NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD APRILE 2014

Acta Med Iran. 2014 Jan;52:49-51.

ASSOCIATION OF ADHD SYMPTOMS SEVERITY WITH HIGHER PATERNAL AND LOWER MATERNAL AGE OF A CLINICAL SAMPLE OF CHILDREN.

Ghanizadeh A.

This study examines the association of father's and mother's age with the severity of inattention and hyperactivity/impulsivity. Participants are 470 children with attention deficit hyperactivity disorder (ADHD) diagnosed according to DSM-IV diagnostic criteria. Moreover, parents reported the severity of ADHD symptoms through completing ADHD checklist. Mother's and father's age was associated with the score of hyperactivity/impulsivity. Lower father's age and advanced maternal age are associated with higher severity of hyperactivity/impulsivity in children and adolescents with ADHD. None of mothers' and fathers' age is associated with ADHD inattentiveness severity in children. Maternal and paternal education levels are not associated with ADHD severity. Older mothers and younger fathers have ADHD children with higher hyperactivity/impulsivity severity. It should be investigated whether the father's and mother's age are risk factors for ADHD.

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Addict Health. 2010;2:89-94.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND CONDUCT DISORDER IN CHILDREN OF DRUG DEPENDENT PARENTS.

Parvaresh N, Ziaaddini H, Kheradmand A, et al.

BACKGROUND: Attention deficit hyperactivity disorder and conduct disorder are amongrelatively prevalent disorders during childhood and adolescence.Considering the negative impact of the parents' drug dependency andbipolar disorder, the present study aimed to determine the prevalence of ADHD and conduct disorder in children of drug-dependent and bipolar parents.

METHODS: In this case-control study, the case group included two groups ofpatients with drug dependency and bipolar disorder hospitalized in Shahid Beheshti hospital in Kerman who had 7 to 11-year-old children.The control group included healthy individuals without any drugdependency or other psychiatric disorders. Data were collected using Rutter scale Form A (parents' form) and a demographic questionnaire.Data were analyzed with ANOVA, Chi-square and Tamhane's post-hoc test.

FINDINGS: Rutter's abnormal scores were generally 7.11% in children of drugdependent parents, 14% in children of bipolar parents and 1.6% in childrenof healthy parents demonstrating no significant difference. The frequencyof conduct disorder in the bipolar and drug dependent group was higherthan the healthy group, but the difference was not significant. Thefrequency of ADHD was 8.9% in the drug dependency group and 1% inthe control group which shows a significant difference.

CONCLUSION: Drug dependency in parents may be a leading factor to mentaldisorders such as ADHD and conduct disorder in children.

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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. 2014.

FINDINGS FROM THE OBSERVATIONAL COMPLY STUDY IN CHILDREN AND ADOLESCENTS WITH ADHD: CORE SYMPTOMS, ADHD-RELATED DIFFICULTIES, AND PATIENTS' EMOTIONAL EXPRESSION DURING PSYCHOSTIMULANT OR NONSTIMULANT ADHD TREATMENT.

Dittmann RW, Banaschewski T, Schacht A, et al.

The aim of this study was to explore the course of attention-deficit/hyperactivity disorder (ADHD) core symptoms, ADHD-related difficulties, and emotional expression during ADHD pharmacotherapy and associations between them. This prospective, observational study examines pediatric patients with ADHD who newly initiated stimulant, atomoxetine or a combination of both treatments. Data were collected at baseline; weeks 1, 2, and 4; and months 3, 6, 9, and 12. Physicians rated ADHD core symptoms using the ADHD Rating Scale (ADHD-RS); patients, parents, and physicians rated ADHD-related difficulties using the Global Impression of Perceived Difficulties (GIPD) Scale; and patients and parents rated emotional expression using the Expression of Emotion Scale for Children (EESC). Results were analyzed using mixed model repeated measures. Associations are presented by Spearman's correlations. Overall, 504 patients, mean age 9.6 years, 72.6 % males, were analyzed. Fifty percent of patients started atomoxetine, 49.0 % stimulant and 1 % a combination of both. ADHD-RS, GIPD, and EESC scores decreased significantly in both monotherapy groups. Correlations between ADHD-RS and parent- or physician-rated GIPD scores were at-best moderate and increased over time but remained low to moderate for patient-rated GIPD [patient, r=0.43 (95 % CI 0.34, 0.51); parent, r=0.58 (0.50, 0.64); physician, r=0.55 (0.48, 0.62)]. Correlations between ADHD-RS and patient- or parent-rated EESC scores were low at baseline (r<0.2) and increased over time mostly for parent ratings [patient, r=0.35 (0.26, 0.44); parent, r=0.41 (0.32, 0.50)]. These data support the effectiveness of ADHD pharmacotherapy. The at-best moderate correlations between ADHD core symptoms and ADHD-related difficulties or emotional expression assessed by different raters indicate potentially important patient outcomes beyond core symptoms.

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Adolesc Health Med Ther. 2011;2:105-12.

SAFETY AND EFFICACY OF CLONIDINE AND CLONIDINE EXTENDED-RELEASE IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDERS.

Ming X, Mulvey M, Mohanty S, et al.

Clonidine has been used off-label in children and adolescents with attention deficit and hyperactivity disorders (ADHD) with or without comorbidities. Clonidine extended-release was recently approved by the US Food and Drug Administration for ADHD in children. This review evaluates the efficacy and safety of clonidine extended-release and clonidine in children and adolescents with ADHD. A search of the Medline database and clinical trials register from 1996-2011 yielded ten clinical trials for critical evaluation of efficacy and safety. Eight of the ten trials reviewed were double-blinded and placebo-controlled. Nine of the ten trials utilized multiple outcome measures. Both clonidine extended-release and clonidine, as monotherapy or adjunctive therapy, were reported to be efficacious in treating ADHD symptoms in children and adolescents with or without comorbid disorders in nine of the ten clinical trials. One study showed clonidine to be ineffective in improving performance of a single task, at a specific point in time, in a small number of subjects. All of the studies that evaluated safety reported clonidine and clonidine extended-release to be well tolerated. The side effects of clonidine included somnolence, fatigue, headache, bradycardia, hypotension, and clinically insignificant electrocardiographic changes. However, there are historical anecdotal reports of serious cardiac side effects, including death in cases with other risk factors. None of the studies compared clonidine extended-release with clonidine in subjects with ADHD. Therefore, it is not clear whether clonidine extended-release is advantageous over clonidine, with regard to either efficacy or safety. It is equally unclear whether clonidine or clonidine extended-release is more efficacious in treating ADHD in subjects with comorbid disorders than in those without comorbidities. All the studies reviewed had limitations in their designs and methods. Clonidine and clonidine extended-release could be efficacious and safe for the treatment of ADHD both as monotherapy and as adjunctive therapy with

stimulant medications in selected patients. There is a need for clinical trials to determine the long-term efficacy and safety of treatment with clonidine and clonidine extended-release in patients with ADHD.

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Adv Mind Body Med. 2014;28:10-15.

AN OPEN-LABEL STUDY TO ELUCIDATE THE EFFECTS OF STANDARDIZED BACOPA MONNIERI EXTRACT IN THE MANAGEMENT OF SYMPTOMS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Dave UP, Dingankar SR, Saxena VS, et al.

Context* Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous disorder of inattention, hyperactivity, and impulsivity or difficulty in controlling behavior. Psychostimulant medications remain the mainline treatment for children with ADHD; however, the average response rate to these medications is 70%, and up to 30% of children do not respond to these medications or are unable to tolerate such potential adverse effects as nausea, insomnia, and weight loss.

Objective* The study investigated the effectiveness of standardized Bacopa monnieri extract (SBME) in ameliorating the severity of the symptoms of ADHD in children.

Design* The clinical trial was conducted as an open-label study.

Setting* The study was conducted at the Center for Research in Mental Retardation (CREMERE) in Mumbai, India, from 2008 to 2010.

Participants* Thirty-one children were participants in the trial. They were 6-12 y of age, with an age of onset of ADHD before 7 y of age, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD.

Intervention* The children received SBME at a dose of 225 mg/d for a period of 6 mo. The specific SBME used in the study was BacoMind (M/s Natural Remedies, Bangalore, India).

Outcome Measures* Subsequent to the screening of participants, the research team administered the Parent Rating Scale to assess the ADHD symptom scores at baseline, and the team administered it again at the end of the 6 mo of treatment.

Results* SBME significantly reduced the subtests scores of ADHD symptoms, except for social problems. The symptom scores for restlessness were reduced in 93% of children, whereas improvement in self-control was observed in 89% of the children. The attention-deficit symptoms were reduced in 85% of children. Similarly, symptom scores for learning problems, impulsivity, and psychiatric problems were reduced for 78%, 67%, and 52% of children, respectively. It was observed that 74% of the children exhibited up to a 20% reduction, while 26% of children showed between a 21% and a 50% reduction in the total subtests scores.

Conclusion* Standardized extract of B monnieri was found to be effective in alleviating the symptoms of ADHD and was well-tolerated by the children.

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AJOB Prim Res. 2014 Jan;5:44-55.

FOCUSING ON CAUSE OR CURE?: PRIORITIES AND STAKEHOLDER PRESENCE IN CHILDHOOD PSYCHIATRY RESEARCH.

Milner LC, Cho MK.

BACKGROUND: Biomedical research is influenced by many factors, including the involvement of stakeholder groups invested in research outcomes. Stakeholder involvement in research efforts raise questions of justice as their specific interests and motivations play a role in directing research resources that ultimately produce knowledge shaping how different conditions (and affected individuals) are understood and treated by society. This issue is highly relevant to child psychiatry research where diagnostic criteria and treatment strategies are often controversial. Biological similarities and stakeholder differences between attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) provide an opportunity to explore this issue by comparing research foci and stakeholder involvement in these conditions.

METHODS: A subset of ADHD and ASD research articles published between 1970-2010 were randomly selected from the PubMed database and coded for research focus, funding source(s), and author-reported conflicts of interest (COIs). Chi-square analyses were performed to identify differences between and within ADHD and ASD research across time.
RESULTS: The proportion of ADHD research dedicated to basic, description, and treatment research was roughly similar and remained stable over time, while ASD research showed a significant increase in basic research over the past decade. Government was the primary research funder for both conditions, but for-profit funders were a notable presence in ADHD research, while joint-funding efforts between non-profit and government funders were a notable presence in ASD research. Lastly, COIs were noted more frequently in ADHD than in ASD research.
CONCLUSIONS: Our study shows significant differences in research foci and funding sources between the conditions, and identifies the specific involvement of for-profit and non-profit groups in ADHD and ASD, respectively. Our findings highlight the relationship between stakeholders outside the research community and research trajectories and suggest that examinations of these relationships must be included in broader considerations of biomedical research ethics.

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Am J Occup Ther. 2014 Mar;68:149-58.
EFFECTS OF WEIGHTED VESTS ON ATTENTION, IMPULSE CONTROL, AND ON-TASK BEHAVIOR IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Lin HY, Lee P, Chang WD, et al.
OBJECTIVE. In this study, we examined the effectiveness of using weighted vests for improving attention, impulse control, and on-task behavior in children with attention deficit hyperactivity disorder (ADHD).
METHOD. In a randomized, two-period crossover design, 110 children with ADHD were measured using the Conners' Continuous Performance Test-II (CPT-II) task.
RESULTS. In the weighted vest condition, the participants did show significant improvement in all three attentional variables of the CPT-II task, including inattention; speed of processing and responding; consistency of executive management; and three of four on-task behaviors, including off task, out of seat, and fidgets. No significant improvements in impulse control and automatic vocalizations were found.
CONCLUSION. Although wearing a weighted vest is not a cure-all strategy, our findings support the use of the weighted vest to remedy attentional and on-task behavioral problems of children with ADHD.

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Am J Psychiatry. 2014 Feb.
PSYCHIATRIC DISORDERS FROM CHILDHOOD TO ADULTHOOD IN 22Q11.2 DELETION SYNDROME: RESULTS FROM THE INTERNATIONAL CONSORTIUM ON BRAIN AND BEHAVIOR IN 22Q11.2 DELETION SYNDROME.
Schneider M, Debbane M, Bassett AS, et al.
OBJECTIVE Chromosome 22q11.2 deletion syndrome is a neurogenetic disorder associated with high rates of schizophrenia and other psychiatric conditions. The authors report what is to their knowledge the first large-scale collaborative study of rates and sex distributions of psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome. The associations among psychopathology, intellect, and functioning were examined in a subgroup of participants.
METHOD The 1,402 participants with 22q11.2 deletion syndrome, ages 6-68 years, were assessed for psychiatric disorders with validated diagnostic instruments. Data on intelligence and adaptive functioning were available for 183 participants ages 6 to 24 years.
RESULTS Attention deficit hyperactivity disorder (ADHD) was the most frequent disorder in children (37.10%) and was overrepresented in males. Anxiety disorders were more prevalent than mood disorders at all ages, but especially in children and adolescents. Anxiety and unipolar mood disorders were overrepresented in females. Psychotic disorders were present in 41% of adults over age 25. Males did not predominate in psychotic or autism spectrum disorders. Hierarchical regressions in the subgroup revealed

that daily living skills were predicted by the presence of anxiety disorders. Psychopathology was not associated with communication or socialization skills.
CONCLUSIONS To the authors' knowledge, this is the largest study of psychiatric morbidity in 22q11.2 deletion syndrome. It validates previous findings that this condition is one of the strongest risk factors for psychosis. Anxiety and developmental disorders were also prevalent. These results highlight the need to monitor and reduce the long-term burden of psychopathology in 22q11.2 deletion syndrome.

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Am J Orthopsychiatry. 2014 Mar;84:209-17.
ADOLESCENTS' ADHD SYMPTOMS AND ADJUSTMENT: THE ROLE OF ATTACHMENT AND REJECTION SENSITIVITY.
Scharf M, Oshri A, Eshkol V, et al.
The associations between attachment style, ADHD symptoms, and social adjustments were examined in a community sample of adolescents. Five hundred and eight junior high school students completed questionnaires pertaining to attachment style, ADHD symptoms (inattention and hyperactivity), and rejection sensitivity, and were rated by homeroom teachers on social adjustment. Analyses supported a 3-profile pattern of attachment styles: secure, dismissing, and preoccupied. The 3 attachment profiles showed differential risk on adolescents' social adjustment, as well as on ADHD symptoms. The secure profile showed the most adaptive outcomes on all of the examined adjustment outcomes, compared with the other 2 profiles. In contrast, the preoccupied attachment profile showed the highest levels of ADHD problems, angry and anxious expectations, while displaying a similar level of maladjustment to the dismissing profile. In addition, structural equation modeling was used and supported a model that tested an indirect link between attachment security and adolescent adjustment via an ADHD latent factor. Findings suggest that clinicians and educators should pay attention to relational patterns (attachment styles) in adolescence, as these may serve as a developmental precursor for ADHD and a range of adjustment problems in school.

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Ann Allergy Asthma Immunol. 2014 Apr.
ASSOCIATION BETWEEN CHILDHOOD ALLERGIC DISEASE, PSYCHOLOGICAL COMORBIDITY, AND INJURY REQUIRING MEDICAL ATTENTION.
Garg N, Silverberg JI.
BACKGROUND: Children with allergic disease have multiple risk factors for accidental injuries.
OBJECTIVE: To determine the prevalence of injuries requiring medical treatment in US children with allergic disease.
METHODS: The authors analyzed data from the 2007 to 2008 National Survey of Children's Health, including a nationally representative sample of 27,556 children 0 to 5 years old.
RESULTS: The prevalence (95% confidence interval [CI]) of at least 1 allergic disease was 29.4% (28.0-30.8); 6.6% (5.8-7.4) were diagnosed with asthma, 15.0% (14.0-16.0) with eczema, 11.6% (10.6-12.6) with hay fever, and 6.1% (5.4-6.9) with food allergy. Children with allergic disorders had higher odds of at least 1 comorbid psychiatric and behavioral disorder (PBD; survey logistic regression; odds ratio 2.93, 95% CI 2.13-4.03), including attention-deficit/hyperactivity disorder (4.75, 2.89-7.80), depression (6.03, 1.29-28.27), anxiety (5.54, 2.70-11.37), conduct/oppositional defiant disorder (2.97, 1.88-4.70), and learning delay (2.49, 1.70-3.66), but not autism/Asperger disorder (1.89, 0.98-3.64). The prevalence of injury in the past year requiring medical attention was 10.5% (95% CI 9.5-11.4). The association between allergic disease and injury requiring medical attention was mediated in part by a PBD (Sobel test 0.0021, 95% CI 0.0014-0.0029, P < .0001; bootstrapping approach, indirect effects, odds ratio 1.005, 95% CI 1.003-1.007; Baron-Kenny beta(yx,m) = 0.04, P < .0001, R2 = 0.002). However, children with at least 1 allergic disorder (1.74, 1.23-2.46), including eczema (1.59, 1.01-2.50), asthma (1.91, 1.10-3.31), hay fever (2.05, 1.24-3.39), and food allergies (2.00, 1.10-3.67), had higher odds of sustaining injuries even after controlling for comorbid PBDs and medical disorders.

CONCLUSION: The results suggest that the association between allergic disease and injury is multifactorial, including being secondary to PBD.

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Ann Occup Environ Med. 2013;25:18.

FOUR CASES OF ABNORMAL NEUROPSYCHOLOGICAL FINDINGS IN CHILDREN WITH HIGH BLOOD METHYLMERCURY CONCENTRATIONS.

Hong YS, Kim DS, Yu SD, et al.

BACKGROUND: Methylmercury (MeHg) easily crosses the blood-brain barrier and accumulates in the brain. Accumulated MeHg will cause neurological symptoms. We report four pediatric cases of neuropsychological findings with high blood MeHg concentrations.

CASE PRESENTATION: Four children were admitted for follow-up study because their total mercury (THg) concentration in the blood was found to be high during a national survey. Case 1 was a 9-year-old female with a 16.6 mug/l blood THg concentration in the survey. During admission, the blood THg, hair THg, and blood MeHg concentration(mercury indices) were 21.4 mug/l, 7.2 mug/g, and 20.1 mug/l, respectively. In our neuropsychological examination, cognitive impairment and attention deficit were observed. Her diet included fish intake 2-3 times per week, and she had been diagnosed with epilepsy at 3 years of age. Case 2 was a 12-year-old male with blood THg of 15.4 mug/l in the survey and the mercury indices were 12.7 mug/l, 5.7 mug/g, and 11.8 mug/l, respectively, on admission. He was also observed to have attention-deficit/hyperactivity disorder. Case 3 was a 10-year-old male child with blood THg of 17.4 mug/l in the survey, and the mercury indices on admission were 21.6 mug/l, 7.5 mug/g and 21.5 mug/l, respectively. In his case, mild attention deficit was observed. Case 4 was a 9-year-old male with blood THg of 20.6 mug/l in the survey and the mercury indices were 18.9 mug/l, 8.3 mug/g, and 14.4 mug/l, respectively, on admission. Mild attention difficulty was observed.

CONCLUSION: We suggest that fish consumption may be the main source of MeHg exposure, and that MeHg may have been the cause of the neuropsychological deficits in these cases.

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Appl Neuropsychol Child. 2014;3:94-102.

IS EXECUTIVE FUNCTION SPECIFICALLY IMPAIRED IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1? A NEUROPSYCHOLOGICAL INVESTIGATION OF COGNITIVE FLEXIBILITY.

Roy A, Barbarot S, Roulin JL, et al.

Our study investigated spontaneous versus reactive cognitive flexibility in children with neurofibromatosis type 1 (NF1) and their comorbidity with attention-deficit hyperactivity disorder (ADHD). Thirty children with NF1 aged 7 to 12 years old were compared to 60 healthy controls matched by age, gender, and parental education. On the basis of Eslinger and Grattan's definition (1993), spontaneous shifting was assessed using fluency tests, whereas reactive flexibility was measured by a child adaptation of the Modified Card-Sorting Test and the Brixton Test. IQ and basic skills were taken into account as confounding variables that might influence executive measures. NF1 children performed below the level of healthy children on both reactive flexibility tasks, even when intelligence and basic skills were partialled out, but ADHD symptomatology was not found to adversely affect the performance of patients. Our findings support the hypothesis of a specific executive impairment in NF1, uncovering a dissociation between (impaired) reactive flexibility and (preserved) spontaneous shifting, with no impact of ADHD on executive performance.

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Appl Neuropsychol Child. 2014;3:145-51.

MOTOR SKILLS DEVELOPMENT IN CHILDREN WITH INATTENTIVE VERSUS COMBINED SUBTYPES OF ADHD.

Vasserman M, Bender HA, Macallister WS.

The relations between attention-deficit hyperactivity disorder (ADHD) and motor skills are well documented, with research indicating both early and lifelong motor deficits in children with this disorder. Despite neuroanatomical and neurodevelopmental differences, which may predict differential rates of motor impairment between ADHD subtypes, evaluation of motor skill deficits in children with different presentations are limited in scope and equivocal in findings. The present investigation evaluated early motor development history and objectively measured motor skills in children with ADHD-Inattentive subtype (ADHD-I) and ADHD-Combined subtype (ADHD-C). One hundred and one children with ADHD-I (n = 53) and ADHD-C (n = 48) were included. Variables included Full-Scale IQ (FSIQ), history of motor delays, and utilization of early intervention services, as well as objectively measured motor impairment as assessed via tasks of fine-motor coordination. No between-group differences were found for FSIQ, but differences in age emerged, with the ADHD-I group being older. No differences in early motor delays were observed, though a considerably higher percentage of children with ADHD-C demonstrated early difficulties. Surprisingly, although children and adolescents with ADHD-C reported more frequent utilization of early intervention services, those with ADHD-I exhibited greater levels of current motor impairment on objective tasks. Given the over-representation of older children in the ADHD-I group, data were reanalyzed after excluding participants older than 10 years of age. Although the between-group differences were no longer significant, more than twice the number of parents of children with ADHD-C reported early motor delays, as compared with the ADHD-I group. Overall, children with ADHD-I were more likely to exhibit current objectively measured motor impairment, possibly due to later identification, less intervention, and/or different neurodevelopmental substrates underlying this disorder subtype.

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Arch Clin Neuropsychol. 2014 May;29:217-23.

EFFECTS OF AN AQUATIC EXERCISE PROGRAM ON INHIBITORY CONTROL IN CHILDREN WITH ADHD: A PRELIMINARY STUDY.

Chang YK, Hung CL, Huang CJ, et al.

The purpose of this preliminary study was to examine whether an aquatic exercise intervention that involves both aerobic and coordinative exercises influences restraint inhibition in children with ADHD. Thirty participants were assigned to either an aquatic exercise or a wait-list control group. Participants were assessed by Go/Nogo Task and motor ability prior to and after an 8-week exercise intervention (twice per week, 90 min per session) or a control intervention. Significant improvements in accuracy associated with the Nogo stimulus and the coordination of motor skills were observed over time in the exercise group compared with the control group. Only main effects of group were found for reaction time and accuracy associated with the Go stimulus. These findings suggest that an exercise program that involves both quantitative and qualitative exercise characteristics facilitates the restraint inhibition component of behavioral inhibition in children with ADHD.

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Arch Dis Child. 2014 Apr.

SAFETY OF MEDICINES USED FOR ADHD IN CHILDREN: A REVIEW OF PUBLISHED PROSPECTIVE CLINICAL TRIALS.

Clavenna A, Bonati M.

OBJECTIVE: To assess the long-term safety of drugs for attention deficit hyperactivity disorder (ADHD).

METHODS: A bibliographic search was performed in the MEDLINE, EMBASE and PsycINFO databases for prospective studies evaluating the incidence of adverse events (AEs) in children and adolescents treated for ADHD.

RESULTS: A total of six prospective studies that monitored drug safety during therapy for at least 12 weeks were retrieved. The drugs studied were atomoxetine (two studies, 802 patients), osmotic-controlled released oral methylphenidate formulation (two studies, 512 patients), extended release formulation of

mixed amphetamine salts (one study, 568 patients) and transdermal methylphenidate (one study, 326 patients). Heterogeneity was found in the duration of follow-up (ranging between 1 and 4 years) and in the way data were reported.The rate of treatment-related AEs ranged from 58% to 78%, and the rate of discontinuation due to AEs ranged from 8% to 25% of the children.Decreased appetite, insomnia, headache and abdominal pain were the most common AEs observed.Most AEs and cases of discontinuation occurred during the first few months of treatment.
CONCLUSIONS: Few studies evaluated the long-term safety of drugs for ADHD. Heterogeneity in follow-up duration and in data reporting made comparing different studies and drugs difficult. A systematic monitoring of long-term safety is needed.

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Arts Psychother. 2014;41:233-39.
PSYCHODRAMATIC GROUP PSYCHOTHERAPY AS A PARENTAL INTERVENTION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PRELIMINARY STUDY.
Vural P, Akkaya C, Kucukparlak I, et al.
It is already known that clinical attention deficit hyperactivity disorder (ADHD) is affected by some negative parenting variables. The aim of this study was to investigate the effects of psychodramatic group psychotherapy (PGP) on parenting variables. The study group included seven mothers whose children had been diagnosed with ADHD and were attending a special education and rehabilitation center. Twelve PGP sessions, one per week, were conducted with these mothers. Participants' statements were recorded at each session, and these statements were evaluated to indicate basic parental variables, namely: parental psychopathology, negative parental cognitions, negative parental attitudes, family functionality-marital conflict, and parental stress. The statistical study revealed that statements indicating parental psychopathology and negative parental attitudes showed a statistically significant negative correlation with time. Qualitative data indicate mothers stigmatization, self-stigmatization and harsh punishment toward the children. Parental psychopathology and negative parental attitudes are two parental factors that are known to have a negative impact on the clinical status of ADHD, and PGP might be effective in improving these two factors.

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Asian J Psychiatry. 2014;8:47-51.
ADHD BIFACTOR MODEL BASED ON PARENT AND TEACHER RATINGS OF MALAYSIAN CHILDREN.
Gomez R.
Background: The study used confirmatory factor analysis to ascertain support for the bifactor model of the Attention Deficit/Hyperactivity Disorder (ADHD) symptoms, based on parent and teacher ratings for a group of Malaysian children.
Methods: Malaysian parents and teachers completed ratings of ADHD and Opposition Defiant Disorder (ODD) symptoms for 934 children.
Results: For both sets of ratings, the findings indicating good fit for the bifactor model, and the factors in this model showed differential associations with ODD, thereby supporting the internal and external validity of this model.
Discussion: The theoretical and clinical implications of the findings are discussed.

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Assessment. 2014 Apr.
RELIABILITY AND VALIDITY OF THE ONLINE CONTINUOUS PERFORMANCE TEST AMONG CHILDREN.
Bart O, Raz S, Dan O.
Objective. The study assesses the reliability and validity of a new Online Continuous Performance Test (OCPT) for measuring sustained attention, response inhibition, and response time consistency among children.

Method. The study sample comprised 73 children (6-13 years), 47 children with attention deficit hyperactivity disorder and 24 in the control group. The Diagnostic Interview Schedule for Children was administered to participants' parents to confirm group allocation. Children completed the OCPT in a laboratory setting, and a week later completed the OCPT at home.
Results. Split-half correlation coefficients reflected high levels of reliability in the laboratory and at home. Significant correlations were found between the laboratory- and home-based OCPT scores. Significant differences in OCPT performance were found between children with and without attention deficit hyperactivity disorder on the OCPT in the two settings.
Conclusions. These results support the reliability and validity of the OCPT and suggest that it may serve as an effective tool for the assessment of children's attention function in naturalistic settings.

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Atten Defic Hyperact Disord. 2014 Feb.

CHILDHOOD AND PERSISTENT ADHD SYMPTOMS ASSOCIATED WITH EDUCATIONAL FAILURE AND LONG-TERM OCCUPATIONAL DISABILITY IN ADULT ADHD.

Fredriksen M, Dahl AA, Martinsen EW, et al.

Few studies have examined the impact of childhood attention deficit hyperactivity disorder (ADHD) symptoms on adult ADHD functional outcomes. To address this issue dimensionally, ADHD symptoms in childhood and adulthood and their relation to educational deficits and work disability are studied in a clinical sample of adult patients with previously untreated ADHD. About 250 adults diagnosed systematically with ADHD according to DSM-IV were prospectively recruited. Primary outcomes were high school dropout and being out of the work last year. Childhood ADHD symptoms, sex differences, comorbidities of other mental disorders, and adult ADHD symptoms were examined by historical data, clinician interviews, and questionnaires. High levels of ADHD symptom severity in childhood were related to dropping out of high school [odds ratio (OR) = 3.0], as were higher numbers of hyperactive-impulsive symptoms in childhood. Significantly, more women than men were long-term work disabled (OR = 2.0). After adjusting for age and gender, persisting high levels of ADHD inattention symptoms in adulthood (OR = 2.5), number of comorbid disorders, and particularly anxiety disorders were significantly related to long-term work disability. Childhood hyperactive-impulsive symptoms and overall severity of childhood ADHD symptoms were associated with high school dropout rates; however, persisting ADHD inattention symptoms and comorbid mental disorders in adulthood were more correlated to occupational impairment. These findings underline proposals for studies on early recognition and interventions for ADHD and psychiatric comorbidity. They further suggest that inattentive symptoms be a focus of adult ADHD treatment and that workplace interventions be considered to prevent long-term work disability.

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Aust Occup Ther J. 2014 Apr.

EIGHTEEN-MONTH FOLLOW-UP OF A PLAY-BASED INTERVENTION TO IMPROVE THE SOCIAL PLAY SKILLS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Wilkes-Gillan S, Bundy A, Cordier R, et al.

BACKGROUND/AIM: There is a well-documented need for interventions to successfully address the social difficulties of children with attention deficit hyperactivity disorder. This study aimed to further the development of a previously conducted pilot of a play-based intervention. To achieve this, children's social play outcomes pre-post and 18-month following the intervention were examined by raters unaware of the study's purpose. Additionally, parents' experiences of the intervention were explored.
METHODS: Participants included five children with attention deficit hyperactivity disorder who had participated in a play-based intervention and their typically developing playmates; parents of children with attention deficit hyperactivity disorder also participated. Children and their playmates attended an 18-month follow-up play session and parents participated in semi-structured interviews. The Test of Playfulness was used to measure children's play outcomes in the context of social play with a peer, pre-post and 18-months

following the intervention. Wilcoxon signed-ranks (Z) and Cohen's-d were used to measure effect. Thematic analysis was used to analyse reoccurring themes from parents' interviews.
RESULTS: Children's social play outcomes improved pre-post intervention (Z = 2.02; P = 0.04; d = 1.6) and were maintained 18-month post intervention (Z = 0.14; P = 0.89; d = -0.4). Core themes included: the intervention as an enjoyable experience, a common language for talking about play/social interactions, an observable change in children's skills, transference of skills and the need for support to refresh learnt lessons over time.
CONCLUSIONS: The intervention demonstrated preliminary and long-term efficacy in developing the social play skills of children with attention deficit hyperactivity disorder. Further research is required to optimise intervention feasibility and parent involvement prior to conducting a large-scale research.

