP). The TSP included lectures, group assignments with supervision, and bring-home assignments between teaching sessions. The themes for the teaching and supervision programme was; (1) General information on ADHD, (2) Assessment and parent-professional cooperation, (3) Facilitation for children with ADHD symptoms, (4) Effective strategies for challenging behaviours, (5) Risk and success factors for inclusion. The post-programme focus group interviews assessed self-experienced learning and changes in attitudes.
Results: The analysis of focus group interviews and notes of participating teams made during assignments indicates that participants experience increased knowledge on early identification of symptoms associated with ADHD in preschool-aged children. Further, the analysis clearly indicated that participation in the TSP lead to increased knowledge on facilitation and education of preschool children with symptoms associated with ADHD, and that the participation in this study leads to changes in educational practices.
Conclusions: This study implemented a model to increase competence in professionals and parents on ADHD-related behaviours. This study indicates that this model is effective in increasing knowledge and alter practices

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ADHD Atten Deficit Hyperact Disord. 2017;9:S30-S31.

WHITE MATTER MICROSTRUCTURAL CHARACTERISTICS AND GENETIC RISK FOR ADHD.

Wu Z, Hoogman M, Cao Q, et al.

Objectives: To investigate, whether the genetic risk for Attention-Deficit/Hyperactivity Disorder (ADHD) contributes to white matter microstructural characteristics in patients and healthy adolescents.

Methods: Three different cohorts were used in the current study: 1) Primary cohort: 206 children recruited in Beijing (ADHD and controls, aged 8-15 years); 2) NeuroIMAGE cohort: 165 adolescents and young adults recruited in The Netherlands (ADHD and controls, aged 11-26 years); 3) IMAGEN cohort: 1232 adolescents of European descent (general population, aged 14 years). All individuals underwent diffusion tensor imaging (DTI), and blood samples of 1.52 individuals were collected and genotyped. Tract-based spatial statistics (TBSS) analysis was performed after careful data preprocessing and quality control. Data analysis was performed in several steps: 1) Voxel-based case-control comparison in the primary cohort to generate regions of interest (ROIs); 2) mean fractional anisotropy (FA) was extracted from all ROIs that came out of Step1 in both primary and NeuroIMAGE cohort; 3) candidate gene-set-based analyses were performed with genes involved in dopamine/norepinephrine, serotonin, and neurodevelopment pathways in both Chinese and NeuroIMAGE cohorts. In a second approach, we calculated a biologically informed polygenic risk score (PRS) of the target gene sets in the IMAGEN cohort using a genome-wide association study of a Chinese cohort (n Γê+ 2000) as a reference; whole TBSS skeleton voxel-based regression was done with the PRS score in male and female subjects separately since more males ADHD were present in discovery samples.

Results: Decreased FA in anterior corona radiata in children with ADHD revealed in step 1 was associated with the dopamine/norepinephrine pathway in the primary cohort, but this was not replicated in the NeuroIMAGE cohort. The whole skeleton TBSS analysis in IMAGEN showed negative correlation between PRS and FA values in widespread regions in males but not females.

Conclusions: ADHD-relevant, biologically informed genetic analysis revealed potential associations with white matter microstructure development in cases as well as in the general population

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ADHD Atten Deficit Hyperact Disord. 2017;9:S35.

MULTILEVEL MODELLING OF NEUROFEEDBACK EEGLEARNING IN CHILDREN AND ADOLESCENTS WITH ADHD.

Zuberer A, Minder F, Drechsler R, et al.

Objectives: Over the past years neurofeedback (NF) has gained increasing popularity as a training method for children and adults with ADHD. Analyses of NF training efficacy usually focus on clinical pre-post improvements, but ignore specificity, e.g. whether or not children with ADHD gain control over their brain activity during the training sessions. It is still unknown why some children are good learners, while others seem unable to regulate their brain activity. The goal of the present study was to evaluate factors that might influence EEG-learning performance and to analyse the impact of EEG-learning on clinical outcome.

Methods: Forty-eight children with ADHD (aged 8-16 years; mean 11.1y, SD 2.1) participated in 15 double sessions of NF training of slow cortical potentials (SCPs). SCP NF training may be used to promote self-regulation of brain activity independently from individual EEG patterns, as short term changes of brain activity-either activation or deactivation-are fed back and trained. Stimulants were allowed on condition that the dose was kept stable during the training period. Severe comorbidities were excluded. For the analysis, a multilevel modelling approach with linear mixed effects models was deployed.

Results: We found differential EEG-learning effects for both training conditions: children learned better to activate than to deactivate their brain activity. Moreover,EEG-learningwas highly dependent on age and on medication. The inclusion of ADHD symptom severity or pre/post changes in ADHD symptom ratings did not improve the model fit.

Conclusions: By using a linear mixed models approach, this analysis takes into account inter- and intra-subject variability and thereby results in more precise findings as compared to traditional methods. We also conclude that the association between EEG-learning and clinical outcome in NF training deserves further examination

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ADHD Atten Deficit Hyperact Disord. 2017;9:S31.

THE POTENTIAL SEX DIFFERENCES IN THE RESTINGSTATE FRACTIONAL AMPLITUDE OF LOW FREQUENCY FLUCTUATION IN CHILDREN WITH ADHD.

Yanfei W, Li S, Lu L, et al.

Objectives: To find out if the fractional amplitude of low frequency fluctuation (fALFF) is different between boys and girls with ADHD in resting-state functional magnetic resonance imaging.
Methods: There were 38 children with ADHD in our study including 31 boys and seven girls. Forty-two well developed children were involved too, including 29 boys and 13 girls. Total scores of C-WISC and ADHD rating scale were used to measure intelligence quotient and the severity of ADHD. fALFF was measured for each child. Analysis of covariance (ANCOVA) was used to find out the difference between the group and the sex with intelligence quotient as covariance. Multiply comparison correction was made by +¦-sim ($P < 0.05$ corrected).
Results: Sex-by-group analysis reveal that fALFF is lower in the boys with ADHD in the left cerebellum ($t = -4.76$, $t = -3.47$) when compared to boys without it; girls with ADHD show a higher fALFF in bilateral cerebellum ($t = 4.87$, $t = 6.22$, $t = 4.60$, $t = 4.16$) when compared to girls without it. Only in girls with ADHD, fALFF in the insula ($t = -4.41$, $t = -4.05$) is lower and in the thalamus ($t = 4.58$) is higher than girls without ADHD. The correlation analysis indicates that there is a negative relationship ($r = -0.89$, $P < 0.05$ corrected) between the fALFF of the left cerebellum of girls with ADHD and the scores of inattention symptoms.
Conclusions: Sex difference existed potentially in the fALFF of children with ADHD. The decreased fALFF of the cerebellum might deteriorate the attention deficit symptom of girls with ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S17.

TRAIT ANHEDONIA: A RISK FACTOR FOR UNDETECTED ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SUICIDE IN ADULT DEPRESSED PATIENTS.

Sternat T, Fotinos K, Fine A, et al.

Objectives: Depression and suicide are among the leading causes of disability and death respectively. Research suggests that approximately 11% of adolescents experience depression. Depressed adolescents are six times more likely to attempt suicide compared to non-depressed counterparts. Adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD) are more likely to develop adult depression. As core symptom of depression, anhedonia, is common in ADHD and associated with poorer treatment response to antidepressants. The aim of this study was to determine predictive factors and clinical features associated with the development of treatment-resistant depression (TRD) and suicidal symptoms in adults.
Methods: Data was collected from consecutive referrals ($n = 160$) to a mood and anxiety clinic. Patients referred for ADHD were excluded from the analysis. Diagnosis was established through the mini international neuropsychiatric interview plus 5.0.0 and a semi-structured interview. One-way analysis of variance and t-tests were performed to examine predictive factors related to TRD and increased risk for suicide.
Results: The results indicated that 34% of patients referred for TRD had undiagnosed ADHD and 55% presented with chronic anhedonia. Clinical features included SSRI failure (44%), suicide ideation (62%), and suicide attempts (16%). The number of failed psychiatric medications ($p < 0.001$), SSRI failures ($p = 0.020$), and number of SSRI failures ($p = 0.032$) was predictive of ADHD. Chronic ($p = 0.002$) and present ($p = 0.003$) anhedonia predicted SSRI failure. Chronic anhedonia predicted increased suicide ideation ($p = 0.05$) and attempts ($p = 0.036$).
Conclusions: This study demonstrated that trait anhedonia or low hedonic tone may be a link between TRD and ADHD, which may predict poorer treatment outcomes in a subset of patients treated with SSRIs. Low hedonic tone may increase the risk of suicidality. These findings emphasise the importance of screening depressed patients who fail SSRI treatment for ADHD and low hedonic tone in order to assure safety and optimal outcomes

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ADHD Atten Deficit Hyperact Disord. 2017;9:S41.

WEIGHT AND HEIGHT IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A LONGITUDINAL DATABASE STUDY ASSESSING THE IMPACT OF GUANFACINE, STIMULANTS OR NO PHARMACOTHERAPY.

Spalding W, Banaschewski T, Feldman B, et al.

Objectives: This study assessed the real-world impact of long-term guanfacine therapy administered alone or adjunctive to a stimulant on weight and height in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: Using data from anonymized U.S. Department of Defense electronic medical records (January 2009-June 2013), mixed-model regression analyses of longitudinal weight and height measurements normalised to z-scores were conducted for three cohorts: guanfacine (first interval of guanfacine exposure), first-line stimulant monotherapy (first interval of stimulant exposure), and unmedicated (post-diagnosis interval). Patients were diagnosed with ADHD, were aged 4-17 years at index date (initiation of any ADHD medication, or diagnosis if unmedicated), and had weight/height measurements in the year before index date and during the analysis period. Patients in the guanfacine cohort were allocated to subgroups based on previous/concurrent stimulant exposure.

Results: Across all cohorts, 47,294 patients were included in weight analyses (66.7% male) and 40,738 in height analyses (67.1% male). Guanfacine monotherapy did not lead to clinically meaningful deviations from normal z-score trajectories for weight (first-line, n = 943; non-first-line, n = 174) or height (first-line, n = 741; non-first-line, n = 138). For guanfacine adjunctive to a stimulant, weight (n = 1663) and height (n = 1.339) z-scores followed declining trajectories. First-line stimulant monotherapy led to declining weight (n = 32,999) and height (n = 28,470) z-score trajectories during the first 1-2 years and 3-4 years, respectively; weight z-scores subsequently returned to pre-index date levels. In patients not receiving ADHD medication, weight (n = 11,515) and height (n = 10,050) z-scores were stable.

Conclusions: This study found little evidence that long-term guanfacine monotherapy, administered first-line or non first-line, was associated with deviations from normal growth. As expected, stimulant monotherapy resulted in initial reductions in growth which attenuated over time. Guanfacine adjunctive to a stimulant led to declining trajectories in weight and height z-scores

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ADHD Atten Deficit Hyperact Disord. 2017;9:S8.

THE EFFECT OF ITGA1 ON BRAIN WHITE MATTER AND COGNITIVE PHENOTYPE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sun X, Zhao C, Cao Q, et al.

Objectives: According to recent genome-wide association studies and meta-analysis of ADHD, ITGA1 gene plays a significant role in neuron projection morphogenesis, which may be involved in neurodevelopment. We aimed to investigate the association of ITGA1 with ADHD on brain and cognitive phenotype.

Methods: 115 individuals (age 8.3-15.8 years) were recruited, including 55 ADHD patients and 60 control boys. Magnetic resonance scanner (3T, Siemens) was used to collect MRI data in the Imaging Center for Brain Research, Beijing Normal University. Three hypotheses were assumed to explain the phenomenon: 1) diagnosis 9 polymorphisms interaction effect; 2) diagnosis main effect; 3) polymorphism main effect. Voxel-based analysis were performed, which analysed the whole brain white matter fractional anisotropy (FA) images. As for cognitive score and FA value of every individual, a general liner model was applied to confirm the existence of the significant interaction. The diagnosis and SNP main effect have to be tested if the interaction did not exist.

Results: The ADHD patients and health control boys showed significant diagnose main effect in ADHD-RS-IV score (full scale, inattentiveness and hyperactivity/impulsivity: $p < 0.001$), one behavioural score of executive function (inhibition: $p = 0.019$), and Rey complex figure test (recall structure score and recall detail score: $p < 0.001$). Significant SNP main effect was discovered in one behavioural score of executive function (working memory: $p = 0.013$). Significant interaction on FA value were uncovered in one cluster covering the left posterior corona radiate, the posterior of thalamic radiation, splenium of corpus callosum.

Conclusions: A variant of ITGA1 gene might be involved in the biological mechanism of ADHD through influencing the corona radiate and corpus callosum, then neuropsychological phenotype of inhibition and working memory

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ADHD Atten Deficit Hyperact Disord. 2017;9:S5.

THE INTERACTION OF ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR LIKE (BMAL1) AND ACETYLSEROTONIN O-METHYLTRANSFERASE (ASMT) AFFECTS THE COGNITIVE FUNCTIONS OF MALE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jin J, Liu L, Li H, et al.

Objectives: To explore the correlation between interaction of aryl hydrocarbon receptor nuclear translocator like (BMAL1) and acetylserotonin O-methyltransferase (ASMT) and the cognitive functions of male children with Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: A total of 870 Chinese Han ADHD children were recruited. Cognitive functions were evaluated using Rey-Osterrieth complex figure test (RCFT) for working memory, and intelligence test (IQ) was conducted using the C-WISC. Correlation between genes and cognitive functions was analysed using generalised multifactor dimensionality reduction (GMDR).

Results: Significant interaction effect of BMAL1 and ASMT was found on cognitive functions (p values varied from 0.005 to 0.033). In detail, the interaction of rs12421530 and rs1982350 of BMAL1 and rs6588810 of ASMT has effect on total IQ (test accuracy = 57.83%, p = 0.005), verbal IQ (test accuracy = 56.22%, p = 0.008), AIQ (test accuracy = 55.55%, p = 0.016) and BIQ (test accuracy = 56.63%, p = 0.009) in male children with ADHD. What's more, the interaction of rs1982350 of BMAL1 and rs6588807 and rs6588810 of ASMT has effect on structural forgotten score of RCFT (test accuracy = 60.07%, p = 0.008), and the interaction of rs1982350 and rs12421530 of BMAL1 and rs6588807 of ASMT has effect on detail forgotten score of RCFT (test accuracy = 57.17%, p = 0.033) in male children with ADHD as well.

Conclusions: Our present results suggest the influence of interaction of ASMT and BMAL1 on cognitive functions in male ADHD children

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ADHD Atten Deficit Hyperact Disord. 2017;9:S23.

PERIODIC LIMB MOVEMENTS ONSET LATENCY AND FERRITIN LEVELS IN CHILDREN WITH ADHD.

Konofal E, Janka D, Lecendreux M, et al.

Objectives: There is evidence that Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with sleep problems in children. Impressive publications have previously described restless legs syndrome (RLS) and periodic limb movements during sleep (PLMS) in children with ADHD. It has been reported that RLS at rest, during the evening, temporary removed during mental occupation or movement and PLMS, at a rate of > 5 per hour of sleep, affected mostly severe cases of ADHD. In these children, direct correlations between symptoms of ADHD and mechanism of sleep disruption, iron status dysregulation, underlying a hypothetical common dopaminergic deficit, has been hypothesised. However, this association was only analysed by using actigraphy or polysomnography, but not by using the simple PLMS index. The temporal evolution of periodic leg movements (PLM) and the relationship of their severity effect on diurnal ADHD symptoms has never been investigated. The aim of our study was to evaluate the predictive impact on RLS and ADHD symptoms severity of the temporal evolution of PLM patterns during sleep.

Methods: A group of 50 school-aged (10.3 ± 2.7 years) randomised children (14G, 36B) with ADHD, without specific sleep complaints expressed, not clinically referred for a diagnosis of RLS underwent systematic one-night video-polysomnography. PLM were detected following standard criteria and the PLMS index calculated. PLM analysis was done separately by each sleep cycle. PLMs nocturnal variation was also considered in light of slow wave activity (SWA).

Results: Most of these children with ADHD (65%) had a PLMS index > 5 (range 1.2.7-28.1). A tendency of positive correlation between PLMS index (11 ± 10) and ADHD-RS score (42 ± 10) is found, but above all, with the application of the PLM temporal analysis, we showed that the distribution PLM declined from the

first to the last sleep cycle, and especially in those with the most severe diurnal symptoms of ADHD. Children with a ADHD-RS score up to 40 (14/31) expressed polysomnographically a very short PLM Onset Latency (< 1 min after sleep onset latency) associated with a decrease in SWS period at each sleep cycle (> 20% of total sleep time) and the lowest ferritin (< 30 microg/L) ($p < 0.01$).
Conclusions: The PLM temporal analysis and PLM distribution during sleep seem to indicate that the most severe ADHD children have a short PLMOL, the lowest ferritin levels and a reduction of SWS density. Low ferritin level and common mechanism generating RLS, PLM and ADHD should be speculated. This study suggests that there is an association between PLMOL, SWS reduction, the severity of ADHD symptoms and iron deficiency expressed by low ferritin levels. Sleep recording and temporal analysis of PLMs could play a role in pharmacological management and demonstrate a causal association between ADHD, RLS and PLMS. Iron supplementation should be suggested also

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ADHD Atten Deficit Hyperact Disord. 2017;9:S35.

EFFICACY OF A DEVICE THAT COMBINES NEUROFEEDBACK, MOTION BIOFEEDBACK AND COGNITIVE ATTENTION TRAINING FOR ADHD IN CHILDREN: A RANDOMISED SINGLE-BLIND, CONTROLLED INTERVENTIONAL STUDY.

Johndrow J, Vaishnavi S.

Objectives: To assess the impact of a device (NeuroPlus) that combines neurofeedback and motion biofeedback with cognitive attention training on cognitive and behavioural symptoms in children with ADHD.
Methods: Subjects aged 8-13 years diagnosed with ADHD were randomised into the treatment group or control group. Out of 60 subjects screened, 26 subjects enrolled in the treatment group and 23 subjects in the control group. Subjects in the interventional group used the NeuroPlus system for 30 min, three times per week, for ten consecutive weeks (for a total of 30 sessions, with 900 min of system use). The control group had treatment as usual. Subjects could be on or off ADHD medications, but had to maintain their treatment as long as for the duration of the study. The outcome measures included objective testing results from the Quotient ADHD system, as well as results from the Conners-3 parent assessment.
Results: The treatment group performed significantly better than the control group on Quotient Motor ($p = 0.006$, effect size 1.22), Quotient Attention ($p = 0.026$, effect size 0.54), and Quotient Global Index ($p = 0.031$, effect size 1.00). The treatment group also was significantly better than the control group on the following Conners-3 parent scores: Global index ($p = 0.007$, effect size 0.86), inattention ($p = 0.006$, effect size 0.86), Hyperactivity ($p = 0.026$, effect size 0.70), and learning problems ($p = 0.031$, effect size 0.67). The treatment group was not significantly different from the control group on oppositional defiance, executive functioning, and aggression on Conners-3.
Conclusions: This study showed that a device that combines multiple modalities (neurofeedback, motion-based feedback, and cognitive attention training) can significantly improve core ADHD symptoms in children over ten weeks. The improvement was seen with both objective measures (as measured by the Quotient ADHD system), as well as subjective measures (as measured by the Conners-3 parent assessment). A larger trial with a longer assessment period may be beneficial to assess for long-term benefits

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ADHD Atten Deficit Hyperact Disord. 2017;9:S15.

TOWARDS EVIDENCE-BASED ASSESSMENTS: CLINICAL UTILITY OF RATING SCALES AND COGNITIVE TEST METHODS IN DIAGNOSTIC ASSESSMENT AND TREATMENT EVALUATIONS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gustafsson P, Tallberg P.

Objectives: The aim of this study was to examine if clinical utility in diagnostic assessments and treatment evaluations could improve by combining different methods.
Methods: Two populations from two different child and adolescent psychiatry (CAP) clinics in Sweden were studied. Retrospective data were collected from clinical records. Concerning diagnostic utility, we compared children with (n = 78) and without (n = 40) ADHD. Sensitivity, specificity, and the area under the receiver operator characteristic (ROC) curve were calculated to evaluate classification accuracy of the Swanson,

Nolan and Pelham-IV questionnaire (SNAP-IV), the Conners continuous performance test (Conners; CPT II) and the quantitative behaviour test (Qb test). Concerning treatment evaluation, we compared the results from parent ratings of SNAP-IV and Qb test before and after initiation of medical treatment and in the follow-up one year later for 43 children with ADHD. Dose titration for 56 children were assessed with the Qb test. The Mann-Whitney U-test was used for group comparisons and Spearman rank-correlation and logistic regression for analysing associations. Sensitivity, specificity, positive predictive values and negative predicted values were calculated for the SNAP-IV parameters, the different Qb test scores and their combinations.
Results: The Conners CPT II and the SNAP-IV showed statistically significant diagnostic classification accuracy. A combination of SNAP-IV and Conners CPT II variables yielded better classification accuracy compared with either method alone. Using the Qb test when parent ratings were inconclusive, led to a good sensitivity when predicting treatment outcome one year later.
Conclusions: The SNAP-IV and Conners CPT II contributed to the diagnostic assessment of ADHD. Qb test was found to be useful in evaluating central stimulant treatment when parent ratings were inconclusive. To combine rating scales and performance-based assessment methods seems useful

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ADHD Atten Deficit Hyperact Disord. 2017;9:S7-S8.

PARENTING FACTORS AND FAMILY-LEVEL ADVERSITY AS PREDICTORS OF ADHD SYMPTOM TRAJECTORIES IN CHILDHOOD AND ADOLESCENCE AND OUTCOMES.

Gonzalez R, Pastrana MV, Bird H, et al.

Objectives: Parental characteristics and behaviours may impact the course of childhood ADHD. Cross-sectional studies suggest that early family adversity may moderate ADHD outcomes. Nevertheless, there is a paucity of longitudinal research that explores the relationship between early parenting factors and family-based adversity and ADHD symptom trajectories. We examine the role of parenting factors and early maltreatment on ADHD symptom trajectories and their outcomes using a well-characterized and ample longitudinal sample.
Methods: We analysed data from 2.491 children followed for three waves from the Boricua youth study, a longitudinal study of children and adolescents of Puerto Rican background. ADHD diagnosis was measured at each wave using the diagnostic interview schedule for children-IV. We describe the average and classes of developmental trajectories of ADHD symptoms through childhood and adolescence from first wave (ages 5-13) and examine family-level predictors and outcomes at third wave associated with the trajectories. Predictors include: Parental distress, parent-child relationship, monitoring, physical and emotional abuse and adverse life events. Outcomes include comorbidity, substance misuse and delinquency. Models were adjusted by age, sex and time-varying income, household education, parental psychopathology and ADHD medication status.
Results: Preliminary results using structural equation modelling show the average trajectory and slope were significant ($p < 0.001$), suggesting variability in initial values of ADHD symptoms and in their rate of change (fit indices: V2 3.52(1), RMSEA 0.032, CFI 0.99 and TLI 0.98). Emotional ($p < 0.01$), physical abuse ($p < 0.001$), and number of adverse life events ($p < 0.001$) at wave one were associated with the population average trajectory of symptoms. Using general growth mixture modelling, we identified four trajectories of ADHD symptoms (high, increasing, decreasing, and low). We are currently examining predictors of the four symptom trajectories and outcomes at wave 3.
Conclusions: Results underscore the role of parenting factors, early adversity and family environment in the course and development of offspring ADHD

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ADHD Atten Deficit Hyperact Disord. 2017;9:S21.

ARE THERE SIGNIFICANT ASSOCIATIONS BETWEEN THE SEVERITY OF ADHD SYMPTOMS AND OF AUTISTIC TRAITS IN CHILDREN AND ADOLESCENTS WITH ADHD?

Jespersen RAF, Neystab+© +, Kier A, et al.

Objectives: To examine potential relationships between the severity of ADHD symptoms and that of autistic trait (AT).

Methods: Sample: 93 children (59% boys; age range 5-17) ICD-10 diagnoses: F.90.0 Disturbance of attention and activity (N:66) F.90.1 Hyperkinetic conduct disorder (N:3) or F.98.8 Attention deficit disorder without hyperactivity (N:24). Exclusion criterion: Autism spectrum disorder (ASD) diagnosis. The children were consecutively recruited as they were referred for clinical evaluations in an outpatient clinic at the national hospital of the Faroe Islands. The severity of ADHD symptoms was operationalised by using the ADHD-RS questionnaire and AT was operationalized by using the social responsiveness scale. The children's parents completed both questionnaires. We used Pearson bivariate correlation analyses and linear multiple regression analysis to examine the associations of interest.

Results: There was a significant positive correlation between the severity of AT and that of the total ADHD symptoms (r =.650; p <.001). Both the severity of the inattentive symptoms (r =.527; p <.001) and that of the impulsive/hyperactive (I/H) symptoms (r =.609; p <.001) correlated significantly with the severity of AT. A multiple regression analysis with AT as the dependent variable and the inattentive and I/H symptoms severity as independent variables showed a significant association between AT and both ADHD symptom dimensions-with the I/H symptoms (± =.457; p <.001) contributing more to the model than the inattentive symptoms (± =.278; p =.004).

Conclusions: In line with previous reports (Kotte et al. 2013; Taylor, Charman, & Ronald 2015) the ADHD symptoms severity is significantly associated with that of subclinical AT in children and adolescents with ADHD and without comorbid ASD. The significant associations between the severity of ADHD symptoms and that of AT may reflect impairments in underlying neural systems that lead to both types of behaviour

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ADHD Atten Deficit Hyperact Disord. 2017;9:S25.

TEMPERAMENTAL DIFFERENCES IN ADULTS WITH AND WITHOUT A CHILDHOOD DIAGNOSIS OF ADHD.

Jain U, Jain S.

Objectives: Adults identified with ADHD in adulthood are often denied a diagnosis unless there has been a confirmed diagnosis in childhood (very relevant to insurance coverage of medications). The DSM-V has changed the criterion to having symptoms before the age of 12 but, in fact, temperamental differences using the temperament and character inventory can be compared to determine their relevance.

Methods: As a secondary finding in a study looking at personality disorders comorbid with ADHD, n = 154 ADHD adults-five groups: A) n = 65 (noADHDinattentive (ADHD-I) as a child) + ADHD-I adult B) n = 39 (no ADHD combined (ADHD-C) as a child + ADHD-C adult), C) n = 12 ADHD-I as child/adult, D) n = 32 ADHD-C as child/adult and E) n = 6 ADHD-C as child and ADHD-I as adult. Group A and C were compared as were groups B and D. Group E was too small.

Results: No differences in age and gender between groups. In looking at temperamental differences groupAversusC = NS, groupBversusDNS.

Conclusions: A pre-existing diagnosis should not be used to determine the stability or validity of the diagnosis. It is reasonable that the underlying temperamental characteristics of adult patients with ADHDremain stable

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ADHD Atten Deficit Hyperact Disord. 2017;9:S42.

CLINICAL INVESTIGATION OF CHILDREN WITH ADHD TREATED WITH ATOMOXETINE ORAL SOLUTION.

Ichiyama T, Ishikawa N, Matsufuji H, et al.

Objectives: Atomoxetine oral solution has been developed for patients who have difficulty swallowing capsules, and was first sold in Japan in November 2013. We investigated clinical features including validity, safety, and tolerability of the atomoxetine oral solution for children with ADHD.

Methods: The subjects were 42 children with ADHD (male: female = 35: 7) who were treated with the atomoxetine oral solution in our hospital from December 2013 to November 2016. We investigated their clinical records retrospectively to analyse clinical features of the affected children, and validity, safety and tolerability of the atomoxetine oral solution.

Results: The ages of diagnosing ADHD of the subjects were median 6.5 years (ranges 4.3-10.1 years). The ages of starting treatment with the atomoxetine oral solution for the subjects were median 6.9 years (ranges 4.3-13.6 years). The subjects who could continue to take the atomoxetine oral solution were 23 of 42 children (55%). The solution worked well in 18 of the 23 children (78%). Nineteen children discontinued to take the solution. The reasons were as follows: Twelve (12) children disliked taking the solution tasting bitter, four children were in bad humour, two children had suspected drug eruptions, and one child had continuous nausea.

Conclusions: Our results suggest that the atomoxetine oral solution is useful for children with ADHD who cannot take capsules. It is likely that a bitter taste of the solution is its weakness

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ADHD Atten Deficit Hyperact Disord. 2017;9:S13.

A COMPARISON OF SCREENING INSTRUMENTS TO IDENTIFY ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kim D, Kim K-Y, Kim H-J, et al.

Objectives: The aim of this study was to determine the validity of three screening instruments for adult Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: This study included 52 adults with ADHD-like symptoms who visited Severance hospital in South Korea. All patients completed Conners adult ADHD rating scale-Korean (CAARS-K). Among them, 45 patients conducted digit span (DS) and 31 patients conducted continuous performance test (CPT). Each patient completed a clinical interview with an expert psychiatrist and diagnosis was made according to the diagnostic and statistical manual for mental disorder-IV (DSM-IV). Sensitivity and specificity were calculated for each of the tools to examine the validity of the screening instruments.

Results: Of the 52 patients, 32 were diagnosed with ADHD. Nine patients (45%) of the Non-ADHD group had mood disorder. Male to female ratio was higher in the ADHD group compared with that of the non-ADHD group. Sensitivity and specificity of the individual tools were; for CAARS-K 0.750 and 0.40; for digit span 0.037 and 0.889; for CPT 0.333 and 0.770 respectively. The sensitivity increased to 0.889 when CAARS-K and CPT were both conducted.

Conclusions: Adult ADHD affects a great deal in daily function. Variety of comorbidity and difference in symptomatology compared with that of a child delays the detection. CAARS-K is an adequate screening tool for adult ADHD which could advance the diagnosis. Using CPT additionally could effectively identify ADHD in adult

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ADHD Atten Deficit Hyperact Disord. 2017;9:S20-S21.

GAZE MOVEMENTS FOR SOCIAL ATTENTION DISSOCIATING CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER IN A VISUAL EXPLORATION TASK.

Ioannou C, Seernani D, Hill H, et al.

Objectives: According to a recent review and meta-analysis (Chita-Tegmark, 2016), the main factor determining gaze control of patients with autism spectrum disorder (ASD) in tasks requiring social attention is social content, defined as the number of people in the scene, as well as their relationship, level of activity and interaction. However, to our knowledge, the study of gaze movements for social attention has been

restricted to patients with ASD and rarely included those with Attention-Deficit/Hyperactivity Disorder (ADHD). Given current discussions of potential aetiological overlap between ASD and ADHD (Biscaldi et al. 2015; Rommelse et al. 2011), the present study compares these two clinical groups with regard to their gaze movements during visual exploration of social stimuli differing in complexity.
Methods: The subjects of the study are children and adolescents with ADHD, ASD and healthy controls (n = 90; 10-13 years; all native German speakers). Pictures of real-life social interactions, differing in complexity (one person vs. four persons interacting, two pictures each) were presented for 120 s each. To ensure task engagement, participants were told to pay attention to the pictures so as to answer questions following their presentation. Groups will be compared across levels of social complexity in fixation durations, dwell times, transitions between areas of interest and further parameters of gaze control.
Results: Preliminary results suggest ASD and ADHD patients differ in both dwell times for socially significant areas of interest and in transitions between them. Scatter of fixations in clinical groups will be further investigated.
Conclusions: Our study compares for the first time ASD and ADHD in gaze movements during exploration of social interactions and will therefore contribute to the discussion of potential overlap between these disorders regarding the dynamics of gaze behaviour

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Am J Intellect Dev Disabil. 2017 Mar;122:97-117.
IMPACT OF ATTENTION TRAINING ON ACADEMIC ACHIEVEMENT, EXECUTIVE FUNCTIONING, AND BEHAVIOR: A RANDOMIZED CONTROLLED TRIAL.
Kirk H, Gray K, Ellis K, et al.
Children with intellectual and developmental disabilities (IDD) experience significant difficulties in attention, learning, executive functions, and behavioral regulation. Emerging evidence suggests that computerized cognitive training may remediate these impairments. In a double blind controlled trial, 76 children with IDD (4-11 years) were randomized to either an attention training (n = 38) or control program (n = 38). Both programs were completed at home over a 5-week period. Outcome measures assessed literacy, numeracy, executive functioning, and behavioral/emotional problems, and were conducted at baseline, post-training, and 3-month follow-up. No training effects were observed at post-training; however, children in the training group showed greater improvements in numeracy skills at the 3-month follow-up. These results suggest that attention training may be beneficial for children with IDD; however, the modest nature of the intervention effects indicate that caution should be taken when interpreting clinical significance

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Am J Psychiatry. 2017 Aug;174:785-94.
PSYCHOSOCIAL STRESS AND BRAIN FUNCTION IN ADOLESCENT PSYCHOPATHOLOGY.
Quinlan EB, Cattrell A, Jia T, et al.
OBJECTIVE: The authors sought to explore how conduct, hyperactivity/inattention, and emotional symptoms are associated with neural reactivity to social-emotional stimuli, and the extent to which psychosocial stress modulates these relationships.
METHOD: Participants were community adolescents recruited as part of the European IMAGEN study. Bilateral amygdala regions of interest were used to assess the relationship between the three symptom domains and functional MRI neural reactivity during passive viewing of dynamic angry and neutral facial expressions. Exploratory functional connectivity and whole brain multiple regression approaches were used to analyze how the symptoms and psychosocial stress relate to other brain regions.
RESULTS: In response to the social-emotional stimuli, adolescents with high levels of conduct or hyperactivity/inattention symptoms who had also experienced a greater number of stressful life events showed hyperactivity of the amygdala and several regions across the brain. This effect was not observed with emotional symptoms. A cluster in the midcingulate was found to be common to both conduct problems and hyperactivity symptoms. Exploratory functional connectivity analyses suggested that amygdala-precuneus connectivity is associated with hyperactivity/inattention symptoms.

CONCLUSIONS: The results link hyperactive amygdala responses and regions critical for top-down emotional processing with high levels of psychosocial stress in individuals with greater conduct and hyperactivity/inattention symptoms. This work highlights the importance of studying how psychosocial stress affects functional brain responses to social-emotional stimuli, particularly in adolescents with externalizing symptoms

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Am J Public Health. 2017 Feb;107:322-28.

FAMILIAL FACTORS, VICTIMIZATION, AND PSYCHOLOGICAL HEALTH AMONG SEXUAL MINORITY ADOLESCENTS IN SWEDEN.

Donahue K, Langstrom N, Lundstrom S, et al.

OBJECTIVES: To determine the influences of victimization experience and familial factors on the association between sexual minority status and psychological health outcomes among adolescents.

METHODS: We used data from the Child and Adolescent Twin Study in Sweden, a prospective, population-based study of all twins born in Sweden since 1992. Cross-sectional analyses included individuals who completed assessments at age 18 years (n = 4898) from 2000 to 2013. We also compared psychological health among sexual minority adolescents and their nonminority co-twins.

RESULTS: Sexual minority adolescents were more likely than were unrelated nonminority adolescents to report victimization experiences, including emotional abuse, physical abuse or neglect, and sexual abuse. Sexual minority adolescents also reported significantly more symptoms of anxiety, depression, attention-deficit/hyperactivity disorder, disordered eating, and substance misuse in addition to increased parent-reported behavior problems. Victimization experience partially mediated these associations. However, when controlling for unmeasured familial confounding factors by comparing sexual minority adolescents to their same-sex, nonminority co-twins, the effect of sexual minority status on psychological health was almost entirely attenuated.

CONCLUSIONS: Familial factors-common genetic or environmental influences-may explain decreased psychological adjustment among sexual minority adolescents

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Anadolu Psikiyatr Derg. 2017;18:379-86.

EFFECT OF GENDER DIFFERENCES ON IMPULSIVITY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Gökçe S, et al.

Objective: Impulsiveness has been considered the core symptom of attention-deficit/hyperactivity disorder (ADHD). In this study, we aimed to assess effect of gender differences on impulsivity in adolescents diagnosed with ADHD.

Methods: One hundred and fifty-six adolescents (91 males, 65 females) who were admitted to the Erenköy Research and Training Hospital for Psychiatry and Neurology Child and Adolescent Clinic between 01.01.2016 and 01.05.2016 and diagnosed with ADHD were recruited to participate in this study. Adolescents filled out Barratt Impulsiveness Scale and parents completed the SNAP IV ADHD Scale.

Results: Of the participants, 41.6% (n=65) were female and 58.3% (n=91) were male. The mean age of girls was 14.3±1.7 years, and the mean age of boys was 14.4±1.7 years. The Barratt impulsivity mean total scores, the Barratt attentive impulsivity subscale mean scores, and the Barratt motor impulsivity subscale mean scores were significantly higher in the female ADHD group than in the male ADHD group. In multiple linear regression analysis, gender was significantly correlated with the Barratt impulsivity total mean score, the Barratt attentive impulsivity mean score, and the Barratt motor impulsivity mean score.

Conclusion: The finding of greatest interest in this analysis is that the adolescent girls who were diagnosed with ADHD had greater attentive and motor impulsivity scores than boys as measured by the BIS-11.

Although, some previous research reported inconsistent findings of impulsivity levels by gender, our findings confirm prior reports of higher impulsivity in the female clinical population

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Anadolu Psikiyatr Derg. 2017;18:611-20.

RELATION OF EMOTION REGULATION AND EMPATHY SKILLS WITH MATERNAL EMOTION REGULATION AND ATTACHMENT IN CHILDREN DIAGNOSED WITH ADHD.

Özyurt G, Öztürk Y, Akay A.

Objective: Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood neurodevelopmental disorder. Difficulties in the areas of emotion regulation and empathy were found in prior studies. Mother child attachment is important in the development of emotion regulation and empathy. We aimed to examine the relation emotional regulation and empathy skills in children with ADHD and emotion regulation and attachment properties in their mothers and to compare with healthy controls.

Methods: The study group consisted of 61 children (8-12 years old) diagnosed with ADHD. The control group (87 children) comprised patients of other clinics at hospital and was matched for gender and age to the ADHD patients. The Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL) was used to diagnose ADHD and allowed comorbidities. We evaluated disorder severity at the time of assessment using the DuPaul Attention Deficit and Hyperactivity Disorder Rating Scale. All patients were treatment-naive. Emotional Regulation Checklist (ERC) and KA-SI empathy scale were used to examine children emotional regulation and empathy. Difficulties in Emotion Regulation Scale (DERS) was used to indicate maternal emotional dysregulation status and Experiences in Close Relationship Scale-II was used to evaluate attachment properties in mothers.

Results: Children with ADHD had statistical significant lower scores in the areas of affective empathy, cognitive empathy, total empathy score and emotion regulation and cases had statistical significant higher scores in emotion lability. Mothers of children with ADHD had higher scores in anxious and avoidant attachment styles and all subscales of DERS. The correlation between, ADHD symptoms, KA-SI Empathy, ERC, Attachment Scale, and DERS was evaluated by Pearson's correlation analysis. Negative correlation was found between both attention deficit and hyperactivity scores of Du Paul scale and affective, cognitive empathy scores of KA-SI Emphatic Tendency Scale and emotion regulation scores of ERC; a positive correlation was determined between attention deficit and hyperactivity scores of Du Paul scale, mothers' anxious and avoidant attachment andDERS total scores, and emotional lability scores of ERC.

Discussion: Mother-child attachment and maternal emotion regulation skills have important roles in the emotion regulation and empathy skills of children. Better understanding of neuropsychologic development process of attachment, empathy and emotion regulation skills and their relations with each other may contribute to the treatment of children with ADHD

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Anadolu Psikiyatr Derg. 2017;18:495-502.

ASSESSMENT OF ELECTRONIC MEDIA USE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gormez V, et al.

Objective: Electronic media use is an emerging area of research interest, however its relationship with Attention Deficit hyperactivity disorder (ADHD) is neglected in Turkish literature. We therefore aimed to examine its relationship with certain variables and ADHD subtypes.

Methods: A total of 360 participants aged between 6-18 years, who attended Bezmialem University, Child and Adolescent Psychiatry Outpatient Clinic between January 2016 and October 2016, were screened with the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS) interview to ascertain diagnoses and a sociodemographic information tool was used to collect the relevant data.

Results: The mean age of the sample was 9.47±2.67 years, and 81.9% of them consisted of males. 20.6% of the sample was reported to spend between 2 and 4 hours a day using electronic media gadgets (TV viewing, cell phone and/or tablet/computer use), while 4-6 hours of use was reported in 15.8%, 6-8 hours in

11.4%, 8-10 hours in 9.4% and more than 10 hours/day in 18.2% of the total sample. Heavy users of electronic media (>6 hours/day) reportedly had significantly higher academic achievement and lower socioeconomic status as compared to those who used it at medium (2-6 hours/day) and low levels (<2 hours/day). Gender, the content of TV viewing and total electronic media use within the household also significantly differed between the heavy, medium and low intensity users. Regression analyses revealed that total daily electronic media use for 10 hours and above was significantly and independently associated with the current family psychiatric illness and low academic achievement of the child.
Conclusion: To the best of our knowledge, this is the first study reporting use of a variety of electronic media gadgets in a Turkish clinical sample of children and adolescents with ADHD. Results are in line with the existing international literature and highlights the excessive electronic media use in this clinical population. We recommend a routine screening for electronic media exposure in ADHD minors and increase awareness in their families and schools. Longitudinal and methodologically more robust studies are needed to examine cause-effect relationships

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Anadolu Psikiyatr Derg. 2017;18:478-84.
PREVALENCE OF ADHD IN NORTHERN CYPRUS.
Hekim B, Dirik E, et al.
Objective: We evaluated the prevalence of attention-deficit/hyperactivity disorder (ADHD) among primary school children in Nicosia, a province of the Turkish Republic of Northern Cyprus (TRNC).
Methods: ADHD screening scales were filled out by the teachers and parents of primary school children aged 6-11 years. The study was conducted in two stages. In the first stage, the Turgay DSM-IV-Based Disruptive Behavior Disorders Child and Adolescent Rating & Screening Scale (T-DSM-IV-S) was sent to the parents of 1140 students and also given to the teachers of children whose parents filled out the T-DSM-IV-S. For the second stage, children and parents whos e children had 12 points from the ADHD scales, either bythe parents or teachers report, were invited to our clinic for a semi-structured interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime; K-SADS-PL). ADHD was diagnosed with use of the K-SADS-PL in both children and their parents as well as in accordance with DSM-IV-TR ADHD criteria.
Results: The response rate for parents in stage I was 49.9%. A total of 125 children fulfilled the positive screening criteria. Ninety-eight parents were interviewed. The prevalence of ADHD was 12.8%. The major subtype was combined type (61.1%); the inattentive type was present in 33% of the sample, and the hyperactive-impulsive type in 5.6%.
Discussion: The prevalence of ADHD in primary school-aged children in a province in the TRNC was 12.8%. This is the first study to assess ADHD prevalence and subtype distribution in the TRNC

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Arq Neuropsiquiatr. 2017 Apr;75:204-08.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE IMPACT OF METHYLPHENIDATE ON WORKING MEMORY, INHIBITION CAPACITY AND MENTAL FLEXIBILITY.
Bolfer C, Pacheco SP, Tsunemi MH, et al.
Objective: To compare children with attention-deficit/hyperactivity disorder (ADHD), before and after the use of methylphenidate, and a control group, using tests of working memory, inhibition capacity and mental flexibility.
Methods: Neuropsychological tests were administrated to 53 boys, 9-12 years old: the WISC-III digit span backward, and arithmetic; Stroop Color; and Trail Making Tests. The case group included 23 boys with ADHD, who were combined type, treatment-naive, and with normal intelligence without comorbidities. The control group (n = 30) were age and gender matched. After three months on methylphenidate, the ADHD children were retested. The control group was also retested after three months.
Results: Before treatment, ADHD children had lower scores than the control group on the tests (p </= 0.001) and after methylphenidate had fewer test errors than before (p </= 0.001).

Conclusion: Methylphenidate treatment improves the working memory, inhibitory control and mental flexibility of ADHD boys

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Arq Neuro-Psiquiatr. 2017;75:563-69.

VALIDATION OF THE EXPRESSION AND EMOTION SCALE FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER INTO BRAZILIAN PORTUGUESE.

Simon MAVP, Reed UC, Vaughan B, et al.

Objective: To validate the parent-rated Expression and Emotion Scale for Children (EESC) for patients with attention-deficit/hyperactivity disorder (ADHD).

Methods: The EESC was applied to parents of children with and without ADHD. The children were divided into age groups: Group A, between six and eight years old; Group B, between nine and 11 years old; and Group C, between 12 and 15 years old. The validation was carried out according to the steps proposed by Guillemin et al. For the statistical calculation, Cronbach's ±, Pearson's correlation, the ICC and ROC curve were used.