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Autism. 2014 Mar.

WORKING MEMORY ARREST IN CHILDREN WITH HIGH-FUNCTIONING AUTISM COMPARED TO CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RESULTS FROM A 2-YEAR LONGITUDINAL STUDY.

Andersen PN, Skogli EW, Hovik KT, et al.

The aim of this study was to analyse the development of verbal working memory in children with high-functioning autism compared to children with attention-deficit/hyperactivity disorder and typically developing children. A total of 34 children with high-functioning autism, 72 children with attention-deficit/hyperactivity disorder and 45 typically developing children (age 9-16 years) were included at baseline and followed up approximately 25 months later. The children were given a letter/number sequencing task to assess verbal working memory. The performance of children with high-functioning autism on verbal working memory did not improve after 2 years, while improvement was observed in children with attention-deficit/hyperactivity disorder and typically developing children. The results indicate a different developmental trajectory for verbal working memory in children with high-functioning autism compared to children with attention-deficit/hyperactivity disorder and typically developing children. More research is needed to construct a developmental framework more suitable for children with autism spectrum disorder.

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Autism. 2014 Mar.

EXPLORING THE AGREEMENT BETWEEN QUESTIONNAIRE INFORMATION AND DSM-IV DIAGNOSES OF COMORBID PSYCHOPATHOLOGY IN CHILDREN WITH AUTISM SPECTRUM DISORDERS.

Gjevik E, Sandstad B, Andreassen OA, et al.

Autism spectrum disorders are often comorbid with other psychiatric symptoms and disorders. However, identifying psychiatric comorbidity in children with autism spectrum disorders is challenging. We explored how a questionnaire, the Child Behavior Check List, agreed with a Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)-based semi-structured interview, the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kiddie-SADS). The sample comprised 55 children and adolescents (age 6 to 18 years) with autism spectrum disorders, including the main autism spectrum disorder subgroups and the broad range of cognitive and language functioning. High rate of psychopathology was found both through questionnaire and interview assessment. Using predefined Child Behavior Check List cutoffs, we found good agreement between the Child Behavior Check List and the Kiddie-SADS for identifying attention deficit/hyperactivity disorder, depressive disorders, and oppositional defiant disorder. However, overall the specificity of the Child Behavior Check List was low. The Child Behavior Check List was not useful for identifying anxiety disorders. The Child Behavior Check List may capture core symptoms of autism spectrum disorders as well as comorbid psychopathology, and clinicians should be aware that the Child Behavior Check List may be unspecific when used in children and adolescents with autism spectrum disorders.

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Behav Neurol. 1992;5:149-54.

SLEEP DISTURBANCES AND EPILEPTIFORM ACTIVITY IN A SUBPOPULATION OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A LITERATURE REVIEW GENERATING AN HYPOTHESIS WITH IMPLICATIONS FOR DRUG THERAPY.

Miller LG, Kraft IA.

The use of electroencephalography and sleep studies in attention deficit hyperactivity disorder (ADHD), and the associated behavioral disorders is reviewed. Based on the available literature, we propose a hypothesis indicating four subtypes of ADHD. The usefulness of EEGs and sleep laboratory indices in detecting a subgroup of patients with submaximal responses to methylphenidate is also discussed.

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BJOG. 2014 Mar.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER IN CHILDREN BORN TO MOTHERS WITH THYROID DYSFUNCTION: A DANISH NATIONWIDE COHORT STUDY.

Andersen S, Laurberg P, Wu C, et al.

OBJECTIVE: To examine the association between maternal hyper- and hypothyroidism and the risk of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in the child.
DESIGN: A population-based cohort study.
SETTING: Singletons liveborn in Denmark between 1991 and 2004.
POPULATION: A total of 857 014 singletons alive and living in Denmark at the age of 3 years.
METHODS: Information on the diagnosis and/or treatment of maternal thyroid disease and the neurodevelopmental disorders ADHD and ASD in the child was obtained from Danish nationwide registers. The Cox proportional hazards model was used to estimate the hazard ratio (HR) with 95% confidence interval (95% CI) for risk of ADHD and ASD in children born to mothers with thyroid dysfunction, adjusting for potential confounding factors.
MAIN OUTCOME MEASURES: ADHD and ASD in the child.
RESULTS: Altogether, 30 295 singletons (3.5%) were born to mothers with thyroid dysfunction. Maternal hyperthyroidism diagnosed and treated for the first time after the birth of the child increased the risk of ADHD in the child (adjusted HR 1.23; 95% CI 1.05-1.44), whereas hypothyroidism increased the risk of ASD (adjusted HR 1.34; 95% CI 1.14-1.59). No significant association was seen for maternal diagnosis and treatment prior to the birth of the child.
CONCLUSIONS: Children born to mothers diagnosed and treated for the first time for thyroid dysfunction after their birth may have been exposed to abnormal levels of maternal thyroid hormone already present during the pregnancy, and this untreated condition could increase the risk of specific neurodevelopmental disorders in the child

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BMC Psychiatry. 2014;14.

THE ASSOCIATIONS BETWEEN ADHD AND ASTHMA IN KOREAN CHILDREN.

Kwon HJ, Lee MY, Ha M, et al.

Background:The aim of this study was to investigate the associations between attention deficit hyperactivity disorder (ADHD), the most common neuropsychiatric disorder in school children, and childhood allergic disease by evaluating their respective prevalence.
Methods:Subjects were comprised of first and second grade students in twenty two elementary schools in a city in the Republic of Korea. The mode of measurement for ADHD was based on DSM-IV from clinical interviews conducted by child psychiatrists. Along with the diagnostic interviews, we also used the epidemiological questionnaires, Computerized Attention Deficit-Hyperactivity Disorder Diagnostic System, the abbreviated Conner's Parent Rating Scale (CPRS), and DuPaul's ADHD Rating Scales. Allergic conditions, such as asthma, have been separately evaluated based on the questionnaire items whose validity and reliability were proved by the International Study of Asthma and Allergies in Children (ISAAC). All questionnaires were completed by the subjects' parents.

Results:The lifetime prevalence rate of asthma in ADHD patients was 36.6%, compared to a prevalence of 24.3% in control subjects. The lifetime prevalence rate of allergic rhinitis in ADHD patients was 59.0%, compared to a prevalence of 47.0% in control subjects. Statistically significant difference has been found between the two groups. In the logistic regression model of the ADHD and the control group, the relative risk of asthma was 1.60 times higher (confidence interval 1.301-1.964), the relative risk of allergic rhinitis was 1.38 times higher (confidence interval 1.124-1.681), which showed statistical significance.
Conclusions:The findings of this study suggest significant association between ADHD and childhood asthma and allergic rhinitis. Therefore, appropriate evaluation and treatment are needed for asthmatic children with attention-deficit symptoms, or allergic rhinitis with ADHD. Besides, further research is needed to determine the etiological approach towards ADHD, asthma, and allergic rhinitis.

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Br J Educ Psychol. 2014 Mar;84:108-24.

READING AND LISTENING COMPREHENSION AND THEIR RELATION TO INATTENTION AND HYPERACTIVITY.

Cain K, Bignell S.

BACKGROUND: Children with diagnoses of attention-deficit/hyperactivity disorder (ADHD) frequently have reading problems. To date, it is not clear whether poor reading is associated with both inattention and hyperactivity and also whether poor reading comprehension is the result of poor word reading skills or more general language comprehension weaknesses.
AIMS: We report two studies to examine how reading and listening comprehension skills are related to inattention and hyperactivity/impulsivity.
SAMPLES: Separate groups of 7- to 11-year-olds participated in each study.
METHODS: In both studies, we used teacher ratings of inattention and hyperactivity/impulsivity to identify three groups at risk of ADHD: poor attention, high hyperactivity, poor attention and high hyperactivity, and also same-age controls. In Study 1, we explored how inattention and hyperactivity predicted reading after controlling for non-verbal IQ and vocabulary. In Study 2, we compared listening and reading comprehension in these groups.
RESULTS: Poor attention was related to poor reading comprehension, although the relation was partially mediated by word reading skill (Study 1). Groups with high hyperactivity had weak listening comprehension relative to reading comprehension (Study 2).
CONCLUSIONS: These results indicate that the reading comprehension problems of children with attention difficulties are related to poor word reading and that listening comprehension is particularly vulnerable in children at risk of ADHD.

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Brain. 2014;137:1156-66.

A BIMODAL NEUROPHYSIOLOGICAL STUDY OF MOTOR CONTROL IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A STEP TOWARDS CORE MECHANISMS?

Heinrich H, Hoegl T, Moll GH, et al.

Knowledge about the core neural mechanisms of attention-deficit hyperactivity disorder, a pathophysiologically heterogeneous psychiatric disorder starting in childhood, is still limited. Progress may be achieved by combining different methods and levels of investigation. In the present study, we investigated neural mechanisms of motor control in 19 children with attention-deficit hyperactivity disorder (aged 9-14 years) and 21 age-matched typically developing children by relating neural markers of attention and response control (using event-related potentials) and measures of motor excitability/inhibition (evoked by transcranial magnetic stimulation). Thus, an interplay of processes at a subsecond scale could be studied. Using a monetary incentives-based cued Go/No-Go task, parameters that are well-known to be reduced in attention-deficit hyperactivity disorder were analysed: event-related potential components P3 (following cue stimuli; in Go and No-Go trials) and contingent negative variation as well as the transcranial magnetic stimulation-based short-interval intracortical inhibition measured at different latencies in Go and No-Go trials. For patient and control groups, different associations were obtained between performance,

event-related potential and transcranial magnetic stimulation measures. In children with attention-deficit hyperactivity disorder, the P3 amplitude in Go trials was not correlated with reaction time measures but with short-interval intracortical inhibition at rest (r = 0.56, P = 0.01). In No-Go trials, P3 and short-interval intracortical inhibition after inhibiting the response (at 500 ms post-stimulus) were correlated in these children only (r = 0.62; P = 0.008). A classification rate of 90% was achieved when using short-interval intracortical inhibition (measured shortly before the occurrence of a Go or No-Go stimulus) and the amplitude of the P3 in cue trials as input features in a linear discriminant analysis. Findings indicate deviant neural implementation of motor control in children with attention-deficit hyperactivity disorder reflecting compensatory cognitive mechanisms as a result of a basal motor cortical inhibitory deficit (reduced activation of inhibitory intracortical interneurons). Both deviant inhibitory and attentional processes, which are not related to each other, seem to be characteristic for attention-deficit hyperactivity disorder at the neural level in motor control tasks. The underlying neural mechanisms, which are probably not restricted to the motor cortex and the posterior attention network, may play a key role in the pathophysiology of this child psychiatric disorder. The high classification rate can further be interpreted as a step towards the development of neural markers. In summary, the bimodal neurophysiological concept may contribute to developing an integrative framework for attention-deficit hyperactivity disorder.

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Brain Cogn. 2014;87:30-38.

POSTERIOR P1 AND EARLY FRONTAL NEGATIVITY REFLECT DEVELOPMENTAL CHANGES IN ATTENTIONAL DISTRACTION DURING ADOLESCENCE.

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

Previous studies in adults have revealed that attentional distraction modulates the late positive potential (LPP) during emotion regulation. To determine whether early visual components reflect developmental changes in attentional distraction during adolescence, we collected event-related potentials from 20 young adolescents, 18 older adolescents, and 18 young adults as they performed a distraction task (counting) while viewing affective images. Consistent with previous findings obtained in distraction studies, the distraction task (counting) reduced emotional modulation of the LPP. At an early stage of processing, counting reduced emotional modulation of P1 and increased the negativity bias of early frontal negativity (eFN) for negatively valenced pictures compared to simple viewing with no distraction. sLORETA analyses further revealed eFN indexing of rostral prefrontal cortical activation, a cortical area that has been shown in recent fMRI studies to be activated by distraction. Moreover, P1 amplitudes in young and older adolescents did not differ but were both larger than the P1s in young adults. In addition, eFN amplitudes significantly decreased with age. The dissociable distraction patterns between the posterior P1 and eFN provide evidence not only for the timing hypothesis of emotion regulation but also for different developmental trajectories of visual processing areas and the prefrontal cortex during affective processing in adolescence.

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Brain Dev. 2014 Apr.

IMPROVED PREFRONTAL ACTIVITY IN AD/HD CHILDREN TREATED WITH ATOMOXETINE: A NIRS STUDY.

Araki A, Ikegami M, Okayama A, et al.

Background/Aims: Atomoxetine (ATX), a selective norepinephrine reuptake inhibitor, is the first approved non-stimulant drug for treatment of attention deficit/hyperactivity disorder (AD/HD). The present study examined the effects of long-term treatment with ATX on prefrontal hemodynamic activity in AD/HD children during a continuous performance task (CPT) using near-infrared spectroscopy (NIRS).

Methods: Prefrontal hemodynamic activity was measured in 12 children with AD/HD during experimental sessions conducted before and 6months or more after starting ATX treatment. The average maintenance dose of ATX was 1.6mg/kg/day. Fourteen age-matched typically developing children participated as a control group.

Results: In the control group, the CPT induced a significant increase in oxygenated hemoglobin (oxy-Hb) concentration in the bilateral dorsolateral prefrontal cortex (DLPFC). In the AD/HD group in the pre-ATX

condition, the CPT did not induce a significant increase in oxy-Hb concentration in any of the NIRS channels, but induced a significant decrease in oxy-Hb concentration in the left ventrolateral prefrontal cortex (VLPFC). In the AD/HD group in the post-ATX condition, significant activation was observed in the right DLPFC and the decrease in oxy-Hb concentration in the left VLPFC disappeared.
Conclusions: These results suggest that long-term treatment with ATX improved prefrontal hemodynamic activity in AD/HD children, and NIRS may be useful for assessment of the prefrontal hemodynamic response to ATX treatment.

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Br J Psychiatry. 2014;204:306-15.
VITAMIN-MINERAL TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN ADULTS: DOUBLE-BLIND RANDOMISED PLACEBO-CONTROLLED TRIAL.
Rucklidge JJ, Frampton CM, Gorman B, et al.
Background: The role of nutrition in the treatment of attention-deficit hyperactivity disorder (ADHD) is gaining international attention; however, treatments have generally focused only on diet restriction or supplementing with one nutrient at a time.
Aims: To investigate the efficacy and safety of a broad-based micronutrient formula consisting mainly of vitamins and minerals, without omega fatty acids, in the treatment of ADHD in adults.
Method: This double-blind randomised controlled trial assigned 80 adults with ADHD in a 1:1 ratio to either micronutrients (n=42) or placebo (n=38) for 8 weeks (trial registered with the Australian New Zealand Clinical Trials Registry: ACTRN12609000308291).
Results: Intent-to-treat analyses showed significant between-group differences favouring active treatment on self- and observer- but not clinician-ADHD rating scales. However, clinicians rated those receiving micronutrients as more improved than those on placebo both globally and on ADHD symptoms. Post hoc analyses showed that for those with moderate/severe depression at baseline, there was a greater change in mood favouring active treatment over placebo. There were no group differences in adverse events.
Conclusions: This study provides preliminary evidence of efficacy for micronutrients in the treatment of ADHD symptoms in adults, with a reassuring safety profile.

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Can J Occup Ther. 2013 Dec;80:274-83.
DRIVING INDICATORS IN TEENS WITH ATTENTION DEFICIT HYPERACTIVITY AND/OR AUTISM SPECTRUM DISORDER.
Classen S, Monahan M, Brown KE, et al.
BACKGROUND: Motor vehicle crashes are leading causes of death among teens. Those teens with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), or a dual diagnosis of ADHD/ASD have defining characteristics placing them at a greater risk for crashes.
PURPOSE: This study examined the between-group demographic, clinical, and simulated driving differences in teens, representing three diagnostic groups, compared to healthy controls (HCs).
METHOD: In this prospective observational study, we used a convenience sample of teens recruited from a variety of community settings.
FINDINGS: Compared to the 22 HCs (mean age = 14.32, SD = +/-.72), teen drivers representing the diagnostic groups (ADHD/ASD, n = 6, mean age = 15.00, SD = +/-.63; ADHD, n = 9, mean age = 15.00, SD = +/- 1.00; ASD, n = 7, mean age = 15.14, SD = +/-. 1.22) performed poorer on visual function, visual-motor integration, cognition, and motor performance and made more errors on the driving simulator.
IMPLICATIONS: Teens from diagnostic groups have more deficits driving on a driving simulator and may require a comprehensive driving evaluation.

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Child Psychiatry Hum Dev. 2014 Apr;45:243-53.

CHILD ROUTINES AND PARENTAL ADJUSTMENT AS CORRELATES OF INTERNALIZING AND EXTERNALIZING SYMPTOMS IN CHILDREN DIAGNOSED WITH ADHD.

Harris AN, Stoppelbein L, Greening L, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most common disorders of childhood, and the presence of comorbid externalizing and internalizing symptoms often result in severe negative long-term consequences. Multiple etiological factors contribute to the development of co-occurring symptoms. Family stability and consistency appear to be particularly important in effectively managing behavioral concerns. One important factor in producing consistency and stability is the use of routines. The current study examined how routines may be related to internalizing/externalizing symptoms in a clinical sample (N = 371) of children with ADHD (M age = 9.13, SD = 1.96; 77 % male). After controlling for child age, gender, and parental adjustment, routines predicted both internalizing and externalizing symptoms. Specific subtypes of routines including Household, Discipline, and Homework Routines were found to significantly predict symptomatology. A positive relation was found between parental and child adjustment problems; however, support for routines moderating the relation between parent and child adjustment was not supported.

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Child Psychiatry Hum Dev. 2014 Mar.

ADAPTIVE MULTIMODAL TREATMENT FOR CHILDREN WITH ATTENTION-DEFICIT-/HYPERACTIVITY DISORDER: AN 18 MONTH FOLLOW-UP.

Dopfner M, Ise E, Wolff Metternich-Kaizman T, et al.

The Cologne Adaptive Multimodal Treatment (CAMT) study demonstrated that adaptive and individually tailored multimodal treatment for attention-deficit/hyperactivity disorder (ADHD) [consisting of behavior therapy (BT) and/or stimulant medication] is highly effective. This study reports findings of the 18 month follow-up assessment. Parents and teachers completed broad range behavior scales (Child Behavior Checklist/Teacher Report Form) and standardized ADHD and oppositional defiant disorder/conduct disorder symptom rating scales. Children that used medication to treat ADHD at follow-up (N = 32) and those that did not (N = 34) were analyzed separately. Parents did not report significant changes in child behavior from posttest to follow-up. Teacher ratings revealed some aggravation of ADHD symptoms in children that received medication, but this was not significant after Bonferroni correction. The initial advantage of combined treatment over BT was no longer evident. It can be concluded that treatment for ADHD that is tailored to the assessed needs of children results in large treatment effects that are maintained for at least 18 months.

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Child Psychiatry Hum Dev. 2014 Feb.

VISUOSPATIAL WORKING MEMORY IN 7- TO 12-YEAR-OLD CHILDREN WITH DISRUPTIVE BEHAVIOR DISORDERS.

Saarinen S, Fontell T, Vuontela V, et al.

Very little evidence exists on working memory (WM) deficits in children with disruptive behavior disorders such as Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD). We evaluated the function of visuospatial WM in patients (n=26) with ODD/CD compared with age- and gender-matched controls (n=26) while controlling for the comorbid diagnosis of Attention-Deficit/Hyperactivity-Disorder (ADHD) in patients. The patients were diagnosed by Kiddie-SADS-PL interview, psychiatric symptoms were measured using Child Behavior Checklist and Teacher Report Form. WM was measured by computer-based visuospatial n-back tasks with three difficulty levels. Incorrect responses (reflecting WM performance) in all WM tasks were significantly higher in patients with ODD/CD than in controls. Both patient subgroups, ODD/CD + ADHD and ODD/CD alone, had WM deficits compared with controls. These results suggest that children with ODD/CD have visuospatial WM deficits that are not accounted for by comorbid ADHD.

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Clin EEG Neurosci. 2014 Apr.

SMALL-WORLD BRAIN FUNCTIONAL NETWORKS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER REVEALED BY EEG SYNCHRONY.

Liu T, Chen Y, Lin P, et al.

We investigated the topologic properties of human brain attention-related functional networks associated with Multi-Source Interference Task (MSIT) performance using electroencephalography (EEG). Data were obtained from 13 children diagnosed with attention-deficit/hyperactivity disorder (ADHD) and 13 normal control children. Functional connectivity between all pairwise combinations of EEG channels was established by calculating synchronization likelihood (SL). The cluster coefficients and path lengths were computed as a function of degree K. The results showed that brain attention functional networks of normal control subjects had efficient small-world topologic properties, whereas these topologic properties were altered in ADHD. In particular, increased local characteristics combined with decreased global characteristics in ADHD led to a disorder-related shift of the network topologic structure toward ordered networks. These findings are consistent with a hypothesis of dysfunctional segregation and integration of the brain in ADHD, and enhance our understanding of the underlying pathophysiologic mechanism of this illness.

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Clin Med Insights Pediatr. 2014;8:11-16.

PSYCHIATRIC MORBIDITY AMONG STREET CHILDREN IN DUHOK.

Taib NI, Ahmad A.

BACKGROUND: Due, in part, to family constraints in dealing with the economical burden of raising a family, a wave of street children is sweeping the developing world. Such children are prone to both somatic and mental illnesses. This is the first ever study that has been conducted to explore the psychopathology among street children in the Duhok Governorate.

METHODS: The study was conducted between March 2004 and May 2005 in Duhok City among street children who attended the Zewa Center-the only center for street children in the region at the time of the study. Among a total of 107 eligible children, 100 agreed to participate (93% response rate). A modified family map (genogram) was used to obtain demographic data from the children and their caregivers through semi-structured interviews. In addition, the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) structured interviews were conducted with the children.

RESULTS: The study found that 98% of children worked on the street because of the economic need and pressure on their families. There was high rate of parental illiteracy (90% of fathers and 95% of mothers), and 61% of respondents were shown to have at least one psychiatric disorder. A high percentage (57%) of these children suffered from anxiety disorders including posttraumatic stress disorders (29%). Ten percent had depression, and 5% had attention deficit hyperactivity disorder.

CONCLUSION: Street children in Duhok seem to be working children due to their families' needs.

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Clin EEG Neurosci. 2013;44:E87.

IS EXCESSIVE EEG BETA ACTIVITY ASSOCIATED WITH DELINQUENT BEHAVIOR IN ADULT SUBJECTS WITH ADHD?

Meier NM, Perrig W, Koenig T.

Objective. The attention deficit/hyperactivity disorder (ADHD) shows an increased prevalence in delinquents. In recent studies, a subgroup of subjects with ADHD and delinquents displayed excessive EEG beta activity, which has been associated with antisocial behavior in ADHD children. We investigated whether delinquent behavior in adult ADHD subjects is related to excessive beta activity.

Methods. We compared the resting state EEGs of delinquent and nondelinquent subjects with ADHD and controls regarding power spectra and topography of the EEG.

Results. Offenders with ADHD showed more beta power at frontal, central and parietal brain regions than nondelinquents with ADHD.

Conclusion. Excessive beta power may represent a riskfactor for delinquent behavior in adults with ADHD. The awareness of such a risk-factor may be helpful in the assessment of the risk for delinquent behavior in a psychiatric context and provide a neurobiological background for therapeutic interventions.

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Clin EEG Neurosci. 2013;44:E46.

CONCURRENT EEG-FMRI STUDY OF THE NEURAL SUBSTRATES OF SPATIAL ENCODING IN ADHD.

Lenartowicz A, Lau E, Rodriguez C, et al.

Attention deficit hyperactivity disorder (ADHD) is often associated with atypical performance on tasks requiring spatial working memory (WM). In the present study, we investigated the neural substrates of this deficit, with emphasis on the integrity of the encoding stage, which we had previously found to be associated with attenuated desynchronization of oscillations in the alpha (8-12 Hz) frequency band in ADHD. We hypothesized that this effect was indicative of atypical neural interactions of occipital, parietal, and prefrontal cortices during the encoding stage. To address this question, we tested 20 male adolescents (12-15 years), of whom half were diagnosed with ADHD, on a Sternberg spatial WM task. This task requires participants to encode the locations of dots presented on a screen, the accuracy of which is assessed after a 7- to 9-second delay with the presentation of a probe stimulus either in one of the previous shown location or in a novel location. During the task we concurrently recorded EEG and fMRI signals. We used the EEG indices to assess attention engagement during encoding as indexed by desynchronization of oscillations in the alpha (8-12 Hz) band. We used the fMRI measures to assess the interactions of then network involved in the process of spatial encoding. Our results indicate that alpha desynchronization during spatial encoding may be associated with the activities of occipital, parietal and prefrontal cortices, that these regions form a functional network and that these relationships vary as a function of difficulty during encoding. We describe the relationship of these measures with symptoms and performance. We conclude that alpha desynchronization and its relationship to occipito-parietal-frontal interactions may be used to characterize and refine the sources of deficits of spatial WM in ADHD.

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Clin EEG Neurosci. 2013;44:E12.

ELECTRICAL AND MULTIMODAL NEUROIMAGING IN ADHD: TRANSLATIONAL ASPECTS.

Brandeis D.

Introduction. Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent and persistent neurodevelopmental disorder. Despite its heterogeneity, electroencephalographic/eventrelated potential (EEG/ERP) and hemodynamic (functional magnetic resonance imaging [fMRI]) neuroimaging have revealed consistent deficits of state regulation, inhibition, and motivation in ADHD. Translational neuroimaging draws on these results for diagnostics or subtyping, and learning selfregulation of core brain dysfunctions through neurofeedback. Still, neuroimaging markers may not be sufficiently diagnostic, and the sizeable clinical effects of EEG-neurofeedback treatment in ADHD are partly confounded by expectancy1 and other unspecific factors.2 Neurofeedback using activity from specific dysfunctional regions, like the anterior cingulate cortex (ACC) affected in ADHD, represents a new approach to increase specificity.

Methods. An initial translational study examined the diagnostic utility of topographic EEG markers for ADHD.3 Next, tomographic EEG neurofeedback (tNF3) using frequency (theta and beta bands), and slow cortical potentials (SCP) protocols for bidirectional regulation of ACC brain activity, was observed in 12 ADHD children. The ACC activity across training and rest phases was computed using sLORETA (low-resolution electromagnetic tomography) of the 30-channel EEG.

Results. Topographic EEG spectra reliably indicated developmental lag but were not diagnostic for ADHD. Reduction of ADHD symptoms and movementrelated artifacts were obtained after tNF. Control over ACC activity was learned only in a simple SCP condition, but ACC frequency distribution at rest normalized over the course of tNF training.

Discussion. Clinical improvements support bidirectional self-regulation approaches in ADHD, but the improvements after ACC tNF occurred without substantial learning of ACC control, despite stabilisation of ACC activity. Future translational studies should promote learning of control, use multimodal approaches to improve specificity of diagnostic and treatment, and clarify brain mechanisms underlying nonspecific contribution to NF.

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CNS Spectr. 2014 Feb;1-10.

DAILY LIFE IMPAIRMENTS ASSOCIATED WITH CHILDHOOD/ADOLESCENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AS RECALLED BY ADULTS: RESULTS FROM THE EUROPEAN LIFETIME IMPAIRMENT SURVEY.

Caci H, Asherson P, Donfrancesco R, et al .

Introduction The Lifetime Impairment Survey, conducted in Europe, assessed impairment and symptoms of attention-deficit/hyperactivity disorder (ADHD) in childhood, and experiences of ADHD diagnosis and treatment, as recalled by adults.

METHODS: Adults with ADHD and without ADHD (control group) were invited to participate in an internet-based survey and report on their childhood experiences. History of ADHD diagnosis was self-reported. Groups were compared using impairment and symptom scales.

RESULTS: Overall, 588 adults with ADHD and 736 without ADHD participated. Mean (standard deviation [SD]) age at diagnosis of ADHD was 20.0 (12.6) years (median 18.0) following consultation with 3.8 (5.1) doctors (median 2) over 44.6 (69.3) months (median 17.0). A total of 64.1% (377/588) of adults with ADHD reported frustration or difficulties during the diagnostic process. The ADHD group had a higher mean (SD) score versus control for general (3.3 [1.2] vs 2.1 [1.2]; $p < 0.001$) and school impairment (2.8 [0.7] vs 2.3 [0.6]; $p < 0.001$) but not home impairment (2.1 [0.5] for both groups). Discussion The survey demonstrated that ADHD had a negative impact on all aspects of childhood investigated, as recalled by adults.

CONCLUSIONS: These data provide insights into childhood impairments and identify areas for improvement in the management and treatment of ADHD.

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Cogn Behav Pract. 2014 Feb;21:32-42.

A PARENT-TEEN COLLABORATIVE TREATMENT MODEL FOR ACADEMICALLY IMPAIRED HIGH SCHOOL STUDENTS WITH ADHD.

Sibley MH, Altszuler AR, Ross JM, et al.

The current study pilots a low-intensity behavioral intervention for parents and high school students with ADHD that promotes parent-teen collaboration at home and in session (Supporting Teens' Academic Needs Daily-Group; STAND-G). Twenty-three high school students with ADHD and their parents were randomly assigned to receive an 8-week behavioral treatment beginning in October, January, or March. Weekly data were collected from students' online grade books for 37 weeks of the school year to monitor changes in academic functioning through baseline, posttreatment, and follow-up phases. Students who had not yet received the treatment served as a control group for students who completed treatment. Qualitative and quantitative ratings of satisfaction, improvement, and parent implementation of home-based behavioral strategies were collected. Results indicated parent and teen satisfaction with STAND-G, parent compliance with intervention strategies, and a range of parent-rated therapeutic benefits (i.e., organization and time-management skills, academic conscientiousness, parent-teen communication, adolescent autonomy). Findings for the objective grade book data were mixed, with Group 2 (January), but not Group 1 (October), displaying identifiable acute improvements relative to control students. However, both groups evaluated at follow-up displayed meaningful improvements in the percentage of work turned in up to 2 months out of treatment. With these results in mind, we discuss the importance of tailoring interventions to the lives of high school students with ADHD and the future of treatment development and delivery for this often underserved population.

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Compr Psychiatry. 2013 Oct;54(7):943-52.

ON THE RELATIONSHIP BETWEEN RETROSPECTIVE CHILDHOOD ADHD SYMPTOMS AND ADULT BPD FEATURES: THE MEDIATING ROLE OF ACTION-ORIENTED PERSONALITY TRAITS.

Carlotta D, Borroni S, Maffei C, Fossati A.

A number of studies have reported data suggestive of a significant association between ADHD and BPD, nevertheless, the nature of this relation has not been fully understood yet. In our study, we tried to evaluate if the relationship between retrospectively assessed ADHD symptoms and adult BPD features could mediated by selected temperament/personality traits. Four hundred forty-seven in- and outpatients consecutively admitted to the Clinical Psychology and Psychotherapy Unit of the Scientific Institute H San Raffaele of Milan, Italy, were administered the Italian versions of the following instruments: Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II), Wender Utah Rating Scale (WURS), Temperament and Character Inventory-Revised (TCI-R), Barratt Impulsiveness Scale-11 (BIS-11), and Aggression Questionnaire (AQ). Our mediation analyses showed that the combination of impulsivity, aggression, novelty seeking, and juvenile conduct problems completely mediate the relationship between retrospectively assessed ADHD symptoms and current BPD features.

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Curr Med Res Opin. 2014 Apr.

SYSTEMATIC EVIDENCE SYNTHESIS OF TREATMENTS FOR ADHD IN CHILDREN AND ADOLESCENTS: INDIRECT TREATMENT COMPARISONS OF LISDEXAMFETAMINE WITH METHYLPHENIDATE AND ATOMOXETINE.

Roskell NS, Setyawan J, Zimovetz EA, et al.

Abstract

Objective: Systematically review and synthesize the clinical evidence of treatments for attention deficit hyperactivity disorder (ADHD) by indirectly comparing established treatments in the UK with a drug recently approved in Europe (lisdexamfetamine [LDX]).

Research design and methods:

Population: children and adolescents.

Setting: Europe.

Comparators: methylphenidate (MPH), atomoxetine (ATX), and dexamphetamine (DEX). Electronic databases and relevant conference proceedings were searched for randomized, controlled clinical trials evaluating efficacy and safety of at least one of the comparators and LDX. Quality assessments for each included trial were performed using criteria recommended by the Centre for Reviews and Dissemination. Network meta-analysis methods for dichotomous outcomes were employed to evaluate treatment efficacy.

Main outcome measures: Response, as defined by either a reduction from baseline of at least 25% in the ADHD Rating Scale [ADHD-RS] total score or, separately, as assessed on the Clinical Global Impression-Improvement [CGI-I] scale, and safety (all-cause withdrawals and withdrawal due to adverse events).

Results: The systematic review found 32 trials for the meta-analysis, including data on LDX, ATX, and different formulations of MPH. No trials for DEX meeting the inclusion criteria were found. Sufficient data were identified for each outcome: ADHD-RS, 16 trials; CGI-I, 20 trials; all-cause withdrawals, 28 trials; and withdrawals due to adverse events, 27 trials. The relative probability of treatment response for CGI-I (95% confidence intervals [CI]) for ATX versus LDX was 0.65 (0.53-0.78); for long-acting MPH versus LDX, 0.82 (0.69-0.97); for intermediate release MPH versus LDX, 0.51 (0.40-0.65); and for short-acting MPH versus LDX, 0.62 (0.51-0.76). The relative probabilities of ADHD-RS treatment response also favored LDX.

Conclusions: For the treatment of ADHD, the synthesis of efficacy data showed statistically significant better probabilities of response with LDX than for formulations of MPH or ATX. The analysis of safety data proved inconclusive due to low event rates. These results may be limited by the studies included, which only investigated the short-term efficacy of medications in patients without comorbid disorders

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Curr Ther Res Clin Exp. 2007 Nov;68:432-49.

EVALUATION OF THE EFFECT OF METHYLPHENIDATE BY COMPUTED TOMOGRAPHY, ELECTROENCEPHALOGRAPHY, NEUROPSYCHOLOGICAL TESTS, AND CLINICAL SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PROSPECTIVE COHORT STUDY.

Yildiz OO, Agaoglu B, Sen BF, et al.

Background: Stimulant drugs are the most commonly used treatments for attention-deficit/hyperactivity disorder (ADHD), although the mechanism of action of these drugs is still not entirely understood.

Objective: The aim of this study was to investigate the effects of the psychostimulant drug methylphenidate (MPH) on regional cerebral blood flow (rCBF), electrical activity of the brain, and clinical symptoms in children with ADHD using single-photon emission computed tomography (SPECT), electroencephalography (EEG), and neuropsychological tests.

Methods: In this prospective cohort study, pediatric outpatients received MPH for 3 months at a mean dose of 1 mg/kg . d (range, 0.5-1.5 mg/kg . d). They were then administered the Wechsler Intelligence Scale for Children-Revised, the Bender Visual-Motor Gestalt Test (BGT), EEG, and SPECT of the brain. The parents and/or teacher of each child were asked to complete the Conners' Parent Rating Scale (CPRS), the Conners' Teacher Rating Scale (CTRS), and the Turgay Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S). All of the evaluations were performed at baseline and after 3 months of MPH treatment. Each child underwent a Stroop test as an activation method 15 minutes before the SPECT procedure.

Results: Sixty patients were assessed for inclusion. Twenty-one children (18 boys [85.7%], 3 girls [14.3%]; mean [SD] age, 9.7 [1.7] years; range, 8-13 years) with a diagnosis of ADHD were included in and completed the study. Mean (SD) BGT scores before MPH treatment compared with after MPH treatment were significantly decreased (9.8 [4.2] vs 6.3 [3.4]; Z = -3.27; P = 0.001). After treatment with MPH, the visual SPECT results suggested that low rCBF was normalized in the right frontotemporal areas in 10 children with ADHD. After treatment, 12 patients (57.1%) had no change in EEG activity, 5 (23.8%) had improvement, and 4 (19.0%) had worsening activity. Patients who had improvement or no worsening on EEG after MPH treatment were associated with significant improvement after MPH treatment compared with before treatment in mean (SD) CTRS scores (25.9 [14.3] vs 35.0 [14.4]; P = 0.003), teachers' T-DSM-IV-S total score (25.1 [14.2] vs 38.4 [18.7]; P = 0.005), and CPRS scores (mothers scores: 29.7 [16.6] vs 42.6 [17.2], P = 0.002; fathers' scores: 29.4 [16.8] vs 41.9 [23.7], P = 0.004). No significant difference was found in these scores in the patients whose EEG findings showed deterioration after MPH treatment. The quantitative values for SPECT observed before treatment compared with those observed after 3 months of MPH treatment were not found to be significantly different in any areas of the brain.

Conclusions: MPH use over 3 months was associated with improvement from baseline in visual-motor function and behavioral disorders in these children and adolescents with ADHD. However, no significant difference in rCBF or electrical activity in the brain was observed in this small study.

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Dev Med Child Neurol. 2014 May;56:453-59.

SCREENING FOR CHILDHOOD MENTAL HEALTH DISORDERS USING THE STRENGTHS AND DIFFICULTIES QUESTIONNAIRE: THE VALIDITY OF MULTI-INFORMANT REPORTS.

Johnson S, Hollis C, Marlow N, et al.

AIM: This study investigated the diagnostic accuracy of the Strengths and Difficulties Questionnaire (SDQ) in a population of children born extremely preterm (<26wks gestation).

METHOD: Parents and teachers of 219 extremely preterm children (118 females, 101 males; age 11y) were asked to complete the SDQ to screen for psychological problems. Multi-informant ratings were aggregated using two methods: combined (parent or teacher rated the child with problems) and pervasive (parent and teacher rated the child with problems). Psychiatric diagnoses were assigned using the Development and Well-Being Assessment.

RESULTS: Pervasive ratings had the greatest diagnostic accuracy for emotional disorders (89%), conduct disorders (94%), attention-deficit-hyperactivity disorder (ADHD; 90%), and autism spectrum disorders (ASDs; 94%), but were associated with low sensitivity (</=50%). For clinical use, combined ratings were

best for detecting emotional disorders (sensitivity 77%, specificity 75%), conduct disorders (83%, 88%), and ADHD (85%, 72%). Parent ratings were best for ASDs (93%, 66%). Teacher ratings significantly improved prediction over parent ratings alone for conduct disorders (chi(2) =9.3, p=0.002) and ADHD (chi(2) =24.1, p<0.001) only.
INTERPRETATION: Multi-informant data are preferable for assessing most mental health outcomes using the SDQ. As an outcome measure, pervasive ratings have the best predictive accuracy. For screening, combined ratings are best for detecting ADHD and emotional and conduct disorders. For ASDs, parent ratings were best.

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Dev Neurorehabil. 2014 Apr.
EFFECTS ASSOCIATED WITH ON- AND OFF-LABEL STIMULANT TREATMENT OF CORE AUTISM AND ADHD SYMPTOMS EXHIBITED BY CHILDREN WITH AUTISM SPECTRUM DISORDER.
Barnard-Brak L, Davis TN, Schmidt M, et al.
Abstract
Objective: Families of children with autism spectrum disorder are barraged by different treatment options. Some of these options have the support of empirical evidence while others do not. Stimulant treatments are typically utilized to treat symptoms of ADHD indicating an on-label use of such treatment.
Methods: This study examines the association of stimulant treatment with the on- (symptoms of ADHD) and off- (symptoms of ASD) label symptoms among children with ASD via a non-clinical, population-based sample.
Results: Results indicate no significant association of stimulant treatment with a reduction of on- or off-label symptoms among children with ASD.
Conclusion: Stimulant medications utilized in the treatment of DSM core symptoms of autism spectrum disorder would be considered an off-label use because there is limited evidence to support that stimulants are effective in treating core symptoms of ASD, which is supported by the results of the current study.

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Dev Psychopathol. 2014 Apr;1-19.
EFFECTS OF THE SAFE CHILDREN PREVENTIVE INTERVENTION ON DEVELOPMENTAL TRAJECTORIES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.
Fowler PJ, Henry DB, Schoeny M, et al.
This study examined whether a family-based preventive intervention for inner-city children entering the first grade could alter the developmental course of attention-deficit/hyperactivity disorder (ADHD) symptoms. Participants were 424 families randomly selected and randomly assigned to a control condition (n=192) or Schools and Families Educating Children (SAFE) Children (n=232). SAFE Children combined family-focused prevention with academic tutoring to address multiple developmental-ecological needs. A booster intervention provided in the 4th grade to randomly assigned children in the initial intervention (n=101) evaluated the potential of increasing preventive effects. Follow-up occurred over 5 years with parents and teachers reporting on attention problems. Growth mixture models identified multiple developmental trajectories of ADHD symptoms. The initial phase of intervention placed children on more positive developmental trajectories for impulsivity and hyperactivity, demonstrating the potential for ADHD prevention in at-risk youth, but the SAFE Children booster had no additional effect on trajectory or change in ADHD indicators.

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Dev Sci. 2014 Mar.

PREVIOUS REWARD DECREASES ERRORS OF COMMISSION ON LATER 'NO-GO' TRIALS IN CHILDREN 4 TO 12 YEARS OF AGE: EVIDENCE FOR A CONTEXT MONITORING ACCOUNT.

Winter W, Sheridan M.

Inhibitory control is widely hypothesized to be the cornerstone of executive function in childhood and the central deficit in a number of developmental disorders, including attention-deficit/hyperactivity disorder (ADHD). However, recent evidence from adults indicates that performance on response inhibition tasks may primarily reflect non-inhibitory attentional control (context monitoring) processes. Yet it may be that inhibition plays a more central role in childhood - a time when the architecture of cognitive processes might be more transparent due to wide variability in skill level. Here we directly test inhibitory and context monitoring explanations of task performance on a Go/No-Go task in a large group of children 4-12 years of age. We conclude that traditional inhibitory conceptualizations of task performance on the Go/No-Go task cannot account for our findings, calling into question evidence supporting a central role for inhibitory control in cognitive development or developmental psychopathology.

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Drugs R D. 2013;13:271-80.

CONCOMITANT PHARMACOTHERAPY OF PSYCHOTROPIC MEDICATIONS IN EU CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sikirica V, Fridman M, Bruno A, et al.

Background: With preliminary data suggesting an increasing trend in attention-deficit/hyperactivity disorder (ADHD) prevalence in Europe, the use of psychotropic medications in this population needs to be better understood, particularly among patients with ADHD and no co-morbid psychiatric disorder.

Methods: Medical charts of patients aged 6-17 years with one or more ADHD diagnosis between January 1, 2004 and June 30, 2007, and use of ADHD medication were abstracted by physicians from six European countries. Patients with a history of epilepsy or diagnosis of Tourette syndrome were excluded.

Results: Among a convenience sample of 569 children/adolescent patients (mean age, 12.1 years), 80 (14.1 %) patients used psychotropic concomitant medication (PCM) along with their current on-label ADHD medication. The number of pre-existing co-morbidities, high impairment due to the symptom of anger, and country (France; Italy; the Netherlands; and Spain vs. the reference country, Germany) were significantly associated with PCM use (UK was not significantly different vs. Germany). In particular, in France, Italy, the Netherlands, and Spain, PCM use was highest.

Conclusions: These findings suggest that greater attention to the use of PCM, which are not indicated for the treatment of ADHD, may be warranted in children and adolescents receiving PCM. This highlights the need for further research to assess the impact of PCM use in ADHD patients and to consider alternative, individualized, indicated treatment strategies for patients with ADHD.

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Dusunen Adam. 2014;27:61-68.

VARIOUS ADHD-ASSOCIATED PROBLEMATIC LIFE EVENTS IN PARENTS OF CHILDREN WITH ADHD DIAGNOSIS.

Pazvantoglu O, Akbas S, Sarisoy G, et al.

Objective: The purpose of this study was to establish whether there was any relationship between diagnosis of ADHD and various problematic life events in parents of children monitored with a diagnosis of ADHD.

Method: Two hundred forty nine parents of 167 children followed-up with a diagnosis of ADHD and 146 healthy controls with no diagnosis of ADHD in their children or themselves were included. DSM-IV diagnostic criteria were used in diagnostic evaluation. Diagnostic criteria recommended for DSM-V and ADHD symptom assessment scales (Wender Utah Rating Scale-25, Adult Attention Deficit Hyperactivity Disorder Self-Report Scale) were also used. Problematic life events were recorded on a data form prepared by the authors.

Results: Parents meeting a diagnosis of ADHD experienced nearly all problematic life events at a higher level compared to parents not meeting that diagnosis and to the healthy controls.
Conclusion: Parents of children diagnosed with ADHD are exposed to a high, lifelong level of ADHDassociated life events. These parents should be evaluated in terms of diagnosis of ADHD.

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Encephale. 2014.

IS EMOTIONAL DYSREGULATION A COMPONENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)?

Villemonteix T, Purper-Ouakil D, Romo L.

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents. It is characterized by age-inappropriate inattention/impulsiveness and/or hyperactivity symptoms. ADHD shows a high comorbidity with oppositional defiant disorder (ODD), a disorder that features symptoms of emotional lability. Due to this comorbidity, emotional lability was long considered a secondary consequence of ADHD, which could arise under the influence of environmental factors such as inefficient parenting practices, as part of an ODD diagnosis. In this model of heterotypic continuity, emotional lability was considered not to play any causal role regarding ADHD symptomatology.
Literature findings: As opposed to this view, it is now well established that a large number of children with ADHD and without any comorbid disorder exhibit symptoms of emotional lability. Furthermore, recent studies have found that negative emotionality accounts for significant unique variance in ADHD symptom severity, along with motor-perceptual and executive function deficits. Barkley proposed that ADHD is characterized by deficits of executive functions, and that a deficiency in the executive control of emotions is a necessary component of ADHD. According to this theory, the extent to which an individual with ADHD displays a deficiency in behavioral inhibition is the extent to which he or she will automatically display an equivalent degree of deficiency in emotional inhibition. However, not all children with ADHD exhibit symptoms of emotional lability, and studies have found that the association between emotional lability and ADHD was not mediated by executive function or motivational deficits. Task-based and resting state neuroimaging studies have disclosed an altered effective connectivity between regions dedicated to emotional regulation in children with ADHD when compared to typically developing children, notably between the amygdala, the prefrontal cortex, the hippocampus and the ventral striatum. Morphological alterations of the amygdala have also been reported in previous structural studies in children with ADHD.
Discussion: Emotional lability can result from different neurobiological mechanisms. In particular, bottom-up and top-down processes can be opposed. Bottom-up related emotional dysregulation involves an increased emotional reactivity, and is thought to be linked to the automatic evaluative activity of the amygdala. Top-down mechanisms are associated with the regulation of such activity, and rely on a prefrontal network including the lateral prefrontal cortex, the anterior cingulate cortex and the orbitofrontal cortex. Since various neuropsychological impairments and alterations in multiple brain networks have been implicated in the etiology of ADHD, contemporary models emphasize its neuropsychological heterogeneity. It is therefore likely that some but not all children with ADHD will exhibit neurobiological alterations in circuits dedicated to emotional regulation, possibly at different levels. Future research will have to identify the different causal pathways and to decide whether emotional lability represents a criterion to subtype ADHD diagnoses.
Conclusion: Emotional dysregulation is now known to play a causal role regarding ADHD symptomatology. Along with executive functioning, reaction time variability and potentially delay aversion, emotional dysregulation should therefore be included in future theoretical models of ADHD, as well as in clinical practice when identifying the major impairments in this diagnostic group and when deciding therapeutic strategies.

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Epidemiol Psychiatr Sci. 2014 Jun;23:133-35.

DOES PSYCHOSTIMULANT TREATMENT IN CHILDREN WITH ADHD INCREASE LATER RISK OF SUBSTANCE USE DISORDER?

Purgato M, Cortese S.

Psychostimulants are the first choice medication in children with attention-deficit/hyperactivity disorder (ADHD). Despite the proven high efficacy of psychostimulants, at least in the short term, for ADHD core symptoms, concerns continue to be raised on their adverse effects, including putative increased risk of substance use disorders (SUDs). A recent multicentre, case-control, longitudinal, prospective, European study by Groenman and colleagues found that treatment with psychostimulants in children with ADHD lowered the risk of SUDs in adolescence. However, this finding is at odds with other recent evidence concluding that ADHD children with and without medication treatment history did not significantly differ on any subsequent SUDs rates. In the present paper, we discuss the study by Groenman and colleagues in view of its methodological strengths and limitations, and we suggest possible implications for day-to-day clinical practice.

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Epilepsy Behav. 2014 Mar;32:72-75.

HEADACHE AND ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CHILDREN: COMMON CONDITION WITH COMPLEX RELATION AND DISABLING CONSEQUENCES.

Parisi P, Verrotti A, Paolino MC, et al.

The aim of this review was to analyze literature data on the complex association between headache and attention deficit and hyperactivity disorder (ADHD) in children, in order to explore its possible consequences on child neurological development. Headache and ADHD are two common conditions in the pediatric population. They both are disabling diseases that impact the child's quality of life and are associated with severe cognitive, emotional, and behavioral impairments. To assess and analyze literature data about the association of ADHD and headache in children and possible physiopathogenesis relationships, we searched for the following terms: headache, migraine, tension-type headache, ADHD, and children (MESH or text words). We found different studies that assess the clinical, epidemiological, and physiopathogenetic overlap between these two diseases, with contrasting results and unresolved questions. Structural and functional abnormalities in brain networks have been found to be central in both headache and ADHD pathophysiology. It will be crucial to gain a better understanding of how subcortical-cortical and corticocortical network development is altered during the onset of the disorders.

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Eur Arch Psychiatry Clin Neurosci. 2014 Mar.

SMOKING BEHAVIOR CHARACTERISTICS OF NON-SELECTED SMOKERS WITH CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (AD/HD) HISTORY: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Fond G, Loundou A, Guillaume S, et al.

It is unclear whether adult smokers with childhood attention-deficit/hyperactivity disorder history (CH) have more severe smoking behavior than non-CH smokers, while it is clearly suggested that CH adolescents have more severe smoking behavior than CH adolescents. The aim of the present comprehensive meta-analysis is to determine whether CH smokers have more severe smoking behavior characteristics than those without and the effect of age on the association between CH and smoking behavior. We included all case-control studies and first round data collection of observational studies addressing the difference in smoking behavior characteristics of CH smokers versus non-CH smokers, with validated scales or structured interviews, without any language or date restriction. Nine studies (including 365 smokers with CH and 1,708 smokers without) were included. Compared to non-CH smokers, CH smokers smoked significantly more cigarettes [standardized mean differences (SMD) = 0.15, 95 % CI 0.01-0.28, p = 0.04] and began to regularly smoke earlier (SMD = -0.28, 95 % CI -0.49; -0.07, p = 0.01) but were not significantly more nicotine dependent (SMD = 0.23, 95 % CI -0.04 to 0.48, p = 0.08). After removing the single adolescent study, the significant association between CH and number of daily smoked cigarettes

disappeared, and subgroups analyses confirmed that the significant association between CH and number of daily smoked cigarettes disappeared as age increased. Our meta-analysis illustrates a clinically important link between CH and tobacco smoking in adolescence but not later in life. Further high-quality studies are needed to confirm this finding, as only two studies included participants with a mean age below 20 years.

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Eur Child Adolesc Psychiatry. 2014 Apr.

CHILDREN DIAGNOSED WITH ATTENTION DEFICIT DISORDER AND THEIR HOSPITALISATIONS: POPULATION DATA LINKAGE STUDY.

Silva D, Colvin L, Hagemann E, et al.

Examine the hospital admission risk in young children who are subsequently diagnosed with attention deficit hyperactivity disorder (ADHD). We conducted a population-based, record linkage study. Records of all non-Aboriginal children under 18 years who met the DSMIV/ICD10 criteria for ADHD and prescribed stimulant medication in Western Australia between 2003 and 2007 (n = 11,902) were linked to two other health data systems-the hospital morbidity data system and the midwives notification system (MNS). The non-ADHD reference population (n = 27,304) was randomly selected from the MNS. Compared with controls, children under 4 years who subsequently were diagnosed and treated for ADHD were 70 % [odds ratio (OR) 1.70; 95 % confidence intervals (CI) 1.62-1.77] more likely to be admitted to hospital under 4 years of age. There was an increased risk for injury or poison (OR 1.73; 95 % CI 1.59-1.88), respiratory disease (OR 1.49; 95 % CI 1.40-1.59), ear disease (OR 2.03; 95 % CI 1.86-2.21), infectious diseases (OR 1.68; 95 % CI 1.53-1.85) and neurological conditions (OR 2.03; 95 % CI 1.68-2.44). Admissions under 4 years of age for head injuries, burns, poisons, all other injuries, diseases of the tonsils and adenoids, asthma and early infections were all more common amongst children subsequently diagnosed with and treated for ADHD. There is significant early hospital morbidity for children subsequently diagnosed with ADHD. Multiple aetiologies and causal pathways need to be considered where some of these may include early infections, inflammatory conditions, epilepsy and injuries. Future studies should look at which of these conditions may be on the causal pathway or likely early markers for ADHD.

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Eur Child Adolesc Psychiatry. 2014 Apr.

RISK FACTORS FOR INCIDENT MAJOR DEPRESSIVE DISORDER IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jerrell JM, McIntyre RS, Park YM.

The greater burden of illness in youth with co-occurring attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD) deserves further investigation, specifically regarding the influence of other psychiatric or medical conditions and the pharmacotherapies prescribed. A retrospective cohort design was employed, using South Carolina's (USA) Medicaid claims' dataset covering outpatient and inpatient medical services, and medication prescriptions between January, 1996 and December, 2006 for patients </=17 years of age. The cohort included 22,452 cases diagnosed with ADHD at a mean age 7.8 years; 1,259 (5.6 %) cases were diagnosed with MDD at a mean age of 12.1 years. The probability of a child with ADHD developing MDD was significantly associated with a comorbid anxiety disorder (aOR = 3.53), CD/ODD (aOR = 3.45), or a substance use disorder (aOR = 2.31); being female (aOR = 1.77); being treated with pemoline (aOR = 1.69), atomoxetine (aOR = 1.31), or mixed amphetamine salts (aOR = 1.28); a comorbid obesity diagnosis (aOR = 1.29); not being African American (aOR = 1.23), and being older at ADHD diagnosis (aOR = 1.09). Those developing MDD also developed several comorbid disorders later than the ADHD-only cohort, i.e., conduct disorder/oppositional-defiant disorder (CD/ODD), at mean age of 10.8 years, obesity at 11.6 years, generalized anxiety disorder at 12.2 years, and a substance use disorder at 15.7 years of age. Incident MDD was more likely in individuals clustering several demographic, clinical, and treatment factors. The phenotypic progression suggested herein underscores the need for coordinated

early detection and intervention to prevent or delay syndromal MDD, or to minimize its severity and associated impairment over time.

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European Child & Adolescent Psychiatry. 2014.

CONTINUITY IN FEATURES OF ANXIETY AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN YOUNG PRESCHOOL CHILDREN.

Overgaard KR, Aase H, Torgersen S, et al.

Anxiety disorders and attention deficit/hyperactivity disorder (ADHD) develop before school age, but little is known about early developmental pathways. Here we test two hypotheses: first, that early signs of anxiety and ADHD at 18 months predict symptoms of anxiety and ADHD at age 31/2 years; second, that emotional dysregulation at 18 months predicts the outcome of co-occurring anxiety and ADHD at age 31/2 years. The study was part of the prospective Norwegian Mother and Child Cohort Study (MoBa) at the Norwegian Institute of Public Health. The 628 participants were clinically assessed at 31/2 years. Questionnaire data collected at 18 months were categorized into early behavioural scales of anxiety, ADHD, and emotional dysregulation. We investigated continuity in features of anxiety and ADHD from 18 months to 31/2 years of age through logistic regression analyses. Anxiety symptoms at 31/2 years were predicted by early signs of anxiety (Odds ratio (OR) = 1.41, CI = 1.15-1.73) and emotional dysregulation (OR = 1.33, CI = 1.15-1.54). ADHD symptoms at 31/2 years were predicted by early signs of ADHD (OR = 1.51, CI = 1.30-1.76) and emotional dysregulation (OR = 1.31, CI = 1.13-1.51). Co-occurring anxiety and ADHD symptoms at 31/2 years were predicted by early signs of anxiety (OR = 1.43, CI = 1.13-1.84), ADHD (OR = 1.30, CI = 1.11-1.54), and emotional dysregulation (OR = 1.34, CI = 1.13-1.58). We conclude that there were modest continuities in features of anxiety and ADHD through early preschool years, while emotional dysregulation at age 18 months was associated with symptoms of anxiety, ADHD, and co-occurring anxiety and ADHD at age 31/2 years.

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Eur Child Adolesc Psychiatry. 2014;23:173-77.

SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) LEVELS IN ATTENTION DEFICIT-HYPERACTIVITY DISORDER (ADHD).

Scassellati C, Zanardini R, Tiberti A, et al.

It has been proposed that the neurotrophin brain-derived neurotrophic factor (BDNF) may be involved in attention deficit-hyperactivity disorder (ADHD) etiopathogenesis. Alterations in BDNF serum levels have been observed in childhood/adulthood neurodevelopmental pathologies, but no evidence is available for BDNF serum concentrations in ADHD. The study includes 45 drug-naive ADHD children and 45 age-sex matched healthy subjects. Concentration of serum BDNF was determined by the ELISA method. BDNF serum levels in patients with ADHD were not different from those of controls (mean (plus or minus) SD; ADHD: 39.33 (plus or minus) 10.41 ng/ml; controls: 38.82 (plus or minus) 8.29 ng/ml, t = -0.26, p = 0.80). Our findings indicate no alteration of serum BDNF levels in untreated patients with ADHD. A further stratification for cognitive, neuropsychological and psychopathological assessment in a larger sample could be useful to clarify the role of BDNF in the endophenotype characterization of ADHD.

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Exp Clin Psychopharmacol. 2014;22:100-09.

INTERACTIVE ASSOCIATION OF DOPAMINE RECEPTOR (DRD4) GENOTYPE AND ADHD ON ALCOHOL EXPECTANCIES IN CHILDREN.

Lee SS, Humphreys KL.

Positive and negative alcohol expectancies (AEs) are beliefs about the consequences of alcohol use (e.g., happy, sad, lazy) and they predict patterns of adolescent and adult alcohol engagement in clinical and nonclinical samples. However, significantly less is known about predictors of AE in children, despite

significant variability in AE early in and across development. To identify temporally ordered risk factors that precede AE, we evaluated the independent and interactive association of the functional 7-repeat polymorphism of the dopamine D4 receptor (DRD4) genotype and attention-deficit/hyperactivity disorder (ADHD) with respect to individual differences in positive-social, negative-arousal, sedated/impaired, and wild/crazy AE in school-age children (N=149) prospectively followed from 6-9 to 8-13 years of age. Controlling for age, sex, and wave, DRD4 7+ carriers reported more wild/crazy AE, but DRD4 was unrelated to the remaining AE domains. ADHD symptoms independently predicted higher negativearousal, sedated/impaired, and wild/crazy AE, but not positive-social. We also observed a significant interaction in which ADHD symptoms positively predicted wild/crazy AE only in youth with the 7-repeat DRD4 genotype; the same interaction marginally predicted sedated/impaired AE. No interactive effects were observed for the remaining AE domains. These preliminary results suggest that, among DRD4 youth, early ADHD symptoms predict that children will expect alcohol to have wild/crazy effects. We consider these results within a developmental framework to better understand pathways to and from youth alcohol problems.

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Exp Clin Psychopharmacol. 2014 Apr;22:141-43.

ADHD, IMPULSIVITY AND ALCOHOL ABUSE: METHODS, RESULTS, AND IMPLICATIONS.

Clark DB, de Wit H, Iacono WG.

In this Special Section, the relationships among attention deficit hyperactivity disorder (ADHD), impulsivity, and alcohol abuse are explored by 4 diverse studies. Among these excellent studies, the constructs indicated in the issue title varied in definitions, measurement methods, and interpretive implications. The experimental approaches also varied, including cross-sectional examination of candidate genes in children, determination of long-term outcomes, laboratory tasks to measure attention and inhibition, and alcohol administration. These diverse topics and approaches yielded insights into the etiology and effects of alcohol abuse and indicated research directions that will advance this field.

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Exp Clin Psychopharmacol. 2014;22:110-21.

HEAVY ALCOHOL USE IN EARLY ADULTHOOD AS A FUNCTION OF CHILDHOOD ADHD: DEVELOPMENTALLY SPECIFIC MEDIATION BY SOCIAL IMPAIRMENT AND DELINQUENCY.

Molina BSG, Walther CAP, Cheong J, et al.

Frequent heavy drinking in early adulthood, particularly prior to age 21, is associated with multiple health and legal consequences including continued problems with drinking later into adulthood. Children with attention-deficit/hyperactivity disorder (ADHD) are at risk of alcohol use disorder in adulthood, but little is known about their frequency of underage drinking as young adults or about mediational pathways that might contribute to this risky outcome. The current study used data from the Pittsburgh ADHD Longitudinal Study to test social impairment and delinquency pathways from childhood ADHD to heavy drinking in early adulthood for individuals with (n=148) and without (n=117) childhood ADHD. Although ADHD did not predict heavy drinking, indirect mediating effects in opposing directions were found. A delinquency pathway from childhood ADHD to increased heavy drinking included adolescent and subsequently adult delinquent behavior. A social impairment pathway from childhood ADHD to decreased heavy drinking included adolescent, but not adult, social impairment. These findings help explain the heterogeneity of results for alcohol use among individuals with ADHD and suggest that common ADHD-related impairments may operate differently from each other and distinctly across developmental periods.