Results: The statistical tests showed satisfactory coefficients: Cronbach's ± = 0.76; Pearson's correlation r = 0.91 with CI 95%; replicability ICC = 0.66; sensitivity 0.75; specificity 0.67; accuracy 71%.

Conclusion: According to psychometric data on internal and external consistency (reliability, reproducibility), sensitivity, and specificity, the parent-rated EESC for ADHD is useful in assessing emotional expression

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Aust N Z J Psychiatry. 2017 Apr;51:382-92.

ASSOCIATION BETWEEN CHILDHOOD DIMENSIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ADULTHOOD CLINICAL SEVERITY OF BIPOLAR DISORDERS.

Etain B, Lajnef M, Loftus J, et al.

BACKGROUND: Clinical features of attention deficit hyperactivity disorder can be frequently observed in cases with bipolar disorders and associated with greater severity of bipolar disorders. Although designed as a screening tool for attention deficit hyperactivity disorder, the Wender Utah Rating Scale could, given its factorial structure, be useful in investigating the early history of impulsive, inattentive or mood-related symptoms among patients with bipolar disorders.

METHODS: We rated the Wender Utah Rating Scale in 276 adult bipolar disorder cases and 228 healthy controls and tested its factorial structure and any associations with bipolar disorder phenomenology.

RESULTS: We confirmed a three-factor structure for the Wender Utah Rating Scale (' impulsivity/temper', ' inattentiveness' and ' mood/self-esteem'). Cases and controls differed significantly on Wender Utah Rating Scale total score and sub-scale scores (p-values < 10-5). About 23% of bipolar disorder cases versus 5% of controls were classified as ' WURS positive' (odds ratio = 5.21 [2.73-9.95]). In bipolar disorders, higher Wender Utah Rating Scale score was associated with earlier age at onset, severity of suicidal behaviors and polysubstance misuse; multivariate analyses, controlling for age and gender, confirmed the associations with age at onset (p = 0.001) and alcohol and substance misuse (p = 0.001).

CONCLUSION: Adults with bipolar disorders who reported higher levels of childhood symptoms on the Wender Utah Rating Scale presented a more severe expression of bipolar disorders in terms of age at onset and comorbidity. The Wender Utah Rating Scale could be employed to screen for attention deficit hyperactivity disorder but also for ' at-risk behaviors' in adult bipolar disorder cases and possibly for prodromal signs of early onset in high-risk subjects

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Behav Res Ther. 2017;97:163-69.

DO PARENTAL ADHD SYMPTOMS REDUCE THE EFFICACY OF PARENT TRAINING FOR PRESCHOOL ADHD? A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL.

Forehand R, Parent J, Peisch VD, et al.

Previous studies have suggested that children with Attention-Deficit/Hyperactivity Disorder (ADHD) may benefit less from behavioral parent training (BPT) if their parents have high levels of ADHD symptoms. We conducted a secondary analysis of data from a randomized controlled trial to test the hypothesis that parental ADHD symptoms reduce the efficacy of two BPT programs in a sample of preschoolers with ADHD. One intervention was specifically designed for children with ADHD (NFPP: New Forest Parenting Programme) and one was designed for children with Oppositional Defiant Disorder (ODD) (HNC: Helping the Noncompliant Child). Neither intervention was adapted to address parental ADHD symptoms. This secondary analysis included data from 164 parents and their 3-4 year-old children who were randomly assigned to one of the two programs or a waitlist group. Children were compared on ADHD and ODD outcomes at post-intervention and a 6-month follow-up. The presence of parent ADHD symptoms reduced the efficacy of BPT in only one of 16 analyses. Implications and limitations (e.g., low baseline rate of parental ADHD symptoms) of the findings are provided

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Biol Psychiatry. 2017 Mar;81:452-59.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN OFFSPRING OF MOTHERS WITH INFLAMMATORY AND IMMUNE SYSTEM DISEASES.

Instanes JT, Halmoy A, Engeland A, et al.

BACKGROUND: Prenatal inflammatory mechanisms may play a role in the pathogenesis of psychiatric disorders and could be relevant for attention-deficit/hyperactivity disorder (ADHD). We investigated maternal chronic somatic diseases with immune components as possible risk factors for ADHD in offspring.

METHODS: We performed a population-based nested case-control study by linking data from longitudinal Norwegian registers. We included all individuals born during the period 1967-2008 and alive at record linkage (2012). Individuals receiving ADHD medication during the years 2004-2012 were defined as patients with ADHD (N = 47,944), and all remaining individuals (N = 2,274,713) were defined as control subjects. The associations between maternal diseases and ADHD in offspring were analyzed using logistic regression models.

RESULTS: The following chronic diseases with immune components were related to ADHD in offspring: multiple sclerosis (adjusted odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.2-2.5), rheumatoid arthritis (adjusted OR = 1.7; 95% CI = 1.5-1.9), type 1 diabetes (adjusted OR = 1.6; 95% CI = 1.3-2.0), asthma (adjusted OR = 1.5; 95% CI = 1.4-1.6), and hypothyroidism (adjusted OR = 1.2; 95% CI = 1.1-1.4). In contrast, chronic hypertension and type 2 diabetes showed no significant associations. Estimates were almost unchanged with additional adjustment for parental ADHD, infant birth weight, and gestational age. Although point estimates for male and female offspring were different for some diseases (e.g., maternal asthma [adjusted OR = 1.7; 95% CI = 1.5-1.8 for female offspring and adjusted OR = 1.5; 95% CI = 1.4-1.6 for male offspring]), none of the associations differed significantly by offspring sex.

CONCLUSIONS: Several maternal somatic diseases with immune components were found to increase the risk of ADHD in offspring. The associations could involve several causal pathways, including common genetic predisposition and environmental factors, and increased insight into the mechanisms behind these relationships could enhance our understanding of the etiology of ADHD

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Biol Psychol. 2017;128:82-88.

ATYPICAL INTERFERENCE CONTROL IN CHILDREN WITH AD/HD WITH ELEVATED THETA/BETA RATIO.

Zhang D-W, Roodenrys S, Li H, et al.

The theta/beta ratio (TBR) is a major area of interest within electroencephalogram (EEG) research in AD/HD. While researchers suggest a prognostic role for TBR in AD/HD, its relationship to behavior remains uncertain.

Recent evidence suggests that elevated TBR in AD/HD may be related to atypical inhibition, particularly at an attentional level. This study aimed to examine the performance on three inhibitory tasks of children with AD/HD. Fifty-eight children with AD/HD participated, divided into an elevated TBR (ET) group and a control group (CT). A behavioral disassociation was found compared to CT, ET showed more difficulty in inhibiting surrounding stimuli but had less day-to-day inhibitory issues measured by BRIEF. There was no significant group difference on response inhibition. The results support the prognostic value of TBR in AD/HD. Elevated TBR may be an inhibitory biomarker; further studies are needed to explore the behavioral implications in patients without elevated TBR

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Biomedical Signal Processing and Control. 2018;39:204-12.

CLASSIFICATION OF ADHD AND NON-ADHD SUBJECTS USING A UNIVERSAL BACKGROUND MODEL.

Marcano JL, Bell MA, Beex AAL.

ADHD affects a major portion of our children, predominantly boys. Upon diagnosis treatment can be offered that is usually quite effective. Diagnosis is generally based on subjective observation and interview. As a result, an objective test for the detection or presence of ADHD is considered very desirable. Based on EEG, across multiple channels, using autoregressive model parameters as features, ADHD detection is approached here in analogy with the imposter problem known from speaker verification. Gaussian mixture models are used to define ADHD and universal background models so that a likelihood ratio detector can be designed. The efficacy of this approach is reflected in the traditional detector performance measures of the area-under-the-curve and equal-error-probability. The results ΓÇô based on a limited database of males, approximately 6 years of age ΓÇô indicate that high probability of detection and low equal error rate can be achieved simultaneously with the proposed approach, when using EEG collected during an attention network task. The effect of using contaminated data is investigated as well

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Body, Movement and Dance in Psychotherapy. 2017;1-15.

EMBODIMENT OF A FICTIONAL CHARACTER DURING DANCE MOVEMENT THERAPY WITH AN ADOLESCENT ADD-ÁPATIENT: CASE STUDY.

Selissky MA.

In dance movement therapy, we may work with metaphors that originate from the movement itself, or with symbolic images and situations. What happens, though, if a patient is to choose to embody a random fictional character from their favourite book or film? This case study illustrates the potential of embodiment work with an image of a fictional character, even if this character is not one of the recurrent motifs in literature or mythology and does not bear generally recognised symbolism. The author uses the Emotorics movement analysis system to assess the patient's body and motion profile transformation. The change of the patient's movement and behaviour in the course of a year's long therapy suggests a possibility of therapeutically effective application of the embodiment technique, provided that the choice of the character is based on the patient's actual challenges and subjective experience

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Cereb Cortex. 2017;27:4267-76.

STRUCTURAL COVARIANCE NETWORKS IN CHILDREN WITH AUTISM OR ADHD.

Bethlehem RAI, Romero-Garcia R, Mak E, et al.

Background: While autism and attention-deficit/hyperactivity disorder (ADHD) are considered distinct conditions from a diagnostic perspective, clinically they share some phenotypic features and have high comorbidity. Regardless, most studies have focused on only one condition, with considerable heterogeneity in their results. Taking a dual-condition approach might help elucidate shared and distinct neural characteristics.

Method: Graph theory was used to analyse topological properties of structural covariance networks across both conditions and relative to a neurotypical (NT; n = 87) group using data from the ABIDE (autism; n = 62) and ADHD-200 datasets (ADHD; n = 69). Regional cortical thickness was used to construct the structural covariance networks. This was analysed in a theoretical framework examining potential differences in long and short-range connectivity, with a specific focus on relation between central graph measures and cortical thickness.
Results: We found convergence between autism and ADHD, where both conditions show an overall decrease in CT covariance with increased Euclidean distance between centroids compared with a NT population. The 2 conditions also show divergence. Namely, there is less modular overlap between the 2 conditions than there is between each condition and the NT group. The ADHD group also showed reduced cortical thickness and lower degree in hub regions than the autism group. Lastly, the ADHD group also showed reduced wiring costs compared with the autism groups.
Conclusions: Our results indicate a need for taking an integrated approach when considering highly comorbid conditions such as autism and ADHD. Furthermore, autism and ADHD both showed alterations in the relation between inter-regional covariance and centroid distance, where both groups show a steeper decline in covariance as a function of distance. The 2 groups also diverge on modular organization, cortical thickness of hub regions and wiring cost of the covariance network. Thus, on some network features the groups are distinct, yet on others there is convergence

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Child Neuropsychol. 2017;1-21.
GREATER DELAY DISCOUNTING AMONG GIRLS, BUT NOT BOYS, WITH ADHD CORRELATES WITH COGNITIVE CONTROL.
Patros CHG, Sweeney KL, Mahone EM, et al.
Cognitive neuroscience models suggest both reward valuation and cognitive control contribute to reward-based decision-making. The current study examined the relationship between cognitive control and delay discounting (i.e., choosing smaller, immediate over larger, delayed rewards) in a large sample of boys and girls diagnosed with attention-deficit/hyperactivity disorder (ADHD; N-á=-á95) and typically developing control children (TD; N-á=-á59). Specifically, we examined performance on multiple measures of cognitive control (i.e., Go/No-Go task, Stop Signal task, and Spatial Span task) and delay discounting (i.e., Classic Delay Discounting and Real-Time Delay Discounting tasks), as well as the relationship between these measures. Results indicated that sex moderated the effects of group on task performance. Specifically, girls with ADHD, but not boys with the disorder, exhibited atypical delay discounting of real-time rewards. Results from correlational analyses indicated that delay discounting and cognitive control were not significantly correlated in the overall sample. Multiple regression analyses demonstrated that among girls with ADHD poorer spatial working memory and inhibitory control predicted greater real-time discounting. Collectively, findings provide support for distinct patterns of cognitive control and delay discounting among school-aged girls and boys with ADHD. Additionally, findings suggest that among girls with ADHD, those who exhibit relatively poor working memory and inhibitory control might be a particularly vulnerable subgroup with the greatest propensity to exhibit maladaptive decision-making

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Chinese Mental Health Journal. 2017 Jun;31:454-60.
ASSOCIATION BETWEEN SET SHIFTING IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND NRXNL GENE.
Lu Q, Liu L, Li HM, et al.
Objective: To study the association between set shifting in ADHD and NRXNl gene.
Methods: According to the diagnostic standard of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Totally 756 Han Chinese ADHD children and 133 Han Chinese unaffected children were involved in the analysis. Set shifting, including number connection time (NOTIM), number connection error times (NOERR), number and letter alternant connection time (LETIM), number and letter alternant error times (LEERR), and shifting time(each value was the difference between LETIM and NOTIM), was recorded by trail making test (TMT). Two SNPs (Single Nucleotide Polymorphisms) of NRXNl gene, rsl592728 and

rs4971652, were chose to detect genotype using Sequenom Mass ARRAY system by real time quantitative polymerase chain reaction. Linear regression analysis was applied-to explore the influence of set shifting, then, stratified analysis was used to study the association between set shifting and rsl 592728 as well as rs497l652 in ADHD cases and controls separately.
Results: Linear regression analysis showed that there was a negative correlation between set shifting and month (ß = 0.42, P < 0.001), IQ (ß = 0.34, P < 0.001), group (ß = 0.08, P = 0.004), GG genotype of rs4971652 (ß = 0.06, P = 0.039). Among ADHD children, there was a negative relationship between set shifting and month (ß = 0.46, P < 0.001), IQ (ß = 0.32, P < 0.001), GG genotype of rs4971652 (ß = 0.07, P = 0.018), a positive association was found between set shifting and ADHDSUB (ß = 0.06, P = 0.033), set shifting damaged higher with ADHD-I children than ADHD-C children. While, in controls, set shifting was in inverse relation with month (ß = 0.25, P = 0.002) and IQ (ß = 0.40, P < 0.001).
Conclusion: It suggests that the association between shift in ADHD children and polymorphism of NRXNl gene is existed, set shifting deficit less seriously in GG genotype

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Cleft Palate-Craniofacial Journal. 2015;52:e139-e140.

RELATIONSHIP BETWEEN RECEPTIVE LANGUAGE AND TEACHER AND PARENT REPORTS OF ATTENTION PROBLEMS IN CHILDREN WITH OROFACIAL CLEFTS.

Coppersmith J, Morgan A, Collett B, et al.

Background & Purpose: Children with orofacial clefts (OFC) have increased rates of learning and language disorders compared to the general population. There has been concern that these deficits are sometimes misdiagnosed as attention deficit hyperactivity disorder (ADHD), and as a result, children are not receiving the correct intervention services. This study aims to investigate the relationship between receptive language deficits and teacher and parent report of attention problems.
Methods & Description: The sample included 109 children (Male=58; CL0=13, CPO=18, CLP=78) ages 4-8 years (M=6.6 yrs, SD=1.5). Hearing was screened prior to assessment. Receptive language skills were assessed using the Clinical Evaluation of Language Functioning-Preschool 2 (CELF-P2) for the 4 year old children and CELF-4 for children 5 and up. The Attention Problems syndrome scale and Diagnostic and Statistical Manual-Oriented (DSM)-ADH Problems scale from the age appropriate Child Behavior Checklist (CBCL) were used to assess parent report of attention problems. The same scales were used from the age appropriate Caregiver or Teacher Report Form (TRF) to assess teacher report of attention and DSM-ADH problems. Raw scores were converted to z-scores, using age and sex adjusted norms for parent and teacher measures. Regression analyses with robust standard error were used to measure the association between child receptive language and attention problems, while controlling for parent SES and child age.
Results: Mean scores (SD) on the Attention Problems scale were 55.38 (6.76) for parent report and 56.06 (8.78) for teacher report. On the DSM-ADH Problems scale, they were 54.63 (6.74) and 56.85 (10.41); 18.5% scored above the clinical cutoff (T = 65) on each scale based on parent or teacher report. In the teacher report model, poorer receptive language scores were significantly associated with increased attention problems (Beta =-.361, p =.025) and ADHD behaviors (Beta =-.336, p =.028), over and above age and SES. In the parent report model, receptive language scores were not significantly associated with parent reports of attention problems or DSM-ADH behaviors.
Conclusions: Teachers tend to report more attention problems in children with OFC who had poorer receptive language skills regardless of age and SES. This suggests either co-occurrence of language and attentional problems, or that receptive language delays are sometimes misinterpreted as inattention in the classroom setting. When attentional problems are suspected in this population, screening for language delay may facilitate more appropriate early intervention

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Clin Neuropsychol. 2017 Feb;31:404-22.

PRESCHOOL SELF REGULATION PREDICTS LATER MENTAL HEALTH AND EDUCATIONAL ACHIEVEMENT IN VERY PRETERM AND TYPICALLY DEVELOPING CHILDREN.

Woodward LJ, Lu Z, Morris AR, et al.

OBJECTIVE: To examine the extent to which preschool emotional and behavioral regulatory difficulties were associated with an increased risk of later mental health and educational problems. Of particular interest was whether early regulatory abilities contributed to later risk once baseline child behavioral adjustment and cognitive function were taken into account.

METHOD: Data were drawn from a prospective longitudinal study of 223 children born very preterm (VPT; <32 weeks gestation, n = 110) and full term (37-40 weeks gestation). At corrected ages 2 and 4 years, children's regulatory abilities were assessed using (1) direct observation of child behavior, (2) a modified version of the Emotion Regulation Checklist, and (3) tester ratings of child behavior during neuropsychological testing. At age 9 years, mental health and educational achievement were assessed using the Development and Well-being Assessment interview and the Woodcock Johnson-III Tests of Achievement.

RESULTS: VPT-born children had poorer emotional and behavioral regulation across all measures and time points. They also had higher rates of DSM-IV mental health disorder and educational delay at age 9. Across both study groups, poorer self regulation was associated with an increased risk of ADHD, conduct disorder, anxiety disorders and any disorder net of preschool child behavior problems and social risk. In contrast, only associations between early regulation and later language and any educational delay remained significant after adjustment for preschool cognitive functioning and family social risk.

CONCLUSION: Early assessment of regulation in addition to behavioral screening may improve the early identification of preschool children at mental health risk

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Clinical Epigenetics. 2017;9.

LONG-TERM PRENATAL EXPOSURE TO PARACETAMOL IS ASSOCIATED WITH DNA METHYLATION DIFFERENCES IN CHILDREN DIAGNOSED WITH ADHD.

Gervin K, Nordeng H, Ystrom E, et al.

Background: Epidemiological studies have shown that long-term exposure to paracetamol during pregnancy is associated with attention-deficit/hyperactivity disorder (ADHD). The mechanism by which paracetamol may modulate the increased risk of developing ADHD is currently unknown. We have conducted an epigenome-wide association study (n=384 cord blood samples) and investigated whether prenatal exposure to paracetamol is associated with DNA methylation in children diagnosed with ADHD.

Results: Analyses identified significant differences in DNA methylation (n=6211 CpGs) associated with prenatal exposure to paracetamol for more than 20days in children diagnosed with ADHD compared to controls. In addition, these samples were differentially methylated compared to samples with ADHD exposed to paracetamol for less than 20ays (n=2089 CpGs) and not exposed to paracetamol (n=193 CpGs). Interestingly, several of the top genes ranked according to significance and effect size have been linked to ADHD, neural development, and neurotransmission. Gene ontology analysis revealed enrichment of pathways involved in oxidative stress, neurological processes, and the olfactory sensory system, which have previously been implicated in the etiology of ADHD.

Conclusions: These initial findings suggest that in individuals susceptible to ADHD, prenatal long-term exposure to paracetamol is associated with DNA methylation differences compared to controls

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Clin Psychopharmacol Neurosci. 2017;15:222-28.

THE RELATIONSHIP BETWEEN THE SNAP-25 POLYMORPHISM AND OMISSION ERRORS IN KOREAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kim E, Song D-H, Kim N-W, et al.

Objective: This study aimed to investigate the association between the synaptosomal-associated protein 25 kDa (SNAP-25) genotype and performance on the continuous performance test (CPT) in Korean children with attention-deficit/hyperactivity disorder (ADHD).

Methods: Eighty-seven children with ADHD (mean age, 9.23±1.99 years) participated in this study. Omission errors, commission errors, reaction time, and reaction time variability on the CPT were analyzed. The single-nucleotide polymorphism (SNP) rs3746544 (1065 T>G) of SNAP-25 was genotyped to examine the association with CPT performance.

Results: We found significantly more omission errors on the CPT among children with the TT genotype of SNAP-25 (t=2.56, p=0.012) after correcting for multiple testing.

Conclusion: Our results suggest the possible involvement of the SNAP-25 1065 T>G polymorphism in the inattention phenotype in children with ADHD. Further studies with more refined neuropsychological measures and much larger sample sizes are needed to confirm our findings

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CNS Spectr. 2017 Feb;22:22-30.

ADHD SYMPTOMS IN NON-TREATMENT SEEKING YOUNG ADULTS: RELATIONSHIP WITH OTHER FORMS OF IMPULSIVITY.

Chamberlain SR, Ioannidis K, Leppink EW, et al.

OBJECTIVE: Attention-deficit hyperactivity disorder (ADHD) has been associated with various manifestations of impulsivity in adults, including elevated rates of other impulsive disorders, substance use, questionnaire-based impulsivity scores, and inhibitory dysregulation on neurocognitive tests. The relationship between ADHD and all these other forms of impulsivity has yet to be explored within the context of a single comprehensive study.

METHODS: A total of 423 young adults, who gambled >/=5 times in the preceding year, were recruited using media advertisements and undertook detailed assessment including structured psychiatric interview, questionnaires, and neurocognitive tests. Participants with ADHD symptoms were identified using the Adult ADHD Self-Report Scale Screener (ASRS-V1.1) and were compared to controls using multivariate analysis of variance (MANOVA).

RESULTS: ADHD symptoms were found in 20.3% of the sample, but only 7.3% of these subjects had ever received a formal diagnosis. ADHD symptoms were associated with significantly lower quality of life, lower self-esteem, higher emotional dysregulation, higher impulsivity questionnaire scores, more problematic Internet use, greater occurrence of psychiatric disorders, and impaired stop-signal reaction times. Of these variables, stop-signal reaction times and Barratt attentional impulsiveness were the strongest predictors of group classification.

CONCLUSIONS: ADHD symptoms are common and under-diagnosed in young adults who gamble, and are most strongly linked with certain other types of impulsivity (questionnaire- and cognitive-based measures) and with emotional dysregulation, suggesting that these are each important considerations in understanding the pathophysiology of the disorder, but also potential treatment targets. It is necessary to question whether treatment for adult ADHD could be enhanced by considering self-esteem, emotional reactivity, and impaired inhibitory control as specific treatment targets, in addition to the core diagnostic symptoms of the disorder

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Complement Ther Med. 2017 Feb;30:14-23.

HERBAL MEDICINES IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A SYSTEMATIC REVIEW.

Anheyer D, Lauche R, Schumann D, et al.

OBJECTIVE: The purpose of this review is to identify evidence in herbal therapy in the treatment of ADHD concerning effectiveness and drug tolerability.

METHOD: For this Medline/PubMed, Scopus and the Cochrane Central Register of Controlled Trials (Central) were searched from their inception to 15 July 2016. Only randomized controlled trails (RCT) with children (0-18years) suffering from ADHD were included in this review.

RESULTS: Nine RCTs with 464 patients comparing herbal pharmaceuticals to placebo or active control were included. Seven different herbs were tested in the treatment of ADHD symptoms. Low evidence could be found for Melissa officinalis, Valeriana officinalis and Passiflora incarnata. Limited evidence could be found for pine bark extract and Gingko biloba. The other herbal preparations showed no efficacy in the treatment of ADHD symptoms.

CONCLUSION: While there is still a lack of sufficient numbers of RCTs no concrete recommendations for use can be made so far

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Curr Neurol Neurosci Rep. 2017 Feb;17:11.

TRANSCRANIAL MAGNETIC AND DIRECT CURRENT STIMULATION IN CHILDREN.

Hameed MQ, Dhamne SC, Gersner R, et al.

Promising results in adult neurologic and psychiatric disorders are driving active research into transcranial brain stimulation techniques, particularly transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), in childhood and adolescent syndromes. TMS has realistic utility as an experimental tool tested in a range of pediatric neuropathologies such as perinatal stroke, depression, Tourette syndrome, and autism spectrum disorder (ASD). tDCS has also been tested as a treatment for a number of pediatric neurologic conditions, including ASD, attention-deficit/hyperactivity disorder, epilepsy, and cerebral palsy. Here, we complement recent reviews with an update of published TMS and tDCS results in children, and discuss developmental neuroscience considerations that should inform pediatric transcranial stimulation

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Curr Psychiatry Rep. 2017 Jan;19:7.

USE OF STIMULANTS IN BIPOLAR DISORDER.

Perugi G, Vannucchi G, Bedani F, et al.

Several international guidelines indicate stimulants, including methylphenidate (MPH), amphetamines and derivatives, modafinil, and armodafinil among the second-third-line choices for bipolar depression. Efficacy of stimulants has been also reported for the management of residual depressive symptoms such as fatigue and sleepiness and for the management of affective, cognitive, and behavioral symptoms in children and adult bipolar patients with comorbid ADHD. Few case reports show positive results with MPH in the treatment of resistant mania. Finally, MPH might be an option in some bipolar forms observed in psychiatric presentations of frontotemporal dementia and traumatic brain injury. In spite of these preliminary observations, the use of stimulants in bipolar patients is still controversial. Potential of misuse and abuse and mood destabilization with induction of (hypo)manic switches, mixed states, and rapid cycling are the concerns most frequently reported. Our aims are to summarize available literature on this topic and discuss practical management implications

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Curr Psychiatry Rep. 2017 Feb;19:8.

THE ROLE OF NUTRITIONAL SUPPLEMENTS IN THE TREATMENT OF ADHD: WHAT THE EVIDENCE SAYS.

Lange KW, Hauser J, Lange KM, et al.

Attention-deficit hyperactivity disorder (ADHD) is a common behavioral disorder in children and adolescents and may persist into adulthood. Insufficient nutritional supply of long-chain polyunsaturated fatty acids (LC-PUFAs) and other components including various minerals has been suggested to play a role in the development of ADHD symptoms. This review presents the evidence regarding the role of nutritional PUFA, zinc, iron, and magnesium supplements in the treatment of ADHD with a focus on the critical evaluation of the relevant literature published from 2014 to April 2016. The evaluation of therapeutic nutritional LC-PUFA supplementation in ADHD has shown mixed and inconclusive results and at best marginal beneficial effects. The benefits of PUFAs are much smaller than the effect sizes observed for traditional pharmacological treatments of ADHD. The effectiveness of PUFA supplements in reducing medication dosage has been suggested but needs to be confirmed. Zinc, iron, and magnesium supplementation may reduce ADHD symptoms in children with or at high risk of deficiencies in these minerals. However, convincing evidence in this regard is lacking

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Curr Psychiatry Rep. 2017 Jan;19:1.

PRENATAL RISK FACTORS AND THE ETIOLOGY OF ADHD-REVIEW OF EXISTING EVIDENCE.

Sciberras E, Mulraney M, Silva D, et al.

While it is well accepted that attention-deficit/hyperactivity disorder (ADHD) is a highly heritable disorder, not all of the risk is genetic. It is estimated that between 10 and 40% of the variance associated with ADHD is likely to be accounted for by environmental factors. There is considerable interest in the role that the prenatal environment might play in the development of ADHD with previous reviews concluding that despite demonstration of associations between prenatal risk factors (e.g. prematurity, maternal smoking during pregnancy) and ADHD, there remains insufficient evidence to support a definite causal relationship. This article provides an update of research investigating the relationship between prenatal risk factors and ADHD published over the past 3 years. Recently, several epidemiological and data linkage studies have made substantial contributions to our understanding of this relationship. In particular, these studies have started to account for some of the genetic and familial confounds that, when taken into account, throw several established findings into doubt. None of the proposed prenatal risk factors can be confirmed as causal for ADHD, and the stronger the study design, the less likely it is to support an association. We need a new benchmark for studies investigating the etiology of ADHD whereby there is an expectation not only that data will be collected prospectively but also that the design allows the broad range of genetic and familial factors to be accounted for

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Dev Med Child Neurol. 2017 Mar;59:284-90.

PRELIMINARY EVALUATION OF CHILD SELF-RATING USING THE CHILD TOURETTE SYNDROME IMPAIRMENT SCALE.

Cloes KI, Barfell KS, Horn PS, et al.

AIM: To evaluate and compare how children with Tourette syndrome and parents rate tic and non-tic behavioral related impairment in home, school, and social domains; to compare these with clinician tic ratings; and to identify factors that may predict greater impairment.

METHOD: In a sample of 85 Tourette syndrome and 92 healthy control families, the Child Tourette Syndrome Impairment Scale, designed for parent-report and which includes 37 items rated for tic and non-tic impairment, was administered to parents and, with the referent modified, to children ages 9 to 17 years. Tic severity was rated using the Yale Global Tic Severity Scale (YGTSS). Analyses utilized descriptive and multivariate statistics.

RESULTS: Tourette syndrome children's and parents' impairment ratings were higher than HC ($p<0.001$) and correlated moderately ($r=0.46$ to 0.54; $p<0.001$). Children's and parents' tic impairment ratings correlated with YGTSS ($r=0.36$ to 0.37; $p<0.001$). Parents' average ratings were higher than children's for 19 tic and all

37 non-tic impairment items. For 29 items, children self-rated impairment higher for tics than non-tics. Diagnoses of attention-deficit-hyperactivity disorder and obsessive-compulsive disorder had larger effects on parent impairment ratings.
INTERPRETATION: The Child Tourette Syndrome Impairment Scale appears informative for child self-rating in Tourette syndrome

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Early Child Dev Care. 2017 Jul;187:1147-56.
ETHICAL CONSIDERATIONS FOR RESEARCH INVOLVING BOYS DIAGNOSED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Tucker LA, Govender K.
The 'new sociology of childhood' has activated a growing interest in children as social actors and their level of involvement in activities that affect their lives. In the field of research, debate is underway regarding the consent processes and methodological activities that support child participation. This paper highlights methodological and ethical considerations that emerged while engaging in research with young boys (aged 9–11 years old) with a formal diagnosis of attention-deficit/hyperactivity disorder (ADHD). Key issues include recruitment, informed consent, and participatory activities for data production. Sociocultural theories of childhood and disability are applied to reflect on the power and privilege operating through the research process. Engaging in research that involves children with disabilities, in which discourses of risk, stigma, and protection are elevated, problematizes the researcher–researched relationship and expands considerations of what constitutes ethical practice and 'valuable data'

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Early Hum Dev. 2017;115:9-15.
MATERNAL OBESITY AND ATTENTION-RELATED SYMPTOMS IN THE PRETERM OFFSPRING.
van der Burg JW, Jensen ET, van de Bor M, et al.
Background Maternal pre-pregnancy obesity, in term-born children, is associated with an increased risk of attention problems, however this relationship has not been explored among children born extremely preterm.
Aim To estimate the risk of attention problems at age 10 years in children born very preterm to overweight (i.e., body mass index (BMI) 25ΓÇô29 kg/m2) and obese (i.e., BMI 30 kg/m2) women relative to the risk among children born to women who were neither overweight nor obese (i.e. BMI < 25 kg/m2). Study design Multi-center prospective cohort study.
Methods A total of 764 children born before the 28th week of gestation and whose mother's pre-pregnancy height and pre-pregnancy weight were obtained at birth had an IQ 70 at age 10 years when parents and teachers completed Child Symptom Inventory-4 questionnaires that included items about the presence of ADHD.
Results Compared to children whose mother's pre-pregnancy weight was in the normal range (BMI < 25 kg/m2), children were at increased risk of parent-identified ADHD behaviors if their mother was overweight (odds ratio (OR) = 1.9; 95% confidence interval (CI): 1.1, 3.3), or obese (OR = 2.3; 95% CI: 1.4, 3.9). They were not at increased risk of teacher-identified ADHD characteristics if their mother was overweight before her pregnancy (OR = 1.0; 95% CI: 0.6, 1.8), or obese (OR = 1.0; 95% CI: 0.6, 1.6).
Conclusion Maternal overweight and obesity are associated with increased risk of parent-identified ADHD characteristics at 10 years of age in children born extremely preterm

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Eat Behav. 2017 Aug;26:148-54.

VALIDITY AND RELIABILITY OF THE ATTENTION DEFICIT HYPERACTIVITY DISORDER SELF-REPORT SCALE (ASRS-V1.1) IN A CLINICAL SAMPLE WITH EATING DISORDERS.

Carlucci S, Ivanova I, Bissada H, et al.

Individuals with eating disorders (EDs) commonly experience comorbid attention deficit hyperactivity disorder (ADHD). The shared features of EDs and ADHD, such as inattention, impulsivity and hyperactivity, may exacerbate ED symptomatology and pose challenges to treatment. It is important to screen patients with EDs for symptoms of ADHD to optimize their treatment outcomes. However, the psychometrics of common measures of ADHD have not yet been examined within an ED population. An example of such a measure is the ADHD self-report scale (ASRS-v1.1) symptom checklist, which identifies the presence of ADHD symptoms. This study reports a psychometric study of the ASRS-v1.1 in a clinical sample of 500 adults with an ED. A confirmatory factor analysis indicated the ASRS-v1.1 maintained its two-factor structure of inattention and impulsivity/hyperactivity. The item loadings demonstrated path invariance across ED diagnostic groups indicating construct validity. Further, the subscales exhibited good internal consistency and they were significantly correlated with other measures of impulsivity indicating convergent validity. The ED sample had significantly higher mean scores than published nonclinical norms indicating predictive validity, but the ASRS-v1.1 scores were not significantly different among ED diagnostic groups. Results suggest the ASRS-v1.1 is a valid and reliable screening tool for identifying symptoms of ADHD among adults seeking treatment for ED

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Environ Res. 2017 Oct;158:677-84.

CHILDHOOD POLYBROMINATED DIPHENYL ETHER (PBDE) EXPOSURE AND NEUROBEHAVIOR IN CHILDREN AT 8 YEARS.

Vuong AM, Yolton K, Xie C, et al.

BACKGROUND: Prenatal polybrominated diphenyl ether (PBDE) exposure has been associated with decrements in IQ and increased attention deficit/hyperactivity disorder related behaviors in children; however, data are limited for the role of postnatal exposures.

OBJECTIVES: We investigated the association between a series of childhood PBDE concentrations and Full-Scale Intelligence Quotient (FSIQ) and externalizing problems at 8 years.

METHODS: We used data from 208 children in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort. Child serum PBDEs were measured at 1, 2, 3, 5, and 8 years; missing serum PBDE concentrations were estimated via multiple imputation. The Wechsler Intelligence Scales for Children-IV and the Behavior Assessment System for Children-2 was used to assess intelligence and externalizing behavior, respectively, in children at 8 years. We used multiple informant models to estimate associations between repeated lipid-adjusted PBDEs and child neurobehavior and to test for windows of susceptibility.

RESULTS: Postnatal exposure to PBDE congeners (- 28, - 47, - 99, - 100, and - 153) at multiple ages was inversely associated with FSIQ at 8 years. For instance, a 10-fold increase in BDE-153 concentrations at 2, 3, 5, and 8 years were all related to lower FSIQ at age 8 (beta for 3 years: - 7.7-points, 95% CI - 12.5, - 2.9; beta for 8 years: - 5.6-points, 95% CI - 10.8, - 0.4). Multiple PBDE congeners at 8 years were associated with increased hyperactivity and aggressive behaviors at 8 years.

CONCLUSIONS: Postnatal PBDE exposure was associated with decrements in FSIQ and increases in hyperactivity and aggressive behaviors

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Epilepsy Behav. 2017.

PHYSICAL EXERCISE TO MANAGE SLEEP PROBLEMS IN PEDIATRIC PATIENTS WITH EPILEPSY AND ADHD.

de Lira CAB, Andrade MS, de Mello MT, et al.

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Epilepsy Behav. 2017.

RESPONSE TO "PHYSICAL EXERCISE TO MANAGE SLEEP PROBLEMS IN PEDIATRIC PATIENTS WITH EPILEPSY AND ADHD".

Ekinci O, Okuyaz.

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Epilepsy Behav. 2017;74:161-66.

RESPONSE TO ADRENOCORTICOTROPIC IN ATTENTION DEFICIT HYPERACTIVITY DISORDER-LIKE SYMPTOMS IN ELECTRICAL STATUS EPILEPTICUS IN SLEEP SYNDROME IS RELATED TO ELECTROENCEPHALOGRAPHIC IMPROVEMENT: A RETROSPECTIVE STUDY.

Altunel A, Altunel E.+û., Sever A.

Introduction Encephalopathy with electrical status epilepticus in sleep (ESES) syndrome is a rare epilepsy syndrome of childhood that is characterized by sleep-induced epileptiform discharges and problems with cognition or behavior. The neuropsychiatric symptoms in ESES syndrome, among which the ADHD-like symptoms are prominent, bear a close resemblance to symptoms in various developmental disorders. Positive response to adrenocorticotropic hormone (ACTH) is associated with the normalization of the EEG and improvement of neuropsychiatric function. This study aimed to determine the improvement in ADHD-like symptoms in response to ACTH and establish a relationship between improvement in clinical symptoms and EEG parameters.

Methods Seventy-five patients with ESES syndrome, who had clinically displayed ADHD-like symptoms, had been treated with ACTH for ESES, and their medical records were retrospectively reviewed. Sleep EEGs were recorded at referral and follow-up visits, and short courses of ACTH were administered when spike wave index (SWI) was 15%. The assessment of treatment effectiveness was based on reduction in SWI and the clinician-reported improvement in ADHD-like symptoms. Statistical analyses were conducted in order to investigate the relationship between the clinical and EEG parameters.

Results Following treatment with ACTH, a reduction in SWI in all the patients was accompanied by a mean improvement of 67% in ADHD-like symptoms. Disappearance/reduction of foci and cessation/reduction of seizures were achieved in patients with formerly antiepileptic-resistant seizures. Multiple linear regressions established that pretreatment SWI and treatment delay predicted posttreatment SWI, while reduction in SWI, treatment delay, and the presence of foci predicted improvement in ADHD-like symptoms.

Discussion Improvement in ADHD-like symptoms showed high correlation and was timely with the resolution of ESES. It is suggested that ESES and ADHD may be the two different expressions of a common neurobiological abnormality. With enhanced interpretation of sleep EEG, a more thorough assessment and treatment of neurodevelopmental disorders is possible

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Epilepsy Behav. 2017 Feb;67:13-19.

SELF AND INFORMANT REPORT RATINGS OF PSYCHOPATHOLOGY IN GENETIC GENERALIZED EPILEPSY.

Loughman A, Bowden SC, D'Souza WJ.

The psychological sequelae of genetic generalized epilepsies (GGE) is of growing research interest, with up to a third of all adults with GGE experiencing significant psychiatric comorbidity according to a recent systematic review. A number of unexplored questions remain. Firstly, there is insufficient evidence to determine relative prevalence of psychopathology between GGE syndromes. Secondly, the degree to which self-report and informant-report questionnaires accord in adults with epilepsy is unknown. Finally, while epilepsy severity is one likely predictor of worse psychopathology in GGE, evidence regarding other possible contributing factors such as epilepsy duration and antiepileptic drugs (AEDs) has been equivocal. The potential impact of subclinical epileptiform discharges remains unexplored. Self-report psychopathology symptoms across six DSM-Oriented Subscales were prospectively measured in 60 adults with GGE, with informant-report provided for a subset of 47. We assessed the burden of symptoms from both self- and informant-report, and the relationship between clinical epilepsy variables and self-reported symptoms. Results showed elevated symptoms in almost half of the sample overall. Depression and anxiety were the

most commonly reported types of symptoms. There was a trend towards greater symptoms endorsement by self-report, and relatively modest interrater agreement. Symptoms of ADHD were significantly positively associated with number of AEDs currently prescribed. Other psychopathology symptoms were not significantly predicted by epilepsy duration, seizure-free duration or total duration of epileptiform discharges over a 24-hour period. The high prevalence of psychological needs suggests that routine screening of psychopathology and provision of psychoeducation may be essential to improving patient care and outcomes. Further investigation is required to better understand predictive and causal factors for psychopathology in GGE

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Eur Arch Psychiatry Clin Neurosci. 2017;1-9.

THE INFLUENCE OF GENERALIZED ANXIETY DISORDER ON EXECUTIVE FUNCTIONS IN CHILDREN WITH ADHD.

Menghini D, Armando M, Calcagni M, et al.

The present study was aimed at verifying whether the presence of generalized anxiety disorder (GAD) affects executive functions in children with attention-deficit hyperactivity disorder (ADHD). Two groups of children with ADHD were selected for the study according to the presence or absence of GAD. The first group of 28 children with ADHD with GAD (mean age: 9 ± 1.2; males/females: 24/4) was matched for gender, age, IQ, psychiatric comorbidity with a second group of 29 children with ADHD without GAD (mean age: 8.8 ± 0.7; males/females: 26/3). The two groups with ADHD were compared to 28 typically developing children (mean age: 8.3 ± 1.3; males/females: 23/5) on different measures involving processes especially important in inhibitory control such as rule maintenance, stimulus detection, action selection and action execution. Our results indicated that, differently from children with ADHD with GAD, only the group with ADHD without GAD showed a deficit in inhibitory control. Comorbid subgroups should be differentiated, especially, to develop specific and efficient therapeutic interventions in ADHD

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Eur Child Adolesc Psychiatry. 2017;1-12.

POTENTIAL FOR DIAGNOSIS VERSUS THERAPY MONITORING OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NEW EPIGENETIC BIOMARKER INTERACTING WITH BOTH GENOTYPE AND AUTO-IMMUNITY.

Adriani W, Romano E, Pucci M, et al.

In view of the need for easily accessible biomarkers, we evaluated in ADHD children the epigenetic status of the 5'-untranslated region (UTR) in the SLC6A3 gene, coding for human dopamine transporter (DAT). We analysed buccal swabs and sera from 30 children who met DSM-IV-TR criteria for ADHD, assigned to treatment according to severity. Methylation levels at six-selected CpG sites (among which, a CGGCGGCGG and a CGCG motif), alone or in combination with serum titers in auto-antibodies against dopamine transporter (DAT aAbs), were analysed for correlation with CGAS scores (by clinicians) and Conners' scales (by parents), collected at recruitment and after 6 weeks. In addition, we characterized the DAT genotype, i.e., the variable number tandem repeat (VNTR) polymorphisms at the 3'-UTR of the gene. DAT methylation levels were greatly reduced in ADHD patients compared to control, healthy children. Within patients carrying at least one DAT 9 allele (DAT 9/x), methylation at positions CpG2 and/or CpG6 correlated with recovery, as evident from delta-CGAS scores as well as delta Conners' scales ('inattentive' and 'hyperactive' subscales). Moreover, hypermethylation at CpG1 position denoted severity, specifically for those patients carrying a DAT 10/10 genotype. Intriguingly, high serum DAT-aAbs titers appeared to corroborate indications from high CpG1 versus high CpG2/CpG6 levels, likewise denoting severity versus recovery in DAT 10/10 versus 9/x patients, respectively. These profiles suggest that DAT 5'UTR epigenetics plus serum aAbs can serve as suitable biomarkers, to confirm ADHD diagnosis and/or to predict the efficacy of treatment

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Eur Neuropsychopharmacol. 2017.

EFFECT OF TOBACCO SMOKING ON FRONTAL CORTICAL THICKNESS DEVELOPMENT: A LONGITUDINAL STUDY IN A MIXED COHORT OF ADHD-AFFECTED AND -UNAFFECTED YOUTH.

Akkermans SEA, Van RD, Rommelse N, et al.

Smoking rates are particularly high during adolescence and young adulthood, when the brain is still undergoing significant developmental changes. Cross-sectional studies have revealed altered brain structure in smokers, such as thinner frontal cortical areas. Attention-deficit/hyperactivity disorder (ADHD) increases the risk of becoming nicotine-dependent, and has also been associated with abnormalities in frontal gray matter structure. The present study examines the relationships between smoking, cortical thickness and ADHD symptoms in a longitudinal design that compares adolescent and young adult smokers (n=44; 35 ADHD-affected) and non-smokers (n=45; 32 ADHD-affected) on frontal cortical thickness. Average frontal cortical thickness was estimated through structural magnetic resonance imaging (MRI) at two time points (mean ages 17.7 and 21.1 years), on average 3.4 years apart. Smokers had a 2.6% thinner frontal cortex than non-smokers and this difference was not explained by ADHD or other confounding factors. The rate of cortical thinning across the 3.4-year MRI measurement interval was similar in the total group of smokers compared to non-smokers. However, speeded thinning did occur in smokers who had started regular smoking more recently, in between the two measurements. These novel regular smokers did not differ significantly from the non-smokers at baseline. This suggests that the thinner frontal cortex was not a predisposing factor but rather a consequence of smoking. Although smokers had more ADHD symptoms overall, smoking did not influence the developmental course of ADHD symptoms

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Exp Brain Res. 2017 Mar;235:799-807.