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Front Hum Neurosci. 2014;8:119.

COMPLEXITIES IN UNDERSTANDING ATTENTIONAL FUNCTIONING AMONG CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER.

Lane KA, Stewart J, Fernandes T, et al.

Parental reports of attention problems and clinical symptomatology of ADHD among children with fetal alcohol syndrome disorder (FASD) were assessed in relation to performance on standardized subtests of attentional control/shifting and selective attention from the Test of Everyday Attention for Children (TEA-Ch; Manly etal., 1998). The participants included 14 children with FASD with a mean chronological age (CA) of 11.7 years and a mean mental age (MA) of 9.7 years, and 14 typically developing (TD) children with no reported history of prenatal exposure to alcohol or attention problems with a mean CA of 8.4 years and a mean MA of 9.6 years. The children with FASD were rated by their caregivers as having clinically significant attention difficulties for their developmental age. The reported symptomatology for the majority of the children with FASD were consistent with a diagnosis of ADHD, combined type, and only one child had a score within the average range. These reports are consistent with the finding that the children with FASD demonstrated difficulties with attentional control/shifting, but inconsistent with the finding that they outperformed the TD children on a test assessing selective attention. These findings are considered within the context of the complexity in understanding attentional functioning among children with FASD and discrepancies across sources of information and components of attention.

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Front Human Neurosci. 2014;8.

TOPOLOGICAL ORGANIZATION OF THE "SMALL-WORLD" VISUAL ATTENTION NETWORK IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Xia S, Foxe JJ, Sroubek AE, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood psychiatric disorder. Disrupted sustained attention is one of the most significant behavioral impairments in this disorder. We mapped systems-level topological properties of the neural network responsible for sustained attention during a visual sustained task, on the premise that strong associations between anomalies in network features and clinical measures of ADHD would emerge.

Methods: Graph theoretic techniques (GTT) and bivariate network-based statistics (NBS) were applied to fMRI data from 22 children with ADHD combined-type and 22 age-matched neurotypicals, to evaluate the topological and nodal-pairing features in the functional brain networks. Correlation testing for relationships between network properties and clinical measures were then performed.

Results: The visual attention network showed significantly reduced local-efficiency and nodal-efficiency in frontal and occipital regions in ADHD. Measures of degree and between-centrality pointed to hyper-functioning in anterior cingulate cortex and hypo-functioning in orbito-frontal, middle-occipital, superior-temporal, supra-central, and supra-marginal gyri in ADHD. NBS demonstrated significantly reduced pair-wise connectivity in an inner-network, encompassing right parietal and temporal lobes and left occipital lobe, in the ADHD group.

Conclusions: These data suggest that atypical topological features of the visual attention network contribute to classic ADHD symptomatology, and may underlie the inattentiveness and hyperactivity/impulsivity that are characteristics of this syndrome.

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Indian J Psychol Med. 2013 Oct;35:346-51.

IMPACT OF COMORBIDITY ON THREE MONTH FOLLOW-UP OUTCOME OF CHILDREN WITH ADHD IN A CHILD GUIDANCE CLINIC: PRELIMINARY REPORT.

Srinivasaraghavan R, Mahadevan S, Kattimani S.

CONTEXT: Attention deficit hyperactivity disorder (ADHD) is one of the common neurodevelopmental disorders.

AIMS: Study objective is to report impact of comorbidities on short-term outcome in children with ADHD followed in a child guidance clinic.
SETTINGS AND DESIGN: This was done in a child guidance clinic run jointly by the pediatric and psychiatry department at a tertiary teaching hospital. This is a 3 month prospective follow-up study to assess the outcome in ADHD children.
MATERIALS AND METHODS: Children attending pediatric department with behavioral problems or poor scholastic performance were screened for ADHD and further confirmation of diagnosis was done by semistructured interview of the child and parent. Children functional assessment and ADHD symptom profile was compared at baseline and at follow-up. We screened for and excluded those showing autistic spectrum disorder and having worse than mild mental retardation. Baseline variables were compared between improved and not improved subgroups and impact of these variables on outcome at 3-month follow-up was analyzed.
STATISTICAL ANALYSIS: Descriptive statistics.
RESULTS: Of the 25 children completing the study, at the end of 3 months, 15 improved (not fulfilling criteria for ADHD) and 10 did not improve. Applying Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) for diagnosis of psychiatric comorbidities, six had associated psychiatric comorbidities. This was significantly higher in those who did not improve.
CONCLUSIONS: Presence of comorbidities at baseline was found to affect outcome at 3 month assessment in this preliminary study. Future studies with larger sample and longer follow-up are needed for finding the predictors of outcome in ADHD children in developing nations.

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Indian Journal of Community Psychology. 2014 Mar;10:19-31.
ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A CONCEPTUAL OVERVIEW.
Singh MK, Mukhopadhyay A.
ADHD is the most commonly diagnosed disorder with one or more comorbid conditions of childhood. Research showed that prevalence rate is 4.67% to 15.5% and male to female ratio is 6.4: 1 to 7: 4.47 in India. Several factors have been found to be responsible for ADHD such as genetic, head injuries, neurological, neurochemical, dietary factor, parenting style. Many intervention options are available for reducing ADHD symptoms like pharmacological, behavioural, cognitive-behavioural, parent skill training, educational interventions and various combinations of these. In the present scenario ADHD is becoming a most terrifying disorder in toddlers and school going children so, children with ADHD and its co-occurring disorders need to be identified at an early age to prevent poor school performance and other behavioural problems.

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Indian J Pharmacol. 2013;45:S121.
BACOMIND(REGISTERED TRADEMARK) FOR THE MANAGEMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.
Dave UP, Dingankar SR, Saxena VS, et al.
Objective: Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by inattention, hyperactivity, and impulsivity. Although modern medications are available, not all children respond to medications or have adverse effects. For these reasons, the need for effective and safe alternative remedy has risen and Bacopa monnieri remains a promising alternative intervention for ADHD. The present study hence evaluated efficacy of BacoMind(registered trademark), an enriched phytochemical composition of B. monnieri in alleviating the severity of ADHD symptoms in children. Materials and
Methods: In the present study, thirty one children aged 6-12 years with onset of ADHD below 7 years meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD received 225 mg of BacoMind(registered trademark) for six months. Seven subtests of ADHD symptoms for children were selected from three domains (Inattention, Hyperactivity and Impulsivity) of DSM-IV diagnostic criteria and subsequently these were assessed by parent rating scale for ADHD pre- and post- treatments.

Results: BacoMind(registered trademark) administration resulted in significant reduction (P? 0.05) in all the subtests scores of ADHD symptoms viz., restlessness, impulsivity, attention deficit, self control, psychiatric problems and learning problems except social problems, in which there was a non-significant decrease.
Conclusion: BacoMind(registered trademark) significantly reduced the severity of symptoms in ADHD children.

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Infant Ment Health J. 2014 Mar;35:123-31.

PSYCHOPATHOLOGY IN YOUNG CHILDREN IN TWO TYPES OF FOSTER CARE FOLLOWING INSTITUTIONAL REARING.

Tibu F, Humphreys KL, Fox NA, et al.

Institutional rearing of young children has been demonstrated to increase risk for a broad range of psychiatric disorders and other impairments. This has led many countries to consider or to invest in foster care. However, no study to date has explored potential differences in psychiatric symptoms in children placed in different types of foster care. We assessed internalizing disorders, externalizing disorders, and attention deficit hyperactivity disorder (ADHD) in 54-month-old children living with foster families. We compared one group of children living in high-quality foster families who had benefited from specialized training and support to another group of children placed with government-sponsored foster care in Bucharest, Romania. After controlling for duration of time spent in foster care, there was a main group effect in predicting ADHD (p=.021) and a marginal group × gender interaction effect. No effects were noted for signs of externalizing disorders. There was, however, a significant group × gender interaction effect of signs of internalizing disorders (p=.007), with the girls in high-quality foster care having less severe symptomatology than did their counterparts in the government-sponsored group. Governments must invest in quality interventions for their most vulnerable citizens to prevent serious and potentially lasting problems.

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Int J Radiat Oncol Biol Phys. 2014 Mar;88:814-21.

EMOTIONAL AND BEHAVIORAL FUNCTIONING AFTER CONFORMAL RADIATION THERAPY FOR PEDIATRIC EPENDYMOMA.

Willard VW, Conklin HM, Boop FA, et al.

PURPOSE: The standard of care for pediatric patients with ependymoma involves postoperative radiation therapy. Prior research suggests that conformal radiation therapy (CRT) is associated with relative sparing of cognitive and academic functioning, but little is known about the effect of CRT on emotional and behavioral functioning.
METHODS AND MATERIALS: A total of 113 patients with pediatric ependymoma underwent CRT using photons as part of their enrollment on an institutional trial. Patients completed annual evaluations of neurocognitive functioning during the first 5 years after CRT. Emotional and behavioral functioning was assessed via the Child Behavior Checklist.
RESULTS: Before CRT, emotional and behavioral functioning were commensurate with those of the normative population and within normal limits. After 5 years, means remained within normal limits but were significantly below the normative mean. Linear mixed models revealed a significant increase in attention problems over time. These problems were associated with age at diagnosis/CRT, tumor location, and extent of resection. A higher-than-expected incidence of school problems was present at all assessment points after baseline.
CONCLUSIONS: The use of photon CRT for ependymoma is associated with relatively stable emotional and behavioral functioning during the first 5 years after treatment. The exception is an increase in attention problems. Results suggest that intervening earlier in the survivorship period-during the first year posttreatment-may be beneficial.

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Ir Med J. 2014 Feb;107:41-43.

SAFE AND JUDICIOUS PAEDIATRIC PSYCHOTROPIC PRESCRIBING.

McNicholas F, Orakwue N.

Psychotropic medications are now a well-established and evidenced based treatment for increasing number of child mental health disorders prescribed at increasing frequencies and by increasing number of professional groups. Clinicians' perceived levels of competence and standardised monitoring lag behind prescribing practice and should be addressed by regular continuous professional development. A study specific questionnaire on psychotropic prescribing practice in children was mailed to all child psychiatrists and paediatricians working in Ireland and GPs from a selected Dublin CAMHS catchment area. Of the 116 who replied, (39% response rate), antidepressants (58.7%), antipsychotics (57.1%) and ADHD medications (36.5%) were most commonly prescribed. Results suggest increasing trends of monitoring amongst Irish clinicians over time, but with some lack of specificity. Commensurate with the wish of clinicians, ongoing training in paediatric psychopharmacology is considered essential in order to benefit from the increasing advances in pharmacology.

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Iran J Psychiatry. 2013 Aug;8:131-37.

COMPARING ICONIC MEMORY IN CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ahmadi N, Goodarzi MA, Hadianfard H, et al.

OBJECTIVE: Children with attention deficit hyperactivity disorder (ADHD) do not process most information due to inattention and loss of the opportunity to save and retrieve information. Therefore, these children experience memory impairment. Although visual memory has been previously studied in children with ADHD, iconic memory in these children has been less evaluated. We aimed to study the possibility of iconic memory impairment in children with ADHD, and compare the results with that of children without ADHD.

METHODS: The experimental group of this study were 6-9 year-old children who referred to the Imam Hosein Clinic and were diagnosed as having ADHD by a psychiatrist during 2011-2012 (n=30).The subjects were interviewed clinically by a psychologist; and in order to diagnose ADHD, their parents and teachers were asked to complete the child symptom inventory-4 (CSI-4). The comparison group were 6-9 year-old children without ADHD who studied in 1st and 2nd educational district of Yazd (n=30). Subjects' iconic memory was assessed using an iconic memory task. Repeated measure ANOVA was used for data analysis.

RESULTS: Based on the iconic memory test, the mean score of ADHD children was significantly lower than that of children without ADHD ($P < 0.001$). Moreover, the performance of the experimental group differed significantly when the duration of the presentation differed from 50 ms to 100 ms as compared to the control group ($P < 0.001$). The number of correct answers increased in the experimental group as the duration of presentation increased. However, children with ADHD scored less than children without ADHD at 50 ms as well as 100 ms. The means of ADHD children increased as the duration of the presentation increased from 50 ms to 100 ms to 300 ms ($P < 0.001$).

CONCLUSION: Visual memory is weaker in children with ADHD, and they have weaker performance than normal children in both visual and auditory symbols at presentation durations of 50 and 100 ms. The performance of ADHD children improves as the stimulation time increases.

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Iran J Psychiatry Behav Sci. 2012;6:26-32.

COMPARISON OF TWO BRANDS OF METHYLPHENIDATE (STIMDATE((R)) VS. RITALIN((R))) IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL.

Khodadust N, Jalali AH, Ahmadzad-Asl M, et al.

Objective: To compare the effectiveness and safety of the methylphenidate produced in Iran (Stimdate(R)) with its original brand (Ritalin(R)) in children with Attention deficit hyperactivity disorder (ADHD).

Methods: In this double-blinded randomized clinical trial, 30 patients with ADHD who were 6 to 16 years old, were divided into two groups: 15 in Stimdate(R) and 15 in Ritalin(R) group. The two groups were compared for side effects profile, Conner's Parent's Rating Scale-Persion version (CPRS-R), Child Symptom Inventory-4 (CSI-4), Clinical Global Impressions (CGI), and Children's Global Assessment Scale (CGAS), at baseline and at the 4(th) and 6(th) weeks.
Results: The subjects showed significant decreases in the CPRS-Rand CSI-4 scores and significant increase of CGAS scores during the follow-up, but there were no significant difference between Stimdate(R) and Ritalin(R) group, regarding the pattern of changes observed. The mean therapeutic dose and the number of side effects were not significantly different between the two studied groups.
Conclusions: Both Stimdate(R) and Ritalin(R) had comparable clinical efficacy and safety in children with ADHD.

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J AAPOS. 2014 Feb;18:10-14.

PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AMONG CHILDREN WITH VISION IMPAIRMENT.

Decarlo DK, Bowman E, Monroe C, et al.

PURPOSE: To evaluate the prevalence of parent-reported attention-deficit/hyperactivity disorder (ADHD) in two clinics in Alabama serving children with vision impairment.
METHODS: The medical records of children 4-17 years of age attending the Alabama School for the Blind (ASB) during the 2010-2011 school year or seen at the University of Alabama at Birmingham (UAB) Center for Low Vision Rehabilitation between 2006 and 2010 were retrospectively reviewed. Sociodemographics, ocular characteristics, and parental report of ADHD diagnosis were obtained. The prevalence of ADHD was compared to national and state figures for age-similar children regardless of comorbidities. The prevalence of ADHD, sociodemographic, and ocular characteristics was also compared between clinical sites.
RESULTS: A total of 264 children participated in the study (95 from ASB and 169 from UAB). The prevalence of ADHD among children with visual acuity better than hand motion (n=245) was 22.9%, which is higher than reported state (14.3%) and national prevalence (9.5%) for children in this age range. The prevalence was similar at ASB (22.4%) and UAB (23.1%). Those with ADHD were similar to those without ADHD with respect to age, sex, and race. Children with ADHD were significantly less likely to have nystagmus and more likely to have better visual acuity ($P < 0.05$). The prevalence of ADHD among the 19 participants with total or near total vision loss (all from ASB) was 10.5%.
CONCLUSIONS: Our analyses suggest that children with vision impairment may be more likely to be diagnosed with ADHD than children in the general population.

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J Abnorm Child Psychol. 2014 Apr.

STABILITY AND CHANGE OF ODD, CD AND ADHD DIAGNOSIS IN REFERRED PRESCHOOL CHILDREN.

Bunte TL, Schoemaker K, Hessen DJ, et al.

Longitudinal studies have shown that preschool children's diagnosis of Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are likely to persist into school age. However, limited attention has been paid to instability of diagnosis. The aim of the present study, therefore, was to investigate both stability and change of ODD, CD and ADHD diagnosis in children aged 3.5-5.5 years. For diagnosing these disorders, a semi-structured diagnostic parent interview, i.e., the Kiddie-Disruptive Behavior Disorder Schedule (K-DBDS), was used at the first assessment and at follow-up assessments (9 and 18 months). Five diagnostic stability groups (chronic, partial remission, full remission, new onset, no diagnosis) were compared with regard to impairment and number of symptoms. Participants were referred preschool children with externalizing behavioral problems (N = 193; 83 % male) and typically developing (TD) children (N = 58; 71 % male). Follow-up assessments allowed to distinguish children belonging to the chronic group of ODD, CD or ADHD from those belonging to one of the remission groups. In addition, there was a substantial number of children with a new onset diagnosis. In conclusion, as a complement to studies showing stability of ODD, CD and ADHD diagnosis into school age, present findings

point to changes of diagnosis in the preschool and early school period. Diagnostic reassessments therefore are needed in this age group.

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J Abnorm Child Psychol. 2014 Jan.

A DOSE-RANGING STUDY OF BEHAVIORAL AND PHARMACOLOGICAL TREATMENT IN SOCIAL SETTINGS FOR CHILDREN WITH ADHD.

Pelham WE, Burrows-MacLean L, Gnagy EM, et al.

Placebo and three doses of methylphenidate (MPH) were crossed with 3 levels of behavioral modification (no behavioral modification, NBM; low-intensity behavioral modification, LBM; and high-intensity behavior modification, HBM) in the context of a summer treatment program (STP). Participants were 48 children with ADHD, aged 5-12. Behavior was examined in a variety of social settings (sports activities, art class, lunch) that are typical of elementary school, neighborhood, and after-school settings. Children received each behavioral condition for 3 weeks, order counterbalanced across groups. Children concurrently received in random order placebo, 0.15 mg/kg/dose, 0.3 mg/kg/dose, or 0.6 mg/kg/dose MPH, 3 times daily with dose manipulated on a daily basis in random order for each child. Both behavioral and medication treatments produced highly significant and positive effects on children's behavior. The treatment modalities also interacted significantly. Whereas there was a linear dose-response curve for medication in NBM, the dose-response curves flattened considerably in LBM and HBM. Behavior modification produced effects as large as moderate doses, and on some measures, high doses of medication. These results replicate and extend to social-recreational settings previously reported results in a classroom setting from the same sample (Fabiano et al., School Psychology Review, 36, 195-216, 2007). Results illustrate the importance of taking dosage/intensity into account when evaluating combined treatments; there were no benefits of combined treatments when the dosage of either treatment was high but combination of the low-dose treatments produced substantial incremental improvement over unimodal treatment.

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J Am Acad Child Adolesc Psychiatry. 2014 Mar;53:311-19.

A FOLLOW-UP STUDY OF MATERNAL EXPRESSED EMOTION TOWARD CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): RELATION WITH SEVERITY AND PERSISTENCE OF ADHD AND COMORBIDITY.

Richards JS, Vasquez AA, Rommelse NN, et al.

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is associated with conflicted parent-child relationships. The underlying mechanisms of this association are not yet fully understood. We investigated the cross-sectional and longitudinal relationships between externalizing psychopathology in children with ADHD, and expressed emotion (EE; warmth and criticism) and psychopathology in mothers.

METHOD: In this 6-year follow-up study, 385 children with an ADHD combined subtype were included at baseline (mean, 11.5 years, 83.4% male), of which 285 children (74%) were available at follow-up (mean, 17.5 years, 83.5% male). At both time points, measures of child psychopathology (i.e., ADHD severity, oppositional, and conduct problems), maternal EE, and maternal psychopathology (i.e., ADHD and affective problems) were obtained.

RESULTS: EE was not significantly correlated over time. At baseline, we found a nominally negative association (p </= .05) between maternal warmth and child ADHD severity. At follow-up, maternal criticism was significantly associated with child oppositional problems, and nominally with child conduct problems. Maternal warmth was nominally associated with child oppositional and conduct problems. These associations were independent of maternal psychopathology. No longitudinal associations were found between EE at baseline and child psychopathology at follow-up, or child psychopathology at baseline and EE at follow-up.

CONCLUSIONS: The results support previous findings of cross-sectional associations between parental EE and child psychopathology. This, together with the finding that EE was not stable over 6 years,

suggests that EE is a momentary state measure varying with contextual and developmental factors. EE does not appear to be a risk factor for later externalizing behavior in children with ADHD.

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J Am Acad Child Adolesc Psychiatry. 2014 Feb;53:174-87.

EFFICACY AND SAFETY OF ATOMOXETINE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RESULTS FROM A COMPREHENSIVE META-ANALYSIS AND METAREGRESSION.

Schwartz S, Correll CU.

OBJECTIVE: To comprehensively evaluate the efficacy and safety of atomoxetine (ATX) in pediatric attention-deficit/hyperactivity disorder (ADHD).

METHOD: Meta-analysis of all double-blind randomized controlled trials (DBRCTs) evaluating the efficacy and tolerability of ATX for ADHD. Pooled, random-effects analyses were conducted, calculating standardized mean difference (SMD), yielding effect sizes (ES), relative risk (RR), and number-needed-to-treat/harm (NNT/NNH).Moderator/mediator analyses were also conducted, including metaregression.

RESULTS: Across 25 DBRCTs (56 treatment arms, N=3,928), ATX outperformed placebo regarding overall ADHD symptoms (ES = -0.64, 95% confidence interval [CI] = -0.56 to -0.71, p < 0.0001), hyperactivity/impulsivity (ES = -0.67, CI = -0.53 to -0.81, p < 0.0001), and inattention (ES = -0.59, CI = -0.51 to -0.67, p < 0.0001). Altogether, 44.4% versus 21.4% of patients improved by >/=40% (NNT = 4), whereas 39.9% versus 65.9% improved by <25% (NNT = 4). Oppositional defiant disorder symptoms (ES = -0.33) and quality-of-life-related outcomes (ES = -0.48 to -0.25) improved somewhat less. A higher percentage of treatment-naive patients moderated the efficacy of ATX for overall ADHD symptoms (p = 0.017). All-cause discontinuation with ATX was similar to that for placebo (p = 1.00), with lower discontinuation because of inefficacy (relative risk [RR] = 0.51, CI = 0.36-0.74, p < 0.0001, NNT = 34), but higher discontinuation because of adverse effects (AEs) (RR = 1.89, CI = 1.08-3.31, p = 0.03, NNH = 50) with ATX. At least 1 adverse effect (AE) (70.4% versus 56.1%, p < 0.01, NNH = 6) and >/=1 psychiatric AE (21.5% versus 7.4%, NNH = 7, p < 0.01) were more frequent with ATX, whereas serious AEs (1.5% versus 1.0%), aggression (7.5% versus 6.0%), and suicidal ideation (1.3% versus 0.9%) were not different from placebo.

CONCLUSIONS: Short-term ATX treatment is safe and superior to placebo for overall ADHD symptoms and key secondary outcomes, with a medium ES. However, a relevant patient subgroup (40%) continues to have significant symptomatology, requiring additional clinical attention.

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J Am Acad Child Adolesc Psychiatry. 2014 Apr;53:425-36.

CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS ARE RISK FACTORS FOR OBESITY AND PHYSICAL INACTIVITY IN ADOLESCENCE.

Khalife N, Kantomaa M, Glover V, et al.

OBJECTIVE: To prospectively investigate the association and directionality between attention-deficit/hyperactivity disorder (ADHD) symptoms and obesity from childhood to adolescence in the general population. We examined whether obesogenic behaviors, namely, physical inactivity and binge eating, underlie the potential ADHD symptom-obesity association. We explored whether childhood conduct disorder (CD) symptoms are related to adolescent obesity/physical inactivity.

METHOD: At 7 to 8 years (n=8,106), teachers reported ADHD and CD symptoms, and parents reported body mass index (BMI) and physically active play. At 16 years (n=6,934), parents reported ADHD symptoms; adolescents reported physical activity (transformed to metabolic equivalent of task [MET] hours per week) and binge eating; BMI and waist-hip ratio (WHR) were measured via clinical examination. Obesity was defined using the International Obesity Task Force (IOTF) cut-offs for BMI and the 95th percentile cut-off for WHR.

RESULTS: Childhood ADHD symptoms significantly predicted adolescent obesity, rather than the opposite. Inattention-hyperactivity symptoms at 8 years were associated with indices of obesity at 16 years (obese BMI: odds ratio [OR]=1.91, 95% confidence interval [CI] = 1.10-3.33; 95th percentile WHR: OR=1.71, 95%

CI =1.05-2.78), adjusted for gender, baseline BMI, physical activity, family structure change, and maternal education. Child CD symptoms associated with indices of adolescent obesity. Reduced physically active play in childhood predicted adolescent inattention (OR=1.61, 95% CI=1.16-2.24). Childhood ADHD and CD symptoms were linked with physical inactivity in adolescence (inattention-hyperactivity; OR=1.60, 95% CI=1.20-2.13), but not binge eating. Physical inactivity mediated the associations.
CONCLUSIONS: Children with ADHD or CD symptoms are at increased risk for becoming obese and physically inactive adolescents. Physical activity may be beneficial for both behavior problems and obesity.

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J Am Acad Child Adolesc Psychiatry. 2014 Mar;53:274-96.
INFLAMMATION IN CHILDREN AND ADOLESCENTS WITH NEUROPSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW.
Mitchell RH, Goldstein BI.
OBJECTIVE: There has been rapid growth in research regarding inflammation in neuropsychiatric disorders as it relates to youth. We therefore set out to systematically review the literature on inflammation and neuropsychiatric disorders in children and adolescents.
METHOD: A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were included if proinflammatory markers (PIMs) in children and/or adolescents with neuropsychiatric disorders were measured.
RESULTS: Sixty-seven studies were included, involving 3,952 youth. Evidence for a proinflammatory state is strongest for autism spectrum disorders (ASD). PIMs are elevated in children and adolescents with major depressive disorder (MDD), bipolar disorder (BD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), Tourette's disorder (TD), attention-deficit/hyperactivity disorder (ADHD), and schizophrenia (SZ). However, the data are inconsistent. Evidence for specific PIMs is equivocal at this stage, although the findings in youth with MDD, BD, and PTSD converge with the extant adult literature in these areas. Definitive conclusions are limited by methodologic factors including cross-sectional and retrospective study design, between-study differences in specific markers and methods of analysis, small sample size, and other sources of heterogeneity.
CONCLUSION: The literature regarding inflammation among children and adolescents with neuropsychiatric disorders represents nearly 4,000 youth. There is preliminary evidence for elevated markers of inflammation in this population. Larger, prospective studies are needed to realize the goal of inflammatory markers informing clinical practice. In the interim, present findings suggest that further examination of this topic is warranted.

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J Am Osteopath Assoc. 2014 May;114:374-81.
EFFECT OF OSTEOPATHIC MANIPULATIVE THERAPY IN THE ATTENTIVE PERFORMANCE OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Accorsi A, Lucci C, Di ML, et al.
CONTEXT: Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder most commonly affecting children and teenagers. It is characterized by the coexistence of attention problems and impulsivity and hyperactivity. Although several studies have been conducted on the efficacy of conventional and alternative therapies in children with ADHD, few studies have specifically investigated the efficacy of osteopathic manipulative therapy (OMTh).
OBJECTIVE: To evaluate the efficacy of OMTh in the treatment of children with ADHD.
METHODS: Children aged 5 to 15 years with a primary diagnosis of ADHD who were admitted to a single neuropsychiatry unit from November 2008 to September 2009 were randomly assigned to an intervention group (OMTh + conventional care) or a control group (conventional care only). Biancardi-Stroppa Modified Bell Cancellation Test accuracy and rapidity scores were recorded for both groups at baseline and after 10 weeks. Statistical analyses included univariate tests and multivariate linear regressions.
RESULTS: A total of 28 participants were included in the study: 14 in the OMTh group and 14 in the control group. Univariate statistical analysis showed no statistically significant differences between the intervention

and control groups in terms of characteristics measured at baseline, except for psychosocial intervention (P=.05). Multivariate linear regression showed that OMTh was positively associated with changes in the Biancardi-Stroppa Test accuracy (beta=7.948 points; P=.04) and rapidity (beta=9.089 points; P=.03) scores.
CONCLUSION: Participants who received OMTh had greater improvement in Biancardi-Stroppa Test scores than participants who received conventional care only, suggesting that OMTh can potentially increase performances of selective and sustained attention in children with ADHD. To confirm these findings, studies of larger and more diverse populations are warranted.

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J Atten Disord. 2014 Jan.
PREVALENCE OF ADHD IN QATARI SCHOOL-AGE CHILDREN.
Bradshaw LG, Kamal M.
Objective: The purpose of this quantitative survey study is to provide current accurate estimates of the number of students with ADHD in Qatar Independent and English Medium Private Schools, so that adequate support will be available to assist in the educational growth and development of these students.
Method: This cross-sectional descriptive study of teacher observational ratings used a standardized rating scale. Teachers completed the SNAP-IV. Rating Scales for more than 5,000 students from Qatar Independent Schools and private English Medium Schools between November 2011 and November 2012 in Qatar Grades 1 through 12.
Results: Results align with and extend the previous study of ADHD in Qatar and the current worldwide prevalence.
Conclusion: Enhanced analyses were conducted to identify differences between age groups, genders, and between Private and Independent Schools. Implications for teachers, administrators, and medical personnel are discussed.

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J Atten Disord. 2014 Feb.
THE OUTSMARTERS PROGRAM FOR CHILDREN WITH ADHD: A PILOT STUDY ON THE EFFECTS OF SOCIAL SKILLS, SELF-REGULATION, AND EXECUTIVE FUNCTION TRAINING.
Hannesdottir DK, Ingvarsdottir E, Bjornsson A.
Objective: This study examined the effects of the OutSMARTers program on social skills, self-regulation, and executive functions compared with a Waitlist group and a parent training program.
Method: Participants were 41 children with ADHD, aged 8 to 10 years. All groups were assessed with behavioral checklists and neuropsychological measures at baseline and post-treatment. The two treatment groups were reassessed with behavioral checklists after 3 months.
Results: Findings revealed decreased ADHD symptoms, improved social skills, and better emotion regulation at post-treatment for the OutSMARTers compared with the Waitlist group on subjective measures. No differences were found on objective tasks or between the OutSMARTers and Parent groups after treatment but both treatment groups showed some improvement. In addition, most of the post-treatment changes were maintained for both groups 3 months later.
Conclusion: The results indicate that the OutSMARTers program seems to benefit children with ADHD, but further research and treatment development is needed.

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J Atten Disord. 2014 Apr.

UNDERSTANDING AND MEASURING FUNCTIONAL IMPAIRMENT IN DIVERSE CHILDREN WITH ADHD: DEVELOPMENT OF THE ADHD-FX SCALE WITH AN AT-RISK, COMMUNITY SAMPLE.

Haack LM, Gerdes AC, Lawton KE, et al.

Objective: The current study sought to develop a culturally appropriate measure of functional impairment related to ADHD for diverse families, as research suggests that functional impairment may be a more culturally universal construct than symptomatology.
Method: Seventy-four low-acculturated Latino parents (49 mothers and 25 fathers) of school-aged children provided quantitative and qualitative responses about problem recognition after viewing a language-free video of a child displaying symptoms and behaviors consistent with ADHD.
Results: Thirty-two items were developed for the ADHD-FX scale based on most common responses given from participants. The scale is available in Spanish and English and instructs parents to consider how much each item affects their child in his or her everyday life (from 0 = not at all to 3 = a lot).
Conclusions: The scale can provide an overall impairment score, as well as subscale scores in the theoretically derived domains of academic, peer, and familial impairment.

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J Atten Disord. 2014 Jan.

THE DEVELOPMENT OF COMORBID CONDUCT PROBLEMS IN CHILDREN WITH ADHD: AN EXAMPLE OF AN INTEGRATIVE DEVELOPMENTAL PSYCHOPATHOLOGY PERSPECTIVE.

Danforth JS, Connor DF, Doerfler LA.

Objective: We describe interactions among factors that contribute to the development of conduct problems among children with ADHD.
Method: An integrative developmental psychopathology analysis combines various approaches and posits one model of how diverse risk factors operate together to contribute to the development of conduct problems among children with ADHD.
Results: Substantial genetic risk increases covariation between ADHD and conduct problems. Candidate genes are associated with CNS monoaminergic neurotransmission. Subsequent neurodevelopmental impairment interferes with executive function, with impaired verbal working memory playing an important role. Parent/child bi-directional influences exacerbate the risk for conduct problems when ADHD symptoms increase the likelihood of a coercive parenting style. Parent stress in reaction to child comorbid ADHD and conduct problems, and parent attribution for the child's conduct problem behavior, add to the potential for coercion and reduce constructive parent-child interaction that might otherwise enhance the development of verbal working memory.
Conclusion: In an integrated manner, these variables increase the risk that a child with ADHD will subsequently develop conduct problems.

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J Atten Disord. 2014 Jan.

EFFICACY AND SAFETY OF OMEGA-3/6 FATTY ACIDS, METHYLPHENIDATE, AND A COMBINED TREATMENT IN CHILDREN WITH ADHD.

Barragan E, Breuer D, Dopfner M.

Objective: To compare efficacy of Omega-3/6 fatty acids (Equazen eye q) with methylphenidate (MPH) and combined MPH + Omega-3/6 in children with ADHD.
Method: Participants (N=90) were randomized to Omega-3/6, long-acting MPH, or combination for 12 months. ADHD symptoms were assessed using the ADHD Rating Scale and Clinical Global Impressions-Severity (CGI-S) scale.
Results: ADHD symptoms decreased in all treatment arms. Although significant differences favoring Omega + MPH over Omega-3/6 alone were found for ADHD Total and Hyperactivity-Impulsivity subscales, results on the Inattention subscale were similar. CGI-S scores decreased slowly and consistently with

Omega-3/6, compared with a rapid decrease and subsequent slight increase in the MPH-containing arms. Adverse events were numerically less frequent with Omega-3/6 or MPH + Omega-3/6 than MPH alone.
Conclusion: The tested combination of Omega-3/6 fatty acids had similar effects to MPH, whereas the MPH + Omega combination appeared to have some tolerability benefits over MPH.

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J Atten Disord. 2014 Jan.
CEREBELLAR SYMPTOMS ARE ASSOCIATED WITH OMISSION ERRORS AND VARIABILITY OF RESPONSE TIME IN CHILDREN WITH ADHD.
Goetz M, Schwabova J, Hlavka Z, et al.
Objective: We examined the presence of cerebellar symptoms in ADHD and their association with behavioral markers of this disorder.
Method: Sixty-two children with ADHD and 62 typically developing (TD) children were examined for cerebellar symptoms using the ataxia rating scale and tested using Conners' Continuous Performance Test.
Results: Children with ADHD had significantly more cerebellar symptoms compared with the TD children. Cerebellar symptom scores decreased with age in the ADHD group; in the TD group remained stable. In both groups, cerebellar symptoms were associated with parent-rated hyperactive/impulsive symptoms, variability of response time standard error (RT-SE) and increase of RT-SE as the test progresses. More variables were associated with cerebellar symptoms in the ADHD group including omission errors, overall RT-SE and its increase for prolonged interstimulus intervals.
Conclusion: Our results highlight the importance of research into motor functions in children with ADHD and indicate a role for cerebellar impairment in this disorder.

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J Atten Disord. 2014 Jan.
THE ROLE OF PARENTAL EDUCATION IN THE RELATION BETWEEN ADHD SYMPTOMS AND EXECUTIVE FUNCTIONS IN CHILDREN.
Tillman C, Granvald V.
Objective: Using a population-based sample of 9-year-old children, this study examined whether the relation between symptoms of ADHD and executive functions (EFs) depended on socioeconomic status (SES; indexed by parental education).
Method: Parents and teachers rated the children's ADHD symptoms, and parents also indicated their educational level in a questionnaire. The children performed a comprehensive set of EF tasks.
Results: Whereas working memory was similarly related to ADHD symptoms in the lower and higher parental education group, the relations of inhibition and mental set-shifting with ADHD symptoms were generally stronger in the higher educational group, a pattern that was supported by several significant group differences in correlations.
Conclusion: This suggests that the EF pathway in contemporary multiple pathway models of ADHD etiology may be particularly relevant in higher SES parts of the population.

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J Atten Disord. 2014 Mar.
PRELIMINARY EFFICACY OF A BEHAVIORAL PARENT TRAINING PROGRAM FOR CHILDREN WITH ADHD IN PAKISTAN.
Malik TA, Rooney M, Chronis-Tuscano A, et al .
Objective: In an effort to address the lack of evidence-based interventions for ADHD in developing South Asian countries, we examined the preliminary efficacy of a behavioral parent training program in Pakistan.
Method: A quasi-experimental design was utilized. Eighty-five 4- to 12-year-old children with clinically significant ADHD symptoms participated: 55 were recruited from hospital clinics (active treatment group)

and 30 were recruited from schools (waitlist control group). Parent and teacher ratings of ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) symptoms and impairment were collected.
Results: Using intent-to-treat analyses, the treatment group showed significant pre-post improvement on parent-reported ODD symptoms and ADHD-related impairment. Teacher ratings showed no improvement.
Conclusion: This study provides preliminary evidence for the feasibility and effectiveness of behavioral parenting training for children with ADHD in Pakistan and represents a critical first step in identifying evidence-based treatments for Pakistani children with ADHD.

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J Atten Disord. 2014 Jan.
ACCIDENT PRONENESS IN CHILDREN AND ADOLESCENTS AFFECTED BY ADHD AND THE IMPACT OF MEDICATION.
Lange H, Buse J, Bender S, et al.
Objective: This study aims to ascertain once and for all whether children and adolescents affected by ADHD show a higher risk for accidents, as well as investigating a possible association between the administration of ADHD-specific medication and the occurrence of accidents.
Method: Two exceptionally large sets of data were implemented in this analysis. Participants included children and adolescents representative of the entire German population. Data for Survey 1 was collected through extensive administration of questionnaires. Data for Survey 2 stemmed from the records of a leading German health insurance company. In terms of statistical analysis, chi-square tests as well as logistic regression analyses were applied and odds ratios (ORs) were determined.
Results: Innovative results are presented showing a significantly higher likelihood for ADHD-affected youngsters to be involved in accidents compared with their nonaffected counterparts (Survey 1: OR=1.60; Survey 2: OR=1.89) but lacking an overall significant influence of medication regarding the occurrence of accidents (Survey 1: OR=1.28; Survey 2: OR=0.97). Frequency of accidents could be predicted by ADHD, gender, and age in both samples. Medication intake served as a weak predictor only in Survey 2.
Conclusion: It has been determined in two representative and independent German samples that youngsters with ADHD are at a significantly higher risk of being involved in accidents. In the future, this should always be considered when setting up a treatment plan to ensure a safer and healthier coming of age without relying solely on specific effects of medication.

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J Atten Disord. 2014 Mar.
ATYPICAL ACTIVATIONS OF FRONTO-CEREBELLAR REGIONS DURING FORETHOUGHT IN PARENTS OF CHILDREN WITH ADHD.
Rapin L, Poissant H, Mendrek A.
Objective: Although several studies suggest heritability of ADHD, only a few investigations of possible associations between people at risk and neural abnormalities in ADHD exist. In this study, we tested whether parents of children with ADHD would show atypical patterns of cerebral activations during forethought, a feature of working memory.
Method: Using Functional Magnetic Resonance Imaging (fMRI), we compared 12 parents of children with ADHD and 9 parents of control children during a forethought task.
Results: Parents of children with ADHD exhibited significantly increased neural activations in the posterior lobes of the cerebellum and in the left inferior frontal gyrus, relative to parents of control children.
Conclusion: These findings are consistent with previous reports in children and suggest the fronto-cerebellar circuit's abnormalities during forethought in parents of children with ADHD. Future studies of people at risk of ADHD are needed to fully understand the extent of the fronto-cerebellar heritability.

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J Atten Disord. 2014 Feb.

ATTACHMENT COMPETENCES IN CHILDREN WITH ADHD DURING THE SOCIAL-SKILLS TRAINING AND ATTACHMENT (SOSTRA) RANDOMIZED CLINICAL TRIAL.

Storebo OJ, Skoog M, Darling RP, et al.

Objective: To investigate the effects of social-skills training and a parental training program on children with ADHD as measured by the children's attachment competences.

Method: The SOSTRA trial is a randomized, parallel-group, outcome-assessor-blinded, superiority trial evaluating 8 weeks social-skills training and parental training plus standard treatment versus standard treatment alone for 8- to 12-year old children with ADHD.

Results: There were no significant differences in attachment competences at 6 months between the experimental (n=25) and the control (n=22) groups (odds ratio=1.06, 95% confidence interval=[0.31, 3.58], p=.91). In total, 17 children (36%) changed their entry status, 1 (2%) from secure to insecure attachment, while 16 (34%) changed from insecure to secure attachment.

Conclusion: The experimental treatment does not seem to affect attachment competences compared with standard treatment alone. Children in the SOSTRA trial improved their attachment competences significantly at 6-month follow-up.

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J Atten Disord. 2014 Mar.

POSSIBLE COGNITIVE BENEFITS OF ACUTE PHYSICAL EXERCISE IN CHILDREN WITH ADHD: A SYSTEMATIC REVIEW.

Grassmann V, Alves MV, Santos-Galduroz RF, et al.

Objective: Studies have suggested that even a single session of physical exercise enhances executive functions. ADHD is among the most common developmental disorders in childhood, but little is known about alternative treatments for this disorder. Therefore, we performed a systematic review of the literature to analyze articles that evaluated the executive functions of children with ADHD after an acute exercise session.

Method: We reviewed articles indexed in the PubMed, American Psychiatric Association (APA) psychNET, Scopus, and Web of Knowledge databases between 1980 and 2013.

Results: Of 231 articles selected, only three met the inclusion criteria.

Conclusion: Based on these 3 articles, we concluded that 30 min of physical exercise reportedly improved the executive functions of children with ADHD. Due to the small number of articles selected, further studies are needed to confirm these benefits.

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J Atten Disord. 2014 Apr.

CURRENT MOOD SYMPTOMS DO NOT AFFECT THE ACCURACY OF RETROSPECTIVE SELF-RATINGS OF CHILDHOOD ADHD SYMPTOMS.

Grogan K, Bramham J.

Objective: Given that the diagnosis of adulthood ADHD depends on the retrospective self-report of childhood ADHD symptoms, this study aimed to establish whether current mood affects the accuracy of retrospective self-ratings of childhood ADHD.

Method: Barkley's Adult ADHD Rating Scale (BAARS) was used to assess the retrospective self- and parent-reports of childhood ADHD symptoms of 160 adults with ADHD and 92 adults without ADHD. Self-rated current mood was also measured using the Hospital Anxiety and Depression Scale (HADS).

Results: Higher BAARS self-ratings correlated with higher HADS self-ratings. Strongest correlations were evident between hyperactive/impulsive symptoms and anxiety symptoms. There was no relationship between current mood and accuracy of self-report.

Conclusion: Current mood does not affect the accuracy of retrospective self-ratings of ADHD. Future research should aim to provide new measures of anxiety in ADHD to avoid the double counting of hyperactive/impulsive and anxiety symptoms.

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J Atten Disord. 2014 Apr.

THE SEX RATIO OF FULL AND HALF SIBLINGS OF PEOPLE DIAGNOSED WITH ADHD IN CHILDHOOD AND ADOLESCENCE: A DANISH NATIONWIDE REGISTER-BASED COHORT STUDY.

Mouridsen SE, Rich B, Isager T.

Objective: It has been suggested that high levels of prenatal testosterone exposure are implied in the etiology of male preponderance disorders such as autism spectrum disorder and ADHD. Within this scope, we studied the sex ratio (proportion of males) in siblings of individuals diagnosed with ADHD in childhood and adolescence.

Method: We did a nationwide, register-based cohort study of the sex ratio in siblings of the 16,381 patients in Denmark diagnosed with ADHD at age 17 years and younger and registered in the nationwide Danish Psychiatric Central Register between January 1, 1994 and May 28, 2013.

Results: Among the 33,151 siblings, 17,041 were males and 16,110 females. This yields a sex ratio of 0.514, which is not statistically significant different from the Danish live birth sex ratio of 0.513 during the relevant years (p = .70).

Conclusion: These findings provide no support for the hypothesis that the sex ratio is elevated among the siblings of people with ADHD.

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J Child Adolesc Psychopharmacol. 2014 Apr;24:140-48.

A RANDOMIZED, CONTROLLED, CROSSOVER TRIAL OF FISH OIL TREATMENT FOR IMPULSIVE AGGRESSION IN CHILDREN AND ADOLESCENTS WITH DISRUPTIVE BEHAVIOR DISORDERS.

Dean AJ, Bor W, Adam K, et al.

Abstract

Objective: Epidemiological research links aggression to low serum concentrations of omega-3 fatty acids, such as those found in fish oil. However, no studies have specifically examined whether fish oil supplementation can reduce the frequency and severity of impulsive aggression in children with disruptive behavior disorders.

Methods: Children presenting with impulsive aggression and meeting research criteria for diagnosis of disruptive behavior disorders were randomized to receive either: 1) Fish oil capsules (4 g daily) for 6 weeks followed by placebo (identical-looking capsules) for 6 weeks; or 2) placebo for 6 weeks, followed by fish oil for 6 weeks, in a double-blind, crossover design. Primary outcomes were the Children's Aggression Scale and the Modified Overt Aggression Scale. Secondary outcomes included emotional and behavioral functioning (Strengths and Difficulties Questionnaire [SDQ]), hyperactivity symptoms (Attention-Deficit/Hyperactivity Disorder [ADHD] Rating Scale), family functioning (Family Assessment Device), and cognitive functioning (Stop Signal Task, Trail-Making Task, and Eriksen Flanker Task). Serum concentrations of omega-3 and omega-6 fatty acids were measured at baseline, and at 6 and 12 weeks.

Results: Twenty-one children participated (81% male; mean age 10.3+/-2.2 years; range 7-14). Fish oil treatment increased serum concentrations of eicosapentanoic acid ($F=14.76$, $p<0.05$) and total omega-3s ($F=20.56$, $p<0.05$), but did not influence primary ratings of aggression. In fact, a trend suggested that fish oil worsened a secondary measure of aggression (SDQ Conduct Subscale, $F=4.34$, $p=0.06$). Fish oil treatment was associated with an improvement in one rating of hyperactivity (SDQ Hyperactivity Subscale, $F=2.22$, $p<0.05$), but did not influence any other outcome measures.

Conclusions: These findings suggest that fish oil treatment does not improve aggression in children with disruptive behavior disorders.

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J Child Adolesc Psychopharmacol. 2014 Apr;24:112-19.

ATYPICAL ANTIPSYCHOTIC USE AMONG MEDICAID-INSURED CHILDREN AND ADOLESCENTS: DURATION, SAFETY, AND MONITORING IMPLICATIONS.

Burcu M, Zito JM, Ibe A, et al.

Abstract

Objective: Over the last two decades, the increased use of atypical antipsychotic medications, often for unlabeled indications including attention-deficit/hyperactivity disorder (ADHD), has been profound. This study aims to characterize duration of atypical antipsychotic use by age group and Medicaid eligibility category, and among youth with noncomorbid ADHD.

Methods: Administrative data on 266,590 youth 2-17 years of age, and continuously enrolled in a mid-Atlantic state Medicaid program in 2006, were assessed in terms of median days of atypical antipsychotic use using bivariate analyses and multivariable quantile regression. Also, in a subanalysis of youth diagnosed with ADHD without any reported psychiatric comorbidities (i.e., noncomorbid ADHD), age-specific adjusted odds and adjusted median days of atypical antipsychotic use by Medicaid eligibility category were assessed. Additionally, patterns of use of single atypical antipsychotic regimens and two concomitant atypical antipsychotic regimens were described.

Results: Overall, the median annual duration of atypical antipsychotic use was 180 days (interquartile range: 69-298 days). Children (2-12-year-olds) had longer durations of use than did adolescents (13-17-year-olds) (median 192 vs. 179 days), respectively. In the absence of any comorbid psychiatric diagnosis, ADHD-diagnosed foster care youth had more than threefold greater adjusted odds of atypical antipsychotic use than did youth enrolled in income-eligible Medicaid categories. Nearly one third of such ADHD-diagnosed foster care youth received atypical antipsychotics regardless of age group, with annual duration of use >250 median days in 2-12-year-olds. In concomitant atypical antipsychotic regimens, risperidone, aripiprazole, and quetiapine were the most common.

Conclusions: Exposure to atypical antipsychotics in Medicaid-insured youth, in particular for children in foster care and those diagnosed with ADHD, was substantial, warranting outcomes research for long-term effectiveness, safety, and oversight for appropriate cardiometabolic monitoring.

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J Child Neurol. 2014 Apr.

THE NEUROLOGIC PROFILE OF CHILDREN AND ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE.

Ben-Or O, Zelnik N, Shaoul R, et al.

In recent years, there has been an increasing incidence of inflammatory bowel disease in children and adolescents. Neurologic involvement has been mainly reported in adults, and information in pediatrics is based primarily on individual case reports. In this study, we explored the prevalence and spectrum of neurologic manifestations of 50 children with inflammatory bowel disease in comparison to healthy controls. Based on clinical reports and neurologic evaluation, 34 patients (68%) exhibited neurologic manifestations compared with 10 children (23.8%) in the control group (P < .001). The main symptoms associated with inflammatory bowel disease in comparison to the control subjects were headache: 46% vs 3% (P < 0.001), dizziness: 26% vs none (P < .001), hypotonia: 10% vs none (P = .06), attention-deficit hyperactivity disorder (ADHD): 28% vs 7.1% (P < .001), tics and sensory complaints: 16% vs 2.4% (P = .036). Seizures and neuropsychiatric disorders were less characteristic. A larger-scale prospective study is required to further clarify this association.

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J Child Neurol. 2014 Jan.

REDUCED SHORT INTERVAL CORTICAL INHIBITION CORRELATES WITH ATOMOXETINE RESPONSE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).

Chen TH, Wu SW, Welge JA, et al.

Clinical trials in children with attention-deficit hyperactivity disorder (ADHD) show variability in behavioral responses to the selective norepinephrine reuptake inhibitor atomoxetine. The objective of this study was to

determine whether transcranial magnetic stimulation-evoked short interval cortical inhibition might be a biomarker predicting, or correlating with, clinical atomoxetine response. At baseline and after 4 weeks of atomoxetine treatment in 7- to 12-year-old children with ADHD, transcranial magnetic stimulation short interval cortical inhibition was measured, blinded to clinical improvement. Primary analysis was by multivariate analysis of covariance. Baseline short interval cortical inhibition did not predict clinical responses. However, paradoxically, after 4 weeks of atomoxetine, mean short interval cortical inhibition was reduced 31.9% in responders and increased 6.1% in nonresponders (analysis of covariance t 41=2.88; P=.0063). Percentage reductions in short interval cortical inhibition correlated with reductions in the ADHD Rating Scale (r=0.50; P=.0005). In children ages 7 to 12 years with ADHD treated with atomoxetine, improvements in clinical symptoms are correlated with reductions in motor cortex short interval cortical inhibition.

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J Child Neurol. 2014 Mar.

SOCIAL COMMUNICATION FEATURES IN CHILDREN FOLLOWING MODERATE TO SEVERE ACQUIRED BRAIN INJURY: A CROSS-SECTIONAL PILOT STUDY.

Breau LM, Clark B, Scott O, et al.

We compared the social communication deficits of children with moderate to severe acquired brain injury or autism spectrum disorder, while accounting for the role of attention-deficit hyperactivity disorder (ADHD) symptoms. Parents of 20 children aged 6 to 10 years (10 acquired brain injury; 10 autism spectrum disorder) completed the Social Communication Questionnaire, and Conners 3 Parent Short. A multivariate analysis of covariance revealed significant differences between groups in Social Communication Questionnaire restricted repetitive behavior scores, but not reciprocal social interaction or social communication. Multiple linear regressions indicated diagnosis did not predict reciprocal social interaction or social communication scores and that Conners 3 Parent Short Form hyperactivity scores were the strongest predictor of Social Communication Questionnaire reciprocal social interaction scores after accounting for age and Intelligence Quotient. The lack of difference in social communication deficits between groups may help in understanding the pathophysiology underlying the behavioral consequences of acquired brain injury. The link between hyperactivity and reciprocal interaction suggests that targeting hyperactivity may improve social outcomes in children following acquired brain injury.

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J Child Neurol. 2014 May;29:608-16.

BEHAVIORAL ASSESSMENT OF THE DYSEXECUTIVE SYNDROME FOR CHILDREN: AN EXAMINATION OF CLINICAL UTILITY FOR CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).

Siu AF, Zhou Y.

The present study evaluated the utility of the Behavioral Assessment of Dysexecutive Syndrome for Children for discerning differences in executive functioning between attention-deficit hyperactivity disorder (ADHD) children and normal controls and examined its associations with real-life executive function as rated by parent reports on the Dysexecutive Questionnaire for Children. Sixty-three children diagnosed with ADHD and 60 normal healthy peers were recruited for this study. All participants completed the Behavioral Assessment of Dysexecutive Syndrome for Children, while their parents completed the Dysexecutive Questionnaire for Children. Results revealed that the ADHD group exhibited significantly poorer performance than the controls on 3 subtests of the Behavioral Assessment of Dysexecutive Syndrome for Children (ie, Playing Cards Test, Water Test, and Zoo Map Test 2), as well as on the total Dysexecutive Questionnaire for Children. Significant correlation was found between the total Dysexecutive Questionnaire for Children and the 6-Part Test. Findings suggested that some subtests of the Behavioral Assessment of Dysexecutive Syndrome for Children were particularly useful for detecting real-life executive dysfunction in ADHD. Yet, further studies are needed to provide extended validity data.

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J Child Neurol. 2014 Feb.

PLANNING DEFICIT IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1: A NEUROCOGNITIVE TRAIT INDEPENDENT FROM ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)?

Galasso C, Lo-Castro A, Di CL, et al.

Neurofibromatosis type 1 is associated with executive dysfunctions and comorbidity with attention-deficit hyperactivity disorder (ADHD) in 30% to 50% of children. This study was designed to clarify the neurocognitive phenotype observed in neurofibromatosis type 1 by testing the hypothesis that children with neurofibromatosis type 1 have specific planning deficits independently from intellectual level and ADHD comorbidity. Eighteen children with neurofibromatosis type 1 were pair-matched to 18 children with ADHD and 18 healthy controls. All groups were assessed on the presence of ADHD symptoms (Conners Scales) and planning deficits (Tower of London). Compared with control group, groups with neurofibromatosis type 1 and ADHD demonstrated significant impairment of planning and problem solving. The lack of correlation between Tower of London results and Conners subscale scores in neurofibromatosis type 1 group confirmed that the planning and problem-solving deficit is not directly related to inattention level. These findings suggested that the executive impairment probably represents a peculiar trait of neurofibromatosis type 1 neurocognitive phenotype.

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J Child Psychol Psychiatry. 2014 Jan.

NEUROPSYCHOLOGICAL FUNCTIONING IN CHILDHOOD-ONSET PSYCHOSIS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Brodsky K, Willcutt EG, Davalos DB, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and childhood-onset psychosis (COP) are chronic, heterogeneous disorders with symptoms that frequently co-occur, but the etiology of their comorbidity is unknown. Studies of each disorder indicate that both ADHD and COP are associated with a range of neuropsychological weaknesses, but few neuropsychological studies have directly compared groups with ADHD and COP.

METHODS: Groups with ADHD only (32 F, 48 M), COP only (5 F, 5 M), ADHD + COP (9 F, 21 M), and a control group with neither disorder (25 F, 44 M) completed a neuropsychological battery that included measures of verbal working memory, response inhibition, response speed and variability, and selective attention.

RESULTS: All three clinical groups exhibited significantly lower performance versus the control group on all neuropsychological measures, whereas the only significant difference between the clinical groups was a significantly larger weakness in verbal working memory in the groups with COP.

CONCLUSIONS: The frequent co-occurrence between COP and ADHD may reflect shared neuropsychological weaknesses that are most pronounced on measures of working memory and response variability.

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J Child Psychol Psychiatry. 2014 Mar.

WORKING MEMORY TRAINING IN YOUNG CHILDREN WITH ADHD: A RANDOMIZED PLACEBO-CONTROLLED TRIAL.

Van Dongen-Boomsma M, Vollebregt MA, Buitelaar JK, et al.

ACKGROUND: Until now, working memory training has not reached sufficient evidence as effective treatment for ADHD core symptoms in children with ADHD; for young children with ADHD, no studies are available. To this end, a triple-blind, randomized, placebo-controlled study was designed to assess the efficacy of Cogmed Working Memory Training (CWMT) in young children with ADHD.

METHODS: Fifty-one children (5-7 years) with a DSM-IV-TR diagnosis of ADHD (without current psychotropic medication) were randomly assigned to the active (adaptive) or placebo (nonadaptive) training condition for 25 sessions during 5 weeks. The compliance criterion (>20 sessions) was met for 47 children. The primary outcome measure concerned the core behavioural symptoms of ADHD, measured with the ADHD Rating Scale IV (ADHD-RS). Secondary outcome measures were neurocognitive functioning, daily

executive functioning, and global clinical functioning. The influence of the increase in difficulty level (Index-Improvement) for the treatment group was also analysed. Clinical trial registration information - 'Working Memory Training in Young ADHD Children'; www.clinicaltrials.gov; NCT00819611.
RESULTS: A significant improvement in favour of the active condition was found on a verbal working memory task (p=.041; adapted Digit Span WISC-III, backward condition). However, it did not survive correction for multiple testing. No significant treatment effect on any of the primary or other secondary outcome measurements was found. The Index-Improvement significantly contributed to ADHD-RS and the Behavior Rating Inventory of Executive Function, both rated by the teacher, but revealed no significant group difference.
CONCLUSIONS: This study failed to find robust evidence for benefits of CMWT over the placebo training on behavioural symptoms, neurocognitive, daily executive, and global clinical functioning in young children with ADHD.

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J Child Psychol Psychiatry. 2014 May;55:413-15.
EDITORIAL: THE POWER OF TREATMENT STUDIES TO EXPLORE CAUSAL PROCESSES IN CHILDHOOD DISORDERS.
Anon
We all have a tendency to be easily seduced by Occam's razor, or the desire to accept the simplest hypothesis to explain a given phenomenon. If we observe that children with ADHD come from more impoverished backgrounds or have diets that contain more additives than their peers, then a parsimonious theory would be that poverty and/or diet are causal factors in the development of ADHD. Such theories are all the more attractive because they suggest potential targets for intervention: improve family circumstances and child diet and symptoms of ADHD should diminish. Of course in reality untangling causal relationships is much more complicated. We now accept that many common disorders reflect the confluence of genetic and environmental risk factors, but that any given risk factor is likely to account for only a tiny amount of explained variance in symptom profile. What's more, in order to fulfil the promise of intervention, we must begin to unravel the precise mechanisms by which identified risk factors affect the developing system. This issue showcases two key methodologies for understanding causal influences on developmental disorders: longitudinal designs and well-controlled intervention studies. Both may employ statistical techniques that can identify the mediators of observed associations, elucidating potential mechanistic processes.

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J Clin Child Adolesc Psychol. 2014 Apr.
LONGITUDINAL CHANGES IN INDIVIDUAL SYMPTOMS ACROSS THE PRESCHOOL YEARS IN CHILDREN WITH ADHD.
Harvey EA, Lugo-Candelas CI, Breaux RP.
The present study examined trajectories of individual Diagnostic and Statistical Manual of Mental Disorders (4th ed.) symptoms of attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) across the preschool years in children with ADHD. It also evaluated whether preschool symptoms vary in their ability to discriminate children who later meet criteria for ADHD from typically developing children. ADHD and ODD symptoms were assessed annually in 75 ethnically diverse children (46 boys) who presented with behavior problems at age 3 and met criteria for ADHD 3 years later, and in 51 typically developing children (26 boys). Children with ADHD generally exhibited stable levels of hyperactivity/impulsivity but increases in several symptoms of inattention. Most ADHD symptoms showed at least fair utility in discriminating children with and without ADHD; however, 3 symptoms of inattention (carelessness, losing things, and forgetfulness) and 1 symptom of hyperactivity/impulsivity (blurting out answers) had relatively poor utility. These symptoms demonstrated only somewhat greater utility at age 4, but by the age of 5 were better able to classify children. Children with ADHD exhibited increases in several ODD symptoms, including symptoms related to negative affect. Although most symptoms of

hyperactivity/impulsivity appear to extend well down to age 3, more developmentally appropriate symptoms of inattention may be required to develop more sensitive assessments for 3- and 4-year-old children.

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J Clin Child Adolesc Psychol. 2014 Apr.

IMPLICATIONS OF PARENTAL AFFILIATE STIGMA IN FAMILIES OF CHILDREN WITH ADHD.

Mikami AY, Chong GK, Saporito JM, et al.

This study examined parents' perceptions/awareness and internalization of public courtesy stigma (affiliate stigma) about their children's inattentive and hyperactive/impulsive symptoms, and associations between parental affiliate stigma, parental negativity expressed toward the child, and child social functioning. Participants were families of 63 children (ages 6-10; 42 boys) with attention-deficit/hyperactivity disorder, assessed in a cross-sectional design. After statistical control of children's severity of inattentive and hyperactive/impulsive symptoms (as reported by parents and teachers), parents' self-reports of greater affiliate stigma were associated with more observed negative parenting. The associations between high parental affiliate stigma and children's poorer adult informant-rated social skills and greater observed aggression were partially mediated by increased parental negativity. As well, the positive association between children's adult informant-rated aggressive behavior and parental negativity was partially mediated by parents' increased affiliate stigma. Parental affiliate stigma about their children's inattentive and hyperactive/impulsive symptoms may have negative ramifications for parent-child interactions and children's social functioning. Clinical implications for parent training interventions are discussed.