ABNORMAL CONNECTIVITY IN THE SENSORIMOTOR NETWORK PREDICTS ATTENTION DEFICITS IN TRAUMATIC BRAIN INJURY.

Shumskaya E, van Gerven MA, Norris DG, et al.

The aim of this study was to explore modifications of functional connectivity in multiple resting-state networks (RSNs) after moderate to severe traumatic brain injury (TBI) and evaluate the relationship between functional connectivity patterns and cognitive abnormalities. Forty-three moderate/severe TBI patients and 34 healthy controls (HC) underwent resting-state fMRI. Group ICA was applied to identify RSNs. Between-subject analysis was performed using dual regression. Multiple linear regressions were used to investigate the relationship between abnormal connectivity strength and neuropsychological outcome. Forty (93%) TBI patients showed moderate disability, while 2 (5%) and 1 (2%) upper severe disability and low good recovery, respectively. TBI patients performed worse than HC on the domains attention and language. We found increased connectivity in sensorimotor, visual, default mode (DMN), executive, and cerebellar RSNs after TBI. We demonstrated an effect of connectivity in the sensorimotor RSN on attention ($p < 10\text{-}3$) and a trend towards a significant effect of the DMN connectivity on attention ($p = 0.058$). A group-by-network interaction on attention was found in the sensorimotor network ($p = 0.002$). In TBI, attention was positively related to abnormal connectivity within the sensorimotor RSN, while in HC this relation was negative. Our results show altered patterns of functional connectivity after TBI. Attention impairments in TBI were associated with increased connectivity in the sensorimotor network. Further research is needed to test whether attention in TBI patients is directly affected by changes in functional connectivity in the sensorimotor network or whether the effect is actually driven by changes in the DMN

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Exp Brain Res. 2017 May;235:1593-602.

ATTENTION AND PAIN: ARE AUDITORY DISTRACTORS SPECIAL?

Sloan P, Hollins M.

It is well established that manipulations of attention and emotional state can modulate pain. Some researchers have used olfactory or visual distractors to manipulate these factors in combination, and have found that attention and emotion have different effects on pain intensity and unpleasantness. Specifically,

distraction from pain was found to markedly reduce its intensity while having little effect on its unpleasantness. Other evidence indicates, however, that the strength of intermodal attentional shifts depends on the specific modalities involved, with auditory-somesthetic shifts being relatively weak. The present study was, therefore, undertaken to determine how pain intensity and unpleasantness are affected when auditory, rather than olfactory or visual, distractors are used. Attention was directed either to the pain from noxious thermal stimuli, or to simultaneously presented environmental sounds that had either positive (e.g., bird chirping) or negative (e.g., alarm clock) associations. To manipulate attention, subjects were instructed to make two-alternative forced-choice discrimination judgments concerning the temperature of the thermal stimuli (in heat blocks) or the loudness of the sound clips (in sound blocks). Unpleasant sound clips were used during half of the heat blocks and half of the sound blocks, with pleasant sounds in the other half. Participants rated two components of pain: intensity and unpleasantness, after each block of trials. Although pain unpleasantness was influenced both by attentional direction and by the valence of the sound clips, pain intensity was not affected by either of these experimental manipulations. The failure of auditory distractors to modulate pain intensity differs from the previously documented ability of olfactory distractors to do so. Our findings are, however, consistent with evidence that one can attend simultaneously to auditory and cutaneous stimuli. Thus, environmental sounds are not effective at reducing pain intensity, but are capable of modulating pain unpleasantness, perhaps because it is constructed at a later stage

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Expert Rev Neurother. 2017;1-9.

CONSIDERATIONS FOR ADHD IN THE CHILD WITH EPILEPSY AND THE CHILD WITH MIGRAINE.

Downs J, Giust J, Dunn DW.

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is a common comorbid condition in children with epilepsy and migraine. Treatment of ADHD in children with epilepsy or migraine is essential but clinicians may overlook symptoms of ADHD and avoid appropriate use of medications that may reduce symptoms of ADHD without compromising treatment of epilepsy or migraine. Areas covered: PubMed was searched for articles on ADHD and epilepsy or migraine. Key papers were reviewed for additional articles. Areas of interest were: epidemiology, etiological factors, and treatment with emphasis on therapy. Expert commentary: Stimulant medication, especially methylphenidate, appears to be safe and effective in the treatment of ADHD in children with epilepsy or migraine. Unfortunately, data is limited with very few controlled trials of methylphenidate and very limited information on the use of amphetamines or non-stimulant drugs

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Farmacia. 2017;65:550-56.

DIETARY OMEGA-3 FATTY ACIDS SUPPLIMENTATION FOR ATTENTION DEFICIT WITH HYPERACTIVITY DISORDER IN EPILEPTIC CHILDREN.

Leanca M, et al.

Attention deficit hyperactivity disorder (ADHD) is a highly frequent childhood disease usually treated with neurotropic stimulant drugs, therapy with serious side effects especially for children with neurologic comorbidities. Considering the low levels of essential fatty acids in children□s serum with this disorder, the present study evaluated the effects of dietary omega-3 fatty acids supplementation in ADHD children with epilepsy. 17 children with epilepsy and ADHD have been clinically evaluated concerning neurological, psychiatric, psychological, EEG, biochemical (urinary catecholamines) parameters. They received supplements with omega-3 fatty acids for 6 months (with re-evaluation of the biochemical markers and the psychological tests-Conners questionnaire). 14 children accomplished the study. All patients had high scores of ADHD questionnaires before adding-on the dietary supplement and after 6 months, 75% showed a significant improvement, by measuring the symptoms of inattention and impulsivity, academic and language difficulties. Regarding the catecholamines□ (namely adrenaline, noradrenaline and dopamine), our results showed a significant decrease of their levels in urine, compared to baseline. Regarding the behavioural

benefit in combination with the low risk due to a good safety profile, the dietary supplementation with omega-3 fatty acids offers a promising complementary approach to standard therapy

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Frontiers in Behavioral Neuroscience. 2017;11.

CHILDHOOD TRAUMA ASSOCIATED WITH ENHANCED HIGH FREQUENCY BAND POWERS AND INDUCED SUBJECTIVE INATTENTION OF ADULTS.

Lee S-H, Park Y, Jin MJ, et al.

Childhood trauma can lead to various psychological and cognitive symptoms. It has been demonstrated that high frequency electroencephalogram (EEG) powers could be closely correlated with inattention. In this study, we explored the relationship between high frequency EEG powers, inattention, symptoms of adult attention deficit hyperactivity disorder (ADHD), and childhood traumatic experiences. A total of 157 healthy Korean adult volunteers were included and divided into two groups using the Childhood Trauma Questionnaire (CTQ) score. The subjective inattention scores, ADHD scale, and anxiety and depression symptom were evaluated. EEG was recorded and quantitative band powers were analyzed. The results were as follows: (1) the high CTQ group showed significantly increased delta, beta1, beta2, beta3 and gamma, and significantly decreased low alpha power compared to the low CTQ group; (2) the high CTQ group had higher inattention score compared to the low CTQ group; (3) the high CTQ group had higher adult ADHD scores; (4) CTQ scores showed significant positive correlations with inattention scores, and adult ADHD scores; (5) unexpectedly, the inattention scores showed significant positive correlations with beta powers and a negative correlation with low alpha power; and (6) the moderated mediation model was confirmed: the depression fully mediated the path from state anxiety to inattention, and the CTQ significantly moderated the pathway between anxiety and depression. Our results show the possibility that childhood adversity may cause subjective inattention and adult ADHD symptoms. Depressive symptoms fully mediated the path from anxiety to inattention, especially in those who report severe childhood traumatic experiences

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Front Psychiatry. 2017;8.

THE DIRECT/INDIRECT ASSOCIATION OF ADHD/ODD SYMPTOMS WITH SELF-ESTEEM, SELF-PERCEPTION, AND DEPRESSION IN EARLY ADOLESCENTS.

Kita Y, Inoue Y.

The present study aimed to reveal the influences of attention-deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) symptoms on self-esteem and self-perception during early adolescence and to clarify the spillover effect of self-esteem on depressive symptoms. ADHD symptoms in 564 early adolescents were evaluated via teacher-rating scales. Self-esteem and depressive symptoms were assessed via self-reported scales. We analyzed the relationships among these symptoms using structural equation modeling. Severe inattentive symptoms decreased self-esteem and hyperactive-impulsive symptoms affected self-perception for non-academic domains. Although these ADHD symptoms did not directly affect depressive symptoms, low self-esteem led to severe depression. ODD symptoms had a direct impact on depression without the mediating effects of self-esteem. These results indicated that inattentive symptoms had a negative impact on self-esteem and an indirect negative effect on depressive symptoms in adolescents, even if ADHD symptoms were subthreshold. Severe ODD symptoms can be directly associated with depressive symptoms during early adolescence

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Gene. 2017;630:8-12.

ASSOCIATION OF MITOCHONDRIAL DNA 10398 A/G POLYMORPHISM WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN KOREAN CHILDREN.

Hwang IW, Hong JH, Kwon BN, et al.

Mitochondria are subcellular organelles that contribute to aerobic ATP generation by oxidative phosphorylation (OXPHOS). Previous studies reported that mitochondrial dysfunction and deficiency caused by mitochondrial DNA polymorphisms is associated with various diseases. Especially, mitochondrial DNA 10398 A/G polymorphism is known to affect the regulation of mitochondrial calcium levels related to energy production, and its association with psychiatric disorders such as schizophrenia and bipolar disorder has been reported. However, there are no reports on the genetic relationship between mitochondrial DNA polymorphisms and ADHD. Thus, we evaluated the genetic association between 10398 A/G polymorphism and ADHD in the Korean children. Genotype frequency differences between the case and the control were assessed using Chi-square tests. Independent t-test was used to estimate the effects of genotype on Behavior Assessment System for Children (BASC-2) scales in ADHD children. Our results showed that mitochondrial DNA 10398 A/G polymorphism was significantly associated with the ADHD children ($p < 0.05$). Stratified analyses for gender and subtypes showed a marginal trend toward significance (boys: $p = 0.059$, and combined subtype: $p = 0.068$, respectively). In the BASC-2 analysis, the 10398 A/G polymorphism was significantly associated with aggression behavior and leadership in ADHD boys ($p < 0.05$). These findings suggest that the mitochondrial DNA 10398 A/G polymorphism play a possible role in the genetic etiology of ADHD in Korean children. Larger sample set and functional studies are necessary to further elucidation of our findings

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Int J Adolesc Med Health. 2017 Apr;29.

POSTNATAL TESTOSTERONE MAY BE AN IMPORTANT MEDIATOR OF THE ASSOCIATION BETWEEN PREMATURITY AND MALE NEURODEVELOPMENTAL DISORDERS: A HYPOTHESIS.

Rice TR.

Children born premature are at risk for neurodevelopmental disorders, including autism and schizophrenia. This piece advances the hypothesis that altered androgen exposure observed in premature infants is an important mediator of the neurodevelopmental risk in males associated with prematurity. Specifically, the alterations of normative physiologic postnatal activations of the hypothalamic-pituitary-gonadal axis that occur in preterm males are hypothesized to contribute to the risk of neuropsychiatric pathology of prematurity through altered androgen-mediated organizational effects on the developing brain. The physiology of testosterone and male central nervous system development in full-term births is reviewed and compared to the developmental processes of prematurity. The effects of the altered testosterone physiology observed within prematurity outside of the central nervous system are reviewed as a segue into a discussion of the effects within the nervous system, with a special focus on autism spectrum disorders and attention deficit hyperactivity disorder. The explanatory power of this model is reviewed as a supplement to the preexisting models of prematurity and neurodevelopmental risk, including infection and other perinatal central nervous system insults. The emphasis is placed on altered androgen exposure as serving as just one among many mediators of neurodevelopmental risk that may be of interest for further research and evidence-based investigation. Implications for diagnosis, management and preventative treatments conclude the piece

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Int J Occup Med Environ Health. 2017 May;30:511-20.

IMPACT OF ROAD TRAFFIC NOISE ON SLEEP DISTURBANCES AND ATTENTION DISORDERS AMONGST SCHOOL CHILDREN LIVING IN UPPER SILESIAN INDUSTRIAL ZONE, POLAND.

Skrzypek M, Kowalska M, Czech EM, et al.

OBJECTIVES: Published reports suggest that some adverse health impact may be related to noise exposure, and motor vehicle traffic is considered to be the main source of environmental hazard of noise. The aim of this study has been to assess an association between occurrence of sleep and attention disorders

with exposure to the noise generated by motor vehicle traffic in the case of a large group of children living in an urban environment.
MATERIAL AND METHODS: The data was obtained using a cross sectional study design in Bytom (Silesia, Poland) from 2003-2007 for a selected group of 7-14 year olds (N = 5136). The geographic information system was used for assessing the exposure to noise generated by the motor vehicle traffic. The association between occurrences of sleep disturbances or attention disorders and exposure to the traffic noise was examined by means of multivariable logistic regression.
RESULTS: Sleep disturbances and attention disorders were found to be statistically significantly associated with exposure to the traffic noise. The multivariable logistic regression results suggest that sleep disturbances and attention disorders were more likely to occur in the case of children living in the area with higher traffic density, the odds ratio (OR) = 1.44 (95% confidence interval (CI): 1.05-1.97) and 1.38 (95% CI: 1.03-1.86), respectively.
CONCLUSIONS: The results of the study have confirmed that the exposure to the traffic noise could be a significant risk factor for sleep disturbances and attention disorders among children

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Int J Psychophysiol. 2017 May;115:112-24.

HERITABILITY OF BRAIN ACTIVITY RELATED TO RESPONSE INHIBITION: A LONGITUDINAL GENETIC STUDY IN ADOLESCENT TWINS.

Anokhin AP, Golosheykin S, Grant JD, et al.

The ability to inhibit prepotent but context- or goal-inappropriate responses is essential for adaptive self-regulation of behavior. Deficits in response inhibition, a key component of impulsivity, have been implicated as a core dysfunction in a range of neuropsychiatric disorders such as ADHD and addictions. Identification of genetically transmitted variation in the neural underpinnings of response inhibition can help to elucidate etiological pathways to these disorders and establish the links between genes, brain, and behavior. However, little is known about genetic influences on the neural mechanisms of response inhibition during adolescence, a developmental period characterized by weak self-regulation of behavior. Here we investigated heritability of ERPs elicited in a Go/No-Go task in a large sample of adolescent twins assessed longitudinally at ages 12, 14, and 16. Genetic analyses showed significant heritability of inhibition-related frontal N2 and P3 components at all three ages, with 50 to 60% of inter-individual variability being attributable to genetic factors. These genetic influences included both common genetic factors active at different ages and novel genetic influences emerging during development. Finally, individual differences in the rate of developmental changes from age 12 to age 16 were significantly influenced by genetic factors. In conclusion, the present study provides the first evidence for genetic influences on neural correlates of response inhibition during adolescence and suggests that ERPs elicited in the Go/No-Go task can serve as intermediate neurophysiological phenotypes (endophenotypes) for the study of disinhibition and impulse control disorders

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Int J Pediatr Otorhinolaryngol. 2017;101:178-85.

INTELLIGIBILITY OF DEGRADED SPEECH AND THE RELATIONSHIP BETWEEN SYMPTOMS OF INATTENTION, HYPERACTIVITY/IMPULSIVITY AND LANGUAGE IMPAIRMENT IN CHILDREN WITH SUSPECTED AUDITORY PROCESSING DISORDER.

Ahmmed AU.

Objectives To compare the sensitivity and specificity of Auditory Figure Ground sub-tests of the SCAN-3 battery, using signal to noise ratio (SNR) of +8 dB (AFG+8) and 0 dB (AFG0), in identifying auditory processing disorder (APD). A secondary objective was to evaluate any difference in auditory processing (AP) between children with symptoms of inattention versus combined sub-types of Attention Deficit Hyperactivity Disorder (ADHD).
Methods Data from 201 children, aged 6 to 16 years (mean: 10 years 6 months, SD: 2 years 8 months), who were assessed for suspected APD were reviewed retrospectively. The outcomes of the SCAN-3 APD test

battery, Swanson Nolan and Pelham-IV parental rating (SNAP-IV) and Children's Communication Checklist-2 (CCC-2) were analysed.
Results AFG0 had a sensitivity of 56.3% and specificity of 100% in identifying children performing poorly in at least two of six SCAN-3 sub-tests or one of the two questionnaires, in contrast to 42.1% and 80% respectively for AFG+8. Impaired AP was mostly associated with symptoms of ADHD and /or language impairment (LI). LI was present in 92.9% of children with ADHD symptoms. Children with symptoms of combined ADHD plus LI performed significantly poorly ($p < 0.05$) compared to inattention ADHD plus LI in Filtered Words (FW) sub-test, but not in the rest of the SCAN-3 sub-tests.
Conclusion Speech in noise tests using SNR of 0 dB is better than +8 dB in assessing APD. The better FW performance of the inattention ADHD plus LI group can be speculated to be related to known difference in activity in a neural network between different sub-types of ADHD. The findings of the study and existing literature suggest that neural networks connecting the cerebral hemispheres, basal ganglia and cerebellum are involved in APD, ADHD and LI

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J Behav Ther Exp Psychiatry. 2017 Mar;54:77-87.
EMOTIONAL INTERFERENCE AND ATTENTIONAL PROCESSING IN PREMENSTRUAL SYNDROME.
Eggert L, Kleinstauber M, Hiller W, et al .
BACKGROUND AND OBJECTIVES: Premenstrual syndrome (PMS) is characterized by menstrual cycle-related affective, behavioral, and/or somatic symptoms. By applying the emotional Stroop task (EST) the current study examined if changes in processing emotional information, which have been demonstrated in affective disorders, are also present in PMS.
METHODS: Via online screening, telephone interviews, and daily records over two months 55 women for the PMS group (on the basis of the specific inclusion criteria and a prospectively confirmed PMS) and 55 'non-PMS' controls were recruited. All participants completed three emotional Stroop tasks (EST) with neutral and negative word, picture, and facial stimuli, during the follicular and luteal phase of the menstrual cycle.
RESULTS: Mixed 2 x 2 univariate analyses of variance and post-hoc comparisons showed primarily a greater emotional Stroop effect with respect to picture and facial stimuli in the luteal menstrual cycle phase in women with PMS, compared to the control group. No significant group differences were observed for word stimuli. With respect to the facial stimuli, a kind of paradox effect was revealed (Stroop facilitation) in the PMS group.
LIMITATIONS: This study provides important information regarding cognitive processes in women suffering from PMS that have to be interpreted in the light of the following limitations: a limited representativeness of the sample, the determination of menstrual cycle phases based on symptom diaries but not hormone levels, and a limited interpretability of our results as causal relationships.
CONCLUSIONS: Our findings are in line with the assumption that alterations in cognitive-emotional processes are associated with PMS. Further research on the etiology of PMS should focus more on cognitive-emotional processing and its interaction with biological changes relating to the menstrual cycle

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J Child Adolesc Psychopharmacol. 2017 Apr;27:243-49.
GILLES DE LA TOURETTE SYNDROME, DEPRESSION, DEPRESSIVE ILLNESS, AND CORRELATES IN A CHILD AND ADOLESCENT POPULATION.
Rizzo R, Gulisano M, Martino D, et al.
OBJECTIVE: Gilles de la Tourette syndrome (GTS) and depression are both common disorders. It has been suggested that depression occurs in 13%-76% GTS patients. Despite this, there are few studies into the specific relationships and correlates between the two disorders. There is only some consensus as to the precise relationship between the two disorders.
MATERIALS AND METHODS: We undertook the study to investigate the relationship between depressive symptomatology and the core clinical features of GTS in a well-characterized clinical population of youth with this disorder. Our aim was to verify the association between depression and comorbid obsessive-compulsive

disorder and explore further other potential associations highlighted in some, but not all, of the studies focused on this topic.
RESULTS: Our results demonstrated that (1) the GTS patients were significantly older than the controls, (2) the GTS patients were significantly more depressed than controls, (3) depression was associated with tic severity, (4) the Diagnostic Confidence Index scores were higher in GTS patients without depression, (5) anxiety, attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and behavioral problems were significantly associated with depression, and (6) finally, patients with GTS and depression have a positive family history of depression. However, obsessionality (CY-BOCS) did not differentiate between depressed and not depressed GTS patients.
CONCLUSIONS: Depression is common in patients with GTS and occurs significantly more in GTS than in controls. Depression is significantly associated with GTS factors such as tic severity, comorbidity with ADHD, and the presence of coexistent anxiety, CDs, and behavior problems. Depression is importantly significantly associated with a positive family history of depression. Intriguingly, depression in our sample was not related to obsessionality

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J Child Adolesc Psychopharmacol. 2017 Apr;27:234-42.
CAREGIVER TREATMENT PREFERENCES FOR CHILDREN WITH A NEW VERSUS EXISTING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DIAGNOSIS.
DosReis S, Park A, Ng X, et al.
OBJECTIVES: Parental experiences with managing their child's attention-deficit/hyperactivity disorder (ADHD) can influence priorities for treatment. This study aimed to identify the ADHD management options caregivers most prefer and to determine if preferences differ by time since initial ADHD diagnosis.
METHODS: Primary caregivers (n = 184) of a child aged 4-14 years old in care for ADHD were recruited from January 2013 through March 2015 from community-based pediatric and mental health clinics and family support organizations across the state of Maryland. Participants completed a survey that included child/family demographics, child clinical treatment, and a Best-Worst Scaling (BWS) experiment to elicit ADHD management preferences. The BWS comprised 18 ADHD management profiles showing seven treatment attributes, where the best and worst attribute levels were selected from each profile. A conditional logit model using effect-coded variables was used to estimate preference weights stratified by time since ADHD diagnosis.
RESULTS: Participants were primarily the mother (84%) and had a college or postgraduate education (76%) with 75% of the children on stimulant medications. One-on-one caregiver behavior training, medication use seven days a week, therapy in a clinic, and an individualized education program were most preferred for managing ADHD. Aside from caregiver training and monthly out-of-pocket costs, caregivers of children diagnosed with ADHD for less than two years prioritized medication use lower than other care management attributes and caregivers of children diagnosed with ADHD for two or more years preferred school accommodations, medication, and provider specialty.
CONCLUSIONS: Preferences for ADHD treatment differ based on the duration of the child's ADHD. Acknowledging that preferences change over the course of care could facilitate patient/family-centered care planning across a range of resources and a multidisciplinary team of professionals

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J Clin Child Adolesc Psychol. 2017 Jan;46:59-73.
EFFECTIVENESS OF THE INCREDIBLE YEARS PARENTING PROGRAM FOR FAMILIES WITH SOCIOECONOMICALLY DISADVANTAGED AND ETHNIC MINORITY BACKGROUNDS.
Leijten P, Raaijmakers MA, Orobio de CB, et al.
Families with socioeconomically disadvantaged and ethnic minority backgrounds are often hard to reach for the prevention and treatment of disruptive child behavior problems. We examined whether the Incredible Years parenting intervention can successfully reach and benefit families with socioeconomic disadvantaged and ethnic minority backgrounds in the Netherlands. One hundred fifty-four families from a wide range of

socioeconomic and ethnic backgrounds were recruited in an outpatient clinic for child and adolescent psychiatry and in elementary schools serving deprived neighborhoods. Families were randomly assigned to the BASIC Incredible Years parenting intervention or a waiting list control condition. Children were 3-8 years old (M = 5.59, SD = 1.35; 62% boys, 66% ethnic minorities) and 65% of the children met Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.) criteria for oppositional defiant disorder, conduct disorder, and/or attention-deficit hyperactivity disorder. Incredible Years reduced parent-reported disruptive child behavior and teacher-reported hyperactive and inattentive child behavior and increased parent-reported use of praise and incentives and reduced harsh and inconsistent discipline. Incredible Years did not affect parent-reported hyperactive and inattentive child behavior; teacher-reported child conduct problems; and parent-reported use of appropriate discipline techniques, clear expectations, physical punishment, and parenting stress. Of importance, the effectiveness of Incredible Years did not differ across families with different socioeconomic and ethnic backgrounds. Effects were maintained at 3-month follow-up. This study shows that socioeconomically disadvantaged and ethnic minority families in disadvantaged neighborhoods can be engaged in and benefit from parenting interventions to reduce disruptive child behavior

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J Clin Psychopharmacol. 2017 Jun;37:315-22.

A Phase 3, Multicenter, Open-Label, 12-Month Extension Safety and Tolerability Trial of Lisdexamfetamine Dimesylate in Adults With Binge Eating Disorder .

Gasior M, Hudson J, Quintero J, et al.

BACKGROUND: A 12-month, open-label extension study assessed the long-term safety and tolerability of lisdexamfetamine dimesylate (LDX) in adults with binge eating disorder (BED).

METHODS: Adults (aged 18-55 y) with BED who completed 1 of 3 antecedent studies were enrolled in a 52-week, open-label extension study (dose optimization, 4 weeks [initial titration dose, 30-mg LDX; target doses, 50- or 70-mg LDX]; dose maintenance, 48 weeks). Safety evaluations included the occurrence of treatment-emergent adverse events (TEAEs), vital sign and weight assessments, and Columbia-Suicide Severity Rating Scale responses.

RESULTS: Of the 604 enrolled participants, 599 (521 women and 78 men) comprised the safety analysis set, and 369 completed the study. Mean (SD) LDX exposure was 284.3 (118.84) days; cumulative LDX exposure duration was 12 months or longer in 344 participants (57.4%). A total of 506 participants (84.5%) reported TEAEs (TEAEs leading to treatment discontinuation, 54 [9.0%]; severe TEAEs, 42 [7.0%]; serious TEAEs, 17 [2.8%]). Treatment-emergent adverse events reported in greater than or equal to 10% of participants were dry mouth (27.2%), headache (13.2%), insomnia (12.4%), and upper respiratory tract infection (11.4%). Mean (SD) changes from antecedent study baseline in systolic and diastolic blood pressure, pulse, and weight at week 52/early termination (n = 597) were 2.19 (11.043) and 1.77 (7.848) mm Hg, 6.58 (10.572) beats per minute, and -7.04 (7.534) kg, respectively. On the Columbia-Suicide Severity Rating Scale, there were 2 positive responses for any active suicidal ideations; there were no positive responses for suicidal behavior or completed suicides.

CONCLUSIONS: In this 12-month, open-label, extension study, the long-term safety and tolerability of LDX in adults with BED were generally consistent with its established profile for attention-deficit/hyperactivity disorder

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J Med Internet Res. 2017 Mar;19:e79.

Microsoft Kinect-based Continuous Performance Test: An Objective Attention Deficit Hyperactivity Disorder Assessment.

Delgado-Gomez D, Penuelas-Calvo I, Maso-Besga AE, et al.

BACKGROUND: One of the major challenges in mental medical care is finding out new instruments for an accurate and objective evaluation of the attention deficit hyperactivity disorder (ADHD). Early ADHD identification, severity assessment, and prompt treatment are essential to avoid the negative effects associated with this mental condition.

OBJECTIVE: The aim of our study was to develop a novel ADHD assessment instrument based on Microsoft Kinect, which identifies ADHD cardinal symptoms in order to provide a more accurate evaluation. METHODS: A group of 30 children, aged 8-12 years (10.3 [SD 1.4]; male 70% [21/30]), who were referred to the Child and Adolescent Psychiatry Unit of the Department of Psychiatry at Fundacion Jimenez Diaz Hospital (Madrid, Spain), were included in this study. Children were required to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria of ADHD diagnosis. One of the parents or guardians of the children filled the Spanish version of the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) rating scale used in clinical practice. Each child conducted a Kinect-based continuous performance test (CPT) in which the reaction time (RT), the commission errors, and the time required to complete the reaction (CT) were calculated. The correlations of the 3 predictors, obtained using Kinect methodology, with respect to the scores of the SWAN scale were calculated.
RESULTS: The RT achieved a correlation of -.11, -.29, and -.37 with respect to the inattention, hyperactivity, and impulsivity factors of the SWAN scale. The correlations of the commission error with respect to these 3 factors were -.03, .01, and .24, respectively.
CONCLUSIONS: Our findings show a relation between the Microsoft Kinect-based version of the CPT and ADHD symptomatology assessed through parental report. Results point out the importance of future research on the development of objective measures for the diagnosis of ADHD among children and adolescents

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J Pers Disord. 2017 Feb;31:26-48.

A MULTI-METHOD EXAMINATION OF THE LINKS BETWEEN ADHD AND PERSONALITY DISORDER.

Smith TE, Samuel DB.

An existing relationship between attention-deficit/hyperactivity disorder (ADHD) and personality disorder (PD) has been well documented, yet research has been limited by possible selection and self-report biases as well as PD models of questionable validity. This study examined the relationship of ADHD with adult personality traits and disorders in a sample that included individuals prescreened for elevated childhood ADHD symptoms. Four hundred thirty-nine undergraduates completed retrospective reports of childhood ADHD symptoms as well as current ratings of ADHD symptoms, traditional PD categories, and the DSM-5 alternative PD trait model. To overcome potential biases in self-report, 161 parents of the participants provided ratings of childhood and current functioning. Results suggest that while self-report of ADHD was significantly correlated with several PDs, parent reports obtained somewhat more specific links with adult dependent, borderline, and paranoid PDs. Most importantly, the DSM-5 Section III dimensional trait model provided greater specificity, as the trait of distractibility consistently emerged as a unique predictor, and thus appeared more useful for understanding the developmental pathways of ADHD

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J Psychiatr Ment Health Nurs. 2017 Feb;24:15-27.

THE EFFECTIVENESS OF THERAPEUTIC CONVERSATION INTERVENTION FOR CAREGIVERS OF ADOLESCENTS WITH ADHD: A QUASI-EXPERIMENTAL DESIGN.

Gisladottir M, Svavarsdottir EK.

WHAT IS KNOWN ON THE SUBJECT?: Caregivers of adolescents with ADHD experience major difficulties as care providers and are in need of guidance and support. Adolescents with ADHD may develop oppositional and criminal behaviour. More than 50 % have the symptoms in adulthood, and up to one-fourth with severe emotional or antisocial difficulties. There is a lack of evidence of caregivers' supporting intervention although caregiver groups have been found to contribute to better coping, decreased stress and improvements in ADHD symptoms.
WHAT DOES THIS PAPER ADD TO EXISTING KNOWLEDGE?: Primary caregivers of adolescents with ADHD experienced better quality of life after the Therapeutic Conversation Intervention. The intervention contributed to better social functioning among secondary caregivers.
WHAT ARE THE IMPLICATIONS FOR PRACTICE?: The content of the Therapeutic Conversation Intervention is significant and highlights the utility of a combination of group and private sessions for

caregivers of people with ADHD. The intervention can influence how services for families are organized, such that a Therapeutic Conversation Intervention could be offered on a regular basis.
ABSTRACT: Introduction Caregivers of adolescents with Attention Deficit Hyperactivity Disorder are burdened with tasks and many suffer from distress. Adolescents with ADHD may develop antisocial behaviour and caregiver's group can empower caregiver's supporting role.
Aim/Question To evaluate the effectiveness of a Therapeutic Conversation Intervention on caregivers of adolescents with ADHD regarding strengthening the supportive role.
Method The study utilized a quasi-experimental design. The participants (n = 60) were caregivers of adolescents (13-17 years old) with ADHD. The intervention consisted in-group and parent sessions. The Calgary Family Model and the Family Illness Beliefs Model were used as theoretical frameworks.
Results The study revealed significant differences in the improvement of quality of life; regarding primary caregiver (PC) worry, daily activities, family relationships and collaboration post-intervention, as well emotional functioning at both post-intervention and follow-up. Secondary caregiver (SC) social functioning was significantly improved at follow-up.
Discussion The intervention proved to be beneficial to the caregivers and is filling a gap in much needed intervention. Implication for practice The results will expand health care professionals' knowledge of how to increase PC quality of life when supporting their adolescent with ADHD. This treatment information should improve service at health care centres/hospitals where adolescents with ADHD receive care

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J Psychiatr Res. 2017 Feb;85:15-23.
THE ROLE OF PARENTAL PSYCHOPATHOLOGY AND PERSONALITY IN ADOLESCENT NON-SUICIDAL SELF-INJURY.
Gromatsky MA, Waszczuk MA, Perlman G, et al.
Adolescent non-suicidal self-injury (NSSI), a significant risk factor for suicidal behavior, is strongly associated with adolescent psychopathology and personality traits, particularly those characterized by poor self-regulation. Some parental psychopathology and personality traits have also been identified as risk factors for adolescent NSSI, but specific parental characteristics and mechanisms involved in this association have not been systematically examined. The current study comprehensively investigated the contribution of parental psychopathology and personality to adolescent NSSI using data from the baseline wave of the Adolescent Development of Emotion and Personality Traits (ADEPT) study of 550 adolescent girls (mean age = 14.39 years, SD = 0.63) and their biological parents. We first investigated whether parental lifetime psychiatric diagnoses, and personality and clinical (rumination, self-criticism, emotional reliance) traits were associated with adolescent NSSI. We also tested whether adolescent history of psychiatric illness, personality, and clinical traits mediated the associations between parental characteristics and adolescent NSSI. Parental substance use disorder, adult-ADHD symptoms, self-criticism, and lower agreeableness and conscientiousness were associated with offspring's NSSI. These associations were mediated through adolescent characteristics. In contrast, parental mood and anxiety disorders and neuroticism were unrelated to adolescent NSSI. The results suggest that parental traits and disorders characterized by self-regulatory difficulties and lack of support constitute risk factors for self-injury in adolescent girls, acting via adolescent traits. This demonstrates that parental influences play a significant role in the etiology of adolescent NSSI

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JAMA Pediatr. 2017 Feb;171:181-89.
SPENDING ON CHILDREN'S PERSONAL HEALTH CARE IN THE UNITED STATES, 1996-2013.
Bui AL, Dieleman JL, Hamavid H, et al.
Importance: Health care spending on children in the United States continues to rise, yet little is known about how this spending varies by condition, age and sex group, and type of care, nor how these patterns have changed over time.
Objective: To provide health care spending estimates for children and adolescents 19 years and younger in the United States from 1996 through 2013, disaggregated by condition, age and sex group, and type of care.

Evidence Review: Health care spending estimates were extracted from the Institute for Health Metrics and Evaluation Disease Expenditure 2013 project database. This project, based on 183 sources of data and 2.9 billion patient records, disaggregated health care spending in the United States by condition, age and sex group, and type of care. Annual estimates were produced for each year from 1996 through 2013. Estimates were adjusted for the presence of comorbidities and are reported using inflation-adjusted 2015 US dollars.
Findings: From 1996 to 2013, health care spending on children increased from $149.6 (uncertainty interval [UI], 144.1-155.5) billion to $233.5 (UI, 226.9-239.8) billion. In 2013, the largest health condition leading to health care spending for children was well-newborn care in the inpatient setting. Attention-deficit/hyperactivity disorder and well-dental care (including dental check-ups and orthodontia) were the second and third largest conditions, respectively. Spending per child was greatest for infants younger than 1 year, at $11741 (UI, 10799-12765) in 2013. Across time, health care spending per child increased from $1915 (UI, 1845-1991) in 1996 to $2777 (UI, 2698-2851) in 2013. The greatest areas of growth in spending in absolute terms were ambulatory care among all types of care and inpatient well-newborn care, attention-deficit/hyperactivity disorder, and asthma among all conditions.
Conclusions and Relevance: These findings provide health policy makers and health care professionals with evidence to help guide future spending. Some conditions, such as attention-deficit/hyperactivity disorder and inpatient well-newborn care, had larger health care spending growth rates than other conditions

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JAMA Pediatr. 2017;171:756-63.

MOTOR VEHICLE CRASH RISK AMONG ADOLESCENTS AND YOUNG ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Curry AE, Metzger KB, Pfeiffer MR, et al.

IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) often persists into adolescence, when motor vehicle crash risk peaks.We know little about when adolescents with ADHD get licensed and, once they do, the extent to which they have increased crash risk compared with adolescents without ADHD.
OBJECTIVES To examine the association between ADHD and both driver licensing and crash involvement and whether it varies by sex, licensing age, and/or being prescribed ADHD medication at licensure.
DESIGN, **SETTING, AND PARTICIPANTS** This retrospective cohort studywas conducted at 6 primary care practices of the Children's Hospital of Philadelphia, a large pediatric health care network in southeastern Pennsylvania and southern New Jersey. Using electronic health records, we defined a cohort of 2479 adolescents and young adults with ADHD and 15 865 without ADHD who were (1) born from 1987 to 1997; (2) residents of New Jersey and patients at 1 of 6 New Jersey primary care practices at age 12 years or older; and (3) age-eligible to obtain a driver's license from 2004 through 2014. Electronic health records data were then linked with New Jersey's statewide driver licensing and crash databases for 2004 through 2014.
MAIN OUTCOMES AND MEASURES Acquisition of a driver's license and first involvement as a driver in a police-reported crash. Survival analysis was used to estimate adjusted hazard ratios for licensing and crash outcomes through age 25 years.
RESULTS The median age of individuals at the end of the study was 22.2 years (interquartile range, 19.7-24.8). Compared with individuals without ADHD, the licensing probability of individuals with ADHD 6 months after eligibility was 35%lower (for males: Adjusted hazard ratio, 0.65; 95%CI, 0.61-0.70; females: Adjusted hazard ratio, 0.64; 95%CI, 0.58-0.70). Among individuals with a driver's license, 764 of 1785 with ADHD (42.8%) and 4715 of 13 221 without ADHD (35.7%) crashed during the study period. The adjusted risk for first crash among licensed drivers with ADHD was 1.36 times higher than for those without ADHD (95% CI, 1.25-1.48) and did not vary by sex, licensing age, or over time. Only 129 individuals with ADHD (12.1%) were prescribed medication in the 30 days before licensure.
CONCLUSIONS AND RELEVANCE Adolescents with ADHD get licensed less often and at an older age. Once licensed, this cohort has a greater risk of crashing. Additional research is needed to understand the specific mechanisms by which ADHD influences crash risk

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JAMA Psychiatry. 2017 Jan;74:76-84.

ESTIMATING THE HERITABILITY OF STRUCTURAL AND FUNCTIONAL BRAIN CONNECTIVITY IN FAMILIES AFFECTED BY ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sudre G, Choudhuri S, Szekely E, et al.

Importance: Despite its high heritability, few risk genes have been identified for attention-deficit/hyperactivity disorder (ADHD). Brain-based phenotypes could aid gene discovery. There is a myriad of structural and functional connections that support cognition. Disruption of such connectivity is a key pathophysiologic mechanism for ADHD, and identifying heritable phenotypes within these connections could provide candidates for genomic studies.

Objective: To identify the structural and functional connections that are heritable and pertinent to ADHD.

Design, Setting, and Participants: Members of extended multigenerational families enriched for ADHD were evaluated. Structural connectivity was defined by diffusion tensor imaging (DTI) of white matter tract microstructure and functional connectivity through resting-state functional magnetic resonance imaging (rsfMRI). Heritability and association with ADHD symptoms were estimated in 24 extended multigenerational families enriched for ADHD (305 members with clinical phenotyping, 213 with DTI, and 193 with rsfMRI data). Findings were confirmed in 52 nuclear families (132 members with clinical phenotypes, 119 with DTI, and 84 with rsfMRI). The study and data analysis were conducted from April 1, 2010, to September 1, 2016.

Results: In the 52 nuclear families, 86 individuals (65.2%) were male and the mean (SD) age at imaging was 20.9 (15.0) years; in the 24 multigenerational extended families, 145 individuals (47.5%) were male and mean age at imaging was 30.4 (19.7) years. Microstructural properties of white matter tracts connecting ipsilateral cortical regions and the corpus callosum were significantly heritable, ranging from total additive genetic heritability (h2) = 0.69 (SE, 0.13; P = .0000002) for radial diffusivity of the right superior longitudinal fasciculus to h2 = 0.46 (SE, 0.15; P = .0009) for fractional anisotropy of the right inferior fronto-occipital fasciculus. Association with ADHD symptoms was found in several tracts, most strongly for the right superior longitudinal fasciculus (t = -3.05; P = .003). Heritable patterns of functional connectivity were detected within the default mode (h2 = 0.36; SE, 0.16; cluster level significance, P < .002), cognitive control (h2 = 0.32; SE, 0.15; P < .002), and ventral attention networks (h2 = 0.36; SE, 0.16; P < .002). In all cases, subregions within each network showed heritable functional connectivity with the rest of that network. More symptoms of hyperactivity/impulsivity (t = -2.63; P = .008) and inattention (t = -2.34; P = .02) were associated with decreased functional connectivity within the default mode network. Some cross-modal correlations were purely phenotypic, such as that between axial diffusivity of the right superior longitudinal fasciculus and heritable aspects of the default mode network (phenotypic correlation, rhop = -0.12; P = .03). A genetic cross-modal correlation was seen between the ventral attention network and radial diffusivity of the right inferior fronto-occipital fasciculus (genetic correlation, rhog = -0.45, P = .02).

Conclusions: Analysis of data on multigenerational extended and nuclear families identified the features of structural and functional connectivity that are both significantly heritable and associated with ADHD. In addition, shared genetic factors account for some phenotypic correlations between functional and structural connections. Such work helps to prioritize the facets of the brain's connectivity for future genomic studies

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JAMA Psychiatry. 2017 Feb;74:179-88.

ASSOCIATION OF FLUID INTELLIGENCE AND PSYCHIATRIC DISORDERS IN A POPULATION-REPRESENTATIVE SAMPLE OF US ADOLESCENTS.

Keyes KM, Platt J, Kaufman AS, et al.

Importance: Despite long-standing interest in the association of psychiatric disorders with intelligence, few population-based studies of psychiatric disorders have assessed intelligence.

Objective: To investigate the association of fluid intelligence with past-year and lifetime psychiatric disorders, disorder age at onset, and disorder severity in a nationally representative sample of US adolescents.

Design, Setting, and Participants: National sample of adolescents ascertained from schools and households from the National Comorbidity Survey Replication-Adolescent Supplement, collected 2001 through 2004. Face-to-face household interviews with adolescents and questionnaires from parents were obtained. The data were analyzed from February to December 2016. DSM-IV mental disorders were assessed with the World Health Organization Composite International Diagnostic Interview, and included a

broad range of fear, distress, behavior, substance use, and other disorders. Disorder severity was measured with the Sheehan Disability Scale.
Main Outcomes and Measures: Fluid IQ measured with the Kaufman Brief Intelligence Test, normed within the sample by 6-month age groups.
Results: The sample included 10073 adolescents (mean [SD] age, 15.2 [1.50] years; 49.0% female) with valid data on fluid intelligence. Lower mean (SE) IQ was observed among adolescents with past-year bipolar disorder (94.2 [1.69]; P = .004), attention-deficit/hyperactivity disorder (96.3 [0.91]; P = .002), oppositional defiant disorder (97.3 [0.66]; P = .007), conduct disorder (97.1 [0.82]; P = .02), substance use disorders (alcohol abuse, 96.5 [0.67]; P < .001; drug abuse, 97.6 [0.64]; P = .02), and specific phobia (97.1 [0.39]; P = .001) after adjustment for a wide range of potential confounders. Intelligence was not associated with posttraumatic stress disorder, eating disorders, and anxiety disorders other than specific phobia, and was positively associated with past-year major depression (mean [SE], 100 [0.5]; P = .01). Associations of fluid intelligence with lifetime disorders that had remitted were attenuated compared with past-year disorders, with the exception of separation anxiety disorder. Multiple past-year disorders had a larger proportion of adolescents less than 1 SD below the mean IQ range than those without a disorder. Across disorders, higher disorder severity was associated with lower fluid intelligence. For example, among adolescents with specific phobia, those with severe disorder had a mean (SE) of 4.4 (0.72) points lower IQ than those without severe disorder (P < .001), and those with alcohol abuse had a mean (SE) of 5.6 (1.2) points lower IQ than those without severe disorder (P < .001).
Conclusions and Relevance: Numerous psychiatric disorders were associated with reductions in fluid intelligence; associations were generally small in magnitude. Stronger associations of current than past disorders with intelligence suggest that active symptoms of psychiatric disorders interfere with cognitive functioning. Early identification and treatment of children with mental disorders in school settings is critical to promote academic achievement and long-term success

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J Abnorm Child Psychol. 2017 Aug;45:1235-45.

MODERATORS OF PARENT TRAINING FOR DISRUPTIVE BEHAVIORS IN YOUNG CHILDREN WITH AUTISM SPECTRUM DISORDER.