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J Clin Psychiatry. 2013 Dec;74:1217-23.

ATOMOXETINE TOLERABILITY IN PEDIATRIC AND ADULT PATIENTS RECEIVING DIFFERENT DOSING STRATEGIES.

Wietecha LA, Ruff DD, Allen AJ, et al.

OBJECTIVE: Examine how different dosing schedules and recent stimulant therapy effect incidence, time to onset, and duration of common treatment-emergent adverse events (TEAEs) during atomoxetine treatment.

METHOD: Post hoc analyses including safety data (open-ended questions) from 22 pediatric and 3 adult atomoxetine trials (1998-2009) in patients with attention-deficit/hyperactivity disorder. Most common TEAEs were determined by incidence rates and frequency of consumer and clinician inquiries. Onset and duration of TEAEs with slow versus fast titration, once-daily versus twice-daily dosing, and previous stimulant exposure were compared among treatment groups using Kaplan-Meier methods.

RESULTS: In pediatric patients, the most commonly reported TEAEs were abdominal pain, decreased appetite, fatigue, nausea, somnolence, and vomiting; time to onset of TEAEs was significantly shorter for once-daily versus twice-daily dosing for all TEAEs (P</=.007) and for fast versus slow titration for abdominal pain, decreased appetite, and somnolence (all P values </=.009); duration of TEAEs with once-daily dosing was significantly longer for decreased appetite (P=.001) and nausea (P=.041); and more common in stimulant-naive patients versus patients with prior stimulant use were abdominal pain, decreased appetite, and fatigue (P</=.047). In adult patients, the most commonly reported TEAEs (erectile dysfunction data were excluded) were nausea, insomnia, decreased appetite, urinary hesitation/urinary retention, and fatigue; insomnia had a significantly shorter time to onset and longer duration with twice-daily versus once-daily dosing (P</=.032) and fast versus slow titration (P</=.007).

CONCLUSIONS: Time to onset and resolution of TEAEs appear dependent on dosing schedule and titration speed. These findings can help to better manage tolerability issues and set appropriate expectations for clinicians and patients during atomoxetine titration, potentially improving treatment adherence and success.

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J Egypt Public Health Assoc. 2014 Apr;89:9-15.

EFFICACY OF A PSYCHOSOCIAL INTERVENTION FOR PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, ALEXANDRIA, EGYPT.

Shata ZN, Abu-Nazel MW, Fahmy SI, et al.

BACKGROUND: Childhood attention deficit hyperactivity disorder (ADHD) is a chronic disorder that carries an immense amount of suffering for its victims, their families, and communities. The efficacy of behavioral parent training in the treatment of ADHD has been supported in several studies.
OBJECTIVE: To evaluate the efficacy of a predesigned culturally sensitive psychosocial intervention program for parents of ADHD children in Alexandria, Egypt.
PARTICIPANTS AND METHODS: A pretest-post-test intervention study was carried out at the Child Mental Health Clinic for School Students affiliated to the Health Insurance Organization, Alexandria. The intervention aimed at improving parents' knowledge of ADHD, building their skills in effective parenting, stress management and problem-solving, as well as providing social support. All the participants (50 parents) were assigned to groups, each of five to eight parents. They received a total of eight sessions on a weekly basis. The program was evaluated immediately after completion and 2 months later using the Arabic Version of Conners' Rating Scale to identify ADHD and to assess its severity, Home Situations Questionnaire, Parenting Scale, the Arabic Version of Depression Anxiety Stress Scales (DASS), and parental ADHD-related knowledge questionnaire were used. RESULTS: There was a statistically significant decrease in the mean total scores recorded by parents on Conners' Rating Scale (P<0.001), Home Situations Questionnaire (P<0.05), Parenting Scale (P<0.001), and DASS (P<0.001) immediately after program completion and 2 months later compared with that reported before program initiation. The total scores of participants on the ADHD-related knowledge questionnaire increased significantly after attending the program (P<0.001).
CONCLUSION AND RECOMMENDATIONS: Provision of a psychosocial intervention program for parents of ADHD children proved to be effective in reducing perceived severity of the symptoms and problem situations, as well as improving parents' knowledge, discipline practices, and psychological well-being.

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J Fam Pract. 2014 Feb;63:E1-E5.

STIMULANTS FOR KIDS WITH ADHD--HOW TO PROCEED SAFELY.

Ken MS, Jacobs I.

A cardiac-focused history and physical exam are essential before you write that prescription. But what about an EKG? Should you order one--or not?

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J Family Med Prim Care. 2013 Apr;2:164-68.

A CROSS-SECTIONAL STUDY OF COMMON PSYCHIATRIC MORBIDITY IN CHILDREN AGED 5 TO 14 YEARS IN AN URBAN SLUM.

Patil RN, Nagaonkar SN, Shah NB, et al.

AIM: Study of the prevalence of common psychiatric disorders in children aged 5 to 14 years in a health post area of an urban slum.
OBJECTIVES: (1) To study frequency of specific psychiatric disorders in the study population, (2) To study the relationship between sociodemographic variables and psychiatric morbidity.
SETTINGS AND DESIGN: The present study was conducted in one of the five health posts of an urban slum, which is a field practice area of the teaching medical institute. It was a cross-sectional study.
MATERIALS AND METHODS: Sample size was estimated by using 20% as a prevalence of psychiatric morbidity which was obtained from previous studies done in developing countries. Household was used as a sampling unit and systematic random sampling method was used for selecting household. Total 257 children aged 5 to 14 years were included in the study. A pre-designed, semi-structured diagnostic interview schedule based on DSM-IV criteria was used for data collection.

STATISTICAL ANALYSIS USED: The tests of significance used were Chi-square and Logistic regression analysis.
RESULTS: The prevalence of psychiatric morbidity in this study was 14.8%. Non-organic enuresis, Attention deficit hyperactivity disorder, Conduct disorder, and Mental retardation were identified as the common mental health problems.
CONCLUSIONS: Factors like nuclear family, parents not living together, large family size, and positive family history of psychiatric disorder were associated with psychiatric morbidity in children.

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J Neural Transm. 2014 Apr.

RESPONSIVITY TO FAMILIAR VERSUS UNFAMILIAR SOCIAL REWARD IN CHILDREN WITH AUTISM.

Pankert A, Pankert K, Herpertz-Dahlmann B, et al.

In autism spectrum disorders (ASD), social motivation theories suggest that the core social communication problems seen in children with ASD arise from diminished responsiveness to social reward. Although clinical and experimental data support these theories, the extent to which the reward deficit in ASD is unique for social rewards remains unclear. With the present investigation, we aimed to provide insight into the degree to which sociality as well as familiarity of reward incentives impact motivated goal-directed behavior in children with ASD. To do so, we directly compared the influence of familiar versus unfamiliar social reward relative to nonsocial, monetary reward in children with ASD relative to age- and IQ-matched typically developing controls (TDC) using a visual and auditory incentive go/nogo task with reward contingencies for successful response inhibitions. We found that children with ASD responded stronger to visual familiar and unfamiliar social reward as well as to nonsocial, monetary reward than TDC. While the present data are at odds with predictions made by social motivation theories, individual variations beyond clinical diagnosis, such as reward exposure across various social settings, help explain the pattern of results. The findings of this study stress the necessity for additional research on intra-individual as well as environmental factors that contribute to social reward responsiveness in individuals with ASD versus other neuropsychiatric disorders such as ADHD or conduct disorder.

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J Phys Ther Sci. 2014 Mar;26:345-47.

INFLUENCE OF WORKING MEMORY TASK AND TIME ON POSTURAL CONTROL OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Wu WL, Chen YY, Wang CC, et al.

[**Purpose**] To investigate how balance changes develop across time under different conditions (with or without a memory task) for children with Attention Deficit Hyperactivity Disorder (ADHD).
[**Subjects and Methods**] The participants were 11 children with ADHD and 12 normal children. To determine their static balance ability, a force plate was used to measure the center of the pressure trajectory.
[**Results**] The length of the sway path became slightly greater in both groups when an additional memory task was added, but the difference was not statistically significant. However, it was interesting to note a significant difference in memory task ability across groups with increasing time. The ADHD group showed a decrease sway path with increasing time for the memory task, but in the control group it increased.
[**Conclusion**] At first, the memory task interfered with ADHD children's performance; however, the memory task may improve their performance after a few seconds.

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J Phys Ther Sci. 2014 Feb;26:223-27.

IMPROVEMENT OF VERGENCE MOVEMENTS BY VISION THERAPY DECREASES K-ARS SCORES OF SYMPTOMATIC ADHD CHILDREN.

Lee SH, Moon BY, Cho HG.

[**Purpose**] To determine whether the improvement of vergence movements by vision therapy can decrease the K-ARS scores of symptomatic ADHD children.

[**Methods**] Eighty-one out of 1,123 children surveyed using the K-ARS, a parents'-reported questionnaire, led to 16 of these 81 children being showed scores of >/=19, and measurement of binocular function diagnosed as having convergence insufficiency. The 16 children were divided equally into a control group and a vision therapy group.

[**Results**] After vision therapy for 12 weeks, near point convergence (4.38+/-0.69 cm) significantly neared compared to the near point convergence before vision therapy (11.50+/-2.28 cm), and both the break point (32.38+/-2.53 Delta) and recovery point (19.75+/-2.11 Delta) of near positive fusional vergence significantly improved compared to their values before vision therapy (15.88+/-2.64 Delta, 6.38+/-6.70 Delta, respectively). Near exophoria after vision therapy (7.81+/-2.00 Delta BI) significantly decreased compared to its value before vision therapy (12.00+/-1.16 Delta BI). The K-ARS scores referring to symptomatic ADHD significantly decreased after vision therapy (17.13+/-2.84) compared to before vision therapy (23.25+/-1.49).

[**Conclusions**] Convergence insufficiency symptoms are closely related to symptoms screened for ADHD, and vision therapy to improve vergence movements is an effective method of decreasing the K-ARS scores.

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J Psychopathol Behav Assess. 2014 Mar;36:30-42.

MEASURING CALLOUS UNEMOTIONAL BEHAVIORS IN EARLY CHILDHOOD: FACTOR STRUCTURE AND THE PREDICTION OF STABLE AGGRESSION IN MIDDLE CHILDHOOD.

Willoughby MT, Mills-Koonce WR, Gottfredson NC, et al.

This study sought to replicate the results of our earlier study, which were published in this Journal (Willoughby et. al 2011), that used mother-reported items from the Achenbach System of Empirically Based Assessment to develop a screening measure of callous unemotional (CU) behaviors for use with preschool-aged children. We further sought to extend those results by exploring the predictive validity of the CU measure with aggression trajectories in early-/mid-childhood. The current study involved secondary data analysis of the NICHD Study of Early Childhood and Youth Development (NICHD-SECCYD) dataset. Factor analyses included N=1176 children who participated in the age 3 year assessment of the NICHD-SECCYD. Predictive models included N=1081 children for whom four of the six possible teacher ratings of aggressive behavior were available from annual assessments spanning 1st-6th grades. Consistent with prior work, a three-factor confirmatory factor model, which differentiated CU from oppositional defiant (ODD) and attention deficit/hyperactive-impulsive (ADHD) behaviors, provided the best fit to the data. Among children with disorganized attachment status, the combination of high levels of mother-rated ODD behaviors and CU behaviors, was predictive of stable elevated levels of teacher-rated aggression from 1st-6th grade (predicted probability=.38, compared with a base rate of .07). These results demonstrate that CU behaviors can be reliably measured by parent report in young children and are dissociable from more commonly assessed dimensions of disruptive behavior. Three-year-old children who exhibit elevated levels of ODD and CU behaviors, and who have disorganized attachments, are at increased risk for exhibiting elevated levels of aggression across middle childhood. Results are discussed from the perspective of early assessment and intervention.

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J Stud Alcohol Drugs. 2014 Jan;75:145-52.

DIFFERENTIAL ASSOCIATIONS BETWEEN ALCOHOL EXPECTANCIES AND ADOLESCENT ALCOHOL USE AS A FUNCTION OF CHILDHOOD ADHD.

Pedersen SL, Harty SC, Pelham WE, et al.

OBJECTIVE: Individuals with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for experiencing alcohol-related problems. However, previous research has not examined alcohol expectancies, a widely studied risk factor for alcohol use, in this population. The current study examined mean differences in alcohol expectancies for adolescents with and without a history of childhood ADHD. The differential association between alcohol expectancies and alcohol use 1 year later as a function of ADHD status was also examined.

METHOD: Two hundred and eighty-six adolescents ages 11-17 (ADHD:n=165; non-ADHD:n=121) reported their alcohol expectancies and alcohol use over a 1-year period as part of the Pittsburgh ADHD Longitudinal Study.

RESULTS: Individuals with a history of ADHD had lower mean levels of alcohol expectancies compared with individuals without ADHD. Specifically, at Time 1, individuals with ADHD reported lower levels of sociability, cognitive and behavioral impairment, and liquid courage expectancies than individuals without ADHD. Further, the association between negative alcohol expectancies at Time 1 and alcohol use at Time 2 differed for individuals with and without a history of ADHD.

CONCLUSIONS: These findings highlight the possibility that individuals with a history of ADHD may rely less on explicit cognitions, such as alcohol expectancies, when making decisions to drink alcohol. This is consistent with the dual process model of alcohol cognitions that has posited that individuals with decreased executive control may rely more on implicit cognitions about alcohol.

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JAMA Pediatr. 2014 Mar.

HOURS OF TELEVISION VIEWING AND SLEEP DURATION IN CHILDREN: A MULTICENTER BIRTH COHORT STUDY .

Marinelli M, Sunyer J, Alvarez-Pedrerol M, et al.

IMPORTANCE This study used longitudinal data to examine potential associations between hours of television viewing and sleep duration in children.

OBJECTIVE To examine the association between hours of television viewing and sleep duration in preschool and school-aged children.

DESIGN, SETTING, AND PARTICIPANTS Longitudinal, multicenter study among birth cohorts in Menorca, Sabadell, and Valencia from the Spanish Infancia y Medio Ambiente (environment and childhood) project. The study sample included 1713 children (468 from Menorca, 560 from Sabadell, and 685 from Valencia).

EXPOSURE Parent-reported child television viewing duration measured in hours per day at 2 and 4 years of age in Sabadell and Valencia and at 6 and 9 years of age in Menorca.

MAIN OUTCOMES AND MEASURES Parent-reported child sleep duration measured in hours per day at 2 and 4 years of age in Sabadell and Valencia and at 6 and 9 years of age in Menorca.

RESULTS In cross-sectional analysis, children with longer periods of television viewing reported at baseline (>/=1.5 hours per day) had shorter sleep duration. Longitudinally, children with reported increases in television viewing duration over time (from & lt;1.5 to >/=1.5 hours per day) had a reduction in sleep duration at follow-up visits. Results were similar when examining television viewing duration as a continuous variable, with each 1 hour per day of increased viewing decreasing sleep duration at follow-up visits (beta=-0.11; 95% CI, -0.18 to -0.05). Associations were similar when television viewing duration was assessed during weekends and after adjusting for potential intermediate factors (child executive function and attention-deficit/hyperactivity disorder symptoms) and confounders (child physical activity level, parental mental health status, maternal IQ, and maternal marital status).

CONCLUSIONS AND RELEVANCE Children spending longer periods watching television had shorter sleep duration. Changes in television viewing duration were inversely associated with changes in sleep duration in longitudinal analysis. Parents should consider avoiding long periods of daily television exposure among preschool and school-aged children.

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JAMA Pediatr. 2014;168:313-20.

ACETAMINOPHEN USE DURING PREGNANCY, BEHAVIORAL PROBLEMS, AND HYPERKINETIC DISORDERS.

Liew Z, Ritz B, Rebordosa C, et al.

Importance Acetaminophen (paracetamol) is the most commonly used medication for pain and fever during pregnancy in many countries. Research data suggest that acetaminophen is a hormone disruptor, and abnormal hormonal exposures in pregnancymay influence fetal brain development. Objective to evaluate whether prenatal exposure to acetaminophen increases the risk for developing attention-deficit/hyperactivity disorder (ADHD)-like behavioral problems or hyperkinetic disorders (HKDs) in children. Design, Setting, and Participants We studied 64 322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002. EXPOSURES Acetaminophen use during pregnancy was assessed prospectively via 3 computer-assisted telephone interviews during pregnancy and 6 months after child birth. Main outcomes and measures To ascertain outcome information we used (1) parental reports of behavioral problems in children 7 years of age using the Strengths and Difficulties Questionnaire; (2) retrieved HKD diagnoses from the Danish National Hospital Registry or the Danish Psychiatric Central Registry prior to 2011; and (3) identified ADHD prescriptions (mainly Ritalin) for children from the Danish Prescription Registry.We estimated hazard ratios for receiving an HKD diagnosis or using ADHD medications and risk ratios for behavioral problems in children after prenatal exposure to acetaminophen. Results More than half of all mothers reported acetaminophen use while pregnant. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95%CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95%CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95%CI, 1.01-1.27). Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes (ie, HKD diagnosis, ADHD medication use, and ADHD-like behaviors; P trend < .001). Results did not appear to be confounded by maternal inflammation, infection during pregnancy, the mother's mental health problems, or other potential confounders we evaluated. conclusions and relevence Maternal acetaminophen use during pregnancy is associated with a higher risk for HKDs and ADHD-like behaviors in children. Because the exposure and outcome are frequent, these results are of public health relevance but further investigations are needed. (copyright) 2014 American Medical Association.

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J Abnorm Child Psychol. 2014 Apr;42:489-99.

PREDICTION OF PRESCHOOL AGGRESSION FROM DRD4 RISK, PARENTAL ADHD SYMPTOMS, AND HOME CHAOS.

Farbiash T, Berger A, Atzaba-Poria N, et al.

This study investigated the influence of a child's DRD4 risk, parental levels of ADHD symptoms, and the interactive influence of these factors on the development of preschool aggression. Additionally, the study investigated the role of home chaos as a mediator between parental ADHD symptoms and child aggression. The sample consisted of 84 4.5-year-old children and their parents. Children were genotyped for the DRD4 polymorphism. ADHD symptoms were self-reported by parents when the child was 2 to 6 months old. Parental reports of home chaos and the child's aggression were collected 4 years later. Child's DRD4 risk and parental ADHD symptoms significantly contributed to the prediction of preschool aggression. However, contrary to our hypotheses, no interactions were found between the child's DRD4 risk and the levels of parental ADHD symptoms. Home chaos played a mediating role in the relation between paternal ADHD symptoms and the child's aggression. The relation between maternal ADHD symptoms and the child's aggression was not significantly mediated through the level of home chaos. The current study emphasizes the importance of longitudinally investigating the contribution of parental ADHD symptoms to child aggression, while also exploring the differential contribution of maternal/paternal inattention and hyperactivity-impulsivity symptoms. Moreover, home chaos was found to be a significant environmental mechanism through which paternal ADHD symptoms affect children's aggression in the preschool years.

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J Abnorm Child Psychol. 2014 Apr;42:479-88.

THE EFFECTS OF INSTRUCTIONS ON MOTHERS' RATINGS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN REFERRED CHILDREN.

Johnston C, Weiss MD, Murray C, et al.

Tested whether instructions for how to rate child attention-deficit/hyperactivity disorder (ADHD) symptoms would improve the agreement between mothers' ratings of symptoms in their children and ratings provided by teachers and objective observers. Sixty-eight mothers of 5 to 12 year old children (53 boys and 15 girls) referred for ADHD assessment were randomly assigned to receive or not receive the instructions. Mothers and teachers rated the children on the SNAP-IV Rating Scale and objective observers rated the children's behavior during structured tasks. Relations between mother and teacher, and mother and observer ratings were generally stronger for mothers in the Instruction group compared to mothers in the No Instruction group, in some cases significantly stronger. The instructional materials also improved mothers' knowledge of how to rate ADHD symptoms and reduced some associations between mothers' ratings and family socioeconomic status. These instructions have the potential to improve clinical assessments of child ADHD symptoms.

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Journal of Applied Behavior Analysis. 2014;47:160-64.

EFFECTS OF WHITE NOISE ON OFF-TASK BEHAVIOR AND ACADEMIC RESPONDING FOR CHILDREN WITH ADHD.

Cook A, Bradley-Johnson S, Johnson CM.

We evaluated the effects of white noise played through headphones on off-task behavior, percentage of items completed, and percentage of items completed correctly for 3 students with attention deficit hyperactivity disorder (ADHD). Headphones plus white noise were associated with decreases in off-task behavior relative to baseline and headphones-only (no white noise) control conditions. Little change in academic responding occurred across conditions for all participants.

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Journal of Attention Disorders. 2014 Feb;18:117-22.

PREPULSE INHIBITION OF ACOUSTIC STARTLE AND THE INFLUENCE OF METHYLPHENIDATE IN CHILDREN WITH ADHD.

Schulz-Juergensen S, Thiemann A, Gebhardt J, et al.

Objective: ADHD is common among children with comorbidity of enuresis. Findings concerning prepulse inhibition (PPI) of startle reflexes are controversial. Although PPI is improved through desamino-arginine vasopressin (dDAVP) in enuresis, some patients also improve concomitant ADHD through dDAVP. This study aims to evaluate whether methylphenidate (MPH) also improves PPI in ADHD.

Method: Nineteen ADHD patients were investigated in a prospective, double-blind, crossover study with MPH versus placebo. PPI was measured as a reduction of acoustic startle reflexes. Subgroups of gender, ADHD subtype, and baseline PPI were analyzed.

Results: Median baseline PPI of ADHD patients (51.7%) was below the value of age-matched normal controls (73%, p =.090). MPH showed no improvement in the whole group, or the subgroups gender or subtype. Reduced baseline PPI was significantly improved (22.5%-39.3%, p =.039).

Conclusion: Heterogeneity of ADHD is confirmed with a wide range of baseline PPI. The improvement of reduced baseline PPI through MPH suggests impaired sensorimotor gating in this subgroup.

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Journal of Attention Disorders. 2014 Feb;18:145-57.

NO BENEFICIAL EFFECTS OF ADDING PARENT TRAINING TO METHYLPHENIDATE TREATMENT FOR ADHD + ODD/CD CHILDREN: A 1-YEAR PROSPECTIVE FOLLOW-UP STUDY.

Ercan ES, Ardic UA, Kutlu A, et al.

Objective: The aim of this study was to compare the effect of methylphenidate (MPH) versus MPH + parent training in children with ADHD and oppositional defiant disorder/conduct disorder (ODD/CD) over a 12-month period.

Method: After careful screening, 120 children diagnosed with ADHD + ODD/CD were included in the study. Treatment consisted of ongoing medication management for 12 months, with or without participation in a parent-training program beginning after the 1st month. Participants were not randomly assigned to treatment groups because of ethical, practical, and methodological reasons.

Results: Data analyses revealed that mother–child relationship improvements and symptom severity did not benefit from parent training.

Conclusion: The results of this study highlighted the positive role of MPH in ADHD. No significant effects were observed after the addition of parent training to MPH treatment. Clinicians should carefully follow patients' improvements and titrate the MPH dosage during long-term treatment.

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Journal of Attention Disorders. 2014 Feb;18:105-16.

DOES STIMULANT PRETREATMENT MODIFY ATOMOXETINE EFFECTS ON CORE SYMPTOMS OF ADHD IN CHILDREN ASSESSED BY QUANTITATIVE MEASUREMENT TECHNOLOGY?

Wehmeier PM, Dittmann RW, Banaschewski T, et al.

Objective: To compare the reduction of ADHD symptoms under atomoxetine (ATX) in patients with and without pretreatment with a stimulant medication using a computer-based Continuous Performance Test (cb-CPT) combined with an infrared motion tracking (MT) device.

Method: Double-blind, placebo-controlled study in ADHD patients (6-12 years) treated with ATX (target dose = 1.2 mg/kg per day). The cb-CPT/MT scores were analyzed using ANCOVA (last observation carried forward).

Results: Patient data (n=125) suggested a differential ATX treatment effect between pretreated and stimulant-naïve patients in terms of three cb-CPT/MT parameters.

Conclusion: This secondary analysis provided evidence that ATX reduced ADHD symptom severity measured by cb-CPT/MT parameters regardless of stimulant pretreatment. A few differential effects were seen based on the cb-CPT/MT. However, no clear pattern could be identified and, overall, the observed differences have no larger clinical relevance. The ATX effect in this study seemed to be largely independent of any previous exposure to stimulants.

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Journal of Attention Disorders. 2014 Feb;18:123-32.

THE EFFECTS OF LISDEXAMFETAMINE DIMESYLATE ON EMOTIONAL LABILITY IN CHILDREN 6 TO 12 YEARS OF AGE WITH ADHD IN A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL.

Childress AC, Arnold V, Adeyi B, et al.

Objective: To evaluate the effect of lisdexamfetamine dimesylate (LDX) on emotional lability (EL) in children with ADHD.

Method: Post hoc analyses of a placebo-controlled trial of LDX-stratified children (aged 6-12 years) with ADHD to prominent and not prominent EL at baseline (score>3 or=3, respectively, on Conners' Parent Rating Scale [CPRS] items of anger, loss of temper, and irritability). Efficacy was assessed by change in CPRS EL scores and ADHD Rating Scale-IV (ADHD-RS-IV) total and subscale scores. Safety measures included treatment-emergent adverse events (TEAEs).

Results: LDX showed improvement versus placebo ($p < .0005$) for EL item least squares (LS) mean change scores at endpoint and throughout the day. At baseline, 138 and 73 participants randomized to LDX treatment and having baseline and endpoint CPRS scores were categorized with CPRS-derived

prominent and not prominent baseline EL, respectively; 41 and 31 participants randomized to placebo were categorized with CPRS-derived prominent and not prominent baseline EL, respectively. ADHD-RS-IV total and subscale scores decreased with LDX regardless of baseline EL severity. TEAEs included decreased appetite, insomnia, upper abdominal pain, headache, and irritability.
Conclusion: EL and ADHD symptoms improved with LDX regardless of baseline EL symptom severity. LDX demonstrated a safety profile consistent with long-acting psychostimulant use.

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Journal of Attention Disorders. 2014 Feb;18:95-104.

METHYLPHENIDATE IN CHILDREN WITH ADHD WITH OR WITHOUT LEARNING DISABILITY.

Williamson D, Murray DW, Damaraju CV, et al.

Objective: To explore treatment response to Osmotic Release Oral System[sup]®[/sup] (OROS) methylphenidate in children with ADHD with and without comorbid learning disability (LD).
Method: Data were analyzed from two 6-week, double-blind, randomized, placebo-controlled, crossover studies evaluating individually determined doses of OROS methylphenidate versus placebo in 135 children (ages 9 to 12 years) with ADHD with or without an LD in reading, math, or both. The sample was demographically diverse, with 31% females and more than 40% minority, predominantly African American and Hispanic. On two laboratory school days, participants received either OROS methylphenidate or placebo and were given a battery of cognitive and behavioral tests.
Results: Treatment with OROS methylphenidate led to improvement in ADHD Rating Scale scores for participants with or without comorbid LD. Both groups performed better during treatment with OROS methylphenidate than placebo on measures of cognitive skills (i.e., Test of Variables of Attention, Finger Windows Backwards), academically related tasks (i.e., Dynamic Indicators of Basic Early Literacy Skills, Test of Handwriting Skills–Revised, Permanent Product Math Test), and observed classroom behavior (i.e., Swanson, Kotkin, Alger, M-Flynn, and Pelham Scale).
Conclusion: In children with ADHD with or without comorbid LD, behavior and performance improved during treatment with OROS methylphenidate.

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J Child Adolesc Ment Health. 2014.

DRUG HOLIDAY UTILISATION IN ADHD-DIAGNOSED CHILDREN AND ADOLESCENTS IN SOUTH AFRICA.

Regnart J, McCartney J, Truter I.

Attention deficit hyperactivity disorder (ADHD) is a prevalent disorder affecting people in all age groups. Pharmacological treatment with psychostimulants, specifically methylphenidate, is first line condition management. The ideal dosing regimen of methylphenidate is debatable with daily use being considered harmful by many. However, it is unknown if sporadic drug withdrawal is beneficial to condition management. The primary aim was to investigate drug holiday utilisation incidence.The study comprised a drug utilisation review (DUR) and questionnaire-based survey. The DUR was conducted using a corporate retail pharmacy group database. Methylphenidate prescriptions were evaluated to determine possible drug holiday use through different analyses of dispensing patterns. The survey included several questions relating to drug holiday use.Drug holiday use was identified in both study populations. Weekends and school holidays were identified as common periods for drug holiday observation. Of the participants that provided reasons for drug holiday utilisation, half indicated that methylphenidate was only necessary for school activities. DUR results indicated that drug holidays appeared to be more commonly observed during March and December.Reasons for drug holiday utilisation were variable. This study recommends that these drug free periods are only observed if shown to be beneficial to the patient.

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J Clin Psychiatry. 2014;75:289-90.

THE PROBLEM OF PATIENT HETEROGENEITY AND LACK OF PROPER TRAINING IN A STUDY OF EEG NEUROFEEDBACK IN CHILDREN.

Cannon RL, Pigott HE, Surmeli T, et al.

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J Clin Psychol. 2014 Apr;70:388-403.

SLUGGISH COGNITIVE TEMPO IS ASSOCIATED WITH ACADEMIC FUNCTIONING AND INTERNALIZING SYMPTOMS IN COLLEGE STUDENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Becker SP, Langberg JM, Luebbe AM, et al.

Objectives: The purposes of the present studies were to (a) examine the factor structure of sluggish cognitive tempo (SCT) and attention-deficit/hyperactivity disorder (ADHD) in college students and (b) examine the associations between SCT and academic functioning and internalizing symptoms in college students with and without ADHD.

Method: In Study 1, a confirmatory factor analysis of the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) was conducted in a sample of 768 college students (aged 17–34 years, 68% female). In Study 2, we examined the relation of SCT to academic functioning and internalizing symptoms in a sample of 72 college students rigorously diagnosed with ADHD (aged 17–35 years, 44% female).

Results: Study 1 results supported the factor structure of the BAARS-IV, with the optimal model comprising 4 correlated but distinct factors: SCT, Inattention, Hyperactivity, and Impulsivity. After controlling for correlated demographic variables and ADHD symptoms, SCT was significantly related to academic impairment (including grade point average), anxiety, and depression. In Study 2, SCT again contributed unique variance to internalizing symptoms and academic impairment after controlling for correlated participant characteristics (i.e., sex, age, race, parent education level, family income, ADHD medication use, and mental health service utilization) and ADHD symptom severity.

Conclusions: These results fill an important gap in the literature by (a) confirming SCT to be distinct from ADHD in emerging adulthood, (b) demonstrating SCT to be strongly linked to college student adjustment, and (c) providing support for the hypothesis that SCT is associated with psychosocial functioning in both individuals with and without ADHD.

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J Dev Behav Pediatr. 2014 Feb;35:108-17.

CHILD AND ADOLESCENT PSYCHOPATHOLOGY PREDICTS INCREASED ADULT BODY MASS INDEX: RESULTS FROM A PROSPECTIVE COMMUNITY SAMPLE.

Korczak DJ, Lipman E, Morrison K, et al.

Objective: To examine the relationship between childhood and adolescent symptoms of (1) depression, (2) attention-deficit hyperactivity disorder (ADHD), and (3) conduct disorder (CD) with adult body mass index (BMI) in a prospective longitudinal study of 3294 community participants in the Ontario Child Health Survey.

Methods: One thousand nine hundred ninety-two children aged 4 to 11 years and 1302 adolescents aged 12 to 16 years at study entry in 1983 underwent follow-up in 2000. Body mass index data were available for 1886 adult participants in the year 2000, which comprised the final study sample. Data were collected from youth, parents, and teachers using a combination of parental, youth, and teacher self-report and semistructured interview. Body mass index is a derived variable determined from the self-reported height and weight in 2000.

Results: Adults with depression, ADHD, or CD identified in childhood had increased body weight (BMI=27.2 kg/m^2, 27.7 kg/m^2, and 27.9 kg/m^2, respectively) compared with their nonaffected peers (BMI=24.8 kg/m^2; $p < .001$). Greater depressive symptoms in childhood were associated with increased adult BMI among boys (p=.02). Among adolescents, depression and sex interact in the association with adult BMI (p=.01). The association of childhood ADHD with adult overweight was completely accounted for

by the effect of comorbid child conduct disturbance (p<.001) for both girls and boys. Greater conduct symptoms were associated with increased adult BMI (p=.04) among adolescent girls.
Conclusion: This epidemiologic study suggests that psychopathology in childhood is associated with increased adult BMI. Early identification of psychiatric illness may present key opportunities for targeted prevention of obesity.

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J Dev Behav Pediatr. 2014 Feb;35:100-07.

MEDIATORS OF METHYLPHENIDATE EFFECTS ON MATH PERFORMANCE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Froehlich TE, Antonini TN, Brinkman WB, et al.

Objective: Stimulant medications, such as methylphenidate (MPH), improve the academic performance of children with attention-deficit hyperactivity disorder (ADHD). However, the mechanism by which MPH exerts an effect on academic performance is unclear. We examined MPH effects on math performance and investigated possible mediation of MPH effects by changes in time on-task, inhibitory control, selective attention, and reaction time variability.
Methods: Children with ADHD aged 7 to 11 years (N=93) completed a timed math worksheet (with problems tailored to each individual's level of proficiency) and 2 neuropsychological tasks (Go/No-Go and Child Attention Network Test) at baseline, then participated in a 4-week, randomized, controlled, titration trial of MPH. Children were then randomly assigned to their optimal MPH dose or placebo for 1 week (administered double-blind) and repeated the math and neuropsychological tasks (posttest). Baseline and posttest videorecordings of children performing the math task were coded to assess time on-task.
Results: Children taking MPH completed 23 more math problems at posttest compared to baseline, whereas the placebo group completed 24 fewer problems on posttest versus baseline, but the effects on math accuracy (percent correct) did not differ. Path analyses revealed that only change in time on-task was a significant mediator of MPH's improvements in math productivity.
Conclusions: MPH-derived math productivity improvements may be explained in part by increased time spent on-task, rather than improvements in neurocognitive parameters, such as inhibitory control, selective attention, or reaction time variability.

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J Mental Health Policy Econ. 2013;16:S35.

ASSOCIATION OF MEDICATION COMPLIANCE WITH QUALITY OF LIFE OF CHILDREN WITH ADHD AND THEIR PARENTS MEASURED BY KIDSCREEN-10 AND EQ-5D.

Van Der Kolk A, Bouwmans C, Schawo S, et al.

Background: ADHD in children and adolescents has a major impact on the quality of life (QoL) of the children as well as their parents. Compliance to medication may add to an increase in QoL of the children as well as their parents. However, there is still limited information on the impact of compliance on QoL of children and their parents. Aims of the Study: To study QoL in children and adolescents with ADHD and their parents, focusing on compliance to ADHD medication.
Methods: A cross-sectional survey was performed via the Dutch organization for parents of children with development disorders using an online questionnaire focused on children and adolescents with ADHD (8-18 years). Two generic QoL questionnaires were used: EQ-5D and KIDSCREEN-10. Questionnaires were completed by parents, also for the children (using proxy ratings). Compliance was rated by parents using expert-defined descriptions. Differences between groups were analyzed using Students' Mests, Chi-Square tests and regression analyses.
Results: Analyses were performed on 618 questionnaires (compliant n=428, non-compliant n=190). Mean age was 11.8 years (82.4% boys). On average, EQ-5D score was 0.80 (compliant 0.83, non-compliant 0.74, p=0.000) and KIDSCREEN-10 index was 41.67 (compliant 42.24, non-compliant 40.33, p=0.000). For EQ-5D, co- morbidity and marital status of the parent had an independent significant association with QoL. For KIDSCREEN-10, age category, comorbidity and parents' education had an independent significant

association with QoL. Overall, EQ-5D scores of the parents were 0.83 without a significant difference between compliant and non-compliant subgroups. EQ-5D of the child was correlated with EQ-5D of the parents (r=0.207, p=0.000).
Discussion: QoL of children with ADHD was significantly associated with their medication compliance status. We were unable to verify the diagnosis due to lack of source verification by patient files. Similarly, we did not have information about symptom severity in our sample.
Implications for Health Care Provision and Use: This study stresses the relevance of focussing on achieving compliance in children receiving pharmacological treatment for ADHD. Specific attention has to be paid to children with co-morbidities. QoL and family overall well-being should be a standard part of treatment evaluation.
Implications for Health Policies: ADHD management is a shared process between families, children and clinicians. This requires the availability of a clear description of treatment pathways. In such guidance, compliance and family well-being should be incorporated. QoL should be an integrated part of health policy discussions on ADHD.
Implications for Further Research: Suggestions for further research include the conduct of this study using children's self-report questionnaires, as proxies may be biased.

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J Mental Health Policy Econ. 2013;16:S3-S4.

VALIDITY AND RESPONSIVENESS OF THE EQ-5D AND KIDSCREEN-10 IN CHILDREN WITH ADHD.

Bouwmans C, Van Der Kolk A, Oppe M, et al .

Background: The current debate on the development of child-specific Quality of Life (QoL) instruments concentrates on the appropriate dimensions. Additionally, child-specific instruments including valuations of health states are still in early stages of development. Valuations allow combining QoL with gains or losses in quantity of life into Quality-Adjusted Life Years (QALYs) and are is used in economic evaluations.
Aim of the Study: To compare the psychometric properties of a generic child-specific and a generic preference based instrument for adults in children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD).
Methods: A survey was performed among parents with a child diagnosed with ADHD. Results using proxy versions of the KIDSC-REEN-10 and EQ-5D were used to compare the QoL constructs and responsiveness to different health states. The KIDSCREEN-10 includes 10 items measuring child's health and well-being. The EQ-5D defines general health on five dimensions: mobility, self-care, daily activities, pain and mood. Principal Component Analysis (PCA) with varimax rotation was used for identifying factors underlying the QoL constructs. Responsiveness was assessed by comparing instrument's index scores of respondents with different stimulant medication adherence and co-morbidity profiles using Student's t-tests. Cohen's effect sizes were calculated for an indirect comparison of the instruments' responsiveness.
Results: Analyses were performed on data derived from 738 parents with a child aged 8 years and older (mean age 11.9 years). Almost 75% of the children had one or more co-morbid conditions (e.g. learning disorder, Autism Spectrum Disorder) and 84% of the children used stimulant medication for ADHD. PCA identified five separate factors of QoL. An overlap was found of three EQ-5D dimensions and six KIDSCREEN-10 items representing a physical and a mental factor. No associations of the EQ-5D dimensions 'self-care' and 'usual activities' and KIDSCREEN-10 items were found. Additionally, no association with EQ-5D dimensions was found with KIDSCREEN-10 items related to performance at school and satisfaction with free time activities. Scores on both instruments differed significantly according to respondents' treatment adherence and co-morbidity profile. Cohen's effect sizes indicated comparable responsiveness of the instruments.
Discussion (incl. **limitations**): Despite instruments' different constructs of QoL, the analyses showed comparable responsiveness to different health states. Clinical information regarding diagnosis, severity of the disorder and co-morbidity was lacking as information was based on parents' reports. Additionally, proxies were used to assess QoL of the children. Valuations of the EQ-5D measurements were derived from the general adult population.

Implications for Health Policies: The results suggest that KIDSCREEN-10 and EQ-5D are complementary instruments. The choice for one of these instruments will depend on the study's research questions and the aim of the study.
Implications for further Research: More research is recommended using self-reports of the EQ-5D and the KIDSCREEN-10. In addition, comparison on responsiveness of the instruments on health should be augmented to other disorders in children.

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J Mental Health Policy Econ. 2013;16:S35-S36.
ASSOCIATION OF MEDICATION COMPLIANCE WITH COSTS OF CHILDREN WITH ADHD: RESULTS FROM A DUTCH OBSERVATIONAL STUDY.
Van Der Kolk A, Bouwmans C, Schawo S, et al.
Background: The discussion on compliance versus non-compliance occupies many minds in ADHD. Compliance may have an economic impact.
Aims of the Study: To investigate societal costs among compliant and non-compliant children with ADHD.
Methods: A cross-sectional retrospective survey among parents of a child aged 6-18 (members of the Dutch parent organization) with ADHD was conducted in September 2010. Data were collected on medical and non-medical resource use. Reference prices (2010) from the Netherlands served as unit costs. Differences between groups were analyzed using Students' Mests and regression analyses. Compliance status was based on parent evaluation and based on pre-defined definitions by expert opinion. Work in progress is presented.
Results: Analyses were performed on 692 questionnaires (compliant n=473, non-compliant n=219). (Mean age 11.2, 82.8% boys). Compliance was significantly associated with total treatment costs, with total mean monthly costs being (euro)513 (SD (euro)1088) and (euro)818 (SD (euro)1287) for compliant and non-compliant children, respectively (p=0.002). The most important cost items were medical consultations (18.9% vs. 20.2%), coaching and extra support lessons at school (25.4% vs. 19.9%), skills trainings (19.3% vs. 20.4%), and child day care (14.6% vs. 11.8%). Medication constituted 4.8% and 2.7% of total costs. Next to compliance, regression analysis showed that co-morbidity also had a significant association with total treatment costs (p=0.000). In a regression model in which compliance and co-morbidity were independent variables, both were significant (p=0.003 and p=0.000, respectively). Mean costs were (euro)249 and (euro)615 (compliant vs. non-compliant) for children without co-morbidity and (euro)630 and (euro)883 for children with co-morbidity. Adding a dummy for co-morbiditynull compliance was not a significant addition to the regression model.
Discussion: Children compliant to ADHD medication generate significant lower monthly costs compared to non-compliant children. The sample was retrieved via a parent organization which might be a selective group.
Implications for Health Care Provision and Use: Focusing on achieving compliance may result in lower health care use. Special attention should be paid to children with co-morbidity.
Implications for Health Policies: There is an association between costs and compliance in children receiving ADHD pharmacological treatment. Effective methods or additional measures to improve compliance to medication in this population may be cost-effective.
Implications for Further Research: Further research could be focused on a random sample of the ADHD population beyond members of the parent association. Many children these days have coaching and extra support at school, the relationship of this cost item with ADHD needs to be investigated further.

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Journal of Policy and Practice in Intellectual Disabilities. 2014 Mar;11:58-61.
ATTENTION DEFICIT HYPERACTIVITY DISORDERS SYMPTOMATOLOGY AMONG INDIVIDUALS WITH DOWN SYNDROME.
Edvardson S, Msallam N, Hertz P, et al.
The prevalence of attention deficit hyperactivity disorders (ADHD) among individuals with Down syndrome (DS) has been difficult to ascertain. This is because many of the phenotypic features of DS may resemble

the clinical manifestations of DS and the myriad methodological challenges in diagnosing ADHD in children with intellectual disabilities (ID). With this in mind, the authors set to determine the prevalence of ADHD symptomatology in a cohort of children and young adults in a DS clinic. Subjects were 83 children and adults, ages 5–38, who were attending the Down Syndrome Center at the Hadassah Mount Scopus University Medical Center. All were screened for ADHD. Screening methods included review of medical files, telephone interviews, and use of the ADHD module of the Autism-Tics, Attention-Deficit/Hyperactivity disorder, and other Comorbidities questionnaire. It was found that 26 (31.3%) of the subjects fulfilled the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.) criteria for ADHD. Of these, 17 (65.4%) were diagnosed as predominantly inattentive type. Four (15.4%) were predominantly impulsive-hyperactive, and five (19.2%) had the combined type. No statistically significant association was found between ADHD and age, sex, number of siblings, presence of heart disease, thyroid dysfunction, sleep disorders, or a family history of ADHD. The prevalence of ADHD symptomatology among individuals with DS in this representative sample is high compared with the general population. ADHD may be underdiagnosed in this special population, hence the need for systematic screening.

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J Psychosom Res. 2014.

TOURETTE PATIENTS' MISBELIEF OF A TIC REBOUND IS DUE TO OVERALL DIFFICULTIES IN RELIABLE TIC RATING.

Muller-Vahl KR, Riemann L, Bokemeyer S.

Objective: While in clinical interviews the vast majority of patients with Tourette syndrome (TS) report about a tic rebound after voluntary tic suppression, in recent studies in children no paradoxical tic increase could be found. We hypothesized that in adult patients there is a tic rebound after tic suppression.

Methods: We investigated the tic severity, premonitory urges and influence of attention deficit hyperactivity disorder (ADHD) before, during and after tic suppression in 22 adult patients with TS using both an objective video tic rating and subjective patient ratings for tics and premonitory urges.

Results: According to the video rating, tic suppression resulted in a significant tic reduction, but no rebound. Patients also reported no tic rebound. They erroneously believed in an absolute tic reduction 20 and 30 min after suppression, but paradoxically felt no relative tic change. Premonitory urges remained unchanged. There was no correlation between premonitory urges and tic severity. The potency for tic inhibition did not correlate with premonitory urges and tic severity. ADHD did not influence tic inhibition.

Conclusion: In adults with TS, there is no tic rebound after voluntary tic suppression. Patients also reported no rebound, but erroneously felt a tic reduction in the later course of the study. This misjudgement as well as patients' often reported (mis-)belief of a tic rebound may be caused by overall difficulties in reliable tic rating. Premonitory urges remained unchanged during tic suppression. Tic suppression was not influenced by attention deficits. Premonitory urges are no prerequisite of tic suppression.

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Journal of the American Academy of Child & Adolescent Psychiatry. 2014 Mar;53:351-61.

ABNORMAL AMYGDALA FUNCTIONAL CONNECTIVITY ASSOCIATED WITH EMOTIONAL LABILITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hulvershorn LA, Mennes M, Castellanos FX, et al.

Objective: A substantial proportion of children with attention-deficit/hyperactivity disorder (ADHD) also display emotion regulation deficits manifesting as chronic irritability, severe temper outbursts, and aggression. The amygdala is implicated in emotion regulation, but its connectivity and relation to emotion regulation in ADHD has yet to be explored. The purpose of this study was to examine the relationship between intrinsic functional connectivity (iFC) of amygdala circuits and emotion regulation deficits in youth with ADHD.

Method: Bilateral amygdala iFC was examined using functional magnetic resonance imaging in 63 children with ADHD, aged 6 to 13 years. First, we examined the relationship between amygdala IFC and parent ratings of emotional lability (EL) in children with ADHD. Second, we compared amygdala iFC across subgroups of children with ADHD and high EL (n=18), ADHD and low EL (n=20), and typically developing

children (TDC), all with low EL (n=19). Results: Higher EL ratings were associated with greater positive iFC between the amygdala and rostral anterior cingulate cortex in youth with ADHD. EL scores were also negatively associated with iFC between bilateral amygdala and posterior insula/superior temporal gyrus. Patterns of amygdala-cortical iFC in ADHD participants with low EL were not different from the comparison group, and the effect sizes for these comparisons were smaller than those for the trend-level differences observed between the high-EL and TDC groups.
Conclusions: In children with ADHD and a range of EL, deficits in emotion regulation were associated with altered amygdala–cortical iFC. When comparing groups that differed on ADHD status but not EL, differences in amygdala iFC were small and nonsignificant, highlighting the specificity of this finding to emotional deficits, independent of other ADHD symptoms.

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J Am Acad Child Adolesc Psychiatry. 2014;53:569-78.
PREDICTIVE NEUROFUNCTIONAL MARKERS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER BASED ON PATTERN CLASSIFICATION OF TEMPORAL PROCESSING.
Hart H, Marquand AF, Smith A, et al.
Objective Attention-deficit/hyperactivity disorder (ADHD) is currently diagnosed on the basis of subjective measures, despite evidence for multi-systemic structural and neurofunctional deficits. A consistently observed neurofunctional deficit is in fine-temporal discrimination (TD).
The aim of this proof-of-concept study was to examine the feasibility of distinguishing patients with ADHD from controls using multivariate pattern recognition analyses of functional magnetic resonance imaging (fMRI) data of TD.
Method A total of 20 medication-naive adolescent male patients with ADHD and 20 age-matched healthy controls underwent fMRI while performing a TD task. The fMRI data were analyzed with Gaussian process classifiers to predict individual ADHD diagnosis based on brain activation patterns.
Results The pattern of brain activation correctly classified up to 80% of patients and 70% of controls, achieving an overall classification accuracy of 75%. The distributed activation networks with the highest delineation between patients and controls corresponded to a distributed network of brain regions involved in TD and typically compromised in ADHD, including inferior and dorsolateral prefrontal, insula, and parietal cortices, and the basal ganglia, anterior cingulate, and cerebellum. These regions overlapped with areas of reduced activation in patients with ADHD relative to controls in a univariate analysis, suggesting that these are dysfunctional regions.
Conclusions We show evidence that pattern recognition analyses combined with fMRI using a disorder-sensitive task such as timing have potential in providing objective diagnostic neuroimaging biomarkers of ADHD.

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J Am Acad Child Adolesc Psychiatry. 2014;53:425-36.
CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS ARE RISK FACTORS FOR OBESITY AND PHYSICAL INACTIVITY IN ADOLESCENCE.
Khalife N, Kantomaa M, Glover V, et al.
Objective To prospectively investigate the association and directionality between attention-deficit/hyperactivity disorder (ADHD) symptoms and obesity from childhood to adolescence in the general population. We examined whether obesogenic behaviors, namely, physical inactivity and binge eating, underlie the potential ADHD symptom-obesity association. We explored whether childhood conduct disorder (CD) symptoms are related to adolescent obesity/physical inactivity.
Method At 7 to 8 years (n=8,106), teachers reported ADHD and CD symptoms, and parents reported body mass index (BMI) and physically active play. At 16 years (n=6,934), parents reported ADHD symptoms; adolescents reported physical activity (transformed to metabolic equivalent of task [MET] hours per week) and binge eating; BMI and waist-hip ratio (WHR) were measured via clinical examination. Obesity was

defined using the International Obesity Task Force (IOTF) cut-offs for BMI and the 95th percentile cut-off for WHR.
Results Childhood ADHD symptoms significantly predicted adolescent obesity, rather than the opposite. Inattention-hyperactivity symptoms at 8 years were associated with indices of obesity at 16 years (obese BMI: odds ratio [OR] = 1.91, 95% confidence interval [CI]=1.10-3.33; 95th percentile WHR: OR=1.71, 95% CI = 1.05-2.78), adjusted for gender, baseline BMI, physical activity, family structure change, and maternal education. Child CD symptoms associated with indices of adolescent obesity. Reduced physically active play in childhood predicted adolescent inattention (OR=1.61, 95% CI=1.16-2.24). Childhood ADHD and CD symptoms were linked with physical inactivity in adolescence (inattention-hyperactivity; OR=1.60, 95% CI=1.20-2.13), but not binge eating. Physical inactivity mediated the associations.
Conclusions Children with ADHD or CD symptoms are at increased risk for becoming obese and physically inactive adolescents. Physical activity may be beneficial for both behavior problems and obesity.

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J Formos Med Assoc. 2014.

THE RELATIONSHIP OF NEUROIMAGING FINDINGS AND NEUROPSYCHIATRIC COMORBIDITIES IN CHILDREN WITH TUBEROUS SCLEROSIS COMPLEX.

Huang C-H, Peng SSF, Weng W-C, et al.

Background/Purpose: To clarify the relationship between neuroimaging findings, neuropsychiatric comorbidities, and epilepsy in patients with tuberous sclerosis complex (TSC) in Taiwan.
Methods: Medical records from 32 patients with TSC were retrospectively reviewed, including mutational analysis, neuroimaging findings, electroencephalogram findings, and neuropsychiatric comorbidities.
Results: Of these patients, six (18.75%) were diagnosed to have autism spectrum disorders (ASD), and 10 (31.25%) were diagnosed to have attention-deficit-hyperactivity disorder. In the latter patients, there were no differences in the regional distribution of tuber burden. In addition to a high prevalence of cystic-like tubers, tubers in insular and temporal areas were associated with ASD. Nonsense mutations in the TSC2 gene group had a correlation with autistic behavior. In 26 (81.25%) patients with a history of epilepsy, infantile spasms and partial seizures were the predominant type of epilepsy. Most of them developed seizures prior to age 1 year.
Conclusion: ASD is a common comorbidity in TSC. Cortical tubers in the temporal lobe and insular area were associated with ASD. The presence of cystic-like tubers on magnetic resonance imaging may also offer a structural marker for ASD in TSC.

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Logoped Phoniatr Vocol. 2014 Mar.

LANGUAGE AND PRAGMATIC PROFILE IN CHILDREN WITH ADHD MEASURED BY CHILDREN'S COMMUNICATION CHECKLIST 2ND EDITION.

Vaisanen R, Loukusa S, Moilanen I, et al.

Objective. The aim of this study was to explore whether children with attention deficit hyperactivity disorder (ADHD) have language and/or pragmatic difficulties compared to typically developing children.
Methods. Nineteen children with ADHD (age 5-12 years) and nineteen typically developing children (age 5-8 years) were evaluated using the Finnish version of Children's Communication Checklist 2nd edition (CCC-2). The CCC-2 questionnaire was filled in by their parents.
Results. According to the CCC-2 questionnaire, differences between the groups were found in linguistic abilities, pragmatics skills, and social interaction.
Conclusion. According to the CCC-2 profiles, many children with ADHD may have various kinds of communication difficulties, even if they do not have a diagnosed language disorder.

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Malays J Nutr. 2012 Dec;18:329-35.

EFFECT OF N-3 SUPPLEMENTATION ON HYPERACTIVITY, OXIDATIVE STRESS AND INFLAMMATORY MEDIATORS IN CHILDREN WITH ATTENTION-DEFICIT-HYPERACTIVITY DISORDER.

Hariri M, Djazayery A, Djalali M, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is associated with difficulties in learning, behaviour and psychosocial adjustment that persist into adulthood. Decreased omega-3 fatty acids and increased inflammation or oxidative stress may contribute to neuro-developmental and psychiatric disorders such as ADHD. The aim of this study was to determine the effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with ADHD.

METHODS: In this double blind study, 103 children (6-12 years) with ADHD receiving maintenance therapy were assigned randomly into two groups. The n-3 group received n-3 fatty acids (635 mg eicosapentaenoic acid (EPA), 195 mg docosahexaenoic acid (DHA)), and the placebo group received olive oil capsules which were visually similar to the n-3 capsules. The duration of supplementation was 8 weeks. Plasma C-reactive protein (CRP), interleukin-6 (IL-6) and the activity of glutathione reductase (GR), catalase (CAT) and superoxide dismutase (SOD) were determined before and after the intervention. Likewise the Conners' Abbreviated Questionnaires (ASQ-P) was applied.

RESULTS: After 8-week intervention, a significant reduction was observed in the levels of CRP ($P < 0.05$, 95% CI = 0.72-2.02) and IL-6 ($P < 0.001$, 95% CI = 1.93-24.33) in the n-3 group. There was also a significant increase in activity of SOD and GR ($P < 0.001$). A significant improvement was seen in the ASQ-P scores in the n-3 group ($P < 005$).

CONCLUSION: Eight weeks of EPA and DHA supplementation decreased plasma inflammatory mediators and oxidative stress in the children with ADHD. These results suggest that n-3 fatty acid supplementation may offer a safe and efficacious treatment for children with ADHD.

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Mol Neurobiol. 2014.

IMAGING FUNCTIONAL AND STRUCTURAL BRAIN CONNECTOMICS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Cao M, Shu N, Cao Q, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopment disorders in childhood. Clinically, the core symptoms of this disorder include inattention, hyperactivity, and impulsivity. Previous studies have documented that these behavior deficits in ADHD children are associated with not only regional brain abnormalities but also changes in functional and structural connectivity among regions. In the past several years, our understanding of how ADHD affects the brain's connectivity has been greatly advanced by mapping topological alterations of large-scale brain networks (i.e., connectomes) using noninvasive neurophysiological and neuroimaging techniques (e.g., electroencephalograph, functional MRI, and diffusion MRI) in combination with graph theoretical approaches. In this review, we summarize the recent progresses of functional and structural brain connectomics in ADHD, focusing on graphic analysis of large-scale brain systems. Convergent evidence suggests that children with ADHD had abnormal small-world properties in both functional and structural brain networks characterized by higher local clustering and lower global integrity, suggesting a disorder-related shift of network topology toward regular configurations. Moreover, ADHD children showed the redistribution of regional nodes and connectivity involving the default-mode, attention, and sensorimotor systems. Importantly, these ADHD-associated alterations significantly correlated with behavior disturbances (e.g., inattention and hyperactivity/impulsivity symptoms) and exhibited differential patterns between clinical subtypes. Together, these connectome-based studies highlight brain network dysfunction in ADHD, thus opening up a new window into our understanding of the pathophysiological mechanisms of this disorder. These works might also have important implications on the development of imaging-based biomarkers for clinical diagnosis and treatment evaluation in ADHD.

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NeuroImage Clin. 2014;4:566-75.

FUNCTIONAL CONNECTIVITY OF NEURAL MOTOR NETWORKS IS DISRUPTED IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

McLeod KR, Langevin LM, Goodyear BG, et al.

Developmental coordination disorder (DCD) and attention deficit/hyperactivity disorder (ADHD) are prevalent childhood disorders that frequently co-occur. Evidence from neuroimaging research suggests that children with these disorders exhibit disruptions in motor circuitry, which could account for the high rate of co-occurrence. The primary objective of this study was to investigate the functional connections of the motor network in children with DCD and/or ADHD compared to typically developing controls, with the aim of identifying common neurophysiological substrates. Resting-state fMRI was performed on seven children with DCD, 21 with ADHD, 18 with DCD + ADHD and 23 controls. Resting-state connectivity of the primary motor cortex was compared between each group and controls, using age as a co-factor. Relative to controls, children with DCD and/or ADHD exhibited similar reductions in functional connectivity between the primary motor cortex and the bilateral inferior frontal gyri, right supramarginal gyrus, angular gyri, insular cortices, amygdala, putamen, and pallidum. In addition, children with DCD and/or ADHD exhibited different age-related patterns of connectivity, compared to controls. These findings suggest that children with DCD and/or ADHD exhibit disruptions in motor circuitry, which may contribute to problems with motor functioning and attention. Our results support the existence of common neurophysiological substrates underlying both motor and attention problems.

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Neuropsychiatr Dis Treat. 2014;10:47-54.

(1)H-MAGNETIC RESONANCE SPECTROSCOPY STUDY OF STIMULANT MEDICATION EFFECT ON BRAIN METABOLITES IN FRENCH CANADIAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

BenAmor L.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in school aged children. Functional abnormalities have been reported in brain imaging studies in ADHD populations. Psychostimulants are considered as the first line treatment for ADHD. However, little is known of the effect of stimulants on brain metabolites in ADHD patients.

OBJECTIVES: To compare the brain metabolite concentrations in children with ADHD and on stimulants with those of drug naive children with ADHD, versus typically developed children, in a homogenous genetic sample of French Canadians.

METHODS: Children with ADHD on stimulants (n=57) and drug naive children with ADHD (n=45) were recruited, as well as typically developed children (n=38). The presence or absence of ADHD diagnosis (Diagnostic and Statistical Manual of Mental Disorders IV criteria) was based on clinical evaluation and The Diagnostic Interview Schedule for Children IV. All children (n=140) underwent a proton magnetic resonance spectroscopy session to measure the ratio of N-acetyl-aspartate, choline, glutamate, and glutamate-glutamine to creatine, respectively, in the left and right prefrontal and striatal regions of the brain, as well as in the left cerebellum.

RESULTS: When compared with drug naive children with ADHD, children with ADHD on stimulants and children typically developed were found to have higher choline ratios in the left prefrontal region (P=0.04) and lower N-acetyl-aspartate ratios in the left striatum region (P=0.01), as well as lower glutamate-glutamine ratios in the left cerebellum (P=0.05). In these three regions, there was no difference between children with ADHD on stimulants and typically developed children.

CONCLUSION: Therapeutic psychostimulant effects in children with ADHD may be mediated by normalization of brain metabolite levels, particularly in the left fronto-striato-cerebellar regions.

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Neuropsychiatr Dis Treat. 2014;10:613-18.

ANALYSIS OF CARDIAC AUTONOMIC MODULATION OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

de Carvalho TD, Wajnsztejn R, de Abreu LC, et al.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is characterized by decreased attention span, impulsiveness, and hyperactivity. Autonomic nervous system imbalance was previously described in this population. We aim to compare the autonomic function of children with ADHD and controls by analyzing heart rate variability (HRV).

METHODS: Children rested in supine position with spontaneous breathing for 20 minutes. Heart rate was recorded beat by beat. HRV analysis was performed in the time and frequency domains and Poincare plot.

RESULTS: Twenty-eight children with ADHD (22 boys, aged 9.964 years) and 28 controls (15 boys, age 9.857 years) participated in this study. It was determined that the mean and standard deviation of indexes which indicate parasympathetic activity is higher in children with ADHD than in children without the disorder: high frequency in normalized units, 46.182 (14.159) versus 40.632 (12.247); root mean square of successive differences, 41.821 (17.834) versus 38.150 (18.357); differences between adjacent normal-to-normal intervals greater than 50 milliseconds, 199.75 (144.00) versus 127.46 (102.21) ($P<0.05$); percentage of differences between adjacent normal-to-normal intervals greater than 50 milliseconds, 23.957 (17.316) versus 16.211 (13.215); standard deviation of instantaneous beat-to-beat interval, 29.586 (12.622) versus 26.989 (12.983).