Lecavalier L, Smith T, Johnson C, et al.

We conducted a 6 month, randomized trial of parent training (PT) versus a parent education program (PEP) in 180 young children (158 boys, 22 girls), ages 3–7 years, with autism spectrum disorder (ASD). PT was superior to PEP in decreasing disruptive and noncompliant behaviors. In the current study, we assess moderators of treatment response in this trial. Thirteen clinical and demographic variables were evaluated as potential moderators of three outcome variables: the Aberrant Behavior Checklist-Irritability subscale (ABC-I), Home Situations Questionnaire (HSQ), and Clinical Global Impressions-Improvement Scale (CGI-I). We used an intent-to-treat model and random effects regression. Neither IQ nor ASD severity moderated outcome on the selected outcome measures. Severity of Attention Deficit Hyperactivity Disorder (ADHD) and anxiety moderated outcomes on the ABC-I and HSQ. For instance, there was a 6.6 point difference on the ABC-I between high and low ADHD groups (p = .05) and a 5.3 point difference between high and low Anxiety groups (p = .04). Oppositional defiant disorder symptoms and household income moderated outcomes on the HSQ. None of the baseline variables moderated outcome on the CGI-I. That IQ and ASD symptom severity did not moderate outcome suggests that PT is likely to benefit a wide range of children with ASD and disruptive behavior

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J Abnorm Child Psychol. 2017 Aug;45:1051-62.

CONTROLLED SOCIAL INTERACTION TASKS TO MEASURE SELF-PERCEPTIONS: NO EVIDENCE OF POSITIVE ILLUSIONS IN BOYS WITH ADHD.

Jiang Y, Johnston C.

Studies have suggested that children with Attention-Deficit/Hyperactivity Disorder (ADHD) possess a Positive Illusory Bias (PIB) where they have higher self-perceptions of competence than more objective measures of their competence. However, recent research calls into question the primary methodology of these studies, that is, difference scores. This study investigated the PIB in boys with ADHD within the social domain using a novel methodology that refrains from using difference scores. Eighty-one 8- to 12-year-old boys with and without ADHD completed social interaction tasks where their actual social performance was made comparable, allowing for tests of between-group differences in self-perceptions that do not rely on difference scores. In addition, to examine whether clarity of social feedback moderates the presence of the PIB, the social tasks presented unclear, clear positive, or clear negative feedback. Boys rated how well they performed in each social interaction task, and these ratings were compared between ADHD and non-ADHD groups. Compared to the non-ADHD group, boys with ADHD did not show a PIB in their ratings of performance on the social tasks. There also was no moderation of boys' ratings by type of feedback received. In contrast, when the PIB was calculated using difference scores based on child and parent ratings of child competence, boys with ADHD showed a PIB compared to boys without ADHD. These findings call attention to the need to re-examine the phenomenon of the PIB using methodologies outside of difference scores

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J Abnorm Child Psychol. 2017 Aug;45:1077-89.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, TRAIT IMPULSIVITY, AND EXTERNALIZING BEHAVIOR IN A LONGITUDINAL SAMPLE.

Ahmad SI, Hinshaw SP.

Attention-deficit/hyperactivity disorder (ADHD) is highly comorbid with and predictive of externalizing behavior, yet is most often examined categorically, not dimensionally. We tested a recently proposed trait impulsivity model by dimensionally examining measures of childhood inattention and hyperactivity/impulsivity separately as predictors of later externalizing behavior in an all-female longitudinal sample of 228 young women. We also examined influences of parenting and peer relations, given the transactional nature and importance of environmental factors. We analyzed the relative contribution of hyperactive/impulsive (HI) and inattentive (IA) symptoms of girls with and without childhood-diagnosed ADHD (M age = 9.5; 140 ADHD and 88 Comparison) to the development of externalizing behaviors in adolescence (M age = 14.2) and early adulthood (M age = 19.6). Authoritarian parenting was examined as a moderator and adolescent externalizing behavior as a mediator of the relation between childhood HI and later externalizing behavior. Childhood HI symptoms significantly predicted multiple externalizing behaviors in adolescence and early adulthood, after accounting for IA and covariates (?R 2 ranged from 2.6 to 7.5 %). Mother's authoritarian parenting moderated this relation. Adolescent externalizing behavior mediated the relation between childhood HI symptoms and early adult externalizing behavior. In no case did childhood IA significantly predict externalizing behavior after accounting for HI symptoms. Findings support a trait impulsivity model, as HI symptoms, but not IA symptoms, significantly predicted later externalizing behavior. Results support the importance of dimensional predictors of developmental trajectories. We discuss implications for assessment, intervention, and future research.

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J Abnorm Child Psychol. 2017 Aug;45:1063-75.

IS THE POSITIVE ILLUSORY BIAS COMMON IN YOUNG ADOLESCENTS WITH ADHD? A FRESH LOOK AT PREVALENCE AND STABILITY USING LATENT PROFILE AND TRANSITION ANALYSES.

Bourchtein E, Langberg JM, Owens JS, et al.

The goal of this study was to use novel approaches that do not require the use of arbitrary cut-points (i.e., latent profile/transition analysis) to evaluate the prevalence and stability of the positive illusory bias (PIB) in

young adolescents with attention-deficit/hyperactivity disorder (ADHD). Participants were 326 middle-school students diagnosed with ADHD (Mage = 12.26 years, 71% male, 77% Caucasian). The Self-Perception Profile for Children (SPPC) was completed by participants and their parents at baseline and again 12 and 18 months later. Cross-sectional results revealed four subgroups based on SPPC responses. Only a small subset (18.4%) of youth with ADHD exhibited a global PIB, across the behavioral, scholastic, and social domains, with an additional 29% displaying a PIB in the scholastic domain only. Additionally, average parent/adolescent-rated competence within each subgroup was in line with an objective measure of scholastic competence (i.e., grades). When examined longitudinally, only a PIB in the social domain was stable across the 18-month study period and only for half of the sample. These findings suggest that the PIB is not ubiquitous in youth with ADHD, with many young adolescents rating themselves accurately relative to their parents and their grades. Further, when stability across time is considered, the PIB may be specific to social functioning, as opposed to a global, cross-domain phenomenon. Implications for the future measurement of the PIB are discussed

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J Abnorm Child Psychol. 2017 Aug;45:1091-103.

ARE ELEVATIONS IN ADHD SYMPTOMS ASSOCIATED WITH PHYSIOLOGICAL REACTIVITY AND EMOTION DYSREGULATION IN CHILDREN?

McQuade JD, Breaux RP.

The present study examined whether children with elevated attention-deficit/hyperactivity disorder (ADHD) symptoms display a unique pattern of emotion dysregulation as indexed by both parent report and physiological reactivity during experiences of failure. A sample of 61 children (9 to 13 years; M = 11.62, SD = 1.29; 48 % male) with and without clinical elevations in ADHD symptoms participated. Parent and teacher report of ADHD and oppositional defiant disorder (ODD) symptoms and parent report of internalizing problems were collected. Parents also provided ratings of children's emotional negativity/lability and emotion regulation. Children's physiological reactivity, based on changes in respiratory sinus arrhythmia (RSA) and skin conductance level (SCL), were assessed while they completed a manipulated social rejection task and impossible puzzle task. Regression analyses indicated that ADHD symptoms were associated with higher parent-rated emotional negativity/lability and with blunted RSA withdrawal in response to social rejection; these effects were not accounted for by co-occurring ODD symptoms or internalizing problems. ODD symptoms also were uniquely associated with parent ratings of poor emotion regulation. Internalizing problems were uniquely associated with emotional negativity/lability, poor emotion regulation, and increased SCL activity in response to social rejection. Results suggest that there may be a pattern of emotion dysregulation that is specific to ADHD symptomatology. The importance of contextual factors when examining physiological reactivity to stress in youth with ADHD is discussed

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J Abnorm Psychol. 2017;126:774-92.

HETEROGENEITY IN DEVELOPMENT OF ASPECTS OF WORKING MEMORY PREDICTS LONGITUDINAL ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOM CHANGE.

Karalunas SL, Gustafsson HC, Dieckmann NF, et al.

The role of cognitive mechanisms in the clinical course of neurodevelopmental disorders is poorly understood. Attention Deficit Hyperactivity Disorder (ADHD) is emblematic in that numerous alterations in cognitive development are apparent, yet how they relate to changes in symptom expression with age is unclear. To resolve the role of cognitive mechanisms in ADHD, a developmental perspective that takes into account expected within-group heterogeneity is needed. Method: The current study uses an accelerated longitudinal design and latent trajectory growth mixture models in a sample of children ages 7-13 years carefully characterized as with (n =437) and without (n = 297) ADHD to (a) identify heterogeneous developmental trajectories for response inhibition, visual spatial working memory maintenance, and delayed reward discounting and (b) to assess the relationships between these cognitive trajectories and ADHD symptom change. Results: Best-fitting models indicated multiple trajectory classes in both the ADHD and

typically developing samples, as well as distinct relationships between each cognitive process and ADHD symptom change. Developmental change in response inhibition and delayed reward discounting were unrelated to ADHD symptom change, while individual differences in the rate of visual spatial working memory maintenance improvement predicted symptom remission in ADHD. Conclusion: Characterizing heterogeneity in cognitive development will be crucial for clarifying mechanisms of symptom persistence and recovery. Results here suggest working memory maintenance may be uniquely related to ADHD symptom improvement

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J Child Adolesc Psychopharmacol. 2017;27:474-82.

EFFICACY AND SAFETY OF HLD200, DELAYED-RELEASE AND EXTENDED-RELEASE METHYLPHENIDATE, IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Pliszka SR, Wilens TE, Bostrom S, et al.

Objective: Evening-dosed HLD200 is a delayed-release and extended-release methylphenidate (DR/ER-MPH) formulation consisting of uniform, dual-layered microbeads with an inner drug-loaded core. DR/ER-MPH is designed to delay the initial release of drug by 8-10 hours, and thereafter, provide a controlled, extended drug release to target onset of effect upon awakening that lasts into the evening. This phase 3 study evaluated the safety and efficacy of DR/ER-MPH on symptoms and temporal at-home functional impairment in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: This 3-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group, forced-dose titration trial evaluated DR/ER-MPH (40-80 mg/day) in children aged 6-12 years with ADHD. Primary efficacy endpoint was the ADHD rating scale-IV (ADHD-RS-IV), and the key secondary endpoints were the Before-School Functioning Questionnaire (BSFQ), and Parent Rating of Evening and Morning Behavior-Revised, morning (PREMB-R AM) and evening (PREMB-R PM). Safety measures included spontaneously reported treatment-emergent adverse events (TEAEs) and two TEAEs of special interest, appetite suppression and insomnia (with direct questioning on sleep disturbance).

Results: One hundred sixty-one participants were included in the intent-to-treat population (DR/ER-MPH, n = 81; placebo, n = 80). After 3 weeks, DR/ER-MPH achieved significant improvements versus placebo in ADHD symptoms (least-squares [LS] mean ADHD-RS-IV: 24.1 vs. 31.2; $p = 0.002$), and at-home early morning (LS mean BSFQ: 18.7 vs. 28.4; $p < 0.001$; LS mean PREMB-R AM: 2.1 vs. 3.6; $p < 0.001$) and late afternoon/evening (LS mean PREMB-R PM: 9.4 vs. 12.2; $p = 0.002$) functional impairment. Commonly reported TEAEs (10%) were insomnia and decreased appetite.

Conclusions: DR/ER-MPH was generally well tolerated and demonstrated significant improvements versus placebo in ADHD symptoms and at-home functional impairments in the early morning, late afternoon, and evening in children with ADHD

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J Child Adolesc Psychopharmacol. 2017;27:555-58.

IMPULSIVE AGGRESSIVE BEHAVIOR TRIGGERED BY HEADACHES IN A CHILD WITH SEVERE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Yang TC, Luber MJ, Coffey BJ.

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J Child Psychol Psychiatry. 2017 Aug;58:958-66.

FEMALE-SPECIFIC ASSOCIATION OF NOS1 GENOTYPE WITH WHITE MATTER MICROSTRUCTURE IN ADHD PATIENTS AND CONTROLS.

van Ewijk H, Bralten J, van Duin EDA, et al.

Background: The nitric oxide synthase gene (NOS1) exon 1f (ex1f) VNTR is a known genetic risk factor for Attention-Deficit/Hyperactivity Disorder (ADHD), particularly in females. NOS1 plays an important role in neurite outgrowth and may thus influence brain development, specifically white matter (WM) microstructure,

which is known to be altered in ADHD. The current study aimed to investigate whether NOS1 is associated with WM microstructure in (female) individuals with and without ADHD.
Methods: Diffusion Tensor Imaging (DTI) scans were collected from 187 participants with ADHD (33% female) and 103 controls (50% female), aged 8–26 years, and NOS1-ex1f VNTR genotype was determined. Whole-brain analyses were conducted for fractional anisotropy (FA) and mean diffusivity (MD) to examine associations between NOS1 and WM microstructure, including possible interactions with gender and diagnosis.
Results: Consistent with previous literature, NOS1-ex1f was associated with total ADHD and hyperactivity-impulsivity symptoms, but not inattention; this effect was independent of gender. NOS1-ex1f was also associated with MD values in several major WM tracts in females, but not males. In females, homozygosity for the short allele was linked to higher MD values than carriership of the long allele. MD values in these regions did not correlate with ADHD symptoms. Results were similar for participants with and without ADHD.
Conclusions: NOS1-ex1f VNTR is associated with WM microstructure in females in a large sample of participants with ADHD and healthy controls. Whether this association is part of a neurodevelopmental pathway from NOS1 to ADHD symptoms should be further investigated in future studies

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J Dev Behav Pediatr. 2017 Jul;38:417-23.
SUBSTANCE USE AMONG ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: REASONS FOR USE, KNOWLEDGE OF RISKS, AND PROVIDER MESSAGING/EDUCATION.
Harstad E, Wisk LE, Ziemnik R, et al.
Objective: Adolescents with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for alcohol and marijuana use. This study's objective is to describe adolescents' ADHD-specific reasons for marijuana use, knowledge of ADHD-specific alcohol risks, and reported subspecialty provider messaging/education regarding alcohol use among adolescents with ADHD.
Methods: Youths with ADHD aged 12 to 18 years completed a survey about alcohol and marijuana use, ADHD-specific reasons for marijuana use, knowledge of ADHD-specific alcohol risks, and reported provider messaging/education regarding alcohol use. We assessed knowledge toward substance use using descriptive statistics. We used and t tests to determine whether knowledge or provider messaging/education differed by sociodemographic characteristics.
Results: Of the 96 participants, 61.5% were male, average age was 15.7 years; 31.3% reported past-year alcohol use and 20.8% reported past-year marijuana use. The majority (65.2%) said 'no/don't know' to both 'Can alcohol make ADHD symptoms worse and 'Can alcohol interfere or get in the way of the medications you take Older participants were more likely to correctly answer the medication question 'yes.' Despite most (74%) participants reporting that their provider asked about alcohol use, few youth reported that their providers gave specific messages/education that alcohol could make ADHD symptoms worse (9.4%) or interfere with ADHD medications (14.6%); older participants and past-year alcohol users were more likely to have received these alcohol-specific messages.
Conclusion: Many youth with ADHD are unaware of the risks of alcohol use in relation to ADHD and providers are not consistently discussing these risks in the context of clinical ADHD care

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J Dev Behav Pediatr. 2017 Jul;38:358-68.
ACADEMIC ACHIEVEMENT AND RISK FACTORS FOR ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN MIDDLE SCHOOL AND EARLY HIGH SCHOOL.
Zendarski N, Sciberras E, Mensah F, et al.
Objective: Examine academic achievement of students with attention-deficit hyperactivity disorder (ADHD) during the early high school period and identify potentially modifiable risk factors for low achievement.
Method: Data were collected through surveys (adolescent, parent, and teacher) and direct assessment of Australian adolescents (12–15 yr; n = 130) with ADHD in early high school (i.e., US middle and high school grades). Academic achievement outcomes were measured by linking to individual performance on the

National Assessment Program-Literacy and Numeracy (NAPLAN) tests, direct assessment of reading and math, and teacher report of academic competence. Linear regression models examined associations between adolescent, parent/family, and school factors and NAPLAN domain scores.
Results: Students with ADHD had lower NAPLAN scores on all domains and fewer met minimum academic standards in comparison with state benchmarks. The poorest results were for persuasive writing. Poor achievement was associated with lower intelligence quotient across all academic domains. Adolescent inattention, bullying, poor family management, male sex, and attending a low socioeconomic status school were associated with lower achievement on specific domains.
Conclusion: Students with ADHD are at increased academic risk during the middle school and early high school period. In addition to academic support, interventions targeting modifiable factors including inattention, bullying, and poor family management may improve academic achievement across this critical period

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J Dev Behav Pediatr. 2017 Jul;38:369-77.
ASSOCIATION BETWEEN PARENTING STYLE AND SOCIAL OUTCOMES IN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: AN 18-MONTH LONGITUDINAL STUDY.
Bhide S, Sciberras E, Anderson V, et al.
Objective: In a community-based sample of children with attention-deficit/hyperactivity disorder (ADHD) (n = 179) and non-ADHD controls (n = 212), this longitudinal study explored changes in parenting style over time; and whether parenting style prospectively predicts child functional outcomes.
Methods: Attention-deficit/hyperactivity disorder diagnosis was assessed using the Conners ADHD index and Diagnostic Interview Schedule for Children IV. Children (70.3% boys) were assessed at baseline (mean age: 7.3 yr) and after 18 months (mean age: 8.9 yr) using a range of parent- and teacher-reported measures of child socioemotional and academic functioning. Parenting style was assessed through parent-reported measures of warmth, consistency, and anger.
Results: At 18-month follow-up, there was a small significant decline in parenting warmth and parenting anger, and an increase in parenting consistency across groups. In the ADHD group, parenting warmth at baseline was positively related to 18-month prosocial behavior and responsibility by parent report, whereas parenting consistency predicted these child outcomes by teacher report. Parenting anger was positively associated with peer problems and negatively associated with prosocial behavior, self-control, and responsibility by parent report. Associations were similar for non-ADHD controls and all associations held after adjusting for a range of family, child, and parent factors. After additional adjustment of baseline levels of child functioning, parenting warmth and consistency continued to be associated with 18-month child outcomes. Parenting style was unrelated to emotional problems and academic competence over time.
Conclusion: Parenting style is independently related to aspects of future social outcomes of children with ADHD. Results hold implications for parenting interventions aimed at managing ADHD-related social impairments over time

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J Groups Addict Recover. 2017 Jul;12:135-57.
GENDER DIFFERENCES IN THE PREVALENCE OF ADHD AMONG CLIENTS OF THERAPEUTIC COMMUNITIES FOR DRUG ADDICTS IN THE CZECH REPUBLIC: SECONDARY ANALYSIS OF THE PILOT STUDY.
Kalina K, Rubášová E, Cablová L, et al.
The aim of this study was to identify gender differences between a group with and without attention deficit hyperactivity disorder (ADHD) in the sample of 76 clients of therapeutic communities. The battery of tests contained three questionnaires based on ADHD Self-Report Scale (ASRS), Wender Utah Rating Scale (WURS), and Conners Teacher Questionnaire. Data were analyzed by combining a descriptive approach and sectional processes of qualitative data analysis. Women with ADHD exhibit more complications in the WURS–25 scale and (together with the women without ADHD) in ASRS. Gender differences in ADHD-

related complication in treatment were expressed on a qualitative level; severe complications occurred mainly in themen in both groups. (PsycINFO Database Record (c) 2017 APA, all rights reserved)

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Journal of Medical Imaging and Health Informatics. 2017;7:1005-12.

ELECTROENCEPHALOGRAPHY MU RHYTHM SUPPRESSION ANALYSIS DURING OBSERVATION-EXECUTION TASKS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sánchez-González, A, García-Zapirain B.

Attention deficit/hyperactivity is widely characterized by inadequate inhibitory control, problems related to task execution, motivation or impaired attention control. Electroencephalographic alpha wave power suppression above the somatosensory cortex is thought to reveal a movement or attention type pattern when contrasted to a baseline. The proposed research attempts to reveal whether there are ADHD-related differences in the activity and nature of alpha EEG wave oscillations during observation-execution tasks. To do so, alpha power suppression through time, frequency and spatial analysis was performed. It is reasonable to assume that different processes may be present in the alpha band, but new research advises about the strong relevance of the somatosensory system during observation-execution processes and indeed, a disruption of this mechanism can lead to some developmental disorders. The results show significant differences in suppressing Mu rhythm for the control group and ADHD group, and also for the combined and inattentive subtypes. Differences were detected for 8-10 and 10-12 Hz frequency ranges in the case of the ADHD group and the combined subtype, and 8-10, 8-12 and 10-12 Hz in the case of the inattentive and hyperactive subtypes. Hence, from these findings it could be interpreted that the ADHD groups have a different conceptualization of external stimuli, and this was perceived in different EEG activity within the somatosensory area. In conclusion, this research could help to understand the mechanism underlying conceptual representation and behavioral performance associated with this disorder

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Journal of Pediatric Epilepsy. 2017.

FACTORS ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH FRONTAL LOBE EPILEPSY.

Kanemura H, Sano F, Ohyama T, et al.

The relationship between attention deficit/hyperactivity disorder (ADHD) and frontal lobe epilepsy (FLE) in children is not well understood. Patients with FLE between 6 and 15 years of age were studied. Scores on the ADHD rating scale (ADHD-RS) and Wisconsin card sorting test (WCST) were obtained at baseline. Behavioral changes were evaluated using the ADHD-RS scores at 6, 12, and 24 months after seizure onset. Perseverative errors of Nelson (PEN) scales on WCST were also evaluated at same time periods. The relationships between clinical manifestations and neuropsychological disturbances were analyzed. In 34 patients, the ADHD-RS score at 24 months after onset was most strongly associated with the presence of status epilepticus (SE, $p = 0.004$, $\beta = 0.490$) followed by seizure frequency ($p = 0.021$, $\beta = 0.382$). The increase in ADHD-RS score was most strongly associated with seizure frequency ($p < 0.001$, $\beta = 0.635$). The PEN score on WCST at 24 months was most strongly associated with seizure frequency ($p = 0.001$, $\beta = 0.724$). The increase in PEN score on WCST was most strongly associated with seizure frequency ($p = 0.001$, $\beta = 0.872$). The only clinical factor associated with both the ADHD-RS and the PEN scores on the WCST was seizure frequency. Seizure frequency may be correlated with risk for ADHD in children with FLE

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J Psychiatr Res. 2017;94:202-07.

DOES THE INCREASING PLACEBO RESPONSE IMPACT OUTCOMES OF ADULT AND PEDIATRIC ADHD CLINICAL TRIALS? DATA FROM THE US FOOD AND DRUG ADMINISTRATION 2000-2009.

Khan A, Fahl MK, Brown WA.

In a study of recent antidepressant clinical trial data, it was found placebo response had grown significantly over time and that contrary to expectations, trial outcome measures and success rate were not impacted. The aim of this paper was to evaluate if this trend of increasing placebo response and stable outcome measures could be seen in clinical trial data for Attention-Deficit Hyperactivity Disorder, a different psychiatric condition with susceptibility to placebo response. For this reason, we evaluated efficacy data reported in the FDA Medical and Statistical reviews for 10 ADHD medication programs (4917 patients, 17 trials, 29 treatment arms). Placebo and medication response were measured as percent symptom reduction and effect sizes and drug-placebo differences were calculated for each treatment arm and analyzed in relation to year of approval. We also investigated the potential role of age and medication class on trends and outcomes. Results showed a similar pattern to antidepressants wherein the placebo response is rising significantly over time ($r = 0.636$, $p = 0.006$) and effect size ($r < 0.0001$, $p = 1.0$), drug-placebo difference ($r =$ Γêǽ0.238, $p = 0.214$), and success rate (28/29 97%) have remained unaffected, likely due to a parallel, although not statistically significant increase in medication response ($r = 0.326$, $p = 0.085$). Age and medication class did not alter these observed time trends but pediatric trials and stimulants were found to have more robust treatment effects than adult trials and non-stimulants. The results of this study suggest that like antidepressants, the relationship between placebo response and the outcomes of ADHD clinical trials is weak at best

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J Psychopharmacol. 2017;31:1070-77.

ASSOCIATION OF THE GRIN2B RS2284411 POLYMORPHISM WITH METHYLPHENIDATE RESPONSE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kim JI, Kim J-W, Park J-E, et al.

Objective: We investigated the possible association between two NMDA subunit gene polymorphisms (GRIN2B rs2284411 and GRIN2A rs2229193) and treatment response to methylphenidate (MPH) in attention-deficit/hyperactivity disorder (ADHD).

Methods: A total of 75 ADHD patients aged 6-17 years underwent 6 months of MPH administration. Treatment response was defined by changes in scores of the ADHD-IV Rating Scale (ADHD-RS), clinician-rated Clinical Global Impression - Improvement (CGI-I), and Continuous Performance Test (CPT). The association of the GRIN2B and GRIN2A polymorphisms with treatment response was analyzed using logistic regression analyses.

Results: The GRIN2B rs2284411 C/C genotype showed significantly better treatment response as assessed by ADHD-RS inattention ($p=0.009$) and CGI-I scores ($p=0.009$), and there was a nominally significant association in regard to ADHD-RS hyperactivity-impulsivity ($p=0.028$) and total ($p=0.023$) scores, after adjusting for age, sex, IQ, baseline Clinical Global Impression - Severity (CGI-S) score, baseline ADHD-RS total score, and final MPH dose. The GRIN2B C/C genotype also showed greater improvement at the CPT response time variability ($p<0.001$). The GRIN2A G/G genotype was associated with a greater improvement in commission errors of the CPT compared to the G/A genotype ($p=0.001$).

Conclusions: The results suggest that the GRIN2B rs2284411 genotype may be an important predictor of MPH response in ADHD

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J Psychopharmacol. 2017;31:1061-69.

VERBAL WORKING MEMORY-RELATED FUNCTIONAL CONNECTIVITY ALTERATIONS IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THE EFFECTS OF METHYLPHENIDATE.

Wu Z-M, Bralten J, An L, et al.

Objective: Few studies have investigated verbal working memory-related functional connectivity patterns in participants with attention-deficit/hyperactivity disorder (ADHD). Thus, we aimed to compare working memory-related functional connectivity patterns in healthy children and those with ADHD, and study effects of methylphenidate (MPH).

Method: Twenty-two boys with ADHD were scanned twice, under either MPH (single dose, 10 mg) or placebo, in a randomised, cross-over, counterbalanced placebo-controlled design. Thirty healthy boys were scanned once. We used fMRI during a numerical n-back task to examine functional connectivity patterns in case-control and MPH-placebo comparisons, using independent component analysis.

Results: There was no significant difference in behavioural performance between children with ADHD, treated with MPH or placebo, and healthy controls. Compared with controls, participants with ADHD under placebo showed increased functional connectivity within fronto-parietal and auditory networks, and decreased functional connectivity within the executive control network. MPH normalized the altered functional connectivity pattern and significantly enhanced functional connectivity within the executive control network, though in non-overlapping areas.

Conclusion: Our study contributes to the identification of the neural substrates of working memory. Single dose of MPH normalized the altered brain functional connectivity network, but had no enhancing effect on (non-impaired) behavioural performance

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Laryngoscope. 2017;127:2113-19.

CHARACTERISTICS OF TINNITUS IN ADOLESCENTS AND ASSOCIATION WITH PSYCHOEMOTIONAL FACTORS.

Kim SY, Jeon YJ, Lee J-Y, et al.

Objectives/Hypothesis: The characteristics and underlying mechanisms of tinnitus remain more elusive in the pediatric population than in adults. We investigated the prevalence of tinnitus, its characteristics, and associated factors, with a focus on psychoemotional problems in adolescents.

Study Design: Cross-sectional study.

Methods: In total, 962 adolescents were surveyed for tinnitus and possibly related otologic and socioeconomic factors. The participants completed a visual analog scale (VAS) pertaining to various aspects of tinnitus, as well as the Tinnitus Handicap Inventory, Children's Depression Inventory (CDI), State Anxiety Inventory for Children, Trait Anxiety Inventory for Children (TAIC), Internet Addiction Test, Conners' Abbreviated Parent Rating Scale, and a learning disability score. Characteristics of tinnitus were analyzed, and psychoemotional and other factors were compared between tinnitus and nontinnitus groups.

Results: Approximately one-third of subjects reported experiencing tinnitus. A family history of tinnitus, subjective hearing loss, dizziness, and CDI and TAIC abnormalities were significantly associated with tinnitus. In the tinnitus-always group, tinnitus showed significant relationships with subjective hearing loss, bilateral tinnitus, and VAS, CDI, and TAIC scores.

Conclusions: The results suggest that about one-third of adolescents experience tinnitus, which may be related to psychoemotional factors. In particular, anxiety and depression may be important factors to consider in managing tinnitus in adolescents. Further study of tinnitus in adolescents, including efforts toward diagnosis and management, is needed to determine whether there is a causal relationship with anxiety and depression, and the extent to which adverse outcomes may be associated with these psychoemotional factors

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Laryngoscope. 2017 May;127:1224-30.

MULTIMODALITY ASSESSMENT OF UPPER AIRWAY OBSTRUCTION IN CHILDREN WITH PERSISTENT OBSTRUCTIVE SLEEP APNEA AFTER ADENOTONSILLECTOMY.

Clark C, Ulualp SO.

OBJECTIVES/HYPOTHESIS: Children with obstructive sleep apnea (OSA) may have multiple sites of upper airway obstruction (UAO). A wide variety of techniques has been used to evaluate UAO. Our aim was to compare findings of cine magnetic resonance imaging (MRI) and drug-induced sleep endoscopy (DISE) in identifying UAO sites in children with persistent OSA after adenotonsillectomy (AT).
STUDY DESIGN: Retrospective chart review.
MATERIAL AND METHODS: The medical records of children who underwent DISE and cine MRI were reviewed. Data pertaining to demographics, past medical history, body mass index, polysomnography, findings of DISE, and cine MRI were obtained.
RESULTS: Fifteen children (11 boys, 4 girls; age range, 7-18 years) were identified. Comorbid conditions were Down syndrome in nine patients, cerebral palsy in one, attention deficit hyperactivity disorder in two, and asthma in three. Severity of OSA was moderate in five, and severe in 10. DISE and cine MRI showed the same UAO site in 10 patients: a single site (tongue) in nine and multiple sites (tongue and oropharynx/lateral walls) in one. DISE showed additional UAO sites undetected by cine MRI in three patients. Cine MRI showed additional UAO sites undetected by DISE in one patient. DISE and cine MRI showed different sites of obstruction in one patient.
CONCLUSIONS: Cine MRI and DISE documented single and multiple sites of UAO in children with persistent OSA after AT. Cine MRI and DISE findings were similar in the majority of the children. Assessment of the sensitivity and specificity of cine MRI and DISE in detecting sites of UAO merits further investigation.

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Mindfulness (N Y). 2017 Aug;8:859-72.

MINDFULNESS-BASED INTERVENTION FOR CHINESE CHILDREN WITH ADHD AND THEIR PARENTS: A PILOT MIXED-METHOD STUDY.

Zhang D, Chan SKC, Lo HHM, et al.

This was a pilot pre–post-intervention study with added qualitative focused group discussions and interviews to examine the feasibility, acceptability, and effects of a mindfulness-based intervention (the 8-week MYmind course) for Chinese children with attention deficit hyperactivity disorder (ADHD) aged 8 to 12 years (n = 11) and one of their parents (n = 11). Outcomes included feasibility and acceptability of MYmind, objective measures of children's attention and related problems, parent-reported child executive function and behavior problems, and parents' parental stress, parenting styles, and mindful parenting. The attendance rate of MYmind (=6 out of 8 sessions) was 91%: only one family withdrew from the course. Participants expressed overall positive views about MYmind. They also expressed their changes after the course, barriers and facilitators for course participation and completion, and suggestions on course improvement. The overall satisfaction scores were 7.3 (2.1) and 8.0 (1.2) out of 10 among the children and parents, respectively. With respect to the quantitative results, after multiple testing correction, positive results with large effect sizes only occurred on the objective attention tests: 'time per target,' 'attention score,' and 'map mission' of the Test of Everyday Attention for Children (TEA-Ch) and 'omissions' of the computerized Conners' Continuous Performance Test 3rd Edition (CPT 3), whereas no statistically significant changes were seen in other measures, i.e., children's other results in the TEA-Ch and CPT 3, parents' perceived child problems on the Eyberg Child Behavior Inventory (ECBI) and the Behavior Rating Inventory of Executive Function (BRIEF), as well as parents' scores of the Parenting Stress Index (PSI), Parenting Scale (PS), and Interpersonal Mindfulness in Parenting (IM-P). The MYmind course is a feasible and acceptable intervention among Chinese children with ADHD and their parents. The preliminary significant quantitative results should be interpreted with much caution due to potential effects from learning on neurocognitive outcomes. Larger studies with a control group are needed

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Mindfulness (N Y). 2017 Aug;8:1018-35.

MECHANISMS OF ACTION IN CONCURRENT PARENT-CHILD MINDFULNESS TRAINING: A QUALITATIVE EXPLORATION.

Haydicky J, Wiener J, Shecter C .

This study examined potential processes of change and mechanisms of action in an 8-week manualized mindfulness intervention for adolescents with attention-deficit/hyperactivity disorder (ADHD) and their parents. Five families (five adolescents aged 13–18 and seven parents) participated in semi-structured interviews about their lived experiences of mindfulness 1 to 3 months after the intervention. Thematic analysis guided by a phenomenological approach revealed several potential underlying mechanisms of action contributing to improved peer and family relationship quality after mindfulness training. Themes were consistent among parents and adolescents. Participant descriptions were indicative of enhanced present-focused awareness and detached self-observation, contributing to improved self-monitoring and self-regulation of attention, behavior, and emotions. Participants reported becoming more adept at implementing adaptive emotion regulation strategies (e.g., cognitive reappraisal, problem-solving, and acceptance) and relying less on maladaptive emotion regulation strategies (e.g., rumination). Parents and adolescents described a parallel process of enhanced self-awareness and self-regulation that conjointly contributed to increased empathy, reduced emotional reactivity, improved communication, and reductions in the intensity and duration of conflicts. Furthermore, as individuals in the parent-child dyad became more adept at regulating their emotions, they mutually reinforced the emotion regulation skills of their social partner. A model of the co-regulatory process of change in parent-adolescent mindfulness training is proposed

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Molecular Autism. 2017;8.

ADHD-RELATED SYMPTOMS AND ATTENTION PROFILES IN THE UNAFFECTED SIBLINGS OF PROBANDS WITH AUTISM SPECTRUM DISORDER: FOCUS ON THE SUBTYPES OF AUTISM AND ASPERGER'S DISORDER .

Chien Y-L, Chou M-C, Chiu Y-N, et al.

Background: The presence of attention-deficit/hyperactive disorder (ADHD) symptoms and impaired attention performance are commonly noted in individuals with autism spectrum disorder (ASD). However, little is known about attention performance in their unaffected siblings. This study aimed to investigate the ADHD-related traits and attention performance in unaffected siblings of probands with autism and Asperger syndrome (AS), as well as the clinical correlates of ADHD-related traits.

Methods: We assessed the intention, hyperactivity-impulsivity, and oppositional symptoms, and attention profiles of 199 probands with a diagnosis of ASD (122 autism, 77 AS), their unaffected siblings, and 196 typically developing controls (TD) by their parents' reports on the ADHD-related symptoms and the Connors' Continuous Performance Test (CCPT), respectively.

Results: Compared to TD, unaffected siblings of ASD probands were more hyperactive/impulsive and oppositional, particularly unaffected siblings of AS probands. In CCPT, unaffected siblings of AS have intermediate levels of performance between probands with AS and TD on focused attention and sustained attention but were not statistically different from AS probands or TD in these attention profiles. In contrast, unaffected siblings of autism probands have significantly better CCPT performance when compared to autism probands but not to TD. In addition, stereotyped behaviors predicted ADHD-related traits in both sibling groups, but distinctive patterns of other correlates for ADHD-related traits were found between the two sibling groups.

Conclusions: This work suggested that unaffected siblings of AS, but not autism, have more hyperactive/impulsive traits and a trend of pervasive attention deficits assessed by CCPT which might serve as potential endophenotypes for genetic studies in AS.

Trial registration: ClinicalTrials.gov, NCT01582256

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NASN Sch Nurse. 2017 Jan;32:36-38.

SCHOOL NURSES' ROLE IN HELPING CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDERS.

AlAzzam M, Suliman M, ALBashtawy M.

Attention-deficit/hyperactivity disorder (ADHD) is a multifaceted disease characterized by core symptoms of hyperactivity, inattention, and impulsivity, affecting children across every socioeconomic and ethnic group. An estimated 40% to 60% of children with ADHD have comorbidities such as anxiety, depression, and learning disabilities. School nurses must be an integral part of the process of increasing awareness about ADHD through improving the service delivery model for affected children and their families. There is a solid foundation of research on which they can build to improve the benefits through study, workshops, community programs, and national screening programs

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Neuroepidemiology. 2017;155-63.

THE ASSOCIATION OF POOR ACADEMIC PERFORMANCE WITH TIC DISORDERS: A LONGITUDINAL, MAINSTREAM SCHOOL-BASED POPULATION STUDY.

Cubo E, Gonzalez C, Ausin V, et al.

Background: Little is known about the academic performance of students with tic disorders (TD). Our aim was to investigate the association of TD and poor academic performance over time.

Methods: Longitudinal, observational study of mainstream schoolchildren comparing grade retention (GR) and learning disorders (LD) in students with vs. without TD between 2010 and 2014. Students with vs. without TD based on DSM-IV-TR criteria, or with vs. without GR and LD were compared in terms of comorbidities, school, and environmental characteristics. The association of TD with GR was analyzed using hazard ratios (HRs) with 95% CIs, and with LD using logistic regression analysis [Odds ratio (OR)].

Results: Two hundred fifty-eight students were included (mean age 14.0 ± 1.71 years, 143 [55.4%] males). The incident rate for TD and GR was 2.6 and 3.3 per 100 persons-year, respectively. LD found in 21 (9.9%) students was associated with TD (OR 11.62, 95% CI 2.21-60.90, p = 0.004), and attention deficit hyperactivity disorder (ADHD; OR 6.63, 95% CI 1.55-28.37, p = 0.01). Low psychological support (HRs 12.79, 95% CI 3.39-48.17) and low sport participation (HRs 6.41, 95% CI 1.54-26.78) were risk factors for GR.

Conclusions: TD was associated with academic difficulties, namely, LD in conjunction with ADHD but not GR. The diagnosis of TD and comorbidities, and the initiation of proper treatment could have a favorable impact on school performance, and consequently on social development

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Neuropsychiatr Dis Treat. 2017 Jul;13.

ATTENTION–MEMORY TRAINING YIELDS BEHAVIORAL AND ACADEMIC IMPROVEMENTS IN CHILDREN DIAGNOSED WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER COMORBID WITH A LEARNING DISORDER.

Carlos Farias A, Cordeiro ML, Felden EPG, et al.

Background: Recent studies have suggested that children with attention-deficit hyperactivity disorder (ADHD) may benefit from computerized cognitive training. Therapy implementation is especially complicated when ADHD is associated with learning disorders (LDs). This study tested the efficacy of a computer-based cognitive training program, namely, computerized cognitive training (CCT), in children with ADHD comorbid with an LD (ADHD-LD), with or without psychostimulant medication.

Materials and methods: After diagnostic evaluations, 27 children with ADHD-LD (8 unmedicated and 19 medicated) participated in CCT, which is intended to improve attention, memory, reasoning, visual processing, and executive functioning. The participants completed 24 1-hour sessions over 3 months. Neuropsychometric and standardized academic test results before and after training were compared to assess treatment efficacy. Shapiro–Wilk normality tests were applied, and subsequent Wilcoxon tests were used to identify significant differences in preversus post-training performance.

Results: After CAT, children diagnosed with ADHD-LD showed 1) improvements in trained skills, measured directly within the software and indirectly by external psychometric tests; 2) improvements in attention,

memory, and some executive functioning; 3) improvements in academic performance, particularly in mathematics; and 4) reductions in maladaptive behavioral features.
Conclusion: The present findings suggest that cognitive training programs should be explored further as potential adjunctive therapies to improve outcomes in children with ADHD-LD

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Neuropsychology. 2017 Feb;31:160-72.
NEUROPSYCHOLOGICAL FUNCTIONING IN COLLEGE STUDENTS WITH AND WITHOUT ADHD.
Weyandt LL, Oster DR, Gudmundsdottir BG, et al.
OBJECTIVE: Increasing numbers of students with attention-deficit/hyperactivity disorder (ADHD) are attending college; however, little empirical information is available concerning the functional impairment experienced by these students. Although preliminary studies suggest that college students with ADHD are more likely to experience a variety of psychosocial and academic difficulties compared to their peers without the disorder, findings regarding neuropsychological functioning have been inconsistent with some studies reporting that college students with ADHD perform more poorly on various cognitive and neuropsychological tasks while others report no differences compared to their peers without ADHD.
METHOD: The purposes of the present study, the Trajectories Related to ADHD in College project, a longitudinal study following the 4-year outcomes of college students with and without ADHD, were to (a) examine the performance of 436 first-year college students with and without ADHD (51.6% female) on measures of executive function (EF) and intelligence and (b) investigate the association of self-reported use of stimulant medication and neuropsychological performance in students with ADHD. Participant data from their first year of involvement in the study were analyzed.
RESULTS: Participants with ADHD performed more poorly on task-based and self-report EF measures relative to the comparison group. In contrast, no significant group differences were found with respect to intellectual performance. Within the ADHD group, use of prescription stimulant medication was associated with improved performance on some, but not all, neuropsychological tasks. Additional analyses also revealed significant group differences in EF based on clinical diagnostic status.
CONCLUSION: College students with ADHD demonstrated poorer EF than their peers without ADHD and psychostimulant medication was associated with improved EF performance. No group differences were found with respect to intellectual functioning, Lastly, having one or more comorbid psychiatric diagnoses in addition to ADHD was associated with poorer EF outcomes

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NeuroRehabilitation. 2017;40:11-21.
A SERIES OF N-OF-1 TRIALS OF STIMULANTS IN BRAIN INJURED CHILDREN.
Nikles J, Mitchell G, McKinlay L, et al.
BACKGROUND: There is controversy about whether central nervous system stimulant (CNS) medication is an effective method of treating acquired attention deficits in children with acquired brain injury (ABI). OBJECTIVE: The primary objective was to determine the effectiveness of stimulants on attention, concentration and executive function in children with ABI.
METHODS: Randomised, double-blind, placebo-controlled, multi-centre n-of-1 trials of stimulants assessing effect on attention, concentration and executive function in 53 children and adolescents with ABI who were outpatients of three tertiary hospitals in Australia. Trials consisted of 3 two-week cycles, each cycle consisting of stimulant medication at doses titrated by physician (1 week) and placebo (1 week) in random order. The effect on parent and teacher Conners' 3 and Behaviour Rating Inventory of Executive Function (BRIEF) was analysed using hierarchical Bayesian methods.
RESULTS: Overall, Teacher Conners' Hyperactivity/Impulsivity and Teacher BRIEF Global Executive scales showed important improvement (T-score mean change 2.6; 95% credible interval (CI): 0.4, 4.9; posterior probability of mean change >0 : 0.99; T-score mean change 3.1; 95% CI: -0.1, 6.4; posterior probability of mean change >0 : 0.97). There were no important improvements in parent/guardian-reported primary outcomes. There was heterogeneity in response identified through individual results of the N-of-1 trials.

CONCLUSIONS: N-of-1 trials have a clear role in identifying those children/adolescents with ABI and secondary Attention Deficit Hyperactivity Disorder (ADHD) who have important improvements, or worsening on stimulants. The results can only be generalized to children/adolescents who have an apparent pre-trial clinical effect from stimulants

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No To Hattatsu. 2017;49:S294.

THE ALTERED CORTICO-CEREBELLAR NETWORK INVOLVED WITH COMT POLYMORPHISM IN CHILDREN WITH ADHD.

Mizuno Y, Jung M, Fujisawa T, et al.

Introduction-The cerebellum, traditionally considered a motor structure, has been increasingly recognized to regulate executive function (EF), dysfunction of which is a widespread conceptual factor in ADHD, Additionally catechol-O-methyltransferase(COMT) polymorphism has been reported to be associated with EF. However it remains unclear whether cortico-cerebellar network involved with EF is altered in children with ADHD, and COMT polymorphism is associated with the altered network.-Methods-Thirty-one children with ADHD(aged 7-13 years) and thirty age, IQ matched typical developing(TD) controls(aged 7-14 years) underwent imaging by using resting state functional MRI, and the functional connectivity of Crus I/II in the cerebellum involved with EF was analyzed. COMT Val-158Met genotype data were also obtained from children with ADHD.-Results-Children with ADHD showed significantly lower functional connectivity of right Crus I/II with left dorsolateral prefrontal cortex than TD controls. In addition the lower functional connectivity of children with ADHD was modulated by COMT polymorphism, with Met-carriers exhibiting significantly lower functional connectivity than the Val/Val genotype.-Conclusion-These results suggest that there is gene-brain interaction between cortico-cerebellar network involved with EF and COMT polymorphism on the background of heterogeneity in ADHD. Further imaging genetics studies may lead to fundamental therapy according to the pathophysiology

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NORD J PSYCHIATRY. 2017 APR;71:210-16.

SELF-RATED PSYCHOPATHIC TRAITS IN A SAMPLE OF TREATMENT-SEEKING ADOLESCENT GIRLS WITH INTERNALIZING AND EXTERNALIZING DISORDERS: COMPARISONS TO GIRLS IN THE COMMUNITY.

Oshukova S, Kaltiala-Heino R, Miettunen J, et al.

BACKGROUND: Psychopathy research has thus far focused mostly on child, male, and delinquent samples, but the results are most likely non-generalizable to adolescent girls with mental health disorders.

AIM: The present study aimed to compare self-rated psychopathic traits between female psychiatric outpatients and girls in the community, and to investigate how psychopathic traits relate to psychiatric disorders.

METHOD: The outpatient sample comprised 163 girls aged 15-17-years recruited from municipal mental health services. Psychiatric diagnoses were assessed based on the ICD-10 classification. The community sample comprised 355 girls from secondary, vocational, and high schools. The Youth Psychopathic trait Inventory (YPI) served as a self-assessment tool.

RESULTS: Treatment-seeking girls exhibit a more impulsive and irresponsible lifestyle than do girls in the community. Girls with externalizing psychopathology, unlike those with an internalizing disorder, exhibit more deficient affective experience than do girls in the community. Psychopathic traits associate with having a psychiatric disorder, a depressive disorder, ADHD, and a conduct disorder. CONCLUSIONS: The psychiatric examination of treatment-seeking adolescent girls would likely benefit from screening for psychopathy and its underlying components

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Pediatrics. 2017 Jul;140.

BEHAVIORAL PATTERNS IN ADOLESCENTS BORN AT 23 TO 25 WEEKS OF GESTATION.

Samuelsson M, Holsti A, Adamsson M, et al.

BACKGROUND: This study examined mental health outcomes in extremely preterm children (EPT) born at 23 to 25 weeks of gestation between 1992 and 1998 at 2 Swedish tertiary care centers that offered regional and active perinatal care to all live-born EPT infants.

METHODS: We assessed 132 (98%) of the 134 EPT survivors at 10 to 15 years of age alongside term-born controls. Behavioral and emotional problems were evaluated by using Achenbach's Child Behavior Checklist and Teacher Report Form and Conners' Parent and Teacher scales for attention-deficit/hyperactivity disorder.

RESULTS: Parents and teachers reported significantly more problems with internalizing behaviors as well as attention, social, and thought problems in EPT children than in controls, even when those with major neurodevelopmental disabilities (NDDs) were excluded. Multivariate analysis of covariance of the behavioral problems reported by parents and teachers revealed no interactions, but significant main effects emerged for group status (EPT versus control) and sex, with all effect sizes being medium to large and accounting for 8% to 14% of the variance. Compared with the controls, EPT children without NDDs had significantly increased rates of >/=90th percentile for total Conners' attention-deficit/hyperactivity disorder problem scores (parents: 40% vs 15%, odds ratio: 3.7, P < .001) (teachers: 24% vs 9%, odds ratio: 3.3, P = .005). The corresponding rates were higher in the total population.

CONCLUSIONS: EPT children with or without NDDs had behavioral problems characterized by a higher risk for anxiety and attention, social, and thought problems. These findings further strengthen the proposition that a preterm behavioral phenotype is recognizable in adolescents born EPT

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Pediatrics. 2017 Apr;139:S38-S49.

NEURODEVELOPMENT: THE IMPACT OF NUTRITION AND INFLAMMATION DURING PRECONCEPTION AND PREGNANCY IN LOW-RESOURCE SETTINGS.

Vohr BR, Poggi DE, Wanke CA, et al.

The rapid pace of fetal development by far exceeds any other stage of the life span, and thus, environmental influences can profoundly alter the developmental course. Stress during the prenatal period, including malnutrition and inflammation, impact maternal and fetal neurodevelopment with long-term consequences for physical and mental health of both the mother and her child. One primary consequence of maternal malnutrition, inflammation, and other sources of prenatal stress is a poor birth outcome, such as prematurity or growth restriction. These phenotypes are often used as indications of prenatal adversity. In fact, the original evidence supporting the fetal programming hypothesis came from studies documenting an association between birth phenotype and the development of subsequent physical and mental health problems. Fetal growth restriction in both term and preterm infants is associated with neonatal morbidities and a wide variety of behavioral and psychological diagnoses in childhood and adolescence, including attention-deficit/hyperactivity disorder, anxiety, depression, internalizing and thought problems, poor social skills, and autism spectrum disorder. Improving maternal-child health requires interventions that begin before pregnancy and continue throughout gestation and into the postpartum period. Such interventions might include supporting pregnancy intention, maternal nutrition, health/medical care, mental health, and providing social support. This article discusses the impact of maternal nutrition and inflammation during preconception and pregnancy among women living in low-resource settings, with an emphasis on key knowledge gaps that need to be addressed to guide program and policy decisions at local, regional and global levels

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Pediatrics in Review. 2017;38:383.
PROGRESSIVE HYPOTONIA AND DECREASED ALERTNESS IN AN 8-MONTH-OLD GIRL.
Paul M, Shehab K, Nguyen T.

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PLoS ONE. 2017;12.
THE PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW WITH NETWORK META-ANALYSES OF RANDOMISED TRIALS.
Catalá-López F, Hutton B, Núñez-Beltrán A, et al.
Background Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed psychiatric disorders in childhood. A wide variety of treatments have been used for the management of ADHD. We aimed to compare the efficacy and safety of pharmacological, psychological and complementary and alternative medicine interventions for the treatment of ADHD in children and adolescents.
Methods and findings We performed a systematic review with network meta-analyses. Randomised controlled trials (3 weeks follow-up) were identified from published and unpublished sources through searches in PubMed and the Cochrane Library (up to April 7, 2016). Interventions of interest were pharmacological (stimulants, non-stimulants, antidepressants, antipsychotics, and other unlicensed drugs), psychological (behavioural, cognitive training and neurofeedback) and complementary and alternative medicine (dietary therapy, fatty acids, amino acids, minerals, herbal therapy, homeopathy, and physical activity). The primary outcomes were efficacy (treatment response) and acceptability (all-cause discontinuation). Secondary outcomes included discontinuation due to adverse events (tolerability), as well as serious adverse events and specific adverse events. Random-effects Bayesian network meta-analyses were conducted to obtain estimates as odds ratios (ORs) with 95% credibility intervals. We analysed interventions by class and individually. 190 randomised trials (52 different interventions grouped in 32 therapeutic classes) that enrolled 26114 participants with ADHD were included in complex networks. At the class level, behavioural therapy (alone or in combination with stimulants), stimulants, and non-stimulant seemed significantly more efficacious than placebo. Behavioural therapy in combination with stimulants seemed superior to stimulants or non-stimulants. Stimulants seemed superior to behavioural therapy, cognitive training and non-stimulants. Behavioural therapy, stimulants and their combination showed the best profile of acceptability. Stimulants and non-stimulants seemed well tolerated. Among medications, methylphenidate, amphetamine, atomoxetine, guanfacine and clonidine seemed significantly more efficacious than placebo. Methylphenidate and amphetamine seemed more efficacious than atomoxetine and guanfacine. Methylphenidate and clonidine seemed better accepted than placebo and atomoxetine. Most of the efficacious pharmacological treatments were associated with harms (anorexia, weight loss and insomnia), but an increased risk of serious adverse events was not observed. There is lack of evidence for cognitive training, neurofeedback, antidepressants, antipsychotics, dietary therapy, fatty acids, and other complementary and alternative medicine. Overall findings were limited by the clinical and methodological heterogeneity, small sample sizes of trials, short-term follow-up, and the absence of high-quality evidence; consequently, results should be interpreted with caution.
Conclusions Clinical differences may exist between the pharmacological and non-pharmacological treatment used for the management of ADHD. Uncertainties about therapies and the balance between benefits, costs and potential harms should be considered before starting treatment. There is an urgent need for high-quality randomised trials of the multiple treatments for ADHD in children and adolescents

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PLoS ONE. 2017;12:e0170982.

CAREGIVER-RELATED PREDICTORS OF THERMAL BURN INJURIES AMONG IRANIAN CHILDREN: A CASE-CONTROL STUDY.

Sadeghi-Bazargani H, Mohammadi R, Ayubi E, et al.

PURPOSE: Burns are a common and preventable cause of injury in children. The aim of this study was to investigate child and caregiver characteristics which may predict childhood burn injuries among Iranian children and to examine whether confounding exists among these predictors.

METHODS: A hospital based case-control study was conducted using 281 burn victims and 273 hospital-based controls, which were matched by age, gender and place of residence (rural/urban). The characteristics of the children and their caregivers were analyzed using crude and adjusted models to test whether these were predictors of childhood burn injuries.

RESULTS: The age of the caregiver was significantly lower for burn victims than for the controls (P<0.05). Further, the amount of time the caregiver spent outdoors with the child and their economic status had a significant positive association with the odds of a burn injury (P<0.05). A multivariate logistic regression found that Type A behaviour among caregivers was independently associated with the child's odds of suffering a burn injury (OR = 1.12, 95% CI: 1.04-1.21). The research also found that children with ADHD (Inattentive subscale: Crude OR = 2.14, 95% CI: 1.16-3.95, Adjusted OR = 5.65, 95% CI: 2.53-12.61; Hyperactive subscale: Crude OR = 1.73, 95% CI: 1.23-2.41, Adjusted OR = 2.53, 95% CI: 1.65-3.87) also had increased odds of suffering a burn injury. However, several variables were identified as possible negative confounder variables, as the associations were stronger in the multivariate model than in the crude models.

CONCLUSION: The caregiver's characteristics which were predictors of burn injuries among Iranian children were: being younger, high socio-economic status, Type A behavioural pattern and spending more time outdoors. In addition, the relationship between a child's ADHD scores and the odds of a burn injury may be negatively confounded by the caregivers predictor variables

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PLoS ONE. 2017;12:e0169277.

DIET AND ADHD, REVIEWING THE EVIDENCE: A SYSTEMATIC REVIEW OF META-ANALYSES OF DOUBLE-BLIND PLACEBO-CONTROLLED TRIALS EVALUATING THE EFFICACY OF DIET INTERVENTIONS ON THE BEHAVIOR OF CHILDREN WITH ADHD.

Pelsser LM, Frankena K, Toorman J, et al.

INTRODUCTION: Attention-deficit/hyperactivity disorder (ADHD) is a debilitating mental health problem hampering the child's development. The underlying causes include both genetic and environmental factors and may differ between individuals. The efficacy of diet treatments in ADHD was recently evaluated in three reviews, reporting divergent and confusing conclusions based on heterogeneous studies and subjects. To address this inconsistency we conducted a systematic review of meta-analyses of double-blind placebo-controlled trials evaluating the effect of diet interventions (elimination and supplementation) on ADHD.

METHODS: Our literature search resulted in 14 meta-analyses, six of which confined to double-blind placebo-controlled trials applying homogeneous diet interventions, i.e. artificial food color (AFC) elimination, a few-foods diet (FFD) and poly-unsaturated fatty acid (PUFA) supplementation. Effect sizes (ES) and Confidence intervals (CI) of study outcomes were depicted in a forest plot. I2 was calculated to assess heterogeneity if necessary and additional random effects subgroup meta-regression was conducted if substantial heterogeneity was present.

RESULTS: The AFC ESs were 0.44 (95% CI: 0.16-0.72, I2 = 11%) and 0.21 (95% CI: -0.02-0.43, I2 = 68%) [parent ratings], 0.08 (95% CI: -0.07-0.24, I2 = 0%) [teacher ratings] and 0.11 (95% CI: -0.13-0.34, I2 = 12%) [observer ratings]. The FFD ESs were 0.80 (95% CI: 0.41-1.19, I2 = 61%) [parent ratings] and 0.51 (95% CI: -0.02-1.04, I2 = 72%) [other ratings], while the PUFA ESs were 0.17 (95% CI: -0.03-0.38, I2 = 38%) [parent ratings], -0.05 (95% CI: -0.27-0.18, I2 = 0%) [teacher ratings] and 0.16 (95% CI: 0.01-0.31, I2 = 0%) [parent and teacher ratings]. Three meta-analyses (two FFD and one AFC) resulted in high I2 without presenting subgroup results. The FFD meta-analyses provided sufficient data to perform subgroup analyses on intervention type, resulting in a decrease of heterogeneity to 0% (diet design) and 37.8% (challenge design).

CONCLUSION: Considering the small average ESs PUFA supplementation is unlikely to provide a tangible contribution to ADHD treatment, while further research is required for AFC elimination before advising this

intervention as ADHD treatment. The average FFD ES is substantial, offering treatment opportunities in subgroups of children with ADHD not responding to or too young for medication. Further FFD research should focus on establishing the underlying mechanisms of food (e.g. incrimination of gut microbiota) to simplify the FFD approach in children with ADHD

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PLoS ONE. 2017;12.

NOVEL SUBGROUPS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IDENTIFIED BY TOPOLOGICAL DATA ANALYSIS AND THEIR FUNCTIONAL NETWORK MODULAR ORGANIZATIONS.

Kyeong S, Kim J-J, Kim E.

Attention-deficit/hyperactivity disorder (ADHD) is a clinically heterogeneous condition and identification of clinically meaningful subgroups would open up a new window for personalized medicine. Thus, we aimed to identify new clinical phenotypes in children and adolescents with ADHD and to investigate whether neuroimaging findings validate the identified phenotypes. Neuroimaging and clinical data from 67 children with ADHD and 62 typically developing controls (TDCs) from the ADHD-200 database were selected. Clinical measures of ADHD symptoms and intelligence quotient (IQ) were used as input features into a topological data analysis (TDA) to identify ADHD subgroups within our sample. As external validators, graph theoretical measures obtained from the functional connectome were compared to address the biological meaningfulness of the identified subtypes. The TDA identified two unique subgroups of ADHD, labelled as mild symptom ADHD (mADHD) and severe symptom ADHD (sADHD). The output topology shape was repeatedly observed in the independent validation dataset. The graph theoretical analysis showed a decrease in the degree centrality and PageRank in the bilateral posterior cingulate cortex in the sADHD group compared with the TDC group. The mADHD group showed similar patterns of intra- and inter-module connectivity to the sADHD group. Relative to the TDC group, the inter-module connectivity between the default mode network and executive control network were significantly increased in the sADHD group but not in the mADHD group. Taken together, our results show that the data-driven TDA is potentially useful in identifying objective and biologically relevant disease phenotypes in children and adolescents with ADHD

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Postgrad Med. 2017;1-10.

A CLINICIAN'S GUIDE TO ADHD TREATMENT OPTIONS.

Mattingly GW, Wilson J, Rostain AL.

Attention deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition of children and adolescents that often persists into adulthood. Primary care physicians are commonly the first to diagnosis ADHD and initiate a treatment plan with the patient. Guidelines recommend psychostimulant treatment as a first-line therapy in the management plan because it has a substantial impact on alleviating the core symptoms of ADHD. The recent development of a variety of methylphenidate and amphetamine formulations provides many options to meet individual patient lifestyle needs. Liquid, chewable, sprinkled capsule, wearable patch, and orally disintegrating tablet formulations are currently available for patients who may be noncompliant with or have difficulty swallowing traditional pills. This review provides a resource for physicians to identify the stimulant delivery formulation that best suits the patient. Formulations in development are also discussed

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2017;77:202-08.

SLC6A1 GENE INVOLVEMENT IN SUSCEPTIBILITY TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CASE-CONTROL STUDY AND GENE-ENVIRONMENT INTERACTION.

Yuan F-F, Gu X, Huang X, et al.

Attention-deficit/hyperactivity disorder (ADHD) is an early onset childhood neurodevelopmental disorder with an estimated heritability of approximately 76%. We conducted a case-control study to explore the role of the

SLC6A1 gene in ADHD. The genotypes of eight variants were determined using Sequenom MassARRAY technology. The participants in the study were 302 children with ADHD and 411 controls. ADHD symptoms were assessed using the Conners Parent Symptom Questionnaire. In our study, rs2944366 was consistently shown to be associated with the ADHD risk in the dominant model (odds ratio [OR] = 0.554, 95% confidence interval [CI] = 0.404ΓÇô0.760), and nominally associated with Hyperactive index score (P = 0.027). In addition, rs1170695 has been found to be associated with the ADHD risk in the addictive model (OR = 1.457, 95%CI = 1.173ΓÇô1.809), while rs9990174 was associated with the Hyperactive index score (P = 0.010). Intriguingly, gene-environmental interactions analysis consistently revealed the potential interactions of rs1170695 with blood lead (Pmul = 0.044) to modify the ADHD risk. Expression quantitative trait loci analysis suggested that these positive single nucleotide polymorphisms (SNPs) may mediate SLC6A1 gene expression. Therefore, our results suggest that selected SLC6A1 gene variants may have a significant effect on the ADHD risk

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Psychiatr Invest. 2017;14:452-57.

BALANCE DEFICIT AND BRAIN CONNECTIVITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kim SM, Hyun GJ, Jung T-W, et al.

Objective We aimed to assess disturbances in postural and gait balance and functional connectivity within the brain regions controlling balance in children with attention-deficit/hyperactivity disorder (ADHD).

Methods Thirteen children with ADHD and 13 ageand sex-matched controls were recruited. Gait balance was assessed by the difference in the center of pressure (COP) between the left and right foot, as well as the difference in plantar pressure between the left and right foot during gait. Neuroimaging data were acquired using a 3.0 Tesla MRI scanner. Functional connectivity between the vermis of the cerebellum and all other brain regionswas assessed.

Results The difference in plantar pressure between the left foot and right foot in the ADHD group was greater than that observed in the control group. The average COP jerk score of the right foot in the ADHD group was higher than that observed in the control group. A higher functional connectivity between the cerebellum and the right middle frontal gyrus (premotor cortex) and medial frontal gyrus (cingulate gyrus) was observed in the control group relative to the ADHD group. In the ADHD group, the difference in plantar pressure between the left and right foot was also negatively correlated with the beta-value within the middle frontal gyrus.

Conclusion Children with ADHD had disturbance of balance as assessed by plantar pressure. Decreased brain connectivity from the cerebellum to the premotor cortex and anterior cingulate was associated with disturbances of posture and balance in children with ADHD

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Res Dev Disabil. 2017 Jan;60:187-97.

MEASURING SOCIAL SKILLS OF CHILDREN AND ADOLESCENTS IN A CHINESE POPULATION: PRELIMINARY EVIDENCE ON THE RELIABILITY AND VALIDITY OF THE TRANSLATED CHINESE VERSION OF THE SOCIAL SKILLS IMPROVEMENT SYSTEM-RATING SCALES (SSIS-RS-C).

Cheung PP, Siu AM, Brown T.

The Social Skills Improvement System-Rating Scales (SSIS-RS; Gresham & Elliott, 2008) are designed to assist in the screening and classification of students (aged 5-18 years) who are suspected of presenting with social skills deficits and to offer guidelines in the development of interventions to remediate those types of problems. The objective of this study is to examine the preliminary reliability and validity of the translated Chinese version of the SSIS-RS, referred to as the SSIS-RS-C. In this study, parent-reported social skills and problem behaviors among students with typical development (n=79) were compared with those of age- and gender-matched students with a known developmental disability (n=79) using the SSIS-RS-C. The results indicated that the SSIS-RS-C subscale scores in all the disability groups were significantly different except for those in the Assertion scale for one disability group. Furthermore, the normative sample of typically developing children and adolescents (aged 5-12 and 13-18 years, n=567) from Hong Kong was established to improve the psychometric properties of the SSIS-RS-C. There were moderate to strong relationships

between the common subscales across all forms of the SSIS-RS-C. Acceptable to excellent levels of internal consistency across all common subscales was also obtained. The scores for the Hong Kong sample (n=567) derived from the use of the SSIS-RS-C were then compared to the normative sample scores from the American version of the SSIS-RS. It was found that there were statistically significant differences on five out of the seven SSIS-RS-C Social Skill subscales for children aged 5-12 years and on four out of the seven SSIS-RS-C Social Skills subscales for the adolescent group (aged 13-18 years). Also, there were statistically significant differences between the American and Hong Kong samples on all of the SSIS-RS-C Problem Behavior scale scores. It was concluded that the SSIS-RS-C is a promising instrument for clinicians to be able to differentiate social skills and problem behaviors among students presenting with and without developmental disabilities in Hong Kong contexts

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Res Social Adm Pharm. 2017 Jan;13:172-86.

THE EVALUATION OF A QUESTION PROMPT LIST FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PEDIATRIC CARE: A PILOT STUDY.

Ahmed R, McCaffery KJ, Silove N, et al.

BACKGROUND: Of the available treatment options for attention-deficit/hyperactivity disorder (ADHD), the use of medications remains the most controversial and it is often difficult for parents to make decisions about treatment. Provision of relevant, reliable information about treatment during consultations may help address parents' concerns about treatment options. Question prompt lists are structured lists of disease and treatment-specific questions intended for use by patients during consultations to encourage communication with clinicians. They may prove useful in empowering parents to ask questions during consultations and to make informed decisions about treatments for ADHD.

OBJECTIVES: To evaluate the acceptability and usefulness of a question prompt list (QPL) for attention-deficit/hyperactivity disorder (ADHD) during consultations between parents of diagnosed children and their pediatricians.

METHODS: Parents of children recently diagnosed with ADHD (n = 17) received a copy of the QPL 7 days before their child's appointment and completed questionnaires before and after their consultations to elicit: satisfaction with the consultation and QPL; situational anxiety levels; achievement of decision-making and information preferences. Pediatricians (n = 3) completed questionnaires after each consultation to determine the impact of the QPL on consultation flow and to ascertain their willingness to incorporate the QPL into their practice.

RESULTS: All parents reported that the QPL helped them to ask more questions, was easy to understand and would be useful to them in future. After receiving the QPL and seeing the pediatrician, parents' anxiety decreased significantly. All described their decision-making roles as 'just right' and were satisfied with the information obtained during their consultations. All pediatricians agreed that the QPL was helpful for parents, made communication easier, and helped parents to initiate discussion about difficult topics. The QPL was not found to impede flow of the consultation. All agreed QPL provision was feasible as part of routine clinical care.

CONCLUSIONS: The QPL received strong support from parents and pediatricians and may be a useful tool in facilitating communication and shared decision-making in this setting. The findings warrant further investigation in a larger randomized controlled study

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Res Dev Disabil. 2017;69:77-84.

THE ROLE OF INATTENTION AND HYPERACTIVITY/IMPULSIVITY IN THE FINE MOTOR COORDINATION IN CHILDREN WITH ADHD.

Fenollar-Cortés J, Gallego-Martinez A, Fuentes LJ.

OBJECTIVE: Deficits in fine motor coordination have been suggested to be associated with Attention-Deficit/Hyperactivity Disorder (ADHD). However, despite the negative impact of poor fine motor skills on

academic achievement, researchers have paid little attention to this problem. The aim of this study was to explore the relationship between ADHD dimensions and fine motor performance.
METHOD: Participants were 43 children with a diagnosis of ADHD aged between 7 and 14 years (M=9.61; 81% male) and 42 typically developing (TP) children in the same age range (M=10.76; 75.2% male).
RESULTS: Children with ADHD performed worse than TP on all tasks (δFine_motor_tasks, -0.19 to -0.44). After controlling for age and ADHD-HY (hyperactivity/impulsivity), higher scores on ADHD-IN (inattentiveness) predicted a larger number of mistakes among all psychomotricity tasks and conditions (β 0.39-0.58, ps<0.05).
CONCLUSION: The ADHD group showed poorer fine motor performance than controls across all fine motor coordination tasks. However, lower performance (more mistakes), was related to the inattention dimension but not to the hyperactivity/impulsivity dimensions. Authors recommend including training and enhancement of the fine motor skills for more comprehensive ADHD treatment

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Scand J Occup Ther. 2017 Jan;24:32-40.
OCCUPATIONAL IDENTITY OF ADOLESCENTS WITH ADHD: A MIXED METHODS STUDY.
Levanon-Erez N, Cohen M, Traub Bar-Ilan R, et al.
BACKGROUND: Occupational identity (OI) is shaped by occupational experiences over time and has been studied among individuals with a variety of health conditions. Adolescents with ADHD face numerous challenges in their occupational performance that may threaten their OI.
OBJECTIVE: This study sought to compare the occupational identities of adolescents with and without ADHD and to gain a deeper understanding of the characteristics of OI among adolescents with ADHD.
METHODS: Sixty-four adolescents with (n = 21) and without ADHD (n = 43) were interviewed using the Occupational Performance History Interview (OPHI-II). A mixed methodology was applied, using quantitative and subsequent qualitative content analyses of 10 interviews, with a directed approach.
RESULTS: OPHI-II OI interval scores and 7/11 items of the OI scale were significantly lower in the ADHD group compared to controls. In the qualitative content analyses, three major themes were found: (i) the meaning of success in academic participation, (ii) the consequences of not succeeding in academic participation and (iii) self-explanations for not succeeding in academic participation.
CONCLUSION: Findings demonstrate the presence of OI challenges among adolescents with ADHD. Occupational therapy intervention may be needed in order to promote occupational adaptation

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Sleep Med. 2017;37:180-86.
THE ASSOCIATION BETWEEN DISRUPTIVE MOOD DYSREGULATION DISORDER SYMPTOMS AND SLEEP PROBLEMS IN CHILDREN WITH AND WITHOUT ADHD.
Waxmonsky JG, Mayes SD, Calhoun SL, et al.
Background Many youth experience persistent irritability and recurrent temper outbursts, conceptualized by DSM-5 as Disruptive Mood Dysregulation Disorder (DMDD). Sleep deprivation impairs emotion regulation which could increase rates of DMDD symptoms, especially in those with preexisting regulatory impairments, as seen with ADHD. However, there has been little examination of the relationship between chronic sleep problems and DMDD symptoms.
Methods Associations between DMDD symptoms and sleep parameters in children were assessed using parent-report and objective measures of sleep in a general population sample (N = 665) and an ADHD sample (N = 784). Irritability, temper outbursts, sleep problems and other psychological problems were assessed with the Pediatric Behavior Scale. The general population study also completed overnight polysomnography (PSG).
Results DMDD symptoms were reported in 9.2% of the community sample and 31.4% of the ADHD sample. In both samples, children with DMDD symptoms had significantly higher parent-reported sleep problems than children without DMDD symptoms. Children with sleep problems had significantly higher DMDD scores than children without sleep problems. However, DMDD symptoms were most strongly associated with oppositional

behavior. Sleep problems were not a significant contributor. Hyperactivity-impulsivity was most strongly associated with sleep problems, and DMDD was not a significant contributor. Children with and without DMDD symptoms did not differ significantly on any PSG parameter.
Conclusions Associations between parent-reported sleep problems and DMDD symptoms were due to their shared relationship with other behavioral problems. Therefore, chronic sleep problems do not appear to be a primary source of DMDD symptoms in children with or without ADHD

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Soc Psychiatry Psychiatr Epidemiol. 2017 Jan;52:87-94.
CHILDHOOD HYPERACTIVITY AND MOOD PROBLEMS AT MID-LIFE: EVIDENCE FROM A PROSPECTIVE BIRTH COHORT.
Stuart-Smith J, Thapar A, Maughan B, et al.
PURPOSE: Childhood hyperactivity leads to mental health problems, but it is not known whether there are long-term risks for adult mood problems in unselected population cohorts that extend to mid-life. Aims were to examine links between childhood hyperactivity and mood problems up to age 50 years and to consider confounding factors and gender differences in associations.
METHODS: The National Child Development Study (NCDS) is a UK cohort of children born in 1958. Children with (N = 453) and without (N = 9192) pervasive and persistent hyperactivity were followed to age 50. Adult mood was assessed using the Malaise Inventory at ages 23, 33, 42, and 50 years and the CIS-R interview at 45 years.
RESULTS: Childhood hyperactivity predicted low mood at all adult assessments (ES = 0.27-0.45), including after covariate adjustment (childhood adversity, emotional and behavioural problems, and attainment).
CONCLUSION: Hyperactivity has enduring risk effects on low mood throughout the life course that extend to middle age

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Subst Use Misuse. 2017 Aug;52:1266-74.
THE IMPACT OF PHARMACOTHERAPY ON SUBSTANCE USE IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: VARIATIONS ACROSS SUBTYPES.
Upadhyay N, Chen H, Mgbere O, et al.
Objective: The primary purpose of this study was to investigate the impact of attention-deficit/hyperactivity disorder (ADHD) pharmacotherapy on the risk of substance use within each ADHD subtype.
Methods: The study used data from the National Comorbidity Survey-Adolescent supplement, a nationally representative sample of US adolescents (ages 13–18) collected from 6,483 adolescent-parent interviews conducted between 2001 and 2004. ADHD was categorized into three subtypes: ADHD-predominantly hyperactive-impulsive type (ADHD-H); ADHD-predominantly inattentive type (ADHD-I); and ADHD-combined type (ADHD-C) using Diagnostic and Statistical Manual of Mental Disorders-IV criteria. Substance use information was obtained from the adolescents' interview. The impact of ADHD-pharmacotherapy on substance use was examined using multivariable logistic regression analysis.
Results: Among the adolescents with ADHD, ADHD pharmacotherapy significantly associated with reduced risk of substance use (OR = 0.53, 95%CI [0.31–0.90]); with regards to ADHD subtypes, ADHD pharmacotherapy is negatively associated with substance use in adolescents with ADHD-C (OR = 0.53, 95%CI [0.24–0.97]) and those with ADHD-H (OR = 0.23, 95% CI [0.07–0.78]), but it did not have statistically significant effect on risk of substance use in those with ADHD-I subtype (OR = 0.49, 95%CI [0.17–1.39]). Among the group who never received ADHD-pharmacotherapy before the interview, individuals with ADHD-H and ADHD-C had a similar risk of substance use compared to adolescents with ADHD-I (ADHD-C: OR = 1.5, 95%CI [0.77–2.95] and ADHD-H: OR = 2.10, 95%CI [0.87–4.95]).
Conclusions: Adolescents with ADHD were equally susceptible to future substance use disregard their ADHD subtypes. Receipt of pharmacotherapy could decrease risk of substance use in adolescents with ADHD-H and ADHD-C, but it may not affect risk of substance use among individuals with ADHD-I

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Tijdschr Psychiatr. 2017;59:439.
PERSISTENT EFFECTS OF METHYLPHENIDATE ON THE DOPAMINERGIC SYSTEM IN CHILDREN WITH ADHD.
Schrantee A.

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Turk Psikiyatri Derg. 2017;28:25-32.
ASSOCIATION BETWEEN PARENTING STYLES AND SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Cop E, Cengel Kultur SE, Senses DG.
OBJECTIVE: We aimed to study characteristics of child and mother reported parenting styles of children with Attention Deficit Hyperacitivity Disorder (ADHD) and association of parenting styles of mothers with demographic and clinical variables like ADHD symptoms, sex, age, ADHD subtype, and comorbidity.
METHOD: 58 children with ADHD and 30 healthy children were included in this study. All children were assessed by The Schedule for Affective Disorders and Schizophrenia for School Aged Children- Present and Lifetime Version. ADHD symptom severity was assessed by The Conners Parent Rating Scale and The Conners Teacher Rating Scale. The Parenting Style Inventory (PSI) and The Parental Attitude Research Instrument (PARI) were used to assess parenting styles of mothers.
RESULTS: ADHD group had lower scores on two subscales of PSI (acceptance/involvement and strictness/supervision) and democratic attitude and equality subscale of PARI and higher scores on strict discipline subscale of PARI compared to control group. In ADHD group, higher symptoms of oppositional defiant disorder were associated with higher mother's strict discipline scores and lower child reported mother's acceptance/involvement scores.
CONCLUSION: Our findings supported the idea that there may be an association between parenting attitudes and ADHD symptoms in families having a child with ADHD. These results indicated the importance of integrated approach to ADHD diagnosis and treatment and evaluating the child with ADHD in the context of family environment

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Value Health. 2017;20:A237.
DEMOGRAPHIC TRENDS IN ADHD DIAGNOSIS IN U.S. CHILDREN USING NHANES DATA BETWEEN 2004 AND 2012.
Zamil D, Wang X, Vadhariya A, et al.
OBJECTIVES: To characterize changes in the demographic distribution of attention-deficit hyperactivity disorder (ADHD) diagnosis from 2004 to 2012 in the United States.
METHODS: ADHD diagnosis data was extracted from the National Health and Nutrition Examination Survey (NHANES) Summary Health Statistics for U.S. Children, a source of nationally representative data on children in the United States. The ADHD cases were identified based on ICD9-CM diagnosis codes. Chi square tests were used to investigate differences in ADHD diagnosis rates by demographic characteristics (age, race, and gender) within each year and simple linear regression was applied to determine the extent of change over time. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) at a priori significance level of 0.05.
RESULTS: The ADHD diagnosis rate was higher among males, Whites, and school aged children and adolescents (vs. preschoolers aged 3-4) in each year examined. The total number of ADHD cases as well as all demographic groups with the exception of African Americans and preschoolers aged 3-4 exhibited an increasing trend between 2004 and 2012.
CONCLUSIONS: ADHD diagnosis among youth showed a significant increase in the U.S. between 2004 and 2012. Notable increases and group differences were also observed among demographic subgroups. These findings indicate a need for future research in reasons for such group differences as well as treatment differences

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Value Health. 2017;20:A295.

ECONOMIC BURDEN OF UNCONTROLLED ATTENTION DEFICIT HYPERACTIVITY DISORDER IN THE US: A RETROSPECTIVE ANALYSIS OF DATABASE CLAIMS FROM A COMMERCIALLY INSURED POPULATION.

Pliszka SR, Rajagopalan K, Davis BM, et al.

OBJECTIVES: Despite availability of several treatment options, adequate symptom control remains a major concern in attention-deficit/hyperactivity disorder (ADHD). Lack of symptom control may impose a significant economic burden, yet few studies have quantified the frequency of uncontrolled symptoms and its relation to costs. This retrospective claims database analysis assessed the impact of ADHD symptom control on health care costs.

METHODS: MarketScan Commercial Database claims between January 1, 2010 and June 30, 2015 were used to identify pediatric (age 6-12), adolescent (13-17), and adult (18+) patients with 2 ADHD diagnoses (ICD-9 314.0x), 1 newly-started ADHD medication pharmacy claim, and continuous enrollment 6 months before and 12 months following ADHD medication initiation (index). Symptom control cohorts were defined from 6-month post-index treatment changes: (i) well controlled-without dose increase or treatment switching/augmentation; (ii) partially con-trolled-dose increase; and (iii) poorly controlled-dose increase and/or treatment switching/augmentation. Annual adjusted cost differences were estimated using generalized linear models.

RESULTS: The ADHD patient sample (97,230 pediatric; 58,641 adolescent; 135,177 adults) was 69.7%, 65.0%, and 48.7% male, respectively. Mean (SD) age was 8.9 (1.9), 15.0 (1.4), and 31.2 (12.1) years for the pediatric, adolescent, and adult groups, with percent well- (62.1%, 73.7%, 73.0%), partially- (8.8%, 6.4%, 6.1%), and poorly-controlled (29.1%, 19.9%, 20.9%), respectively. Well-controlled pediatric patients had lower annual mean total costs ($3,709) than partially- ($4,269) and poorly-controlled patients ($5,127) (all p-values < 0.001). Annual mean medical and pharmacy costs were also lower among well-controlled patients ($2,180, $1,572, respectively) than partially- ($2,163, $2,123) and poorly-controlled ($2,776, $2,363) patients. Similar cost trends were observed for adolescent and adult populations.

CONCLUSIONS: Our findings suggest that, after one year of treatment, 20.9% - 29.1% of ADHD patients were poorly controlled, and incurred 20.7% - 38.2% greater costs than well-controlled patients, suggesting better symptom control may have economic benefits

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Z Kinder Jugendpsychiatr Psychother. 2017 Jul;45:335-37.

MILD HYPOTHERMIA IN A CHILD WITH LOW-DOSE RISPERIDONE.

Grau K, Plener PL, Gahr M, et al.

Risperidone is a widely used, second-generation antipsychotic approved for treating schizophrenia as well as for treating aggression in children and adolescents with mental retardation. The substance has a well-established risk profile including alterations of body temperature. Apart from hyperthermia with and without full-blown malignant neuroleptic syndrome, low body temperatures (hypothermia) have also been reported anecdotally, usually appearing in the context of comedication. Here, we report a case of hypothermia associated with a low-dose risperidone monotherapy in a child

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Z Kinder Jugendpsychiatr Psychother. 2017;45:209-17.

PRE- AND PERINATAL RISK FACTORS IN AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Schmitz JC, Cholemkery H, Medda J, et al.

Objective: Epidemiological studies indicate the relevance of pre- and perinatal risk factors for the genesis of attention deficit/hyperactivity disorder and autism spectrum disorder. This study compares potential risk factors in a clinical sample of children with ADHD, ASD, the combination of both diseases, ADHD and oppositional defiant or conduct disorder (ADHD & ODD/CD) and examined whether the existence of additional risk factors promotes the occurrence of combined diseases.

Method: We compared the pre- and perinatal risk factors of 341 patients (299 boys, 42 girls) from a clinical population, differentiating between children with ADHD (n=80), ASD (n=122), ADHD & ASD (n=55), or ADHD & ODD/CD (n=84).
Results: We observed a higher rate of maternal smoking, a higher rate of migration, and lower parental education among the children with ADHD & ODD/CD compared to those with ASD or ADHD. The rate of migration background was higher among the children with ASD compared to children with ADHD. Miscarriage was a specific risk factor for ADHD & ASD.
Conclusion: Numerous risk factors described in epidemiological studies occurred only rarely in our clinical sample. The distribution of most risk factors was comparable between the examined diseases

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Zh Nevrol Psikhiatr Im S S Korsakova. 2017;117:81-84.

A DYAD APPROACH TO THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Chutko LS, Surushkina SY, Anisimova TI.

AIM: To study anxiety in adolescents with attention deficit hyperactivity disorder (ADHD) and their mothers and to evaluate the efficacy of a dyad approach (simultaneous treatment of the mother and the child) to ADHD treatment.
MATERIAL AND METHODS: Thirty-four adolescents, aged 12-15 years, with ADHD and their mothers were studied. All participants of the study received anxiolytic treatment: children were treated with noophen (500 mg per day 45 days) and their mothers received adaptol (1500 mg per day 45 days). In the comparison group with the same clinical/psychological characteristics, anxiolytic therapy with noophen was used only in adolescents.
RESULTS: Symptoms of anxiety were found in 61.7% of adolescents with ADHD and in 79.4% of the mothers. After the dyad therapy, an improvement was noted in 73.5% of adolescents and 69.7% of the mothers. There was an improvement in 63.3% of patients in the comparison group.
CONCLUSION: The results demonstrate the high efficacy of the dyad approach in treatment of ADHD with comorbid anxiety disorders

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Use of Stimulants in Bipolar Disorder

Giulio Perugi[1,2] · **Giulia Vannucchi**[3,4] · **Fulvio Bedani**[5] · **Ettore Favaretto**[5]

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Abstract Several international guidelines indicate stimulants, including methylphenidate (MPH), amphetamines and derivatives, modafinil, and armodafinil among the second-third-line choices for bipolar depression. Efficacy of stimulants has been also reported for the management of residual depressive symptoms such as fatigue and sleepiness and for the management of affective, cognitive, and behavioral symptoms in children and adult bipolar patients with comorbid ADHD. Few case reports show positive results with MPH in the treatment of resistant mania. Finally, MPH might be an option in some bipolar forms observed in psychiatric presentations of frontotemporal dementia and traumatic brain injury. In spite of these preliminary observations, the use of stimulants in bipolar patients is still controversial. Potential of misuse and abuse and mood destabilization with induction of (hypo)manic switches, mixed states, and rapid cycling are the concerns most frequently reported. Our aims are to summarize available literature on this topic and discuss practical management implications.

This article is part of the Topical Collection on *Bipolar Disorders*

✉ Giulio Perugi
giulio.perugi@med.unipi.it

[1] Department of Experimental and Clinic Medicine, Section of Psychiatry, University of Pisa, Via Roma 67, 56100 Pisa, Italy

[2] Institute of Behavioural Science "G.De Lisio", Pisa, Italy

[3] Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA), University of Florence, Florence, Italy

[4] CREA, Research and Clinical Centre, San Sebastiano Foundation, Florence, Italy

[5] Psychiatric Service, General Hospital of Bressanone, Brixen, Italy

Keywords Bipolar disorder · Stimulants · Methylphenidate · Comorbidity

Introduction

Methylphenidate (MPH), amphetamines and derivatives (i.e., the prodrug lisdexamphetamine (LDX)), modafinil, and armodafinil are the stimulant drugs most commonly utilized in the treatment of bipolar disorder. Both MPH and amphetamines have the FDA approval for the treatment of ADHD and narcolepsy, whether LDX is approved only for ADHD. Modafinil and armodafinil are considered wakefulness-promoting agents indicated for narcolepsy, obstructive sleep apnea syndrome, and shift work sleep disorder.

All those compounds via different mechanisms of actions share the property to enhance dopaminergic prefrontal transmission. Amphetamines, which are considered *releasers* in the psychostimulant class on the basis of the interaction with the DAT, enhance central nervous system via not only blocking the reuptake of both dopamine and norepinephrine but also promoting catecholamine release. Indeed, amphetamines occupy the substrate site of catecholamine transporters (DAT and NET) which are K+-Na+ pump channels: they inhibit the reuptake of dopamine and norepinephrine, and the pump may run in reverse actively diffusing neurotransmitters in the synaptic cleft. Moreover, intracellular amphetamines also reduce the metabolism of dopamine via inhibiting the vesicular monoamine transporter (namely VMAT-2) with a mechanism similar to that involving DAT: dopamine is pumped into the cytoplasm also favoring its passive diffusion out of the cell. MPH, classified among the *blockers* [1], shows a similar mechanism of action with subtle but important differences: MPH sits mostly at allosteric site of the protonic pump almost only inhibiting the reuptake of dopamine and norepinephrine. The intracellular effects

(for example the inhibition of VMAT2) are probably lower than amphetamines, although different comparing to other blockers and not completely understood. Both MPH and amphetamines share the property to enhance dopaminergic transmission not only in the reticular activating system and prefrontal cortex but also in the nucleus accumbens, probably responsible for addictive potential of these drugs and worsening/appearance of tics. It is also debated whether the stimulation of nucleus accumbens is involved in the induction of (hypo)manic switches, cycle acceleration, and psychosis.

Modafinil and its R-enantiomer armodafinil are stimulant-like agents promoting dopamine- and norepinephrine-related transmission. The differences with stimulants are the low affinity for the DAT [2], the interaction with neurotransmission of different mediators as GABA, glutamate, serotonin, histamine, and hypocretin with less interactions with monoamines comparing to other stimulants [3]. Moreover, these compounds seem to show a certain selectivity for the brain regions, mostly acting in suprachiasmatic nucleus, anterior hypothalamus, and amygdale, all regions primarily involved in wakefulness. So, the interaction with nucleus accumbens would be less relevant with reduced addictive potential [4].

Bipolar depression is considered difficult-to-treat with standard antidepressant drugs, and its pharmacological treatment still represents a clinical challenge [5, 6]. Several reasons could be identified to explain the failure of standard antidepressant treatments in bipolar depression: resistance per se, antidepressants induced cycle changes, mixed features, and/or "wear-off" phenomenon [6], frequent alterations of daily rhythms as in delayed phase sleep disorder and unrecognized concomitant neurodevelopmental disorders such as ASD and ADHD.

Some randomized-controlled studies and open clinical reports documented the use of stimulants as augmentation treatment for resistant major depressive disorder [7]. The use of these medications in bipolar depression is understudied, and it is debated whether they should be considered safe, especially regarding their potential induction of mood switches, affective instability, mixed features, and rapid cycling [8]. The use of stimulants is controversial also in the subpopulation of BD patients with comorbid ADHD [9], since available evidence is very sparse and controlled studies virtually absent [8]. Stimulants may also have some role in several neuropsychiatric conditions related to BD or with a bipolar-like presentation. This might be the case of the management of some specific neuropsychiatric symptoms in frontotemporal dementia (FTD) and traumatic brain injury (TBI).

Although all these are poorly explored fields, some of the current international guidelines (the World Federation of Societies of Biological Psychiatry (WFSBP) [10] and the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT–ISBD)) [11] support the adjunctive use of stimulants, namely modafinil, as the second-line choice for bipolar depression.

We systematically reviewed the available literature on the use of stimulant drugs in bipolar disorder.

Methods

A systematic PubMed search of the available literature was conducted to evaluate the possible efficacy and tolerability of stimulants in bipolar disorder. Combinations of the following search terms were used: bipolar disorder, treatment, stimulants, methylphenidate, amphetamine, modafinil, and armodafinil along with terms related to each of the areas of focus listed above. We found only five RCTs on the use of stimulant medications in bipolar depressive patients: three of them involved only bipolar patients (one regarding adjunctive modafinil [12], one adjunctive armodafinil [13], and one on the use of LDX [14] in bipolar depressive patients) and two had mixed samples of both bipolar and unipolar probands [15, 16]. Given the paucity of controlled data, we decided also to include information from open-label studies and case reports. Ten open-label, both prospectively and retrospectively designed, studies are available as well as five case reports. Furthermore, reference lists from each article were assessed for additional citations of interest. We excluded articles in languages other than English. Two reviewers (G.V. and G.P.) evaluated the results of the search on the basis of title and/or abstract and assessed them for the suitability for inclusion on the basis of full publications.

Results and Comments

Randomized Controlled Trials on Stimulants in BD

Randomized controlled trials regarding the use of stimulants in bipolar depression are very few, and the results are not conclusive (Table 1). In interpreting the results, several limitations have to be considered. All the studies suffer from selection biases: in fact, included patients have all a treatment-resistant depression and the stimulants are added to various combinations of other medications. Secondly, samples are usually small and heterogeneous. Finally, the follow-up period is too short to evaluate both medium and long-term efficacy and tolerability of these medications. For example, the induction of mood destabilization and cycle acceleration are not easily evaluable in a study of few weeks. In this sense, the data have to be cautiously interpreted and cannot be easily generalized to other clinical populations.

Frye and colleagues [12] evaluated the efficacy and safety of modafinil in add-on for the treatment of depression in a sample of 85 BD patients in whom mood stabilizers and eventually antidepressants had failed. Patients were randomly

Table 1 Randomized controlled and open-label studies on the use of stimulants in bipolar disorder

Study	Patients	Drug(s)	Follow-up period	Response/remission rates
RCTs				
Silberman et al. 1981 [15]	7 depressive BD patients	Amphetamine vs. placebo (crossover)	4 days	*Response of depressive symptoms not significant
Frye et al. 2007 [12]	85 depressive BD patients	Add-on modafinil vs. placebo (+ mood stabilizer and/or antidepressant)	6 weeks	*Response 43.9 vs. 22.7% Remission 39% vs. 18%
Calabrese et al. 2010 [13]	257 depressive BD I patients	Add-on armodafinil vs. placebo	8 weeks	*Response 37 vs. 38%
Calabrese et al.2014 [17]	400 depressive BD I patients	Add-on armodafinil vs. placebo	8 weeks	*Response 46 vs. 34% Remission 21% vs. 17%
McElroy et al. 2015 [14]	25 depressive BD patients	Lisdexamphetamine vs. placebo	8 weeks	*Response 55 vs. 29% Remission 55 vs. 29%
Scheffer et al. 2005 [21]	40 ADHD patients with mania (pediatric sample)	Divalproex ± D-amphetamine vs. placebo	8 + 4 weeks	§Response 80% °Response 89.6 vs. 10%
Findling et al. 2007 [20]	16 ADHD-BD patients (pediatric sample)	(Lithium or divalproex) + - methylphenidate vs. placebo	4 weeks	°Methylphenidate > placebo ES = 0.90
Open-label trials				
El-Mallakh et al. 2000 [19]	14 moderatly depressed BD patients	Add-on methylphenidate (+ mood stabilizer or antipsychotic)	12 weeks	*Moderate response of depressive symptoms, good response for overall psychiatric picture
Nasr et al. 2004 [26]	78 depressive patients	Add-on modafinil	Chart review	*Significant improvement
Nasr et al. 2006 [27]	191 depressive patients (64 BD)	Add-on modafinil	Chart review	*Significant improvement
Carlson et al. 2004 [23]	8 BD patients (residual depression, sedation, weight gain, anergia)	Add-on metylphenidate or amphetamines	Chart review	*Improvement
Lydon and El-Mallakh 2006 [29]	16 (5 with ADHD too) BD patients	Add-on methylphenidate	Chart review	*(°) Significant improvement
Wingo et al. 2008 [30]	34 BD patients (depressive and/or ADHD)	Previous treatment with stimulants	Chart review	40% rate of (hypo)mania switch
Parker et al. 2010 [24]	27 BD treatment-resistant depressive patients	Monotherapy or add-on methylphenidate	Prospective	*66.6%: mild/moderate improvement 14.%: no improvement 22.2%: adverse psychiatric events
Parker et al.2013 [31]	51 BD treatment-resistant melancholic depressive patients	Stimulants	Prospective	*50%: mild/moderate improvement 12%: adverse events requiring suspension
McIntyre et al. 2013 [25]	40 BD-ADHD patients	Add-on lisdexamphetamine	4 weeks	(*)° Improvement in residual depression (ES = 0.26), ADHD (ES = 0.74/0.76), global impression (ES = 0.75)

RCT= Randomized Controlled Trial; *BD*= Bipolar Disorder; *ADHD*= Attention Deficit/Hyperactivity Disorder; *ES*= Effect Size
* The outcome measures were related to variations of depressive symptoms
§ The outcome measures were related to variations of manic symptoms
° The outcome measures were related to variations of ADHD symptoms

assigned to placebo or modafinil and assessed for the following 6 weeks. Modafinil demonstrated to be significantly superior than placebo (response—defined as the reduction >50% in IDS scores—43.9 vs. 22.7%; remission 39 vs. 18%). Modafinil-treated patients showed progressive improvement not only in depressive symptoms but also in the overall clinical picture (as demonstrated by the improvement in CGI-BP).

Add-on armodafinil was also evaluated in an 8-week double-blind placebo-controlled trial in 257 BD type I patients [13]. Armodafinil seemed to improve depressive symptoms

measured with IDS-30 more than placebo. However, the active drug did not differ from placebo in the rates of clinical response and remission. Armodafinil resulted safe, not increasing the incidence and the severity of suicidality, depression, and mania. The same research group published in 2014 the results of the same 8-week RCT relative to add-on armodafinil in BD, enlarging the sample to 400 patients (201 treated with armodafinil at a dosage of 150 mg/day). The armodafinil group showed greater response rates comparing to placebo (46 vs. 34%, respectively; $p = .015$), whether no statistically significant differences were found in remission rates. Armodafinil also showed to be sufficiently tolerable at this dosage [17].

More recently, the efficacy and safety of adjunctive lisdexamphetamine (LDX) was tested in an 8-week, prospective, randomized, double-blind, placebo-controlled, flexible-dose study in 25 bipolar depressive patients [14]. Although LDX did not differ from placebo in reducing MADRAS scores, the authors found LDX to be superior to placebo in reducing self-reported depressive symptoms, daytime sleepiness, fatigue, and binge eating behavior and in ameliorating blood lipid profile; they also detected statistically significant tendency of LDX to globally improve the severity of overall depressive and bipolar symptoms. The active drug resulted well tolerated, not inducing/worsening suicidality or hypomania/mania. Only one out of 25 patients was ruled out from the study for misuse of the drug.

Finally, one old, double-blind, crossover RCT that tested the use of intravenous D-amphetamine in a mixed sample of 18 unipolar and bipolar depressive patients should be mentioned [15]. As the aim of the study was to examine behavioral response to intravenous D-amphetamine in a very short-term period (4 days), the symptomatological changes were not easily interpretable.

An important clinical area needing further research concerns the employ of stimulant drugs in adults with comorbid ADHD and BD. Although controlled data on this issue are substantially lacking, the CANMAT group [18] identified MPH and mixed amphetamine salts as the first- and second-line medications, respectively, for the treatment of ADHD in bipolar adults. This evidence was based on two controlled studies in pediatric samples and one in adults [19–21]. Some case reports [22–24] also support efficacy and safety of stimulants in this specific population, especially highlighting the absence of negative effects on the symptoms and course of the comorbid mood disorder [9].

Open-Label Trials and Case Reports on Stimulants in Bipolar Disorder

Several open-label trials focused on the use of stimulants in bipolar patients (Table 1). In a 4-week open-label trial, positive results were reported for adjunctive LDX in BD patients with comorbid ADHD [25]. The trial showed that adjunctive flexible doses of LDX in stabilized ADHD-BD patients determined significant reduction both in ADHD and residual depressive symptoms, improved the global quality of life, and were not associated with (hypo)manic switches and/or BD destabilization, at least in a short-term period.

Another 12-week open-label study explored the use of adjunctive MPH in 14 moderately depressed bipolar patients (both BD I and II), non-responding to mood stabilizers and/or antipsychotics. MPH demonstrated to ameliorate both depression and overall symptom severity. As expected, an early response, with significant reduction of depressive symptoms during the first week, predicted a positive response during the overall follow-up period. No (hypo)manic switches were reported as well as other psychiatric adverse reactions, such as activation or anxiety. Non-response was associated with BD type II, organic condition related to BD, and previous adverse reactions to antidepressants [19].

Two retrospective chart reviews (the second is the enlargement of the former sample) reported the use of adjunctive modafinil in depressive patients (both unipolar and bipolar) with unsatisfying response to antidepressants [26, 27]. In both papers, the authors found modafinil to be effective in a proportion of depressive patients (almost one fourth of the sample), improving wakefulness, fatigue, and global functioning besides depressive symptoms. No patients showed mood switches during modafinil treatment. Modafinil appears to be more tolerable of some dopaminergic agents currently used as adjunctive treatment in resistant depression, just like pramipexole, as showed in a recent STEP-BD-derived report [28]. This is especially true in the long term (7–9 months), and the low discontinuation rate is mostly due to the lack of physical/somatic adverse effects of modafinil, whereas efficacy and psychiatric adverse effects are similar for the two compounds.

Similarly, two other retrospective chart reviews [23, 29], considering 16 and 8 BD patients, respectively, reported that adjunctive MPH or other amphetamine derivatives were generally well tolerated in a long-term period and effective for the treatment of depressive symptoms and relapses of bipolar depression not completely respondent to usual pharmacotherapy. Sedation, weight gain, low energy, and fatigue represented the symptoms that showed the best response.

Less encouraging results were reported in a retrospective chart review of 137 adult bipolar patients previously receiving stimulants for the treatment of comorbid ADHD or as add-on during depressive episodes [30]. The authors noted that only the 43% were currently treated with a mood stabilizer and that the estimated rate of stimulant-associated (hypo)mania was 40%.

In a prospective open study [24], 50 treatment-resistant depressive patients were treated with monotherapy or add-on stimulants, mostly MPH. Twenty-seven of them were bipolar (5 BD I and 22 BD II): the 66.6% ($n = 18$) of them reported from moderate to mild improvement in depression severity and 14.8% ($n = 4$) did not experience any improvement, whereas the 22.2% ($n = 6$) reported psychiatric adverse events as transient mood elevation and excitement phenomena that in only one case

turned into a manic episode. In 2013, the same research group [31•] published the results of the extension of the abovementioned study, finally enrolling 112 (51 BD) patients with treatment-resistant melancholic depression, followed up for a mean time of 69 weeks. Both unipolar and bipolar patients in the 70% of the cases reported to be from "very" to "somewhat" ameliorated (respectively, 20 and 50%). Although the 40% of the sample reported significant side effects, only the 12% required the interruption of the medication (the most common were irritability/agitation, increased anxiety, impaired concentration, feeling "jazzed up," "jittery" and "buzzy," tachycardia, sedation or fatigue, and worsening of mood). It is important that the 20% of bipolar patients experienced an excitation phase or the worsening in terms of frequency and/or amplitude of the highs.

In addition to the above reported open observations, some information for clinical or research purposes can be derived from case reports. For example, the efficacy of adjunctive stimulants was described in melancholic bipolar depression [32], in catatonia [33], and in the treatment of residual depressive symptoms, such as fatigue, tiredness [34], and hypersomnia [35] in BD.

An interesting case report described the use of methylphenidate in a patient with comorbid ADHD, BD, panic disorder, and substance and alcohol abuse [36]. The patient had been stabilized with her mood and anxiety symptoms with lamotrigine and quetiapine, but she continued reporting attention deficits and severe bulimia. After the addition on MPH, concentration improved and binging purging symptoms completely remitted. Most importantly, in a 1-year follow-up period, no adverse events or recurrences regarding mood symptoms, addiction, and eating disorders emerged.

Stimulants in Bipolar Patients with Comorbid ADHD

BD and ADHD have a tangled relationship; high rates of comorbidity between the two disorders have been shown both in children and adult clinical populations [8, 18, 37–43]. The two disorders shared a wide overlap in symptoms, diagnostic criteria, clinical presentation, and common developmental trajectories and comorbidities (i.e., substance use disorders, borderline, and antisocial personality). All these overlaps contribute to the complexity of the clinical presentations and create difficulties in differential diagnosis and treatment approach.

Systematic data regarding the treatment of ADHD with stimulants in adult bipolar patients are substantially lacking, but some recommendations can be derived from open trials and case reports. The CANMAT group recently drew a "ranking" based on levels of evidence and MPH and amphetamine mixed salts received, respectively, levels 1 and 2 of evidence for the treatment of ADHD in adults with comorbid BD. Level 3 was attributed to bupropion and atomoxetine and level 4 to cognitive behavioral therapy, modafinil, venlafaxine, desipramine, nortriptyline, and LDX [18]. Beyond the relative value of these recommendations, it is important to underline that available data on the safety of these medications in bipolar patients are encouraging. In fact, as illustrated in a recent meta-analysis based on RCTs, the cumulative incidence of psychosis and mania in treated ADHD adults was 1.48 per 100 person/years, with a very high number needed to harm of 526 [44]. Recently, 2307 bipolar patients who initiated a therapy with MPH were found in the Swedish National Registry and grouped on the basis of concomitant mood-stabilizing treatment. In a 12-month follow-up period, the risk of developing an excitatory phase, as severe as it would require the initiation of an antipsychotic, was increased in those patients assuming MPH monotherapy (with a hazard ratio (HR) of 7.0 in the first 3 months). The risk of mania was increased too, during the first 3 months (HR 3.0), but at a non-significant level, and then was unchanged. By the contrary, in those patients assuming both MPH and mood stabilizers, the risk of excitation resulted reduced and unchanged in the first 3 months and in the successive period, respectively (HR = 0.6 and 1.1). Similar results regard the emergency of full-blown mania [45].

Nonetheless, concerns regarding the use of stimulants in ADHD-BD subjects are still present [8]. Many reports have shown manic switches or psychosis in ADHD-BD patients treated with stimulants [8, 46–50], and most importantly, there are no systematic data regarding the long-term use and safety of these drugs in ADHD-BD subjects. Stimulants should be avoided or considered as a second-line treatment for ADHD-BD patients in presence of an active substance use disorder, active eating disorders (especially anorexia nervosa), and pervasive cluster B personality with pronounced malingering features. Usually, a hierarchical approach is the best management strategy. ADHD should be treated only after a sustained stabilization of the mood disorder [8, 51].

Stimulants in Mania

A new interesting research area is focused on the "vigilance regulation model of mania." In this model, mania as well as other psychomotor excitatory phenomena (for example hyperactivity in ADHD) may be related, at least in some vulnerable individuals, to a vicious circle involving the override of the autoregulatory control of the brain arousal. The hypothesis started from the biunivocal relationship between vigilance and behavior: as vigilance influences behavior, so behavior influences vigilance. According to the hypothesis, in excited individuals, the increase of stimulating experiences and behaviors might be interpreted as an attempt to stabilize arousal via intense external stimulations [52–54]. In this perspective, in some patients, stimulant medications, counterintuitively, may represent a concrete option for the treatment of manic episodes. The evidence supporting this hypothesis is mainly derived from case reports of bipolar patients rapidly improved from a manic episode after the administration of stimulants [54–58]. Two reports also associated improvement of manic symptoms to stabilization of

vigilance assessed by means of EEG [59, 60]. Few years ago, a multicenter international study (MEMAP_Methylphenidate in Mania Project) has been constituted in order to systematically verify the utility of stimulants in the treatment of mania [61].

Stimulants in Other Neuropsychiatric Conditions with Bipolar Presentation: the Case of Late Onset Bipolarity, Frontotemporal Dementia and Traumatic Brain Injury

Bipolar diathesis can be elicited by medical conditions (i.e., vitamin B12 deficiency, hyperthyroidism, Cushing's syndrome, and corticosteroid administration) or by many neurologic conditions such as Alzheimer disease, frontotemporal dementia [62], vascular dementia, silent cerebral infarcts and stroke, normal pressure hydrocephalus, brain tumors, brain injury, epilepsy, infections of the central nervous system, Huntington disease, and prion diseases [63–66]. Interestingly, some authors defined a clinical variant of late onset bipolarity elicited by neurodegenerative dementia as bipolar type VI, which is characterized by mixed-labile mood symptoms and cognitive dysfunction associated with hyperthymic/cyclothymic/irritable temperament, family history of bipolarity, refractoriness to antidepressants and acetylcholinesterase inhibitors, response to mood stabilizers, and/or atypical antipsychotics [62].

One of the best example of late onset bipolarity can be associated to the prodromal phases of frontotemporal dementia (FTD) in its frontal variant (fvFTD). The onset of this neurodegenerative condition is usually earlier than that of other types of dementia, and often, it begins with severe changes of personality and mood episodes of both polarities and behavioral disorders [67]. In the prodromal phase of the illness, when frank neurological signs are absent or subclinical, fvFTD may mimic BD in various aspects. Similar mood disturbances can be observed in some traumatic brain injured (TBI) patients.

Clinical reports for both these conditions suggested positive response to psychostimulants in the management of specific symptoms such as depression, fatigue, tiredness, distractibility, and other cognitive dysfunctions. An interesting double-blind, placebo-controlled, crossover RCT showed a significant reduction in impulsive risk-taking behavior (namely gambling) in eight FTD patients treated with MPH. In this sample, the improvement was independent from the effect on cognitive functioning, which remained unchanged [68]. The authors hypothesized that this effect could be related to a possible normalization of frontal electroencephalographic rhythms as found in FTD [69]. MPH is supposed to ameliorate frontal circuitry transmission with a normalization of signal-to-noise ratio [70].

An example of the use of stimulants in TBI with bipolar-like manifestations is a case report showing the "paradoxical" antimanic effect of dextroamphetamine in a brain-injured manic adolescent, previously treated without effect with standard medications (e.g., divalproex, lithium, haloperidol, and carbamazepine) [58, 71, 72]. In a "personalized"-"stratified" medicine perspective [73], this is an area of great interest for clinical practice that deserves closer attention and further study.

Potential Limitations

A specific concern on the use of stimulants in BD patients regards their potential destabilizing effects on the course of the illness. The major problem of the available literature is the short duration of the studies, ranging from a minimum of 4 to a maximum of 12 weeks. This is insufficient period to evaluate the potential destabilization of the illness. It has been advocated that the induction of (hypo)manic switches linked to stimulants/stimulant-like drugs [74–76] may have been related to the absence of adequate concomitant antimanic or mood-stabilizing therapy [23]. High risks of BD destabilization, including earlier onset and more severe course, have been reported for bipolar adolescents, with previous exposure to stimulants [77, 78], and for adults with ADHD-BD comorbidity treated with MPH [8]. Other reports indicated that psychostimulants did not worsen symptoms of mania in most stabilized BD patients [19–21, 23, 29, 79, 80]. In our experience, at least in stabilized BD patients, the risk of precipitating mania or mixed states is reduced, when stimulant medications are used in combination with mood stabilizers.

Misuse and abuse of MPH or amphetamines may be another problem, in particular in BD patients with comorbid ADHD or substance use disorder. Although several of the reviewed studies showed low rates of misuse for MPH over several months or years of observation [23, 24, 29], other reports suggested high risk of abuse and addiction mainly not only for amphetamines but also for MPH. Such different conclusions may be influenced by the exclusion or inclusion of high-risk patients. In BD patients with a past or current substance use disorder, a conservative approach should be preferred, considering if necessary the use of less addictive drugs such as modafinil and armodafinil [81]. The same strategy can be suggested for ADHD-BD patients with a personal history of treatment misuse and malingering.

Conclusions

Although several international guidelines support the adjunctive use of stimulant drugs as the second-third-line choice for bipolar depression [10, 11], their efficacy and safety in bipolar disorder is still poorly explored. Few short-term controlled studies and some open clinical reports documented the potential efficacy of MPH and modafinil as augmentation treatment for resistant bipolar depression. Available data did not sufficiently clarify whether the use of stimulant in depression (not only bipolar) should be considered an effective therapeutic option for specific depressive phenotypes or a sort of palliative, symptomatic medication with

limited indication for the management of residual or specific symptoms such as fatigue and somnolence.

The employ of MPH in adult BD patients with comorbid ADHD is supported by several preliminary observations, although available evidence is very sparse and long-term studies are virtually absent. Clinical reports supporting that MPH may also have some benefit in several neuropsychiatric conditions with a bipolar-like presentation are also anecdotal. This might be the case of the management of some specific neuropsychiatric bipolar presentations in FTD and TBI.

Data on the use of stimulants in BD are still few and sometimes contradictory. Based on the current level of information, we do not recommend stimulants in BD patients in the absence of mood stabilizers. If stimulants are used, patients should be frequently and regularly assessed for possible manic or mixed symptoms, as these symptoms may occur acutely or after several months. If manic or mixed symptoms arise, it is necessary to discontinue stimulants and use mood stabilizers or other antimanic drugs [82••, 83].

Bipolar disorder is probably a heterogeneous condition with many different clinical presentations mostly qualified by the current symptomatology, longitudinal course, and physical and psychiatric comorbidity. The stratification of patients, in both clinical practice and research, may lead to specific treatment strategies. We should expect that specific BD subpopulations such as patients with a history of ADHD or TBI may respond more favorably to a combination of mood stabilizers and stimulants than to other possible treatments. An appropriate "stratification" process should be considered the basis for more refined treatment approaches and the starting point for future research in this field.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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ORIGINAL PAPER

The influence of Generalized Anxiety Disorder on Executive Functions in children with ADHD

D. Menghini[1] · M. Armando[1,2] · M. Calcagni[1] · C. Napolitano[1] · P. Pasqualetti[4,5] · J. A. Sergeant[6] · P. Pani[3] · S. Vicari[1]

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Abstract The present study was aimed at verifying whether the presence of generalized anxiety disorder (GAD) affects executive functions in children with attention-deficit hyperactivity disorder (ADHD). Two groups of children with ADHD were selected for the study according to the presence or absence of GAD. The first group of 28 children with ADHD with GAD (mean age: 9 ± 1.2; males/females: 24/4) was matched for gender, age, IQ, psychiatric comorbidity with a second group of 29 children with ADHD without GAD (mean age: 8.8 ± 0.7; males/females: 26/3). The two groups with ADHD were compared to 28 typically developing children (mean age: 8.3 ± 1.3; males/females: 23/5) on different measures involving processes especially important in inhibitory control such as rule maintenance, stimulus detection, action selection and action execution. Our results indicated that, differently from children with ADHD with GAD, only the group with ADHD without GAD showed a deficit in inhibitory control. Comorbid subgroups should be differentiated, especially, to develop specific and efficient therapeutic interventions in ADHD.

Keywords Internalizing disorders · Comorbid ADHD · Inhibitory control · Response inhibition

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders with a prevalence rate of 5% [56]. The main clinical features of ADHD are hyperactivity (excessive motor activity, persistent and continuous), deficit of concentration and impulsivity [46].

In addition to these clinical features, it is estimated that 60–100% of patients with ADHD also exhibit one or more comorbid disorders [23, 10, 33, 22]. Between 42 and 90% of patients meet criteria for oppositional defiant disorder and/or conduct disorder [23, 19, 8] and about 20% of children with ADHD are additionally suffering from tic disorders [30, 61, 66, 59].

Several studies have examined the comorbidity between ADHD and Autism Spectrum Disorders, which is reported to have a frequency of about 65% [16, 23]. Other disorders frequently observed in patients with ADHD are dyslexia (25–40%), motor coordination deficits (50%), dyscalculia (10–60%), sleep disorders (25–50%), enuresis and/or encopresis (30%) [23, 50, 72].

While it is true that comorbidity between ADHD and externalizing disorders is more prevalent, the comorbidity of ADHD and Anxiety Disorders (ADHD+AD) deserves careful scrutiny in its own right in as much as this comorbidity may have important implications for etiology, assessment, and treatment [28]. The comorbidity of ADHD and

✉ D. Menghini
deny.menghini@opbg.net

1 Child Neuropsychiatric Unit, Department of Neuroscience, Bambino Gesù Children's Hospital, Piazza Sant'Onofrio 4, 00165 Rome, Italy

2 Office Médico-Pédagogique Research Unit, Department of Psychiatry, University of Geneva School of Medicine, Geneva, Switzerland

3 Department of Physiology and Pharmacology, Sapienza University, Rome, Italy

4 Service of Medical Statistics and Information Technology (SeSMIT), Fatebenefratelli Hospital, Rome, Italy

5 Language and Communication Across Modalities Laboratory (LACAM), Institute of Cognitive Sciences and Technologies (ISTC-CNR), Rome, Italy

6 Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, The Netherlands

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AD seems to be a real phenomenon that cannot be explained solely by symptom overlap [68] especially concerning executive functions (EF) and inhibition control. Schatz and Rostain [65] reviewed the comorbidity of ADHD and AD with a particular emphasis on neuropsychological functioning. The authors concluded that AD in ADHD may partially inhibit impulsivity and response inhibition deficits and make working memory deficits worse. While ADHD is characterized as a disorder with reduced inhibition control [25, 48], AD is associated with increased inhibition control [55, 49, 20] and might act as a factor reducing the severity of ADHD symptoms [47], as proposed originally by Quay [57, 58]. This theoretical framework [49, 40, 12] suggests that ADHD is characterized by low activity in the behavioral inhibition system that leads to fast and impulsive responding and poor inhibitory control. Conversely, in AD the behavioral inhibition system is overactive [26], leading to reflective and slow responding as well as better inhibitory control. Along this line of investigation, a recent study [27] in adults found that anxiety is associated with a better performance when response inhibition is required but also with more omissions for the expected responses. Nevertheless, studies on EF provide conflicting evidence as to whether children with ADHD+AD have better inhibitory control compared to children with ADHD without Anxiety Disorders (ADHD−AD). Several studies have shown that children with ADHD+AD have enhanced behavioral inhibition compared to ADHD−AD [55, 49, 40, 12] but other studies did not confirm these findings: Manassis et al. [40] found that children with ADHD+AD and with ADHD−AD did not significantly differ on the Stop task. Korenblum et al. [35] compared children with AD, ADHD, ADHD+AD (i.e., Generalized AD, GAD, and/or separation AD) and Controls on the Stop task and found that AD was not associated with inhibition deficits or performance monitoring once comorbid ADHD was considered. The meta-analysis by Lipszyc and Schachar [37] documented ADHD+AD had a deficit on the Stop task that was greater than that of individual with AD, but slightly less than that of ADHD, suggesting that a phenocopy of ADHD may arise in the presence of AD. These contradictory results have been found not only in the context of inhibition but also in other EF domains. Manassis [39] reported that ADHD+AD and ADHD−AD were similarly impaired relatively to Controls on working memory tasks. However, Jarrett et al. [29] found that children with ADHD+AD performed worse on working memory than ADHD−AD while in a continuous performance test the group with ADHD+AD and the group with ADHD−AD did not differ. Moreover, Bowen et al. [13] found that the children with a comorbid ADHD+AD had more attentional problems, more anxiety and depressive symptoms, and were also less socially competent than children with ADHD−AD. The study by Vloet et al. [70] suggested that anxiety has no mitigating effect on impulsivity in ADHD, but that children with ADHD+AD showed better performance in sustained and selective attention tasks compared to those with ADHD−AD.

In these latter studies [13, 70], no specific subtypes of AD were taken into account and a possible source of confounding in results is this heterogeneity of patients with AD studied. Indeed, the profile and nature of cognitive dysfunction seem to depend on the AD subtype and studies documented the pattern of impairment on cognitive functioning differs among AD subgroups. For example, Airaksinen et al. [1] found deficits in episodic memory only in patients with panic disorder, obsessive–compulsive disorder and social phobia; in a shifting task (the trial making test), a deficit was found only in panic disorder and obsessive–compulsive disorder subgroups while in the verbal fluency task only in the subgroup with social phobia. Authors found that patients with specific phobia and GAD did not display any specific neuropsychological deficit. In the study by Castaneda et al. [15] participants with panic disorder and agoraphobia showed deficits in semantic clustering and participants with GAD, obsessive–compulsive disorder and post-traumatic stress disorder had difficulties in the retention during the short delay. However, the subgroups with AD selected (panic disorder and agoraphobia, GAD, obsessive–compulsive disorder and post-traumatic stress disorder) did not show impairments in other measures of short and long term memory and of executive functioning, as shifting and visual working memory. A recent study [45], examining executive attention in three groups of children (with ADHD, with AD, and Controls), found in children with ADHD worse performances (more errors, longer and more variables reaction times, higher orienting and conflict scores) than Controls. Compared to the group with AD without specific phobia, children with ADHD did not differ in a few measures considered (conflict scores) but differed in some others (higher orienting scores, more variable reaction times and less accurate responses).

Although the role of specific AD in affecting the cognitive functioning, in general, and EF, in particular, is becoming increasingly clear, the majority of the research in ADHD has focused on AD in general, and no study tried to characterize the cognitive profile of children with ADHD with a specific AD subtype. However, in accordance with literature on subtypes, the selection of a group of children with ADHD and a specific subtype of AD could contribute to clarify the heterogeneity in neuropsychological functioning of children with ADHD.

Within AD, GAD seems to be the most frequent in typical population of children and adolescents and the most frequently comorbid with ADHD [62, 9, 32]. Nevertheless, little is known about the GAD effect on EF of children and adolescents with and without GAD who have ADHD comorbidity.

The aim of the present study was to verify whether the presence of GAD affects the magnitude of EF' effects in ADHD. To meet this aim, two groups of children with ADHD were formed based on the presence or absence of GAD. These two groups were matched for age, IQ, gender, ADHD subtype and psychiatric comorbidity, and were compared on several EF tasks to Controls. We particularly focused on EF tasks that involve processes especially important in inhibitory control such as rule maintenance, stimulus detection, action selection and action execution. These functions are critical in everyday life and, if impaired, they prevent individuals to resist distractions, to maintain their behavioral goal or to change behaviors when required, as occurs in the case of ADHD.

Following Pliszka [55], Oosterlaan and Sergeant [49], Manassis et al. [40], Bloemsma et al. [12], we expected that children with ADHD and GAD (ADHD+GAD) showed better performances in EF' tasks involving inhibitory control because their temperamental anxiety improves the ability to control impulses. Conversely, children with ADHD without GAD (ADHD−GAD) should have more difficult in inhibiting impulsivity in EF' tasks requiring higher response inhibition.

The opportunity to compare the neuropsychological functioning of groups of children with ADHD with or without GAD may give us the possibility to limit the heterogeneity of results on EF in ADHD and may have important implications for better define specific assessment and treatment.

Materials and methods

Participants

Of the 354 children with ADHD admitted to the Child Neuropsychiatric Unit at the Children Hospital Bambino Gesù in 2014, a group of 28 children with ADHD+GAD was selected in according to the presence of GAD. The diagnosis of GAD was conducted according to developmental history, extensive clinical examination, K-SADS-PL [31] and the Conners' Rating Scales Long Version Revised [17] for parents and teachers. Only a small number of participants showed a comorbid separation anxiety disorder other than GAD.

Of the remaining 326 children with ADHD, a second group of 29 children with ADHD−GAD was selected to match the former group with ADHD+GAD for age, IQ, gender, psychiatric comorbidity (see Table 1).

As shown in Table 1, the group with ADHD+GAD and with ADHD−GAD significantly differed in terms of the presence of anxiety symptoms, as measured by the Multidimensional Anxiety Scale for Children—MASC [42]. However, the two groups with ADHD did not differ in the children depression inventory—CDI [36]. The two groups with ADHD did not differ also in terms of distribution of ADHD Combined, ADHD Hyperactive and ADHD Inattentive or for psychiatric comorbidity.

A group of 28 Controls was selected and matched with the two groups of ADHD for age, IQ and gender. Comparisons of demographic characteristics (age, IQ, gender) of

Table 1 Demographic characteristics and number of psychiatric comorbidities of participants

	ADHD−GAD	ADHD+GAD	Controls	ADHD−GAD vs controls *p* value	ADHD+GAD vs controls *p* value	ADHD−GAD vs ADHD+GAD *p* value
AGE (M ± SD) range	8.8 ± 0.7 10.5–7.2	9 ± 1.2 12.7–6.9	8.3 ± 1.3 11.4–7.1	0.39	0.12	0.91
IQ (M ± SD) range	98.5 ± 14.9 133–85	100.3 ± 13.9 131–85	101.8 ± 9.9 119–85	0.72	0.96	0.94
SEX (M/F)	26/3	24/40	23/5	0.66	0.72	0.96
MASC	38.21 ± 11.43	47.04 ± 12.1				0.007
CDI	13.48 ± 8.77	14 ± 8.74				0.83
IN (N)	6	6	–			
H/IM (N)	2	2	–			
IN-H/IM (N)	21	20	–			
SAD (N)	2	3	–			
ODD (N)	8	8	–			
TIC (N)	1	1	–			

IQ intelligence quotient, *ADHD−GAD* ADHD and no general anxiety disorder, *ADHD+GAD* ADHD and general anxiety disorder, *MASC* Multidimensional Anxiety Scale for children, *CDI* children depression inventory, *IN* inattentive subtype, *H/IM* hyperactive/impulsive subtype, *IN-H/IM* combined inattentive-hyperactive/impulsive subtype, *SAD* comorbidity with separation anxiety disorder, *ODD* comorbidity with oppositional defiant disorder, *TIC* comorbidity with tic disorders

the two groups with ADHD and Controls were reported in Table 1.

For each participant, exclusion criteria were: brief IQ below 85 (as assessed by the Leiter-R [60], evidence of neurological disorders, pervasive developmental disorders and receptive language disorders. None of the ADHD children were under stimulant medication.

Children with ADHD underwent a child psychiatric examination conducted by experienced developmental psychiatrists and neuropsychologists. ADHD diagnosis was based on developmental history, extensive clinical examination and a semi-structured interview conduct to parent and child separately, K-SADS-PL [31]. Following the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV [4], children with ADHD were characterized as: 41 fulfilled diagnostic criteria for ADHD Combined subtype, 4 for ADHD Hyperactive-Impulsive and 12 for the ADHD Inattentive subtypes. Patients ADHD NOS (Not Otherwise Specified) were not included in the study.

All participants and their parents gave their written informed consent after receiving a comprehensive description of the study. The study was performed in accordance with the Declaration of Helsinki (1964) and was approved by the local ethical committee of the Children Hospital Bambino Gesù.

Psychopathological assessment

The K-SADS-PL [31] is a semi-structured diagnostic interview that provides diagnoses occurring within the past (life time) and current episodes of psychopathology in children and adolescents according to the DSM-IV criteria. The primary diagnoses assessed with the K-SADS-PL include: major depression, dysthymia, mania, hypomania, cyclothymia, bipolar disorders, schizoaffective disorders, schizophrenia, schizophreniform disorder, brief reactive psychosis, panic disorder, agoraphobia, separation anxiety disorder, avoidant disorder of childhood and adolescence, simple phobia, social phobia, overanxious disorder, generalized anxiety, obsessive compulsive disorder, attention-deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder, enuresis, encopresis, anorexia nervosa, bulimia, transient tic disorder, Tourette's disorder, chronic motor or vocal tic disorder, alcohol abuse, substance abuse, post-traumatic stress disorder, and adjustment disorders. The interview was administered to children and their parents separately. This semi-structured interview takes 45–75 min to administer. The majority of items in the K-SADS-PL are scored using a 0- to 3-point rating scale. Scores of 0 indicate no information is available; scores of 1 suggest the symptom is not present; scores of 2 indicate sub-threshold presentation and scores of 3 indicate threshold presentation of symptoms.

The Conners' Rating Scales Long Version Revised [17] was completed by parents and teachers to obtain a measure of ADHD criteria for Hyperactivity and Inattention. The version for teachers was brought to the teachers by parents with a letter of instructions and gave back before the end of the testing sessions. The version for parents contains 80 items while the version for teachers contains 59 items. The parent version contains scales A through N. The teacher version is similar but lacks scale G (psychosomatic) contained on the parent version. The clinician transfers the circled scores into appropriate scales on the middle form and totals each scale at the bottom of the page. Scores can then be converted to a *T* score. The administration's time is 20 min. Both internal consistency and test–retest reliability are very good for the Conners' Rating Scales. Internal consistency coefficients (Cronbach's alpha) range from 0.69 to 0.97, depending on the age of the sample, and the person completing the questionnaire.

The Multidimensional Anxiety Scale for Children (MASC) [42] is designed to address the multidimensional assessment for anxiety in children and adolescent. The final version of the MASC consists of 39 items distributed across four major factors, three of which can be parsed into two subfactors each. Main and subfactors include (1) physical symptoms (tense/restless and somatic/autonomic), (2) social anxiety (humiliation/rejection and public performance fears), (3) harm avoidance (perfectionism and anxious coping), and (4) separation anxiety. Internal consistency coefficients (Cronbach's alpha) range from 0.87 to 0.91 depending on the age of the sample. The time it generally takes for an individual to complete the MASC is 20 min or less. The MASC manual converts raw scores to *T* scores and differentiates anxiety in children as: 45–55 average, 56–60 slightly above average, 61–65 above average, 66–70 much above average, and scoring above 70 would be suggestive of a clinical diagnosis.

The children depression inventory (CDI) [36] is an instrument appropriated for children and adolescent. CDI is a 27-item rating instrument written at the lowest reading level of any measure of depression for children. Respondents are given a group of three sentences and asked to choose the one that best describes him or her in the past two weeks. Children can score 0–54 on the CDI. A cut-off score of 19–20 is generally accepted to reflect a child who has potentially depressive disorder. The 27 items are grouped into five factor areas, including "negative mood", "interpersonal problems", "ineffectiveness", "anhedonia", and "negative self esteem". Internal consistency (Cronbach's alpha) for the CDI is reportedly high, ranging from 0.82 to 0.97 depending on the age of the sample. The time it generally takes for an individual to complete the CDI is 15 min or less.

MASC and CDI were administered to the children in separated sessions.

Neuropsychological assessment

Tasks widely used to make a clinical assessment of EF in children were selected. Particular attention was given to EF' tasks evaluating stimulus detection, action control, task rules maintenance, and motor programming.

From the standardized and normed clinical battery Test of Everyday Attention for Children—TEA-Ch [41] were selected the following two tasks: SCORE! (SCORE) and Opposite Worlds (OPW). In the SCORE task children are required to count silently the tones and indicate the total number of tones at the end of each trial. The number of tones ranged from 9 to 15 with a total of 10 trials in this subtest. The score is the number of trials in which the child gave the correct response. In OPW task children are shown a sheet presenting a mixed, quasi-random array of the digits 1 and 2. In the 'same world' trial, they are required to say the digits actually presented as quickly as possible. In the 'opposite world' trial, they are required to say the opposite digit ('one' for 2 and 'two' for 1) to the digit presented as quickly as possible. The time (in sec) taken to complete OPW task is the score.

In the Verbal Selective Attention (VSA) task [11], children are required to listen silently to sequences of words, in which the word "Sun" occurs. When the children detect the word "Sun", they have to tap a hand on the table to indicate that they have detected the target word. The score taken is the number of false alarms (taps for wrong words).

Tower of London (TOL) [64] is a classical task to evaluate a variety of behaviors and abilities related to planning and strategy use, as well as the maintenance of attention and behavior in the pursuit of some goal. Performance is evaluated by the sum of the total correct moves in the 10 different patterns.

In the Stroop Color Word Test (STROOP) [24], the children were instructed to read the words, name the colors, and finally, name the ink color of the printed words as quickly and as accurately as possible in the three subsequent subtasks. The score is the difference of the total time (in sec) taken to complete the task between the mean of the two control conditions (read the words and name the colors) and the incongruent task (naming the ink color that incongruously named color words are printed in).

The Stop task [38, 44, 52] consists of randomly intermixed Go and stop trials (67 and 33%, respectively). All trials begin with the presentation of a black cross in the center of a laptop computer screen. After 1500 ms, a white arrow inside a blue circle (go signal) replaces the cross. On Go trials, children were instructed to press the space bar as fast as possible after the go signal appearance. In stop trials after a variable delay (stop signal delay, SSD), a stop signal (red way stop) appears after the Go signal. Children were instructed to refrain from responding. The stop signal delay duration is controlled by a simple staircase procedure (50 ms step) to keep the probability of inhibit around 50%. Stop signal delays are increased or decreased by a single step after successful or unsuccessful stopping. The Stop Signal Reaction Time (SSRT) is estimated (in msec) by subtracting a mean estimate of SSDs from the observed mean of the reaction times in no stop trials.

The Go No-Go task evaluates the ability to suppress a dominant response. It consists of randomly intermixed "go" (75%) and "no-go" (25%) trials. All trials commence with the presentation of a black cross (1500 ms duration), on the center of the screen. In go trials one out of three intermingled equiprobable colored circle stimuli (blue, green, yellow) is presented. Subjects are required to quickly press the key bar to respond to the stimulus. In no-go trials, the colored circle is red and subjects are required to not respond. The error rate (probability of uncorrected responses to no-go signals) is measured.

Procedure

Children were evaluated individually in three testing sessions (each approximately 1–1 1/2 h) carried out on separate days. Tasks were administered randomly during the testing sessions.

Statistical design

The main statistical analysis was a mixed model with Subject as random-effects factor, Task as within-subjects repeated measures factor and Group as between-subjects factor. After verifying the Group × Task interaction, pairwise comparisons between groups for each EF measure were corrected according to Sidak's procedure.

Since several EF measures were considered and separate analyses could produce alpha-inflation (increase of false positive findings), the main analysis consisted of all EF measures, after obtaining Z scores for each measure. Z scores were computed by converting raw scores based on the mean and the standard deviation of normative data of the task (for SCORE, TOL and OPW) or, when normative data were not available, on the mean and standard deviation of Controls (for VSA, STROOP, SSRT, Go No-Go).

According to Shapiro-Wilks test and graphical inspection (Q-Q plot and box-plot), the distributions of VSA (false alarms) and Go No-Go (error rate) resulted non-Gaussian and were log-transformed before computing Z scores.

As justification of the sample size, we calculated that a sample of 75 subjects (25 per group) allowed to reach a power >90% of detecting as significant (at alpha level set at 0.05) a medium standardized effect size ($f = 0.25$) for the overall Group × Task interaction, assuming an average correlation among EF measures of 0.50.

Significant differences were considered for $p < 0.05$.

SPSS 21.0 (International Business Machines Corporation, Armonk, NY, USA for Windows) was used for statistical analysis.

Results

Mean and confidence interval in EF measures (after back-transformation to original measure units for descriptive purpose) of children with ADHD−GAD, with ADHD+GAD and Controls are reported in Table 2.

Results on EF measures, after obtaining *Z* scores, documented a significant main effect for Group $F(2,70.8) = 16.211$; $p < 0.001$, due to the lower overall performance of the group with ADHD−GAD than that of Controls (Sidak $p < 0.001$), as well to the lower overall performance of the group with ADHD+GAD than that of Controls (Sidak $p = 0.006$). The group with ADHD−GAD did not differ from the group with ADHD+GAD (Sidak $p = 0.089$). A significant Group × Task interaction [$F(14,70.5) = 1.987$; $p = 0.024$] was also observed, indicating that inter-groups differences were largely dependent on type of task.

No differences between the group with ADHD+GAD, with ADHD−GAD and Controls were found (see Table 2) for OPW (time), STROOP (time) and Go No-Go (error rate). However, in SCORE (correct score) and in TOL (correct score) groups with ADHD did not differ each other but both showed lower scores than Controls. The group with ADHD+GAD did not differ from Controls with respect to VSA (false alarms) and SSRT (time), while the group with ADHD−GAD showed in VSA (false alarms) and SSRT (time) poorer performance than Controls (eta-squared 0.23 and 0.25, respectively). The groups with ADHD−GAD and with ADHD+GAD differed in VSA (eta-squared 0.15) but not in SSRT.

To check whether the three groups also differed in terms of intra-individual variability (standard deviation, SD) for reaction time variables, a further analysis was performed on SDs of go reaction times in the Stop task (that is of the reaction time obtained from no stop trials) and of go reaction times in Go No-Go task. None of these measures resulted different among the three considered groups (Stop task: ADHD−GAD M ± SD 0.10 ± 0.24; ADHD+GAD M ± SD 0.60 ± 1.33; Go No-Go task: ADHD−GAD M ± SD 0.24 ± 0.52; ADHD+GAD M ± SD −0.23 ± 1.08, consistently, $p > 0.25$ and eta-squared <5%).

Discussion

The aim of the present study was to investigate whether GAD affects EF in children with ADHD. As hypothesized, our results in children with ADHD documented deficits on EF (i.e., on the planning task, TOL, and on the verbal sustained attention task, SCORE), but only children with ADHD−GAD had deficits in tasks mainly requiring inhibitory control. Specifically, children with ADHD−GAD committed more false alarms in VSA than children with ADHD+GAD and Controls, and had slower SSRTs than Controls. Given the large effect sizes of the differences between ADHD−GAD and Controls in VSA and Stop task measures (eta-squared 0.23 and 0.25, respectively), our results can be interpreted as clinically relevant.

As noted previously, neuropsychological studies have provided conflicting results as to whether children with ADHD+AD have better inhibitory control compared to

Table 2 Mean and 95% confidence interval (CI) of raw score of EF measures in groups with ADHD−GAD, with ADHD+GAD and Controls

EF task	ADHD−GAD Mean (95% CI)	ADHD+GAD Mean (95% CI)	Controls Mean (95% CI)	ADHD−GAD vs controls *p* value	ADHD+GAD vs controls *p* value	ADHD−GAD vs ADHD+GAD *p* value
VSA (false alarms)	5.0 (3.8–6.6)	2.2 (1.3–3.3)	1.7 (1.0–2.7)	0.001	0.849	0.009
SCORE (correct)	8.0 (7.1–8.8)	8.2 (7.4–8.9)	9.0 (8.4–9.4)	0.034	0.049	0.938
TOL (correct)	24.4 (23.0–25.8)	24.2 (22.6–25.8)	27.5 (26.1–28.9)	0.002	0.001	0.964
OPW (time)	33.0 (30.0–36.4)	33.1 (29.7–36.9)	34.6 (30.7–38.9)	0.974	0.824	0.97
STROOP (time)	60.4 (51.4–69.4)	52.7 (44.6–60.8)	50.0 (38.4–61.6)	0.446	0.98	0.7
SSRT (time)	317.5 (274.8–360.1)	268.9 (211.3–326.4)	243.8 (214.0–273.6)	0.002	0.582	0.115
Go No-Go (error rate)	0.2 (0.2–0.3)	0.3 (0.2–0.3)	0.2 (0.2–0.3)	0.698	0.643	0.997

ADHD−GAD ADHD and no general anxiety disorder, *ADHD+GAD* ADHD and general anxiety disorder, *VSA* verbal selective attention, *SCORE* verbal sustained attention, *TOL* tower of London, *OPW* opposite worlds, verbal shifting, *STROOP* stroop color word, *SSRT* stop signal reaction time, *Go No-Go* inhibition

p values referred to post hoc comparisons among groups of EF *Z* scores corrected according to Sidak's procedure

children with ADHD−AD [55, 68, 40, 13, 70]. Manassis et al. [40] reported that ADHD+AD and ADHD−AD did not differ in response inhibition. In that study all childhood AD were included, apart from post-traumatic stress disorder and obsessive compulsive disorder. However, it has been argued that each AD subtype may express a distinct cognitive dysfunction [15] and that GAD, as a persistent anxious temperament [2, 3, 7], could influence cognitive processes more than other AD. The better inhibitory control found in our children with ADHD+GAD might be interpreted as a consequence of temperamental anxiety. Indeed, the temperamental anxiety could have the effect of improving different basic cognitive processes involved in inhibitory control, such as stimulus detection, action selection and action execution [53, 67, 69, 63], ameliorating the performance of children with ADHD+GAD in some tasks. Accordingly, it has been suggested that heightened state anxiety facilitates sensory processing and stimulus detection [71, 6, 18, 54]. This would allow children with ADHD+GAD to easily identify the target word and efficiently filter out distractors in the VSA as well as to rapidly detect the stop signal in the Stop task, resulting in shorter SSRT.

In terms of intra-individual variability (SD), the groups with ADHD did not differ from Controls in the Go reaction times of the Stop task and the Go No-Go task. This agrees with studies reporting reaction time variability is not affected by presence of anxiety [5].

In the present study, results on tasks requiring inhibitory control suggested that children with ADHD benefited in some ways of the comorbid GAD. However, we should be cautious about generalizing our results to every context in which inhibitory control is involved. The better inhibitory control in children with ADHD+GAD could have beneficial effects for some behaviors (e.g., when having to suppress a response), but it could be detrimental for others. Particularly, since augmented inhibition has been associated with fearful, passive or avoidant behaviors (Kooijmans et al. 2000) [34], it could be maladaptive in contexts in which the capacity to quickly react appropriately is required.

At our knowledge, only three studies so far investigated the cognitive profile of adults with GAD [1, 14, 27]. The study by Airaksinen et al. [1] found that adults with GAD did not display any specific neuropsychological deficit compared to Controls and to the others subgroups with AD (panic disorder; obsessive–compulsive disorder, and social and specific phobia). Castaneda et al. [14] documented in patients with GAD difficulties only in the retention during the short delay. However, it is important to note that relatively few persons were diagnosed with GAD in both studies (respectively, 7 patients in the first study and only one patient in the second study) and that the small sample sizes could affect the probability to obtain reliable group differences. Similar to our results, in a larger group of 41 adults with AD (GAD and/or social anxiety disorder), Grillon et al. [27] found excessive response inhibition compared to Controls.

To better identify subgroups with ADHD with differences related to EF, the influence of state anxiety should be considered in future studies. A study by Pacheco-Unguetti et al. [51] on the effect of state anxiety in adults with different levels of self-reported state anxiety found that low state anxiety adults were more flexible in adjusting to task demands compared to high state anxiety adults.

Our study suggests that specific AD (i.e. GAD) positively influence certain EF abilities (i.e. response inhibition) in ADHD. Future studies should analyze more in detail which of the basic cognitive processes are affected in inhibitory control in children with ADHD and psychiatric comorbidity. To date, several studies have explored cognitive domains in children with ADHD with comorbid externalizing disorders whereas only few with internalizing disorders. Even fewer have differentiated between distinct subtypes of AD. Our results indicate that the groups with ADHD+GAD and ADHD−GAD have distinct cognitive profiles. Differentiation between comorbid subgroups should be considered, especially, to develop specific and efficient therapeutic interventions [43]. Accordingly, a recent study by Denis et al. [21] revealed in children with ADHD a significant improvement in automatic response inhibition and flexibility, and a decrease in inattention/hyperactivity behaviors following the treatment for AD.

A limitation of the present study is that the EF tasks adopted here are only laboratory measures and that more ecologically tasks are needed to confirm and to generalize the result of the differential cognitive profile between children with ADHD+GAD and children with ADHD−GAD. Speculatively, our results may suggest individualized behavioral treatment aimed at improving very specific cognitive processes and behaviors, and challenges in children with ADHD. In particular, a specific training on metacognitive strategy to improve signal detection, to develop impulse control and to regulate impulsivity should be especially employed with children with ADHD−GAD, who had more difficulties in inhibitory control than children with ADHD+GAD.

Compliance with ethical standards

Conflict of interest This research received no specific grant from any funding agency, commercial or not-for-profit sectors. J. A. Sergeant received educational grant from Novartis, Janssen-Cilag, Lilly, Shire and Vifor. J. A. Sergeant is also on the advisory board of Lilly and Shire.

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ORIGINAL CONTRIBUTION

Potential for diagnosis versus therapy monitoring of attention deficit hyperactivity disorder: a new epigenetic biomarker interacting with both genotype and auto-immunity

Walter Adriani[1,2] · Emilia Romano[1] · Mariangela Pucci[3] · Esterina Pascale[4] · Luca Cerniglia[2] · Silvia Cimino[5] · Renata Tambelli[5] · Paolo Curatolo[6] · Oleg Granstrem[7] · Mauro Maccarrone[8,9] · Giovanni Laviola[1] · Claudio D'Addario[3,9]

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Abstract In view of the need for easily accessible biomarkers, we evaluated in ADHD children the epigenetic status of the 5′-untranslated region (UTR) in the *SLC6A3* gene, coding for human dopamine transporter (DAT). We analysed buccal swabs and sera from 30 children who met DSM-IV-TR criteria for ADHD, assigned to treatment according to severity. Methylation levels at six-selected CpG sites (among which, a CGGCGGCGG and a CGCG motif), alone or in combination with serum titers in autoantibodies against dopamine transporter (DAT aAbs), were analysed for correlation with CGAS scores (by clinicians) and Conners' scales (by parents), collected at recruitment and after 6 weeks. In addition, we characterized the DAT genotype, i.e., the variable number tandem repeat (VNTR) polymorphisms at the 3′-UTR of the gene. DAT methylation levels were greatly reduced in ADHD patients compared to control, healthy children. Within patients carrying at least one DAT 9 allele (DAT 9/*x*), methylation at positions CpG2 and/or CpG6 correlated with recovery, as evident from delta-CGAS scores as well as delta Conners' scales ('inattentive' and 'hyperactive' subscales). Moreover, hypermethylation at CpG1 position denoted severity, specifically for those patients carrying a DAT 10/10 genotype. Intriguingly, high

✉ Walter Adriani
walter.adriani@iss.it

Emilia Romano
romano.emilia@gmail.com

Mariangela Pucci
mariangela.pucci@gmail.com

Esterina Pascale
esterina.pascale@uniroma1.it

Luca Cerniglia
l.cerniglia@uninettunouniversity.net

Silvia Cimino
silvia.cimino@uniroma1.it

Renata Tambelli
renata.tambelli@uniroma1.it

Paolo Curatolo
curatolo@uniroma2.it

Oleg Granstrem
oleg.granstrem@nbioservice.com

Mauro Maccarrone
maccarone@unicampus.it

Giovanni Laviola
giovanni.laviola@iss.it

Claudio D'Addario
cdaddario@unite.it

1 Center for Behavioural Sciences and Mental Health, Istituto Superiore di Sanità, Building 19 Floor D Room 5, viale Regina Elena 299, 00161 Rome, Italy

2 Faculty of Psychology, Università Telematica Internazionale "Uninettuno", Rome, Italy

3 Faculty of Bioscience and Technology for Food, Agriculture and Environment, University of Teramo, Teramo, Italy

4 Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Rome, Italy

5 Dynamic and Clinical Psychology Department, "Sapienza" University of Rome, Rome, Italy

6 Pediatric Neurology Unit, Department of System Medicine, "Tor Vergata" University of Rome, Rome, Italy

7 NBioService Ltd, Saint-Petersburg, Russia

8 Department of Medicine, "Campus Bio-Medico" University of Rome, Rome, Italy

9 European Center for Brain Research, IRCCS "Santa Lucia", Rome, Italy

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serum DAT-aAbs titers appeared to corroborate indications from high CpG1 versus high CpG2/CpG6 levels, likewise denoting severity versus recovery in DAT 10/10 versus 9/*x* patients, respectively. These profiles suggest that DAT 5′UTR epigenetics plus serum aAbs can serve as suitable biomarkers, to confirm ADHD diagnosis and/or to predict the efficacy of treatment.

Keywords Auto-antibodies (aAbs) to neuro-receptors · Epigenetics in neuro-psychiatry · Conners' scales · CGAS scale · Dopamine transporter (DAT) · 10-Repeat allele · 9-Repeat allele · OCD · Tourette's

Introduction

Attention deficit/hyperactivity disorder (ADHD) has been internationally recognized as a serious neuro-developmental alteration [18, 20, 68]. The prevalent ADHD symptoms include problems in maintaining attention, excessive motor activity, and impulsivity, which often lead to poor academic performance and impaired social interactions. These symptoms develop quite early in up to 5% of children [67], and often persist into adolescence and adulthood [8]. Other conditions, frequently comorbid with ADHD, include: externalizing disorders, such as oppositional defiant disorder and conduct disorder; compulsive conditions, such as obsessive–compulsive disorder and Tourette's syndrome [69, 70]; and addictive disorders, such as pathological gambling as well as substance abuse & drug dependence problems [43, 44].

The developmental psychopathology theoretical framework [14, 21] underlined the role of family characteristics in buffering, or even aggravating, ADHD symptomatology. Moreover, among the etiopathogenetic factors for the onset of ADHD, the quality of parent–infant interactions has been proposed to affect the actual phenomenological expression, resulting in a more or less severe constellation of symptoms. As such, in the present work, we took in due account the maternal judgement about their ADHD children, both at recruitment and after 6 weeks of therapy. We are explicitly assuming that Conners' scales compiled by mothers could reflect a combined index, reflecting the quality of interaction between maternal skills and individual ADHD temperament. As such, severe ADHD at recruitment may well reflect a contribution by poor coping ability of the mother; conversely, recovery after 6 weeks may incorporate a relief perceived by the mother, in turn facilitating the recovery itself. However, this notion shall not be seen as a caveat but rather as a more complete account of the dynamic expression of ADHD in real-life situations.

Although the aetiology of ADHD is multi-factorial and still unclear, this syndrome is viewed by some as a motivational dysfunction, due to an altered cross-talk between fronto-striatal circuits [12, 3, 75]. Some evidence exists of imbalanced prefrontal and/or striatal levels of neurotransmitters, especially dopamine [61, 71]. Part of preclinical ADHD research has hence focused on the dopamine transporter (DAT), because modification of expression and/or function of its gene may well lead to specific ADHD symptoms [6, 7, 48]. Unsurprisingly, knockout DAT mice have been extensively used to reproduce behavioral symptoms of ADHD (see [33]). In the same line, knockout DAT rats have been recently generated (Leo and colleagues, manuscript submitted; Cinque and colleagues, manuscript in preparation), although their behavior has still to be fully phenotyped.

Expression of DAT may be determined by the genetic VNTR polymorphism of the 3′ untranslated region (UTR) of its gene *SLC6A3*, and it can be finely tuned by epigenetic mechanisms. The latter are mitotically heritable, but reversible, changes in transcription and/or translation of a gene without modification of genomic DNA sequence [40, 65, 66]. Accumulated evidence supports the pivotal role of epigenetics in neuronal development, differentiation and communication, as well as in synaptic plasticity [51]. In the last decade, a role for epigenetics in psychiatric diseases has been recognized [77]. Among epigenetic mechanisms, DNA methylation is the best characterized, and has been consistently implicated in the development of mental disorders [1, 26, 35]. DNA methylation has been the focus of most recent studies concerning addictive psychiatric disorders (see [41, 46]). For instance, selective changes in DNA methylation of BDNF promoter have been observed in peripheral blood mononuclear cells (PBMCs) of subjects with bipolar disorder type II [23] and major depression [22, 27] as well as in schizophrenic patients [24].

Recently, we proposed that an excessive production of DAT protein, possibly accompanied by altered turnover/degradation, could make DAT or its fragments spill into the blood and generate an auto-immune reaction [34]. Indeed, the presence of detectable auto-antibodies against DAT (DAT aAbs) was confirmed in serum samples from ADHD patients [34]. Notably, observed behavioral changes were nicely segregated between the genotypes. On the one hand, for carriers of two 10-repeat (termed 10/10) VNTR alleles, elevated DAT-aAbs titers were likely associated with most severe ADHD symptoms. On the other hand, for patients carrying at least one 9-repeat allele (termed DAT 9/*x*), the DAT aAbs were rather predicting efficacy of therapy: elevated titers at recruitment were found in subjects showing a considerable behavioral amelioration after 6 weeks of methylphenidate [34]. These data left unanswered the question on how could DAT aAbs serve two apparently opposite functions in either genotype.

Today, diagnoses of ADHD still rely on structured interviews and/or psychometric scales, and there is the need of more objective, possibly biological markers for this condition (see [32, 78]). Purpose of the present study was (1) to ascertain whether DNA methylation at DAT gene 5′-UTR could serve as a biomarker for ADHD and (2) to correlate possible changes in methylation at specific CpG sites with previous data on DAT-aAbs titers [34], as well as with clinical scores of severity (i.e., ADHD symptoms observed at recruitment) and of recovery (i.e., delta-score changes, as observed in ADHD symptoms after 6 weeks of therapy). Our aim was to provide new possible directions to the search of biomarkers, helping clinicians with ADHD diagnosis.

Materials and methods

Recruitment of patients

Participants included 30 children (5 females aged 6–12 years and 25 males aged 6–14 years), with a formal diagnosis of ADHD formulated by the Child Psychiatry Unit of Tor Vergata University (from April 2010 to March 2012). Fifteen children with typical development were used as healthy controls. All subjects had a full Scale IQ over 84, as assessed by the Wechsler Intelligence Scale—III edition. They were evaluated by child neuro-psychiatrists (G. Giana; M. Troianiello; M.C. Porfirio) who determined the diagnosis of ADHD, according to DSM-IV-TR criteria; a medical work-up excluded any auto-immune disorder. Exclusions were made in case of psychiatric comorbidity (conduct disorder, obsessive–compulsive disorder, bipolar disorder, depression, and psychosis), as assessed by a specific Schedule (K-SADS/PL).

Around two-thirds of children with milder symptoms, judged as not in need of pharmacological treatment, underwent cognitive-behavioral therapy and/or periodic follow-up; one-third of children, with a significant impairment of their adaptive functioning in different areas of life, were assigned to pharmacological treatment with methylphenidate (MPH). In the present paper, as we deal with samples collected at recruitment, these two categories based on the therapeutic intervention decided after enrollment were not taken into consideration.

This study was approved by the Ethical Committee of ISS (Prot. CE-ISS 09/270 of 15 July 2009). Informed consent procedures included searching for consent from the child (using age-adequate approaches) and illustrating to parents the standard consent form; the parents gave their signature (i.e., written informed consent) for the child to participate in this study. We confirm that all potential participants who decided not to participate in the study were not disadvantaged in any way by not participating. In addition, we declare that collected biological materials were used solely to the purpose of previous [34] and of this study. The rules set by the Code of Ethics of the World Medical Association (Declaration of Helsinki), which has been printed in the British Medical Journal (18 July 1964), were fully respected.

Clinical assessment

Each patient was evaluated by trained child neuro-psychiatrists at our unit, according to the DSM-IV and ICD-10 criteria for ADHD. Information was gathered from the clinical interviews and questionnaires with the parents, and from direct observations of the patients.

The Children's Global Assessment Scale (CGAS) was used by clinicians to measure the overall severity of social and psychiatric functioning: for children aged 4–16 years, CGAS scores range between 1 and 100, with higher scores indicating better functioning. ADHD symptoms were also determined using Conners' Parent Rating Scale; each item was scored from 0 (not true at all) to 3 (Very much true), giving information about ADHD subtypes (inattentive, hyperactive–impulsive, and combined type).

Parents completed *SNAP-IV* that elicits DSM-IV-TR criteria for ADHD on a four–point scale of frequency. The semi-structured Schedule for Affective Disorders and Schizophrenia—Present and Lifetime version (K-SADS/PL) and the Child Behavior Checklist/4–18 (CBCL) were used separately, to elicit parents' and patients' reports of signs and symptoms that might indicate possible co-morbidities.

Biochemical and genetic assessment

In these children, we were able to collect blood samplings (time T0: basal withdrawal, at recruitment); in addition, we were able to collect buccal swabs using a Catch-all sample collection Swab (Epicentre). As already reported [34], DNA isolated from buccal swabs allowed to determine the DAT genotype, specifically the DAT VNTR polymorphism, well known to be present in the 3′ untranslated region (3′-UTR), rs28363170. Notably, 15 out of 30 patients were homozygous for the 10-repeat allele (DAT 10/10), while 15 of them were carrying at least one 9-repeat allele (DAT 9/*x*, i.e., 9/9 or 9/10). In addition, the same DNAs were used to measure the methylation status of six CpG sites, selected among those present in the 5′ untranslated region (5′-UTR) of the same gene.

Analysis of DNA methylation

Genomic DNA was prepared from buccal swab samples using the BuccalAmp™ DNA Extraction Kit, following the manufacturer instructions (Epicentre, USA). Briefly, after collecting buccal cells, the swab end was placed into a

tube containing QuickExtract DNA extraction solution and rotated a minimum of five times. The tube was vortex mixed for 10 s and incubated at 65 °C for 1 min. After vortex mix for 15 s, the tube was transferred to 98 °C and incubated for 2 min. After vortex mix for 15 s, the DNA was stored until further processing at –20 °C. The yield of DNA is usually between 2 and 14 ng/µl.

The 3′-UTR repeated sequence of the DAT gene was amplified by the polymerase chain reaction (PCR) as it has been described previously [34]. DNAs from the buccal swabs were further processed for assessing amount of methylation in the DAT 5′-UTR sequence (notably, not the transcription promoter region). Amount of methylation was determined in six specific CpG residues (termed M1, M2, M3, M5, M6, and M7; see Fig. 1). Notably, M1–M3 represent a CGGCGGCGG motif, while M5/M6 represents a CGCG motif. The following primers (5′–3′) were used to amplify the gene for DAT: Fwd = AGCTACCATGCCCTA TGTGG; Rev = ATCAGCACTCCAAACCCAAC.

Bisulfite-treated DNA was amplified by PyroMark PCR Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's protocol. PCR conditions were as follows: 95 °C for 15 min, followed by 45 cycles of 94 °C for 30 s, 56 °C for 30 s, 72 °C for 30 s, and, finally, 72 °C for 10 min. PCR products were verified by agarose electrophoresis. Pyrosequencing methylation analysis was conducted using the PyroMark Q24 (Qiagen, Hilden, Germany). The level of methylation was analysed using the PyroMark Q24 Software (Qiagen, Hilden, Germany), which calculates the methylation percentage [mC/(mC + C)] for each CpG site, allowing quantitative comparisons (mC is methylated cytosine and C is unmethylated cytosine).

ELISA methods

As described previously [34], the DAT-EIA-kit (patent details, see below; holder: ISS 100%) was used for the DAT-aAbs detection. Briefly, it is a microtiter immunoplate for ELISA-based determination of natural antibodies (nAbs) to peptide fragments of human dopamine transporter (hDAT) in the serum. Synthetic peptides corresponding to a fragment of DAT serve as the antigen, and have been proven to detect DAT aAbs in the serum of mice as well [2]. This was a kit designed and custom

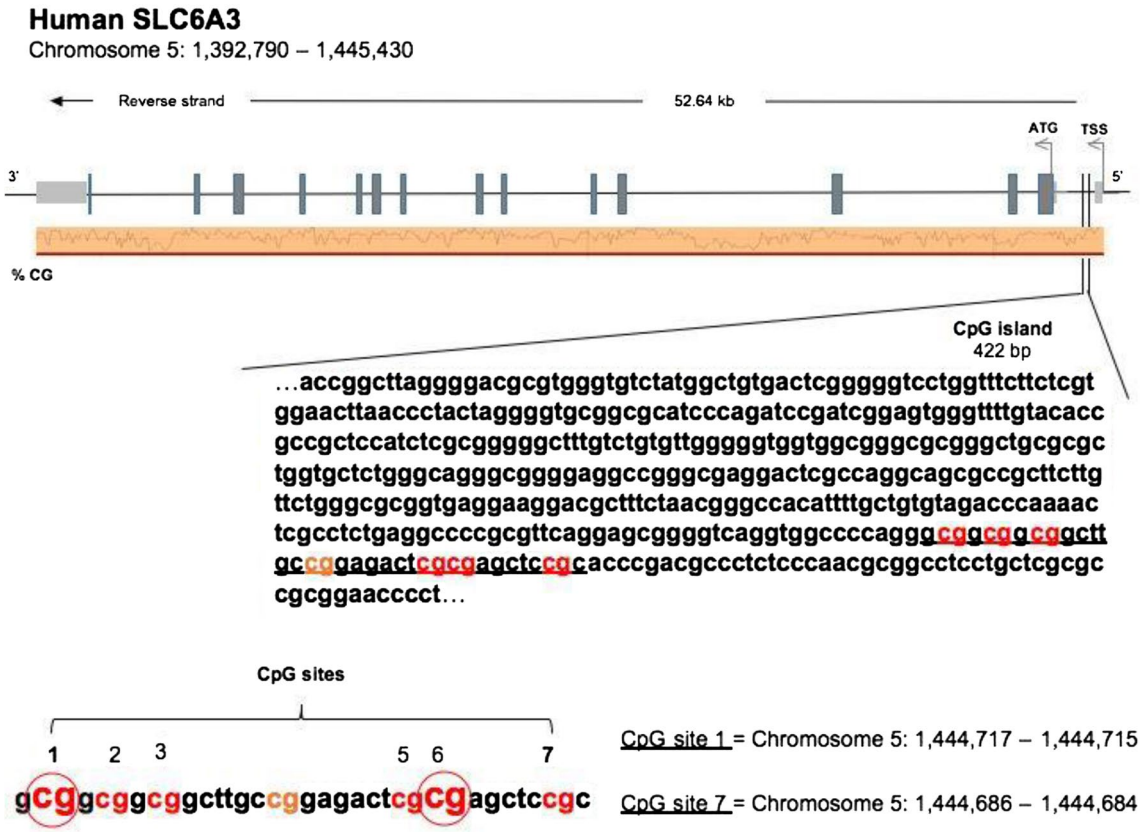

Fig. 1 Sequence of the 5′-UTR in the DAT gene, with localization of six-chosen CpG residues. Our experimental work discovered three out of six residues which are relevant and useful, for the purpose of ADHD severity (diagnosis) and for prediction or verification of recovery after response to therapy (prognosis)

synthesized by one of authors (O.G.), by selecting on the DAT protein an antigenic sequence (namely, a 19-aminoacid most immuno-reactive portion, residing on the best exposed-portion of the wider extra-cellular loop; U.S. Patent and Trademark Office: EFS ID 13464574; Application No: 61681638; Granstrem et al. 10-AUG-2012 provisional turned into Full Patent No. PN810701WO; Int.l Application No. PCT/EP2013/066845; Publication number WO/2014/023852, 10-AUGUST-2013).

Statistical analysis

The following variables, already used for publication [34], were presently re-evaluated:

1. scores obtained in CGAS and in subscales of Conners' scales, both at recruitment and after 6 weeks of therapy; delta scores (value after 6 weeks of therapy minus value at recruitment); and their possible correlation with:
2. semi-quantitative DAT-aAbs titers, obtained through the DAT-EIA-kit assay, in recruited ADHD children.

In detail, we fully investigated the potential correlation between amount of methylation in the six specific CpG residues (see Fig. 1) and the scores obtained in the clinical questionnaires. We also verified the potential correlation between said amounts of methylation and the DAT-aAbs titers found in the serum. These correlations were run for each genotype separately (i.e., DAT 10/10 on one side and DAT 9/*x* on the other hand; $n = 15$ each) by the Pearson's R value (threshold for significance with $n = 15$ is 0.4973 at $p < 0.05$ and 0.4259 at $0.10 < p < 0.05$).

Results

Gross methylation decrease in ADHD

A very first and impressive result (see Fig. 2) shows reduced (nearly halved) levels of methylation, in all six-selected positions, for all of the ADHD patients (see red line, ADHD) compared to healthy controls (see black line, CT). This is a new and unexpected piece of data, since no obvious link is known in the literature, for DAT gene, between a biomarker of epigenetic control (namely, amount of methylation in general) and ADHD.

Statistical correlation between DAT aAbs and clinical scores

We found a correlation between DAT-aAbs titer and CGAS score of −0.186 for 9/*x* patients and −0.395 for 10/10 patients, confirming a weak tendency towards a link between DAT-aAbs titer and ADHD severity, but only within 10/10 patients. These data extend previous findings [34] that, in patients showing the worst severity of ADHD profile, a very high titer could be found in 10/10 carriers only.

We also found a correlation between DAT-aAbs titer and delta-CGAS (i.e., score after 6 weeks minus score at enrolment) of +0.5216 for 9/*x* patients and of +0.2689 for 10/10 patients. These data confirm a strong and significant link between DAT-aAbs titer and likelihood of recovery, but only for 9/*x* patients. Consistently, previous findings [34] showed that, in 9/*x* patients only, a high titer at enrolment was correlated with likelihood of recovery after 6 weeks of therapy.

Therefore, two apparently contradictory pictures segregated along genotypes. It could be asked how can it be that the elevated DAT-aAbs titers are possibly serving as an

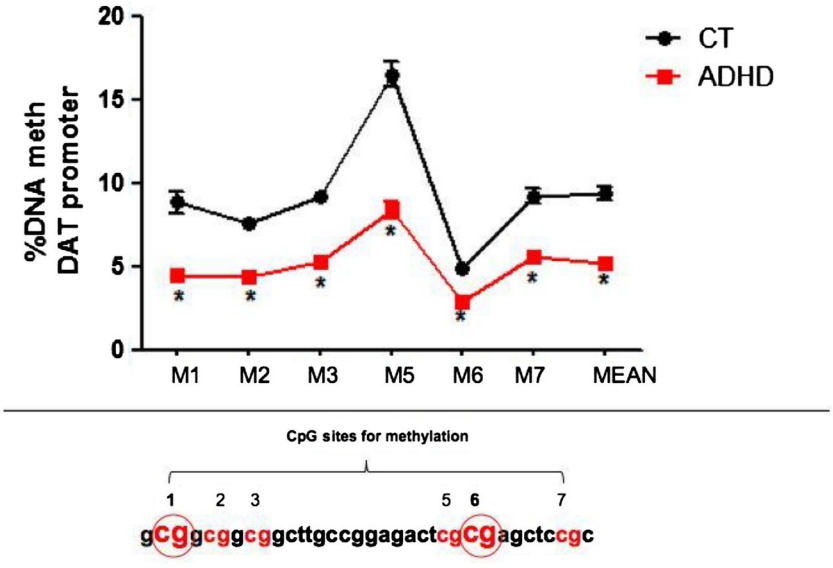

Fig. 2 Methylation level at six specific CpG sites in the 5′-UTR of DAT gene. A gross reduction of overall methylation status is evident in ADHD patients ($n = 30$) compared to healthy controls (CT; $n = 15$)

index of severity (in 10/10 patients), while seemingly are an index of recovery in 9/*x* patients. At this point, we can only speculate that these titers might mirror specific (but yet unknown) molecular features of DAT that in turn depend on the presence or not of the 9-repeat allele.

Statistical correlation between DAT aAbs and methylation

When DAT-aAbs titers were subjected to formal correlations with methylation data, it was clearly evident that the titer correlated with different CpG sites depending on genotype. Specifically, DAT-aAbs titers correlated with methylation of CpG site at position M1 for patients with DAT 10/10 genotype, and conversely with methylation of CpG sites at positions M2 and M6 for patients with a 9/*x* genotype.

Therefore, we could hypothesize that methylation at different sites could well serve a biomarker role similar to DAT aAbs. Specifically, the elevated methylation at CpG M1, alone or jointly with DAT-aAbs titers, may possibly serve as an index of severity (in 10/10 patients), while it serves as an index of recovery in 9/*x* patients when it occurs at CpG M2 or M6, alone or together with titers (see Table 1).

Table 1 Correlation values (Pearson's *R*) between DAT-aAbs titers and methylation levels in six-selected CpG sites at the 5′-UTR of DAT gene, in DAT 10/10 ($n = 15$), and DAT 9/*x* ($n = 15$) patients

	DAT 10/10	DAT 9/*x*
Mean	0.212	0.359
CpG 1	**0.469**	0.285
CpG 2	−0.082	**0.524**
CpG 3	0.022	0.289
CpG 5	0.177	0.248
CpG 6	0.394	**0.455**
CpG 7	0.065	0.117

Bold values trespass the threshold for statistical significance

Statistical correlation between clinical scores and methylation

For DAT 10/10 patients, we confirmed indeed that hypermethylation at CpG M1, as linked to the titer, would have a role in predicting severity. We found indeed that only CpG at position M1 correlated negatively (Pearson's $R = -0.480$) with CGAS value, and slightly with some of the Conners' subscales (see Table 2). Therefore, hypermethylation at CpG M1—much alike high DAT-aAbs titers—denotes a low CGAS score, indexing severity of ADHD symptoms.

For DAT 9/*x* patients, correlations between the six-selected CpG methylation sites and scores from clinical scales (at enrolment) were never significant (data not shown). Therefore, methylation does not appear to serve as a diagnostic index for this genotype.

For DAT 9/*x* patients, we confirmed indeed that hypermethylation at CpG M2 and/or M6, as linked to the titer, would have a role in predicting recovery. We found indeed that the CpG at positions M2 and M6 correlated positively with delta-CGAS value (Pearson's $R = +0.537$ and $+0.648$, respectively), as well as slightly negatively with some of the Conners' subscales (see Table 3). In particular, elevated M2 and/or M6 methylation is associated with positive and larger delta values, suggestive of the amelioration of CGAS scores after a 6-week therapy. In addition, both CpG M2 and (to a lesser extent) M6 were linked to greatly negative delta values, suggestive of amelioration in the scores for the 'inattentive' subscale as well as to less 'hyperactivity' after a 6-week therapy. Overall, hypermethylation at CpG M2 and/or M6, much alike high DAT-aAbs titers, denotes (already at enrolment) the likelihood of a quite quick recovery.

For DAT 10/10 patients, correlations between the six-selected CpG methylation sites and delta scores from clinical scales were never significant (data not shown). Therefore, methylation does not appear to serve a prognostic index for this genotype.

Table 2 Correlations between the methylation levels at six-selected CpG sites, on one side (see rows), and Conners' and CGAS scores at enrollment, on the other side (see columns), in DAT 10/10 ($n = 15$) patients

DAT 10/10	CGAS	Conners' mother			
		Defiant opponent	Inattentive	Hyperactive	ADHD index
Mean	−0.325	0.266	0.237	−0.099	0.331
CpG 1	**−0.480**	0.368	0.361	0.186	0.348
CpG 2	−0.090	0.160	0.296	−0.131	0.415
CpG 3	−0.090	0.180	0.001	−0.212	0.147
CpG 5	−0.132	0.114	0.086	−0.226	0.174
CpG 6	−0.207	0.248	*0.462*	−0.234	0.245
CpG 7	−0.356	0.294	0.129	0.105	0.363

Bold and italic values denote statistical significance, but italic value denotes non-reliable significance: Conner's scales were only considered reliable if also CGAS scale was significant. Thus, higher methylation at M1 mirrors low CGAS

Table 3 Correlations between the methylation levels at six-selected CpG sites, on one side (see rows), and "delta" (score following 6 weeks of therapeutic approach minus score at enrolment) for Conners' and CGAS, on the other side (see columns), in DAT 9/*x* ($n = 15$) patients

DAT 9/*x*	CGAS, delta	Conners' mother, delta				Subscale with best change
		Defiant opponent	Inattentive	Hyperactive	ADHD index	
Mean	0.431	−0.373	−0.560	−0.659	−0.434	−0.6136
CpG 1	0.143	−0.359	*−0.530*	*−0.490*	−0.358	*−0.5645*
CpG 2	**0.537**	**−0.466**	**−0.637**	**−0.758**	**−0.490**	**−0.7198**
CpG 3	0.374	−0.283	−0.283	−0.372	−0.318	−0.3718
CpG 5	0.379	−0.178	−0.434	*−0.593*	−0.309	*−0.5069*
CpG 6	**0.648**	−0.248	**−0.458**	**−0.488**	**−0.487**	−0.4195
CpG 7	0.198	−0.392	−0.401	−0.452	−0.210	−0.3680

Bold and italic values denote statistical significance, but italic values denote non-reliable significance: Conner's scales were only considered reliable if also CGAS scale was significant. Thus, higher methylation at M2 or M6 denotes a likelihood of recovery following 6 weeks of therapeutic approach

Discussion

The present study provides new insights into possible strategies for diagnosing ADHD and/or for predicting (and/or monitoring) treatment efficacy. In particular, we provide preliminary evidence that particular CpG sites are hypomethylated, in the 5′-UTR (transcribed but untranslated region) of the SLC6A3 gene for human DAT. Our data report for the first time an unexpected link between methylation of specific CpG sites and titers of circulating DAT aAbs, which were previously shown to be detectable and linked to ADHD [34]. However, this was not true for all patients but occurred only in association with their genotype, namely, the VNTR polymorphism at 3′-UTR. Specifically, we already demonstrated that the amounts of DAT aAbs, which are detectable in the bloodstream, do correlate with ADHD symptoms' severity in the case of a 10/10 genotype and/or with likelihood to respond positively after treatment in the case of patients carrying at least one 9-repeat allele [34]. In the present study, we were able to extend this observation, further discovering that the amounts of methylation are also correlated with DAT-aAbs titers, depending on genotype, and hence with ADHD symptoms' severity or with likelihood to respond positively to treatment.

There is extensive literature with discordant results on the involvement of 3′-UTR VNTR polymorphism of DAT in ADHD [17, 31, 79] as far as severity is concerned but also for likelihood to respond after treatment [47, 64]. These studies indicate that the 3′ VNTR might not be the functional site itself, but it could act as a tagging marker for an alternative functional site that contributes to the ADHD phenotype [79]. It is, however, quite new to find a role for the 5′-UTR in general and for specific CpG methylation sites in particular, especially as it is clearly a function of VNTR at 3′-UTR; therefore, we deal with factors residing thousands of base pairs apart. It is also quite new to find a link between 5′-UTR methylation, a factor residing on DNA well before it is transcribed, and DAT aAbs, which may well be due to a sort of auto-immune response against a self protein, and anyway implies the translation and cell-surface expression of DAT protein to act as an (auto)-antigen. Such a link is not obvious, since it is not easy to figure out what happened to transcribed mRNA and then to translation into DAT protein (where these steps enhanced or lowered?).

Our data leave also unanswered the question about what levels of promoter methylation as well as DAT protein are expressed in different brain regions of ADHD patients as well as in lymphocytes. With regard to this aspect, there are no consistent data in the literature about VNTR polymorphism and density of DAT protein in the brain and in lymphocytes of ADHD subjects [13, 39, 55, 58]. It could be proposed that DAT aAbs in the bloodstream may somehow mirror the quantity of DAT present on lymphocytes' surface, though this link should be demonstrated. Even more difficult issue is to demonstrate, in humans, that peripheral markers may somewhat mirror central levels of the same markers. Use of animal models is therefore warranted as they permit to compare central and peripheral parameters related to a given behavioral phenotype (see [82]). Overall, our data obtained on epithelial cells support a correlation between DAT-aAbs levels and amount of methylation, in few particular 5′-UTR CpG sites.

A working hypothesis

Consistently with our data, it has been already observed that DNA methylation downstream of the transcription starting site (TSS) more tightly correlates with repression of gene transcription than methylation upstream of the TSS, i.e., in the promoter region [9]. DNA methylation at 5′-UTR should imply less transcription of DNA into mRNA, yet the various CpG sites are related to high DAT-aAbs titers. If indeed titers mirror DAT protein levels in the bloodstream, these may indicate a large extent of translation, at least in the periphery. It is, therefore, unclear how *less* transcription may result in more translation! It

is tempting to speculate that either the 9- or the 10-repeat VNTR (alleles of polymorphism at 3′-UTR) makes it more likely that a few mRNAs generate a lot of DAT protein, for instance, by enhancing mRNA stability. As an alternative explanation, we shall posit that one (or more) of the CpG (when methylated) may act as a binding site for a putative molecule that stimulates transcription (instead of repressing it). Normally, in such a case, we would have more mRNAs (though with a normal stability), thus justifying the 5′-UTR (rather than the 3′-UTR) as promoting expression of DAT protein and hence of DAT aAbs. In this context, it has been shown that methylation at specific sites of a genomic sequence can either reduce [29, 30, 45] or enhance [52] transcription factors attachment to DNA regulatory regions.

One allele only was associated with likelihood of recovery, and it appeared to be the 9-repeat one [34]; in our hands, the 10-repeat allele confers resistance to treatment instead. It is know from our previous paper [34] that 9/*x* patients are showing decreased DAT-aAbs titers combined with a positive outcome of treatment. This notion implies that either the transcription or the translation should perhaps be modulated; namely, we assume that either transcription of mRNAs or their translation may be somewhat reduced or blocked after few weeks of therapeutic, environmental stimulation. We speculate, therefore, of any between either possibility: first, a CpG-favoured (5′-UTR-based) mRNA, whose transcription may be blocked, or second, an over-stable (3′-UTR-based) mRNA which translation can be turned off, by means of appropriate therapeutic interventions. In the case of methylphenidate, where the drug acts by increasing extra-cellular dopamine, a feedback can be proposed, so that the production of further DAT protein is dampened. However, by means of environmental stimulation, also the cognitive and behavioral therapies may turn out to produce quite easily the same effect.

To explain how genotypes interact with mRNAs, it would be enough to elucidate which mechanism, between the 3′-UTR and the 5′-UTR-based ones (just described above), is likely prone to environmental modulation. If environment can switch off translation, when a 3′-UTR VNTR allele confers excessive stability to its mRNAs, the 9-repeat allele is candidate for this role and the 10-repeat allele is then linked to 5′-UTR CpG-based inflexible transcription. If environment can switch off transcription, when a 5′-UTR CpG allele confers allowance to produce its mRNAs, the 9-repeat allele is candidate for this role and the 10-repeat allele is linked to 3′-UTR VNTR-based inflexible translation. By deduction, the second possibility appears much more likely, since an eventual switch off of transcription on one allele (via the 5′-UTR) would leave unaltered translation of over-stable mRNA by the other allele; conversely, the eventual switch off of translation would act on mRNAs from both alleles.

Others already suggested that DNA methylation can be influenced by cis-acting DNA sequence variation located on the same chromosome [5, 28, 57, 59, 81] and our results might thus be seen of relevance in the attempt to integrate genetic variants and DNA methylation. A possible concern might be the distance between the CpG sites under study and the VNTR. These CpG sites are located ≈1000 of bp away from the VNTR; however, it has been demonstrated that regulation in cis arrangement can actually occur at great distances [5].

It is tempting to speculate that 10-repeat VNTR allele confers a great stability to mRNAs, enhancing the likelihood that few mRNAs give still rise to a lot of protein, which production in turn may be out of control. Indeed, as this is an hypothesis based on environmental effects on transcription through the 5′-UTR, there is no way for environment to act on over-stable mRNA produced by 10-repeat 3′-UTR. We shall posit, conversely, that M2 and M6 are sites for binding of a molecule that allows transcription. Normally, when these sites are methylated, many more of normally stable mRNAs are translated; however, it is relatively easy to get them blocked, as environment is able to remove the molecule allowing mRNAs to be translated (after few weeks of therapeutic stimuli).

Specifically, as far as CpG M1 (1,444,716; chromosome 5) methylation is concerned, these levels are closely associated with DAT-aAbs titers in 10/10 patients, as both are indicative of ADHD severity in these patients. To discuss the role of M1, we underline that expansion of a CGG repeat, in the 5′-UTR of the FMR1 gene, is a genetic anomaly that, when accompanied by epigenetic modifications (mainly DNA methylation), results in the inactivation of the FMR1 gene and X-fragile symptoms (see [26, 74]). The importance of DNA 5′-UTR methylation is confirmed by the rare males who are unaffected by X-fragile, since they carry unmethylated full mutations, hence not repressing FMR1 transcription. By applying a similar reasoning to our data, we suppose DAT levels to be very high within the DAT 10/10 patients; as such, hypermethylation at M1 as well as high DAT-aAbs may be two attempts of trying to reduce DAT transcription or function, respectively. This interpretation implies that translation is elevated, as the 3′-UTR confers over-stability to 10-repeat mRNAs.

Conversely, CpG M2 or M6 (1,444,713 or 1,444,685 on chromosome 5) are closely associated with DAT-aAbs titers in DAT 9/*x* patients, as both are indicative of likelihood to respond positively after treatment in these patients. We may suppose DAT levels to be high as well, therefore promoting ADHD, but to possess room for being then diminished. Such interpretation implies that an elevated translation can still be reduced, as the stability of 3′-UTR 9-repeats mRNAs may be modulated. In addition, the CGCG motif (M6) is a putative target for members of a novel family of calmodulin-binding

transcription activators (CAMTAs), reported in various species: CAMTAs regulate transcription through binding to a specific CGCG element [73] and have intriguingly been recognized as integrators of stress responses [60]. As for the present data, the M6 methylation may modulate CAMTAs binding after few weeks of therapy indeed, and hence somewhat reduce or block the excessive mRNA transcription, at least on carriers of that DAT 9-repeat allele (in one copy at least). In support of this notion, we already reported [34] that recovery of ADHD symptoms was also yielding to a decrease of DAT aAbs, which in turn may mirror a reduced expression of DAT protein, at least on lymphocytes.

Remarks on the role of DAT 5′-UTR and/or DAT aAbs

Little attention was given so far to the 5′ untranslated region of SLC6A3 despite potential consequences on gene expression of sequence variation in this region [38, 53]. One work identified many single nucleotide polymorphisms (SNPs), covering exon 1 and intron 1 until the start of exon 2 (+2106). However, the role of the CpG methylation within these sites is less well understood.

In this line, a striking link appears to exist to psycho-immunological interactions [36, 42]. Recent literature provides a clear indication that anti-neuronal antibodies may target a wide range of CNS proteins, including neuroreceptors [25, 37, 49, 50, 80, 83]. Nearly nothing is known for DAT aAbs; yet, in the periphery (namely, in the bloodstream), dopamine can mediate communication between immune cells, and the cross-talk between the immune and nervous systems [10, 72]. Dopamine can probably be important for suppressing T-regulatory cells (Treg) which are involved in auto-immunity [19, 54]. Altered activity of Treg (due to abnormal dopamine) could lead to uncontrolled function of effector T cells and to auto-immunity [62, 63]. Thus, DAT over-expression outside the brain, as in lymphocytes of ADHD children, could lead to dysregulation of neuro-immune systems [4]. The issue of a role for neuro-immune components in ADHD deserves, however, further investigation.

The interactions between genetics, epigenetics, (auto)-immunity on one side, and social as well as familiar environment on the other hands, are at the basis of the concept of multifinality: according to the Developmental Psychopathology framework, a specific risk factor can produce a multiplicity of outcomes depending on other causes or developmental contexts [15, 16, 76]. Thus, the effect of methylation or of a polymorphism, associated with a maladaptive developmental outcome, may well vary depending on other environmental factors such as, e.g., the quality of parent–infant interactions or parental caregiving capacity [11, 56]. It is tempting to propose that methylation levels in correlation with maternal Conners' scores of the present study may provide an index not only for children behavior in itself but more in general for a deviant mother–infant dynamics along the ADHD dimensions.

The importance of such environmental factors and of the proposed biomarkers (genotype, methylation, and aAbs for DAT as well other candidate genes) suggests the need, in future studies, to evaluate them in both parents and children. Moreover, a problematic issue to be addressed would be whether biomarkers found in our clinical sample have a certain degree of stability of if they vary over time during development. Molecular epigenetics as well as auto-antibodies, in fact, may well operate over quick and subtle or slow and persistent processes. Very importantly, it will be crucial to understand whether changes in these biomarkers are indicative of discrete, adverse environmental events (e.g., early traumatic experiences), or more complex, persistent factors (e.g., parental quality of caregiving, neglect, or maltreatment).

Conclusion

Unfortunately, to date, clinical diagnosis of ADHD is solely based on structured interviews or on questionnaires. Nevertheless, reliability of these criteria for ADHD diagnostics remains a matter of debate. This study provides a hint towards a new and potentially very useful biomarker for diagnosis and/or prognosis. Our clinical experimentation demonstrates that determination of DNA methylation levels at specific CpG residues within the 5′-UTR region of the human DAT gene, alone or in combination with quantitation in blood of auto-antibodies (aAbs) against specific peptide fragments of DAT, is a robust and reliable marker of ADHD.

Our present data suggest that CpG methylation and/or DAT aAbs can be used to diagnose ADHD at least in the patients who are homozygous for the 10-repeat VNTR alleles. Instead, in carriers of at least one 9-repeat allele, our available biomarkers can only predict the efficacy of therapeutic approaches, consisting of cognitive and behavioral interventions with or without psycho-stimulant drugs. The main limitation of this study is the relative small sample size. Another limitation may be represented by tools used to classify ADHD symptoms. First, CGAS scores are an estimator of global functioning and thus provide an indirect assay of ADHD severity, and second, Conners' scores by teachers are lacking, which would add an insight into children functioning in a school context. Actually, in our previous paper [34], we report Conners' scales for both teachers and fathers, along with their correlations to aAbs titers. Presently, we decided to limit our investigations to the two scores for which we had a first measure at recruitment and a second measure 6 weeks after, namely, CGAS and mothers' Conners (as we could run formal correlations

with delta-score changes). Further studies in larger series of patient—together with their parents and perhaps also first-degree relatives—and with an extensive psychometric panel are warranted to monitor the effectiveness of the proposed biomarkers, by ascertaining whether or not they show a consistent change during the progress of symptoms' recovery upon various ADHD therapeutic treatments.

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Original Research

Gilles de la Tourette Syndrome, Depression, Depressive Illness, and Correlates in a Child and Adolescent Population

Renata Rizzo, MD, PhD,[1] Mariangela Gulisano, MD, PhD,[1] Davide Martino, MD, PhD,[2,3] and Mary May Robertson, MBChB, MD, DSc [Med], FRCP, FRCPCH, FRCPsych[4]

Abstract

Objective: Gilles de la Tourette syndrome (GTS) and depression are both common disorders. It has been suggested that depression occurs in 13%–76% GTS patients. Despite this, there are few studies into the specific relationships and correlates between the two disorders. There is only some consensus as to the precise relationship between the two disorders.
Materials and Methods: We undertook the study to investigate the relationship between depressive symptomatology and the core clinical features of GTS in a well-characterized clinical population of youth with this disorder. Our aim was to verify the association between depression and comorbid obsessive-compulsive disorder and explore further other potential associations highlighted in some, but not all, of the studies focused on this topic.
Results: Our results demonstrated that (1) the GTS patients were significantly older than the controls, (2) the GTS patients were significantly more depressed than controls, (3) depression was associated with tic severity, (4) the Diagnostic Confidence Index scores were higher in GTS patients without depression, (5) anxiety, attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and behavioral problems were significantly associated with depression, and (6) finally, patients with GTS and depression have a positive family history of depression. However, obsessionality (CY-BOCS) did not differentiate between depressed and not depressed GTS patients.
Conclusions: Depression is common in patients with GTS and occurs significantly more in GTS than in controls. Depression is significantly associated with GTS factors such as tic severity, comorbidity with ADHD, and the presence of coexistent anxiety, CDs, and behavior problems. Depression is importantly significantly associated with a positive family history of depression. Intriguingly, depression in our sample was not related to obsessionality.

Keywords: Gilles de la Tourette syndrome/Tic disorders, affective disorders, obsessive compulsive disorder

Introduction

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder with onset before 18 years of age, characterized by multiple motor and one or more vocal/phonic tics [*Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5) (American Psychiatric Association 2013)] (WHO 1992) and affecting ~1% of the general population (Robertson 2008, 2014). Only 10%–15% of individual patients with GTS have tics only (i.e., pure GTS) in both clinical sample (Freeman et al. 2000) and community (Khalifa and von Knorring 2003, 2005; Hirschtritt 2015), while the remaining patient population (85%+) manifests comorbid obsessive-compulsive behaviors/obsessive-compulsive disorder (OCB/OCD), attention-deficit/hyperactivity disorder (ADHD), autism/autistic spectrum disorders, or other psychopathologies such as conduct disorder (CD), oppositional defiant disorder, and depression (Robertson 2014). A study from Taiwan (Chou et al. 2013) confirmed that GTS patients have a significantly higher risk of developing depression than patients without GTS.

In a recent public health database study, Hirschtritt (2015) estimated the lifetime prevalence of any psychiatric comorbidity among 1374 individuals with GTS to be 85.7%, with 57.7% of patients exhibiting two or more disorders and a mean number of comorbid disorders equal to 2.1. After ADHD and OCD, the most

[1]Section of Child and Adolescent Neuropsychiatry, Department of Experimental and Clinical Medicine, University of Catania, Catania, Italy.
[2]Department of Neurology, King's College Hospital NHS Foundation Trust, London, United Kingdom.
[3]Queen Elizabeth Hospital, Woolwich, Lewisham and Greenwich NHS Trust, London, United Kingdom.
[4]Imperial College London, London, United Kingdom.
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common disorders were mood disorders, anxiety, and disruptive behaviors, each of which occurred in ~30% of GTS patients (especially if the individuals had GTS+OCD).

The presence of depression in GTS remains an area in which further research is warranted. In reviewing the frequency of depressive symptomatology in GTS patients, Robertson (2006) reported a rather broad frequency range of 13%–76%. In this review, studies differed greatly in general design (clinical vs. community-based), diagnostic criteria, patient severity spectrum, and age, with the majority of studies focusing on adult populations. In addition, studies have more consistently reported an association between comorbid depression and comorbid OCD in GTS (Termine et al. 2011; Lebowitz et al. 2012; Rizzo et al. 2014; Hirschtritt 2015), which seemed to account, in large part, also for the genetic correlation between GTS and mood disorders (Hirschtritt 2015). Other studies reported an association of comorbid depression with tic severity (Lewin et al. 2012), including one prospective study on a relatively small patient sample suggesting that depressive symptoms in children and adolescents could predict short-term future tic severity (Lin et al. 2007). Less consistently, comorbid depression was found to be associated in GTS also with ADHD comorbidity (Haddad et al. 2009), CD in childhood (Snijders et al. 2006), and minor life events (Steinberg et al. 2013). It is well demonstrated that GTS patients are exposed to different sources of psychosocial stress that are also potentially linked to depression, among which are social isolation and rejection, peer victimization (Storch et al. 2007; Zinner et al. 2012), illness-related stigma (Davis et al. 2004), and low self-esteem (Thibert et al. 1995). Moreover, symptoms of depression appear to have a widespread negative impact on quality of life (QoL) in GTS patients (Eddy et al. 2011a, 2011b). Robertson et al. (1988) demonstrated that depression in their cohort was not related to medication.

Despite its relative frequency and its impact on QoL, the characteristics of depression in GTS remain insufficiently understood. In particular, little is known about the clinical features of GTS that correlate more strongly with depression as well as the pathobiological basis for these correlations. We conducted a cross-sectional study to investigate the relationship between depressive symptomatology and the core clinical features of GTS, a chronic complex condition, in a well-characterized clinical population of youth with this disorder. Our aim was to verify the association between depression and comorbid OCD and explore further other potential associations highlighted in some, but not all, of the studies focused on this topic.

Materials and Methods

Patient selection

Ninety-eight children and adolescents/young people (CYP) with a diagnosis of having GTS [according to *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, Text Revision (DSM-IV-R) (American Psychiatric Association 2000) or DSM-5 criteria] were consecutively selected among eligible outpatients attending the tertiary referral service for GTS of the University of Catania. GTS patients were deemed eligible to the study if their IQ was within the normal range (110 ± 2 standard deviation [SD]) and if they had received comprehensive neuropsychiatric assessment (as outlined below) both at baseline and after at least 1 year of follow-up (FU). Patients with other neurological or systemic medical illnesses were excluded from the study.

Participating patients were compared with 102 neurologically healthy control (HC) subjects without any history of tics or obsessive-compulsive symptoms, recruited from local schools, who had neither chronic diseases nor psychiatric disorders. All HCs were clinically evaluated by a clinician with expertise in tic disorders. Moreover, family history (first-degree relatives) was obtained from parents with a focus on neuropsychiatric disorders.

Clinical evaluation

The study was approved by the Catania University Hospital Ethics Committee. All parents of the CYP gave written informed consent while the CYP assented. All diagnoses of GTS and associated psychiatric comorbidities were made according to both DSM-IV-TR and DSM-5 criteria by the same senior child neurologist (R.R.). All patients were assessed initially and again after 1–2 years (mean 1.3 SD 0.7) at FU. Data obtained from the clinical assessment at the FU time point were used for the analysis.

Assessment

To diagnose GTS and assess the core tic symptoms and severity, we administered the following list of physician-administered clinical rating instruments: The National Hospital Interview Schedule for Gilles de la Tourette Syndrome (NHIS) (Robertson and Eapen 1996), a semistructured interview used to diagnose GTS and its associated conditions, behaviors, and relevant family history; the GTS Diagnostic Confidence Index (DCI) (Robertson et al. 1999); Yale Global Tic Severity Rating Scale (YGTSS) (Leckman et al. 1989) for tic severity (global score); and Children's Yale–Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al. 1997). CDs were diagnosed using DSM-IV-TR or DSM-5 criteria (American Psychiatric Association 2000, 2013), while echo/paliphenomena, self-injurious behaviors (SIBs), and sleep disorders were evaluated using the NHIS. All patients and HCs were also assessed using the Wechsler Intelligence Scale for Children (WISC-III) (Wechsler 1991).

Patients with GTS and HCs completed several self-rating scales such as the Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (MOVES) scale (Gaffney et al. 1994) used to describe severity of tics and obsessions/compulsions; the Youth Quality of Life Instrument-Research Version (YQOL-R) (Topolski et al. 2003); the Multidimensional Anxiety Scale for Children (MASC) (March et al. 1997); the Conners ADHD/DSM-IV Scale (CADS) (Conners 1978); and the Child Behavior Checklist (CBCL) (Achenbach 1991). Depressive symptomatology was assessed using the patient-administered Child Depression Inventory (CDI) (Kovacs 1988): a cutoff score of 16 was used to predict a diagnosis of depressive disorder based on previous evidence of optimal accuracy (Timbremont et al. 2004).

Parents of patients and HCs completed the Conners ADHD Rating Scale/DSM-IV Scale (Conners 1978), both providing information on ADHD-related symptoms and the CBCL (Achenbach 1991) to assess internalizing and externalizing behaviors. Anxiety was assessed using the self-administered MASC (March et al. 1997).

Statistical analysis

To compare the behavioral and cognitive characteristics among the different groups, statistical analysis was performed using Mann–Whitney U test or chi-squared statistics, as appropriate. A p-value of ≤ 0.05 was considered statistically significant. Data analysis was performed using the PRIMER Statistical Package for Biomedical Sciences (Glanz 2002).

Results

Comparison between GTS patients and healthy volunteers

Ninety-eight GTS patients (81 males, age range 7–18 years; mean ± SD age 12.2 ± 0.7 years) and 103 HCs (53 males; age range 4–18 years; mean ± SD age 15.7 ± 2.5 years) entered the study (Table 1). GTS patients had a mean ± SD age at onset of 6.1 ± 2.3 years and a mean ± SD disease duration of 9.3 ± 4.1 years; their mean ± SD YGTSS score was 26.5 ± 7.9, whereas the mean ± SD CY-BOCS score was 28 ± 7.8. Diagnostic confidence scores were overall very high, with a mean ± SD DCI score of 88.3 ± 4.1.

GTS patients were significantly younger and had a greater percentage of male subjects when compared with healthy volunteers.

Forty-one of the 98 GTS patients (41.8%) had evident depressive symptomatology (i.e., corresponding to a CDI score equal or above 9): 29 of 68 (42.7%) GTS patients with an age between 5 and 12 years at the time of study and 12 of 30 (40%) GTS patients with an age between 13 and 18 years had a CDI score of 9 or above. A CDI score of 16 or above (indicating clinically relevant depression) was found in 15 of our 98 (15.3%) GTS patients, all of whom were older than 13 years at the time of study. CDI scores were significantly greater among GTS patients than among our healthy volunteers ($p = 0.003$). The GTS patients exhibited greater CBCL scores (total, internalizing, and externalizing) as well as greater Conners scores than healthy volunteers, whereas MASC scores were not significantly different between the two groups.

The difference between GTS patients and healthy volunteers was statistically significant in the sections assessing relationships, self, and environment domains of QoL. The difference in general domain did not show any statistically significant differences between the two groups (GTS and HCs).

Finally, GTS patients had lower scores compared with the HC group with regard to QoL (i.e., GTS+Dep, GTS−Dep depression, HCs+Dep HCs−Dep).

Table 1. Demographic and Clinical Characteristics of Gilles de la Tourette Patients and Healthy Control Subjects

	TS (n = 98)	*HC (n = 103)*	p-*Value*
Sex M:F	81:17	53:50	<0.001
Age (years)	12.2 (0.7)	15.7 (2.5)	<0.001
Tic onset (age years)	6.12 (2.2)	—	—
DCI%	88.3 (4.1)	—	—
YGTSS	26.58(7.9)	—	—
CY-BOCS	28 (7.8)	—	—
CDI	8.6 (5.4)	7.3 (2.6)	0.035
MASC	44.8 (13.7)	41.8 (17.2)	0.164
CBCL Total	32.7 (7.4)	22.1 (6.2)	<0.001
CBCL Int	9.9 (2.9)	8.1 (2.2)	<0.001
CBCL Ext	10.9 (2.6)	8.8 (2.7)	<0.001
CONNERS	18.8 (2.7)	14 (2.4)	<0.001
QoL TOT	295.4 (52.7)	320.0 (47.7)	0.000
QoL SELF	94.6 (18.4)	101.2 (20)	0.016
QoL REL	98.4 (21.3)	114.7 (22)	0.000
QoL ENV	90.4 (22)	83.2 (11.4)	0.003
QoL GEN	24.6 (6.4)	25.7 (5.8)	0.204

CBCL, Child Behavior Checklist; CDI, Child Depression Inventory; CY-BOCS, Children's Yale–Brown Obsessive-Compulsive Scale; DCI, Diagnostic Confidence Index; Env, environment; Gen, general; MASC, Multidimensional Anxiety Scale for Children; QoL, quality of life; Rel, relationship; Tot, total.

Comparison between GTS patients with and without clinically relevant depression

Family history and depression. GTS patients with depression GTS+Dep (GTS+Dep: CDI >16) did not differ from patients without depression (GTS−Dep: CDI <16) with respect to tic disorder/GTS, ADHD, and OCB/OCD, whereas there was a statistically significant higher incidence of depression among first-degree relatives of GTS+Dep patients compared with those of GTS patients without clinically relevant depression ($p = 0.02$) (Table 2).

Tic severity and depression. Tic severity was significantly greater ($p = 0.013$) in GTS+Dep compared with GTS−Dep patients (Table 3).

DCI scores provide a figure indicating the lifetime likelihood of suffering from GTS, although some authors suggested this as indicative of lifetime cumulative severity given the documented correlation between DCI and YGTSS scores (Robertson et al. 1999). Our GTS+Dep patients have a significantly lower DCI score than GTS−Dep patients ($p = 0.039$).

A statistically significant difference ($p < 0.0001$) in MOVES scores was observed between GTS−Dep and GTS+Dep patients, with greater scores observed in GTS+Dep patients. With respect to echo-, pali-, and coprophenomena, GTS+Dep patients exhibited significantly higher percentages of palilalia and coprophenomena ($p = 0.014$ and 0.02, respectively), whereas the difference in frequency of echophenomena, although the latter were more prevalent among GTS+Dep patients, did not reach statistical significance ($p = 0.12$).

GTS comorbidities and depression. In our sample, we did not find statistically significant differences between GTS+Dep and GTS−Dep patients ($p = 0.963$) in CY-BOCS scores (Table 3).

On the other hand, our GTS−Dep patients showed significantly higher MASC scores ($p < 0.0001$), higher CADS scores ($p = 0.004$), higher CBCL total, internalizing, and externalizing scores ($p < 0.0001$, 0.03, and <0.0001, respectively), and higher frequency of CDs ($p = 0.04$).

33.3% of the patients in the GTS+Dep group had SIBs compared with 12.5% in the GTS−Dep group, and this difference was statistically significant ($p = 0.035$).

Sleep disorders were reported more frequently by patients in the GTS+Dep group than by patients in the GTS−Dep group (26.7% vs. 12.1%); despite this, it did not reach statistical significance ($p = 0.12$).

Item 9 CDI and depression. Fourteen of the 15 GTS+Dep patients (93.3%) answered positively (item score ≥1) to item 9 of

Table 2. Frequency of Family History (First-Degree Relatives) of Gilles de la Tourette Syndrome and Main Comorbid Psychopathologies in Patients With and Without Depression

	Depressed (%)	*Not depressed (%)*	p-*Value*
GTS/tic	82.1	78.6	0.897
Depression	66.7	34.9	0.020
ADHD	27	36.1	0.233
OCD	69.8	60	0.448

ADHD, attention-deficit/hyperactivity disorder; GTS, Gilles de la Tourette syndrome; OCD, obsessive-compulsive disorder.

Table 3. Comparison of Mean Measure Scores in Patients with Gilles de la Tourette Syndrome With and Without Depression (Child Depression Inventory ≥16)

Measure	*Patients with depression (n = 15)*	*Patients without depression (n = 83)*	p-*Value*
DCI	82.5 (3.9)	86.9 (2.8)	0.039
MOVES	25.3 (11.2)	15.2 (7.8)	0.000
QIT	96.9 (12.7)	94.9 (13.1)	0.627
CBCL TOT	56.7 (24.6)	31.8 (18.3)	0.000
CBCL INT	20 (10.9)	9.2 (7.9)	0.033
CBCL EXT	16.8 (12.1)	11.6 (7.9)	0.000
MASC	57.1 (18.2)	40.9 (14.5)	0.000
CDI	19.1 (2.0)	7.4 (4.5)	0.000
YGTSS	29.6 (5.1)	24.6 (2.1)	0.013
CY-BOCS	27.6 (4.3)	26.9 (3.9)	0.906
CD (%)	61.5	32.53	0.040
Echophenomena (%)	61.6	38.5	0.118
Coprophenomena (%)	69.2	34.9	0.018
SIB (%)	33.3	12.5	0.035
Sleep disorder (%)	26.7	12.1	0.136
Palilalia (%)	46.6	18.1	0.014
OCD (%)	86.6	85.54	0.908
ADHD (%)	73.3	45.7	0.049
CDI item 9 ≥ 1 (%)	93.3	28.9	0.000
CDI item 9 = 2 (%)	40	1.20	0.000
QoL TOT	273.8 (56.3)	317.1 (53.6)	0.005
QoL SELF	87.6 (20.1)	102.4 (16.6)	0.002
QoL REL	81.5 (23.3)	99.3 (21.3)	0.004
QoL ENV	73.4 (14.7)	82.9 (18.6)	0.064
QoL GEN	21 (6)	27.5 (4.7)	0.000

Standard deviation is shown between parentheses.

ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; CD, conduct disorder; CDI, Child Depression Inventory; CY-BOCS, Children's Yale–Brown Obsessive-Compulsive Scale; DCI, Diagnostic Confidence Index; Env, environment; Gen, general; MASC, Multidimensional Anxiety Scale for Children; MOVES, Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey; OCD, obsessive-compulsive disorder; QoL, quality of life; Rel, relationship; SIB, self-injurious behavior; TIQ, total IQ; Tot, total.

the CDI (''I wish I could be dead''), whereas a positive answer to this item was provided by 24/83 (28.9%) of the GTS–Dep patients; this difference was statistically significant ($p < 0.0001$) (Table 3). Six of the 15 GTS+Dep patients (40%) and only 1 of the 83 GTS–Dep patients (1.2%) scored 2 on item 9 of the CDI ($p < 0.0001$).

GTS QoL and depression. GTS+Dep patients reported lower scores than GTS–Dep patients on all QoL domains; differences on total, self, relationship, and general domain scores were statistically significant (Table 3).

Discussion

The present study aimed at enriching the existing literature on the association between depressive symptomatology and other core behavioral features of GTS through the analysis of a well-characterized clinical sample representative of the general population of GTS patients attending a tertiary referral center for this syndrome and related disorders.

As we found, previous authors have also suggested a higher frequency of depressive symptoms in GTS patients compared with the HC group, with a large proportion of GTS patients fulfilling reference diagnostic criteria for major depressive disorder (MDD), (Comings and Comings 1987; Robertson et al. 1993, 1997, 2002; Rickards and Robertson 2003). Interestingly, and again in agreement with our findings, a large body of evidence highlighted the concurrence of depression in GTS with greater tic severity (Robertson et al. 2006; Robertson 2006; Snijders et al. 2006; Lin et. 2007; Cohen et al. 2008) and need for hospitalization (Coffey et al. 2000a), childhood onset OCB/OCD (Robertson et al. 2006; Termine et al. 2011; Lebowitz et al. 2012; Baglioni et al. 2014; Hirschtritt 2015), ADHD (Robertson et al. 2006; Cohen et al. 2008; Haddad et al. 2009), childhood CD (Snijders et al. 2006), and echo/paliphenomena (Robertson et al. 1988). Self-directed aggressive behaviors were found to be associated with depression (Robertson et al. 1988, 1989), while outwardly directed aggressive behaviors were found to be associated with depression by some (Storch et al. 2015), but not others (Robertson et al. 1988).

A clinically relevant impact of depression upon QoL has also been demonstrated previously (Elstner et al. 2001; Müller-Vahl et al. 2010; Eddy et al. 2011a, 2011b). Finally, among demographic features, female gender and older age were detected by some authors as potentially associated with depression in GTS (Robertson et al. 1988, 1989, 1993, 2002, 2006; Elstner et al. 2001; Eapen et al. 2004; Snijders et al. 2006; Robertson and Cavanna 2007).

Robertson (2006) conducted a literature review, which documented in 16 uncontrolled studies from specialist centers examining mood changes among 5409 GTS patients a variable frequency of depressive symptomatology, dysthymia, mood swings, and MDD/depressive illness between 13% and 76%, with MDD as the most prevalent diagnosis; the same systematic review showed that 13 controlled investigations, including patients of different ages with GTS ($n = 741$), overall reported significantly higher rates of depression in patients than in control subjects.

Hirschtritt (2015) recently reported a lifetime prevalence of mood disorders and comorbidity in individuals with GTS of 29.8%, which was lower than the one estimated for the obsessive-compulsive spectrum (66.1%), ADHD (54.3%), or anxiety disorders (36.1%).

Factor analytic studies have confirmed a similar frequency (36%) of depressive disorders in a large clinical population of 639 GTS patients (Cavanna et al. 2011), whereas a previous report by the same authors (Robertson and Cavanna 2007) detected that depressive symptomatology was included in one of four identified factors in association with anxiety, obsessionality, and SIBs. We could also confirm that clinically relevant symptomatology was more likely to be apparent in older patients within the first two decades, in line with previous observations proposing older age as a general risk factor for depression in GTS (Snijders et al. 2006).

Despite the association with the diagnosis of GTS, a surprising finding of our study is the significantly lower DCI score among GTS patients with clinically significant depression scores compared with those with CDI score lower than 16. This finding is particularly striking if we consider that the mean DCI score in our total GTS patient sample was 88.3%, that is, considerably higher than the scores reported in the original publications that used this index, which ranged between 60% (Robertson et al. 1999) and 66% (Rickards and Robertson 2003). This is counterintuitive as the DCI can only increase with age, and the present study was exclusively in CYP, while the others were mixed with CYP and adult cohorts, respectively. We found that GTS–Dep patients had statistically significantly lower scores on the DCI than the GTS+Dep patients

(p-value 0.039). This is in contrast to the results of Robertson et al. (1988) who reported that in GTS patients, depressive symptomatology was significantly higher in those exhibiting echophenomena (note: echo-lalia and echo-praxia each add 5 points each to the DCI).

In our clinical sample, tic severity was significantly higher in patients with clinically relevant depression compared with those without. This finding is in line with several previous studies, which found an association between tic severity (measured using the YGTSS) and depression and anxiety (Comings and Comings 1987; Coffey et. al. 2000b; Cath et al. 2001; Robertson et al. 2006; Snijders et al. 2006; Cohen et al. 2008; Gorman et al. 2010; Conelea et al. 2011).

Lewin et al. (2012), using an Internet-based survey in a nonclinical sample of 460 GTS adults, compared 185 women with 275 men with self-reported GTS and reported that women in the survey reported twice as many comorbid conditions as the men despite similar tic severity.

When comparing the impact of tic severity and depression upon the risk of psychiatric hospitalization in 156 GTS youth, Coffey et al. (2000a) found that comorbid MDD was one of the strongest predictors, whereas tic severity exerted only a marginal predictive effect. Another important recent study (Storch et al. 2015) observed that suicidal thoughts were associated with tic severity and tic-related impairment measured using the YGTSS.

Overall, the majority of the body of evidence suggests that depressive symptomatology and tic severity correlate; the limited longitudinal observations available in the literature (Lin et al. 2007) support a stronger influence of depression upon the severity of tics compared with the influence exerted by tics upon depressive symptomatology, indicating that satisfactory treatment of depression in GTS could have an important beneficial effect on tic management.

Our results confirm the higher incidence of depression in first-degree relatives of depressed GTS patients compared with nondepressed ones. This is in line with previous seminal work by Pauls et al. (1994) and later work by Snijders et al. (2006), who reported a slightly higher frequency (62%) of family history of depression among depressed patients compared with the one reported in those without depression (56%). In the recent community-based study by Hirschtritt (2015), the familial clustering of GTS and mood disorders may be explained, at least in part, by OCD comorbidity.

In our study population, we could not observe any significant association between clinically relevant depression and obsessive-compulsive behaviors or OCD. Although these findings are discrepant with the majority of studies that evaluated concurrence of depression with other psychopathological comorbidities in GTS (Robertson et al. 1993, 2002, 2006), there is also evidence suggesting two distinct psychopathological factors in GTS consisting, respectively, of depression/anxiety and OCB/OCD (Eapen et al. 2004); these two factors accounted for 72% of the overall variance.

The uniformly high frequency of OCB/OCD, which appears to be a much more common trait in GTS patients than depression, indicates that concurrent depression may *not* be a strong determinant of obsessive-compulsive traits in GTS patients. Depressed GTS patients in our population still exhibited a higher rate of OCD comorbidity than nondepressed ones, but the overall high rate of OCD comorbidity in the whole cohort did not allow this difference to reach statistical significance.

We also showed a trend for a higher rate of ADHD comorbidity among depressed GTS patients. This is similar to a previous finding from our group (Rizzo et al. 2007), which showed that pure GTS and GTS+ADHD scored higher than control subjects on both CDI and MASC. In a subsequent study, Rizzo et al. (2012) described 53 pure GTS patients, 44 with GTS+OCD and 3 with GTS+ADHD+OCD; the depression scores on the CDI were lower (4.18) in pure GTS compared with 12.54 in GTS+OCD and 11.91 in GTS+ADHD+OCD. Likewise, Eddy et al. (2011a) reported that young patients with GTS have more depressive symptoms than HCs and patients with epilepsy; at the same time, the CDI scores for the pure GTS group appear to be lower than in other patient groups.

We also confirmed a higher rate of echo/pali- and coprophenomena among depressed GTS patients. Likewise, SIBs were significantly more represented among our GTS patients, in line with a previous work by Robertson et al. (1989).

Our cohort confirms the association between reduced QoL and depressive comorbidity in GTS patients. Previous studies from different groups, including ours, have commented on how tic severity may exert a highly variable degree of impact on QoL (Eddy et al. 2011a). On the other hand, a body of evidence supports the fact that anxiety and depression have a substantial impact on QoL in GTS (e.g., Elstner et al. 2001; Müller-Vahl et al. 2010; Eddy et al. 2011b; Jalenques et al. 2012). Eddy et al. (2011b) reported clinical correlates of QoL in 50 CYP with GTS: symptoms of depression (CDI, CBCL internalizing) were correlated with all four domains of QoL, much in keeping with our findings. Rizzo et al. (2014) showed that in GTS patients, depression was related to comorbidity.

The exact determinants of depression in GTS remain elusive and require more research. Conelea et al. (2014) studied 509 adults using the Tourette Syndrome Impact Survey (TSIS) who completed self-report measures of demographics, tic severity, emotional functioning, QoL, and tic-related general and social activity restriction and found that activity restriction significantly predicted lower QoL. However, it is unclear if this tic-specific activity restriction is part of a more global pattern of avoidance that is consistent with coexisting psychiatric conditions such as anxiety, mood disorders, ADHD, and OCD. Lin et al. (2007) observed higher levels of psychological stress in 45 children and adolescents with GTS and OCD than in HCs. Increases in past depressive symptoms predicted higher levels of current psychosocial stress, which in turn modestly, but significantly, predicted increases in future tic severity. Increases in current depressive symptoms were also predictive of increases in future tic severity. Of note, the impact of stressful life events on the severity of tics and comorbidities was best predicted when stress was measured by parental report. More recently, Steinberg et al. (2013) reported data on 60 patients aged 7–17 years with GTS or TD, showing that minor negative events, mainly those that involved relationships with friends, were moderately but significantly related to the severity of motor tics. Negative minor life events were significantly correlated with depression; there was also an inverse significant correlation between positive life events and depression. Similarly, anxiety symptoms and compulsions were also significantly correlated with negative life events.

Limitations of the Study

We acknowledged a number of limitations in our study. First, our cohort was collected from a tertiary referral clinic and thus the results may not be generalized to the whole population of GTS patients encompassing also patients who do not seek and/ or needed regular medical surveillance. Second, the comprehensive and systematic clinical assessment performed on our patients

within a single center guaranteed uniformity of data collection and patient evaluation, but at the same time posed restrictions on our sample size. The small size of the group of patients with clinically relevant depression ($n = 15$), in particular, did not allow adjustment for potential confounding effects, and future expansion of this single-center clinical cohort will allow to check for spurious results in our case–control comparison. Moreover, it is a cross-sectional study.

Conclusion

Depression is common in GTS patients and is associated with tic severity, comorbid ADHD, coexisting anxiety, CDs and behavioral problems.

Clinical Significance

The diagnoses and management of GTS could be a challenge for the clinician. Early diagnosis and treatment of comorbid depression could prevent severe comorbidities and poor QoL.

Authors' Contributions

Research Project—conception and organization: Renata Rizzo and Mary M. Robertson; patient evaluation: Renata Rizzo and Mariangela Gulisano; and statistical analysis: Mariangela Gulisano and Davide Martino. Manuscript—writing of the first draft: Renata Rizzo and Mary M. Robertson; and review and critique: Renata Rizzo, Mary M. Robertson, and Davide Martino.

Disclosures

Renata Rizzo, Mariangela Gulisano, Davide Martino, and Mary May Robertson have nothing to disclose.

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Address correspondence to:
Mariangela Gulisano, MD, PhD
Section of Child and Adolescent Neuropsychiatry
Department of Experimental and Clinical Medicine
University of Catania
Catania 95123
Italy

E-mail: mariangelagulisano@gmail.com

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Con il patrocinio della:

SINPIA
Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza

Segreteria scientifica:
M. Antonella Costantino – Direttore UONPIA*
Segreteria organizzativa:
Jessica Babboni – Centro ADHD – UONPIA*

* Fondazione IRCCS Ca' Granda – Osp. Maggiore Policlinico – Milano

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MEETING

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

ASST
SPEDALI CIVILI BRESCIA

Audit clinico nell'ambito del Progetto ADHD lombardo: le azioni migliorative

Milano, 27 settembre, 2017
Ore 9.30-18.00 - AULA GUASTI

IRCCS
Istituto di Ricerche Farmacologiche Mario Negri
Via G. La Masa 19 - 20156 Milano

Sistema Socio Sanitario Regione Lombardia ASST Cremona

Sistema Socio Sanitario Regione Lombardia ASST Lecco

Regione Lombardia ASST Santi Paolo e Carlo

PRESENTAZIONE

L'Audit Clinico è l'iniziativa condotta da clinici, che si pone l'obiettivo di migliorare la qualità e gli outcomes dell'assistenza attraverso una revisione strutturata fra pari, per mezzo della quale i clinici esaminano la propria attività e i propri risultati in confronto a standard espliciti e la modificano se necessario, sottoponendo i risultati di tali modifiche a nuove verifiche.

Il nuovo Progetto *Percorsi diagnostici-terapeutici in rete per l'ADHD* si è posto un nuovo importante obiettivo per rafforzare il lavoro e l'impegno degli ultimi anni: consolidare la struttura della rete curante per l'ADHD in Lombardia, ampliarla alla partecipazione di nuovi servizi e garantire risposte terapeutiche e interventi formativi e informativi omogenei ed appropriati in tutto il territorio regionale. Nello specifico si prefigge di implementare l'adesione dei Centri al monitoraggio strutturato e programmato dei percorsi di cura e diffondere modalità di audit clinico. I Centri ADHD nell'ambito del Progetto dovranno assumere un ruolo attivo all'interno della rete UONPIA per implementare e diffondere e coordinare gli obiettivi previsti a livello regionale e garantire un percorso di audit ad essi relativi.

Con questo Audit si cercherà di effettuare il passaggio dall'individuazione e analisi degli scostamenti rispetto agli standard condivisi, che è stata oggetto degli incontri precedenti, alla individuazione e condivisione di possibili azioni correttive.

L'incontro prevede pertanto un momento di sintesi degli audit precedenti (su trattamento farmacologico, su Parent Training e Teacher Training e sul Child training) a partire dal quale definire quali possano essere le azioni migliorative da apportare.

RELATORI

Daniele Arisi
UONPIA, ASST di Cremona
Umberto Balottin
UONPIA IRRCS Mondino, Pavia
Maurizio Bonati
Dipartimento Salute Pubblica, IRCCS Istituto "Mario Negri" di Milano
Antonella Costantino
UONPIA IRCCS Fondazione Policlinico
Gianluca Daffi
UONPIA ASST Spedali Civili di Brescia
Ottaviano Martinelli
UONPIA, ASST di Lecco
Massimo Molteni
IRCCS, Istituto Scientifico Eugenio Medea di Bosisio Parini
Laura Reale
Dipartimento Salute Pubblica, IRCCS Istituto "Mario Negri" di Milano
Monica Saccani
UONPIA ASST SS Paolo e Carlo
Davide Villani
UONPIA, ASST di Lecco
Edda Zanetti
UONPIA ASST Spedali Civili di Brescia

Referenti dei Centri ADHD

Il Progetto: "Condivisione dei percorsi diagnostico-terapeutici per l'ADHD in Lombardia" è stato finanziato dalla Regione Lombardia con Decreto della Dg Welfare N. 1077 del 02 febbraio 2017. Il progetto coinvolge 18 Centri di Riferimento per l'ADHD e il Laboratorio per la Salute Materno Infantile dell'IRCCS - Istituto di Ricerche Farmacologiche Mario Negri. Coordinatore del Progetto è la UONPIA dell'ASST di Brescia.

PROGRAMMA

08:30 – 09:30 Registrazione

09:30 – 10:00
Dall'analisi degli scostamenti alle azioni migliorative
Laura Reale

10:00 – 11:30
TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO:
CHILD TRAINING: CRITERI DI INDICAZIONE, PRIORITÀ ED ESCLUSIONE
*Coordina: **Ottaviano Martinelli** – Discussant: **Antonella Costantino***
*Presentano: **Centro ADHD ASST Rhodense e Referenti Centri ADHD***

11:30 – 13:00
TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO:
CHILD TRAINING: VALUTAZIONE PRE E POST INTERVENTO
*Coordina: **Davide Villani** – Discussant: **Edda Zanetti***
*Presentano: **i Referenti dei Centri ADHD***

13:00- 14:00 Pausa pranzo

14:00- 15:00
TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO:
LE AZIONI MIGLIORATIVE A PARTIRE DAGLI SCOSTAMENTI: REPORT DELL'AUDIT "FARMACOTERAPIA"
*Coordina: **Monica Saccani** – Discussant: **Maurizio Bonati***

15:00-16:00
TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO:
LE AZIONI MIGLIORATIVE A PARTIRE DAGLI SCOSTAMENTI: REPORT DELL'AUDIT "PARENT TRAINING"
*Coordina: **Daniele Arisi** – Discussant: **Massimo Molteni***

16:00-17:00
TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO:
LE AZIONI MIGLIORATIVE A PARTIRE DAGLI SCOSTAMENTI: REPORT DELL'AUDIT "TEACHER TRAINING"
*Coordina: **Gianluca Daffi** – Discussant: **Monica Saccani***

17:00-18:00
CONCLUSIONI
Umberto Balottin, Maurizio Bonati, Antonella Costantino, Ottaviano Martinelli, Massimo Molteni, Monica Saccani, Edda Zanetti, Daniele Arisi, Gianluca Daffi

FONDAZIONE MONDINO
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UNIVERSITÀ DI PAVIA

Dipartimento di Scienze del Sistema Nervoso e del Comportamento

LA MINDFULNESS PER OPERATORI SANITARI

Responsabile Scientifico: Elena Vlacos, IRCCS C. Mondino (Pavia)

Aula 3A – ore 17.00-19.00 - IRCCS C. Mondino - Via Mondino 2 (Pavia)

PROGRAMMA

19 ottobre 2017
Presentazione del Corso
Elena Vlacos, Umberto Balottin

Epistemologia e filosofia della meditazione
Riccardo Zerbetto

26 ottobre 2017
Il punto di vista medico psichiatrico degli effetti della meditazione di Mindfulness
Claudio Pavia

2 novembre 2017
L'integrazione della meditazione di Mindfulness nella relazione terapeutica con il paziente. Il terapeuta consapevole
Elena Vlacos

9 novembre 2017
La ricerca scientifica sugli effetti neurologici della Mindfulness
Cristiano Crescentini

16 novembre 2017
Il ruolo della Mindfulness nella cura delle Dipendenze e dei Disturbi di Personalità
Paolo Antonio Giovannelli

23 novembre 2017
Meditazione di Mindfulness per dirigenti. Un esperto si racconta
Lorenzo Colucci

30 novembre 2017
Pratica di meditazione di Mindfulness, esercizi di meditazione statica e dinamica
Elena Vlacos

"Mia soltanto è la patria della mia anima" M.Chagall

E' stato richiesto il patrocinio di……..

OBIETTIVI FORMATIVI

Il percorso è proposto ai professionisti del settore sanitario, che operano direttamente ed indirettamente con il paziente. Le figure professionali che potranno partecipare saranno quelle di medici, infermieri, psicologi, e fisioterapisti.
Attraverso la comprensione di cosa è la Mindfulness, dei benefici che si possono ottenere attraverso la sua pratica, e grazie all'esperienza personale acquisita durante il percorso, l'operatore sanitario sarà in grado di percepire effetti positivi sulla propria salute psico-fisica, diminuendo notevolmente i livelli di stress, ansia e depressione, sia legati alle difficoltà del proprio lavoro sia dovuti ai problemi della vita quotidiana.
La gestione delle proprie emozioni e la consapevolezza dei propri pensieri e delle proprie azioni favorisce un'esperienza lavorativa migliore, maggiormente serena, ed una relazione con le persone con cui ci si relaziona meno tesa e più gratificante.
Il percorso è organizzato su 7 incontri, durante i quali verrà presentata una parte teorica sul tema trattato ed una parte pratica esperienziale di meditazione guidata dal docente.

ACCREDITAMENTO ECM-CPD

È in atto la pratica di accreditamento per la certificazione dell'evento finalizzata all'attribuzione di Crediti Formativi Regionali Lombardi ECM/CPD, secondo il programma Educazione Continua in Medicina per **Assistente Sanitario, Educatore Professionale, Fisioterapista, Infermiere, Infermiere Pediatrico, Logopedista, Medico Chirurgo** (Tutte Le Discipline), **Psicologo** (Psicologia, Psicoterapia), **Tecnico della Riabilitazione Psichiatrica**
Tecnico di Neurofisiopatologia, Terapista della Neuro e Psicomotricità dell'età evolutiva, Terapista Occupazionale.
Per ottenere i crediti ECM è necessario partecipare ad almeno 6 incontri su 7 e rispondere correttamente all'80% del test di apprendimento.
Sono stati preassegnati **n. 14 crediti ECM-CPD**.

ISCRIZIONI

Iscrizioni on line all'indirizzo http://corsi.mondino.it/corsi_list.php (previa registrazione in piattaforma dei propri dati).
Quote di partecipazione:
Quota standard: euro 240,00 inclusa IVA (euro 196,72 + IVA 22%)
Personale interno Mondino: euro 120,00 inclusa IVA (euro 98,36 + IVA 22%)
Studenti e specializzandi: euro 100,00 inclusa IVA (euro 81,97 + IVA 22%)
Bonifico bancario (IBAN IT10O0311111300000000061736); causale "**Iscrizione evento MOND2517**". Inviare copia del bonifico all'indirizzo ecm@mondino.it. La quota non verrà rimborsata in caso di rinuncia alla partecipazione.

COORDINAMENTO

Ufficio Formazione&Informazione, IRCCS C. Mondino, Pavia (formazione.informazione@mondino.it)

Save the Date

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

To take care of children with ADHD

A therapeutic diagnostic pathway

International Congress

Milan, Thursday 23 November, 2017
9.00-18.00 - AULA A

IRCCS
Istituto di Ricerche Farmacologiche Mario Negri
Via G. La Masa 19 - 20156 Milano

Per ricevere la newsletter iscriversi al seguente indirizzo:
http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-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 e N. 1077 del 02/02/2017) 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 Giuseppe La Masa, 19 - 20156 Milano MI - Italia - www.marionegri.it tel
+39 02 39014.511 - fax +39 02 3550924 - mother_child@marionegri.i