CONCLUSION: Comparison of the autonomic function by analyzing HRV suggests an increase in the activity of the parasympathetic autonomic nervous systems in children with ADHD in relation to the control group.

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Neuropsychology. 2014 Mar.

RULE-BASED AND INFORMATION-INTEGRATION PERCEPTUAL CATEGORY LEARNING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Huang-Pollock CL, Maddox WT, Tam H.

Objective: Suboptimal functioning of the basal ganglia is implicated in attention-deficit/hyperactivity disorder (ADHD). These structures are important to the acquisition of associative knowledge, leading some to theorize that associative learning deficits might be expected, despite the fact that most extant research in ADHD has focused on effortful control. We present 2 studies that examined the acquisition of explicit rule-based (RB) and associative information integration (II) category learning among school-age children with ADHD.

Method and Results: In Study 1, we found deficits in both RB and II category learning tasks among children with ADHD (n=81) versus controls (n=42). Children with ADHD tended to sort by the more salient but irrelevant dimension (in the RB paradigm) and were unable to acquire a consistent sorting strategy (in the II paradigm). To disentangle whether the deficit was localized to II category learning versus a generalized inability to consider more than 1 stimulus dimension, in Study 2 children completed a conjunctive RB paradigm that required consideration of 2 stimulus dimensions. Children with ADHD (n=50) continued to underperform controls (n=33).

Conclusions: Results provide partial support for neurocognitive developmental theories of ADHD that suggest that associative learning deficits should be found, and highlight the importance of using analytic approaches that go beyond asking whether an ADHD-related deficit exists to why such deficits exist.

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NeuroReport. 2014 May;25:618-24.

CHANGES IN NEGATIVE AND POSITIVE EEG SHIFTS DURING SLOW CORTICAL POTENTIAL TRAINING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PRELIMINARY INVESTIGATION.

Takahashi J, Yasumura A, Nakagawa E, et al.

We examined the effects of self-regulation of slow cortical potentials (SCP) in nine children with attention-deficit/hyperactivity disorder (ADHD) by focusing on the changes in electroencephalographic (EEG) shifts during SCP sessions. In SCP training, individuals learn to increase and decrease their cortical excitabilities (enhancement of negative and positive cortical shifts). To examine the efficiency of SCP training, we conducted an attention task and measured contingent negative variation, which relates to the attention maintenance ability. Moreover, to assess training effects at the behavioral level, the Japanese ADHD rating scale (SNAP-J) was completed by the parents. In SCP training, we analyzed changes in EEG shifts during 16 training sessions by calculating the peak amplitudes of positive and negative shifts. The results of EEG data showed that peak amplitudes increased in sessions 11 and 12 for negative shifts and in sessions 9 and 13 for positive shifts. Moreover, we found an enhancement of contingent negative variation amplitude in the attention task before and after training, suggesting that the ability of these children to maintain attention could be modified by SCP training. However, significant behavioral improvements were not observed on the Japanese ADHD rating scale. It has been proposed that the number of additional training sessions may affect both physiological and behavioral improvements. Our present results, however, suggest the possibility that even low numbers of training sessions, such as 16, can bring about physiological improvement, whereas greater numbers of training sessions may be needed to have an influence on behavioral changes.

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Nord J Psychiatry. 2014 Mar.

PSYCHOSIS IN ADULTHOOD IS ASSOCIATED WITH HIGH RATES OF ADHD AND CD PROBLEMS DURING CHILDHOOD.

Dalteg A, Zandelin A, Tuninger E, et al.

Background: Patients diagnosed with schizophrenia display poor premorbid adjustment (PPA) in half of the cases. Attention deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) are common child psychiatric disorders. These two facts have not previously been linked in the literature.

Aims: To determine the prevalence of ADHD/CD problems retrospectively among patients with psychoses, and whether and to what extent the high frequency of substance abuse problems among such patients may be linked to ADHD/CD problems.

Method: ADHD and CD problems/diagnoses were retrospectively recorded in one forensic (n=149) and two non-forensic samples (n=98 and n=231) of patients with a psychotic illness: schizophrenia, bipolar or other, excluding drug-induced psychoses.

Results: ADHD and CD were much more common among the patients than in the general population-the odds ratio was estimated to be greater than 5. There was no significant difference in this respect between forensic and non-forensic patients. Substance abuse was common, but substantially more common among patients with premorbid ADHD/CD problems.

Conclusions: Previous views regarding PPA among patients with a psychotic illness may reflect an association between childhood ADHD/CD and later psychosis. The nature of this association remains uncertain: two disorders sharing some generative mechanisms or one disorder with two main clinical manifestations. Childhood ADHD and particularly CD problems contribute to the high frequency of substance abuse in such groups.

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Nutrients. 2014;6:1539-53.

DIETARY PATTERNS IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Woo HD, Kim DW, Hong YS, et al.

The role of diet in the behavior of children has been controversial, but the association of several nutritional factors with childhood behavioral disorders has been continually suggested. We conducted a case-control

study to identify dietary patterns associated with attention deficit hyperactivity disorder (ADHD). The study included 192 elementary school students aged seven to 12 years. Three non-consecutive 24-h recall (HR) interviews were employed to assess dietary intake, and 32 predefined food groups were considered in a principal components analysis (PCA). PCA identified four major dietary patterns: the "traditional" pattern, the "seaweed-egg" pattern, the "traditional-healthy" pattern, and the "snack" pattern. The traditional-healthy pattern is characterized by a diet low in fat and high in carbohydrates as well as high intakes of fatty acids and minerals. The multivariate-adjusted odds ratio (OR) of ADHD for the highest tertile of the traditional-healthy pattern in comparison with the lowest tertile was 0.31 (95% CI: 0.12-0.79). The score of the snack pattern was positively associated with the risk of ADHD, but a significant association was observed only in the second tertile. A significant association between ADHD and the dietary pattern score was not found for the other two dietary patterns. In conclusion, the traditional-healthy dietary pattern was associated with lower odds having ADHD.

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Pediatr Int. 2014 Jan.

VITAMIN D STATUS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Goksugur SB, Tufan AE, Semiz M, et al.

BACKGROUND: Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of the childhood is an early onset, affecting 2-18 % of the children worldwide. Etiopathogenesis of ADHD is obscure. In recent studies, low levels of vitamin D are found in association with many disorders as well as in neuropsychiatric diseases. In this study, we aimed to investigate serum vitamin D levels in pediatric ADHD patients.

METHODS: A total of 60 ADHD patients and 30 healthy controls were included in the study. Ages of the both groups were in 7 and 18 years old range. Serum levels of 25-OH-Vitamin D, calcium (Ca), phosphorus (P) and alkaline phosphatase (ALP) were investigated.

RESULTS: Serum levels of 25-OH-vitamin D were found to be significantly lower in children and adolescents with ADHD compared to healthy controls and no significant differences were found between the groups in terms of other variables. 25-OH-vitamin D level in ADHD group and control group was respectively; 20.9+/-19.4 ng/mL and 34.9+/-15.4 ng/mL (p=0.001).

CONCLUSION: Our results suggest that there is an association between lower 25-OH-vitamin D concentrations and ADHD in childhood and adolescence. Up to our knowledge this is the first study that investigate the relationship between vitamin D and ADHD in children.

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Pediatr Transplant. 2014 May;18:272-79.

ACADEMIC POTENTIAL AND COGNITIVE FUNCTIONING OF LONG-TERM SURVIVORS AFTER CHILDHOOD LIVER TRANSPLANTATION.

Ee LC, Lloyd O, Beale K, et al.

This cross-sectional study assessed intellect, cognition, academic function, behaviour, and emotional health of long-term survivors after childhood liver transplantation. Eligible children were >5 yr post-transplant, still attending school, and resident in Queensland. Hearing and neurocognitive testing were performed on 13 transplanted children and six siblings including two twin pairs where one was transplanted and the other not. Median age at testing was 13.08 (range 6.52-16.99) yr; time elapsed after transplant 10.89 (range 5.16-16.37) yr; and age at transplant 1.15 (range 0.38-10.00) yr. Mean full-scale IQ was 97 (81-117) for transplanted children and 105 (87-130) for siblings. No difficulties were identified in intellect, cognition, academic function, and memory and learning in transplanted children or their siblings, although both groups had reduced mathematical ability compared with normal. Transplanted patients had difficulties in executive functioning, particularly in self-regulation, planning and organization, problem-solving, and visual scanning. Thirty-one percent (4/13) of transplanted patients, and no siblings, scored in the clinical range for ADHD. Emotional difficulties were noted in transplanted patients but were not different from their

siblings. Long-term liver transplant survivors exhibit difficulties in executive function and are more likely to have ADHD despite relatively intact intellect and cognition.

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Pediatr Cardiol. 2014;35:485-89.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SCREENING ELECTROCARDIOGRAMS: A COMMUNITY-BASED PERSPECTIVE.

Shahani SA, Evans WN, Mayman GA, et al.

Screening electrocardiograms (EKGs) for attention deficit hyperactivity disorder (ADHD) medication administration is controversial. We reviewed our experience as a community-based cardiology group. We reviewed all ADHD screening EKGs during a 2-year period. We evaluated whether screening EKGs resulted in further consultation and if management was altered. We also evaluated differences between patients on ADHD medications and those starting ADHD medications and further stratified the patients into stimulant versus nonstimulant groups. A total of 691 screening EKGs met our criteria. Forty-two patients (6.1 %) were recommended for further consultation. EKG findings requiring consultation included the following: left-ventricular hypertrophy, right atrial enlargement, arrhythmia, prolonged QT, and axis deviation. Studies performed during consultation included 39 echocardiograms, 2 stress tests, 2 Holter monitors, and 1 heart card. Five patients (0.72%) were identified to have cardiac disease, one of whom decided against starting ADHD medications due to an arrhythmia, resulting in a change in management (0.14%). Results comparing mean age, heart rate, and corrected QT interval between patients on medication and patients starting medications were as follows: 10.06 years, 82.87, bpm and 405.24 ms compared with 9.99 years, 80.05 bpm, and 405.82 ms, respectively (p=not significant [NS], p=0.013 [NS], respectively). Results comparing mean age, heart rate, and corrected QT interval between patients on stimulant versus nonstimulant medications were as follows: 9.68 years, 83.10 bpm, and 403.04 ms compared with 9.81 years, 80.10 bpm, and 407.08 ms, respectively (p=NS for all). In our population, screening EKGs rarely resulted in management changes for patients taking or starting ADHD medications.

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Pediatrics. 2014;133:659-67.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN YOUNG CHILDREN: PREDICTORS OF DIAGNOSTIC STABILITY.

Law EC, Sideridis GD, Prock LA, et al.

OBJECTIVES: The goals of this study were (1) to provide estimates of diagnostic stability for a sample of young children diagnosed with attention-deficit/hyperactivity disorder (ADHD) after undergoing comprehensive multidisciplinary assessments and (2) to identify baseline child and family characteristics that predict diagnostic stability over time.

METHODS: Children aged 3 to 6 years, 11 months consecutively diagnosed with ADHD after multidisciplinary consultations at a tertiary care clinic between 2003 and 2008 were recontacted in 2012 and 2013 (N=120). At follow-up, the primary outcome was the proportion of children who continued to meet diagnostic criteria for ADHD. To identify predictors of diagnostic stability, logistic regression models were used. In addition, a latent class model was used to independently classify subjects into distinct clusters.

RESULTS: In this cohort, 70.4% of the children contacted at followup continued to meet diagnostic criteria for ADHD. Predictors of diagnostic stability included externalizing and internalizing symptoms at baseline, parental history of psychopathology, and family socioeconomic status. The latent class model independently identified 3 distinct profiles: (1) children who no longer met ADHD criteria; (2) children with persistent ADHD and high parental psychopathology; and (3) children with persistent ADHD and low family socioeconomic status.

CONCLUSIONS: Young children who underwent comprehensive developmental and psychological assessments before receiving an ADHD diagnosis, had higher rates of diagnostic stability than in previous studies of community samples. Child and family factors that predict diagnostic stability have the potential to guide treatment planning for children diagnosed with ADHD before 7 years of age.

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Pediatrics. 2014 Mar;133:e530-e537.

NEED AND UNMET NEED FOR CARE COORDINATION AMONG CHILDREN WITH MENTAL HEALTH CONDITIONS.

Brown NM, Green JC, Desai MM, et al.

OBJECTIVE: To determine prevalence and correlates of need and unmet need for care coordination in a national sample of children with mental health conditions.

METHODS: Using data from the 2007 National Survey of Children's Health, we identified children aged 2 to 17 years with >/=1 mental health condition (attention-deficit/hyperactivity disorder, anxiety disorder, conduct disorder, or depression) who had received >/=2 types of preventive or subspecialty health services in the past year. We defined 2 outcome measures of interest: (1) prevalence of need for care coordination; and (2) prevalence of unmet need for care coordination in those with a need. Logistic regression models were used to estimate associations of clinical, sociodemographic, parent psychosocial, and health care characteristics with the outcome measures.

RESULTS: In our sample (N=7501, representing an estimated 5,750,000 children), the prevalence of having any need for care coordination was 43.2%. Among parents reporting a need for care coordination, the prevalence of unmet need was 41.2%. Higher risk of unmet need for care coordination was associated with child anxiety disorder, parenting stress, lower income, and public or no insurance. Parents reporting social support and receipt of family-centered care had a lower risk of unmet need for care coordination.

CONCLUSIONS: Approximately 40% of parents of children with mental health conditions who reported a need for care coordination also reported that their need was unmet. Delivery of family-centered care and enhancing family supports may help to reduce unmet need for care coordination in this vulnerable population.

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Pediatrics. 2014 Mar;133:e546-e552.

LONG-TERM MOTOR AND COGNITIVE OUTCOME OF ACUTE ENCEPHALITIS.

Michaeli O, Kassis I, Shachor-Meyouhas Y, et al.

OBJECTIVES: To examine the long-term motor and neurocognitive outcome of children with acute encephalitis and to look at possible prognostic factors.

METHODS: Children who were treated for acute encephalitis in 2000-2010 were reevaluated. All children and their parents were interviewed by using structured questionnaires, and the children underwent full neurologic examinations, along with comprehensive neurocognitive, attention, and behavioral assessments.

RESULTS: Of the 47 children enrolled, 1 died and 29 had neurologic sequelae, including motor impairment, mental retardation, epilepsy, and attention and learning disorders. Children with encephalitis had a significantly higher prevalence of attention-deficit/hyperactivity disorder (50%) and learning disabilities (20%) compared with the reported rate (5%-10%) in the general population of Israel (P<.05) and lower IQ scores. Lower intelligence scores and significantly impaired attention and learning were found even in children who were considered fully recovered at the time of discharge. Risk factors for long-term severe neurologic sequelae were focal signs in the neurologic examination and abnormal neuroimaging on admission, confirmed infectious cause, and long hospital stay.

CONCLUSIONS: Encephalitis in children may be associated with significant long-term neurologic sequelae. Significant cognitive impairment, attention-deficit/hyperactivity disorder, and learning disabilities are common, and even children who were considered fully recovered at discharge may be significantly affected. Neuropsychological testing should be recommended for survivors of childhood encephalitis.

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Pediatrics. 2014;133:e981-e982.

COLLABORATIVE CARE OUTCOMES FOR PEDIATRIC BEHAVIORAL HEALTH PROBLEMS: A CLUSTER RANDOMIZED TRIAL.

Kolko DJ, Campo J, Kilbourne AM, et al.

OBJECTIVE: To assess the efficacy of collaborative care for behavior problems, attention-deficit/hyperactivity disorder (ADHD), and anxiety in pediatric primary care (Doctor Office Collaborative Care; DOCC).

METHODS: Children and their caregivers participated from 8 pediatric practices that were cluster randomized to DOCC (n=160) or enhanced usual care (EUC; n=161). In DOCC, a care manager delivered a personalized, evidence-based intervention. EUC patients received psychoeducation and a facilitated specialty care referral. Care processes measures were collected after the 6-month intervention period. Family outcome measures included the Vanderbilt ADHD Diagnostic Parent Rating Scale, Parenting Stress Index-Short Form, Individualized Goal Attainment Ratings, and Clinical Global Impression-Improvement Scale. Most measures were collected at baseline, and 6-, 12-, and 18-month assessments. Provider outcome measures examined perceived treatment change, efficacy, and obstacles, and practice climate.

RESULTS: DOCC (versus EUC) was associated with higher rates of treatment initiation (99.4% vs 54.2%; P < .001) and completion (76.6% vs 11.6%, P<.001), improvement in behavior problems, hyperactivity, and internalizing problems (P<.05 to .01), and parental stress (P<.05-.001), remission in behavior and internalizing problems (P<.01, .05), goal improvement (P<.05 to .001), treatment response (P <.05), and consumer satisfaction (P<.05). DOCC pediatricians reported greater perceived practice change, efficacy, and skill use to treat ADHD (P<.05 to .01).

CONCLUSIONS: Implementing a collaborative care intervention for behavior problems in community pediatric practices is feasible and broadly effective, supporting the utility of integrated behavioral health care services.

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Pediatrics. 2014 Apr.

ANXIETY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sciberras E, Lycett K, Efron D, et al.

OBJECTIVES: Although anxiety is common in children with attention-deficit/hyperactivity disorder (ADHD), it is unclear how anxiety influences the lives of these children. This study examined the association between anxiety comorbidities and functioning by comparing children with ADHD and no, 1, or >/=2 anxiety comorbidities. Differential associations were examined by current ADHD presentation (subtype).

METHODS: Children with diagnostically confirmed ADHD (N=392; 5-13 years) were recruited via 21 pediatrician practices across Victoria, Australia. Anxiety was assessed by using the Anxiety Disorders Interview Schedule for Children-IV. Functional measures included parent-reported: quality of life (QoL; Pediatric Quality of Life Inventory 4.0), behavior and peer problems (Strengths and Difficulties Questionnaire), daily functioning (Daily Parent Rating of Evening and Morning Behavior), and school attendance. Teacher-reported behavior and peer problems (Strengths and Difficulties Questionnaire) were also examined. Linear and logistic regression controlled for ADHD severity, medication use, comorbidities, and demographic factors.

RESULTS: Children with >/=2 anxiety comorbidities (n = 143; 39%) had poorer QoL (effect size: -0.8) and more difficulties with behavior (effect size: 0.4) and daily functioning (effect size: 0.3) than children without anxiety (n = 132; 36%). Poorer functioning was not observed for children with 1 anxiety comorbidity (n = 95; 26%). Two or more anxiety comorbidities were associated with poorer functioning for children with both ADHD-Inattentive and ADHD-Combined presentation.

CONCLUSIONS: Children with ADHD demonstrate poorer QoL, daily functioning and behavior when >/=2 anxiety comorbidities are present. Future research should examine whether treating anxiety in children with ADHD improves functional outcomes.

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Pediatrics. 2014;133:668-76.

ATTENTION DEFICIT DISORDER, STIMULANT USE, AND CHILDHOOD BODY MASS INDEX TRAJECTORY.

Schwartz BS, Bailey-Davis L, Bandeen-Roche K, et al .

BACKGROUND: Childhood attention-deficit/hyperactivity disorder (ADHD) has been associated with childhood and adult obesity, and stimulant use with delayed childhood growth, but the independent influences are unclear. No longitudinal studies have examined associations of ADHD diagnosis and stimulant use on BMI trajectories throughout childhood and adolescence.

METHODS: We used longitudinal electronic health record data from the Geisinger Health System on 163 820 children ages 3 to 18 years in Pennsylvania. Random effects linear regression models were used to model BMI trajectories with increasing age in relation to ADHD diagnosis, age at first stimulant use, and stimulant use duration, while controlling for confounding variables.

RESULTS: Mean (SD) age at first BMI was 8.9 (5.0) years, and children provided a mean (SD) of 3.2 (2.4) annual BMI measurements. On average, BMI trajectories showed a curvilinear relation with age. There were consistent associations of unmedicated ADHD with higher BMIs during childhood compared with those without ADHD or stimulants. Younger age at first stimulant use and longer duration of stimulant use were each associated with slower BMI growth earlier in childhood but a more rapid rebound to higher BMIs in late adolescence.

CONCLUSIONS: The study provides the first longitudinal evidence that ADHD during childhood not treated with stimulants was associated with higher childhood BMIs. In contrast, ADHD treated with stimulants was associated with slower early BMI growth but a rebound later in adolescence to levels above children without a history of ADHD or stimulant use. The findings have important clinical and neurobiological implications.

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Pediatrics. 2014 Apr.

LANGUAGE PROBLEMS IN CHILDREN WITH ADHD: A COMMUNITY-BASED STUDY.

Sciberras E, Mueller KL, Efron D, et al.

OBJECTIVES: To examine the prevalence of language problems in children with attention-deficit/hyperactivity disorder (ADHD) versus non-ADHD controls, and the impact of language problems on the social and academic functioning of children with ADHD.

METHODS: Children (6 to 8 years) with ADHD (n=179) and controls (n=212) were recruited through 43 Melbourne schools. ADHD was assessed by using the Conners 3 ADHD Index and the Diagnostic Interview Schedule for Children IV. Oral language was assessed by using the Clinical Evaluation of Language Fundamentals, fourth edition, screener. Academic functioning was measured via direct assessment (Wide Range Achievement Test 4) and teacher report (Social Skills Improvement System). Social functioning was measured via parent and teacher report (Strengths and Difficulties Questionnaire; Social Skills Improvement System). Logistic and linear regression models were adjusted for sociodemographic factors and child comorbidities.

RESULTS: Children with ADHD had a higher prevalence of language problems than controls after adjustment for sociodemographic factors and comorbidities (odds ratio, 2.8; 95% confidence interval [CI], 1.5 to 5.1). Compared with children with ADHD alone, those with language problems had poorer word reading (mean difference [MD], -11.6; 95% CI, -16.4 to -6.9; effect size, -0.7), math computation (MD, -11.4; 95% CI, -15.0 to -7.7; effect size, -0.8), and academic competence (MD, -10.1; 95% CI, -14.0 to -6.1; effect size, -0.7). Language problems were not associated with poorer social functioning.

CONCLUSIONS: Children with ADHD had a higher prevalence of language problems than controls, and language problems in children with ADHD contributed to markedly poorer academic functioning.

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Pharmacoepidemiol Drug Saf. 2014;23:534-38.

TRENDS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER DRUGS CONSUMPTION, ISRAEL, 2005-2012.

Ponizovsky AM, Marom E, Fitoussi I .

Purpose: The aim of this study was to describe trends in attention deficit hyperactivity disorder (ADHD) drugs consumption in Israel (Ritalin, Concerta, Daytrana, Vyvanse, Focalin, and Adderall) over the 8years, 2005-2012, and to explore explanations for changes in amounts and patterns of the utilization.

Methods: Data for the period from 2005 to 2012 were extracted from the database maintained by the Israel Ministry of Health's Pharmaceutical Administration. The data were converted into a defined daily dose (DDD) per 1000 inhabitants per day.

Results: Consumption of all ADHD drugs covered by Israel's national health care system doubled over the study period, from 4.02 DDD/1000 inhabitants/day in 2005 to 9.92 DDD/1000 inhabitants/day in 2012. This rise was largely due to a fivefold increase in Concerta consumption (from 0.46 DDD/1000 inhabitants/day in 2005 to 2.28 DDD/1000 inhabitants/day in 2012) and a threefold increase in Ritalin consumption (from 1.43 DDD/1000 inhabitants/day in 2005 to 4.84 DDD/1000 inhabitants/day in 2012). Adderall (amphetamine mixed salts) consumption rose by 30% for the same period. A substantial trend was noted for increased utilization of high-dose formulations together with proportional decline in low-dose consumption. In the same period, cost of the medications has been reduced an average by 20-25%.

Conclusions: There has been a drastic rise in ADHD drugs consumption in Israel over 2005-2012. This has been associated with substantial reduction in cost and changes in the pattern of prescribing that characterized by increased prescription of high-dose long-acting preparations of ADHD drugs and decreased prescription of their low-dose, short-acting formulations.

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Phys Occup Ther Pediatr. 2014 Apr.

ASSESSING SENSORY PROCESSING PROBLEMS IN CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Pfeiffer B, Daly BP, Nicholls EG, et al.

ABSTRACT

Aims: This exploratory study investigated whether children with attention-deficit/hyperactivity disorder (ADHD) are at greater risk than children without ADHD for problems with sensory processing and if certain sensory systems are more closely associated with the core symptoms of ADHD, specifically inattention and hyperactivity/impulsivity.

Methods: The sample included 20 children with ADHD and 27 children without ADHD, ages 5 to 10 years. Assessments included the Sensory Processing Measure-Home Form and the Conners 3rd edition-Parent Short Form.

Results: After controlling for age, children with ADHD exhibited more sensory processing problems on all scales of the Sensory Processing Measure with small to medium effect sizes observed (eta 2 =.27 to .61). For children with ADHD, the Social Participation (r=.50) and Planning and Ideas (r=.73) subtests of the Sensory Processing Measure were significantly associated with hyperactivity/impulsivity, but not with inattention on the subtests of the Conners Parent Short Form.

Conclusion: The results suggest the importance of assessing sensory processing issues in children with ADHD to guide in the intervention process.

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Physical Education and Sport Pedagogy. 2014 Mar;19:205-20.

CHILDREN SAY THE DARNDEST THINGS: PHYSICAL ACTIVITY AND CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Harvey WJ, Wilkinson S, Pressé C, et al.

Background: Physical educators suggested that they are not well-informed about behaviors of children with disabilities, especially attention-deficit hyperactivity disorder (ADHD). Children with ADHD represent a significant number of students in school systems worldwide who often experience difficulties in performing

fundamental movement skills. Reasons for these challenging movement behaviors are not clearly understood. There were no significant effects of stimulant medication on performance of the Test of Gross Motor Development-2 (TGMD-2) for 22 children with ADHD. Six boys with ADHD possessed superficial content knowledge about physical activity (PA) participation. Poor movement skills may be related to a mismatch between content knowledge and specific skill performance, which can be problematic at individual skill levels.
Purpose: To explore how children with ADHD regulate PA participation by listening to PA stories. Participants and setting: Ten children with ADHD participated in this study. They were identified by qualified child psychiatrists from an ADHD clinic at a major mental health institute in a large urban Canadian city.
Research design: A concurrent mixed methods design explored the PA experiences of the children. The qualitative data were given a higher priority. Data collection: The quantitative research component was individualized assessments of fundamental movement skills with the TGMD-2 and Movement Assessment Battery for Children-2. The qualitative research component included: (1) PA self-reporting where each child recorded daily experiences for a two week period and (2) concurrent scrapbook interviews that enhanced participant recall/reflection to generate rich discussions about individual PA experiences.
Data analysis: Quantitative skill assessments provided movement-related descriptions of participants. Individual skill levels were labeled with normative test descriptors linked to each respective assessment instrument. These qualitized descriptors were mixed with interview data only after all movement skill assessments and scrapbook interviews were completed. Interviews were transcribed verbatim and a within group thematic analysis was conducted.
Findings: Many of the children demonstrated movement skill problems on both tests but skill performance was worse on the TGMD-2. Three qualitative themes emerged. The participants with ADHD spoke about their PA experiences in many different individual physical activities (play theme) and various settings (context theme). All children expressed personal wishes to be included in PA with other children in the community. A range of perceived self-regulatory behaviors emerged for planning PA (organization theme). The findings suggest some of the children with ADHD chose and organized their own PA while other children performed PA that was immediately in front of them with minimal organization of their PA behaviors.
Conclusions: Children with ADHD told PA stories that many children without disabilities would tell. However, many of the children with the disorder described experiences related to exclusion from PA. They also lacked conceptual understanding of the purpose and goals related to general participation in various PA. Physical education teacher interventions, leisure counseling and community-based participatory research projects in PA are among the recommendations discussed for children with ADHD.

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PLoS ONE. 2014;9:e95891.

FETAL EXPOSURE TO PERFLUORINATED COMPOUNDS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDHOOD.

Ode A, Kallen K, Gustafsson P, et al.

BACKGROUND: The association between exposure to perfluorinated compounds (PFCs) and attention deficit hyperactivity disorder (ADHD) diagnosis has been sparsely investigated in humans and the findings are inconsistent.
OBJECTIVES: A matched case-control study was conducted to investigate the association between fetal exposure to PFCs and ADHD diagnosis in childhood.
METHODS: The study base comprised children born in Malmo, Sweden, between 1978 and 2000 that were followed up until 2005. Children with ADHD (n=206) were identified at the Department of Child and Adolescent Psychiatry. Controls (n=206) were selected from the study base and were matched for year of birth and maternal country of birth. PFC concentrations were measured in umbilical cord serum samples. The differences of the PFC concentrations between cases and controls were investigated using Wilcoxon's paired test. Possible threshold effects (above the upper quartile for perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) and above limit of detection [LOD] for perfluorononanoic acid (PFNA)) were evaluated by conditional logistic regression.

RESULTS: The median umbilical cord serum concentrations of PFOS were 6.92 ng/ml in the cases and 6.77 ng/ml in the controls. The corresponding concentrations of PFOA were 1.80 and 1.83 ng/ml. No associations between PFCs and ADHD were observed. Odds ratios adjusted for smoking status, parity, and gestational age were 0.81 (95% confidence interval [CI] 0.50 to 1.32) for PFOS, 1.07 (95% CI 0.67 to 1.7) for PFOA, and 1.1 (95% CI 0.75 to 1.7) for PFNA. CONCLUSIONS: The current study revealed no support for an association between fetal exposure to PFOS, PFOA, or PFNA and ADHD.

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PLoS ONE. 2014;9:e95269.

BRAIN MORPHOLOGY IN CHILDREN WITH EPILEPSY AND ADHD.

Saute R, Dabbs K, Jones JE, et al.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is a common comorbidity of childhood epilepsy, but the neuroanatomical correlates of ADHD in epilepsy have yet to be comprehensively characterized.

METHODS: Children with new and recent-onset epilepsy with (n=18) and without (n=36) ADHD, and healthy controls (n=46) underwent high resolution MRI. Measures of cortical morphology (thickness, area, volume, curvature) and subcortical and cerebellar volumes were compared between the groups using the program FreeSurfer 5.1.

RESULTS: Compared to the control group, children with epilepsy and ADHD exhibited diffuse bilateral thinning in the frontal, parietal and temporal lobes, with volume reductions in the brainstem and subcortical structures (bilateral caudate, left thalamus, right hippocampus). There were very few group differences across measures of cortical volume, area or curvature.

CONCLUSIONS: Children with epilepsy and comorbid ADHD exhibited a pattern of bilateral and widespread decreased cortical thickness as well as decreased volume of subcortical structures and brainstem. These anatomic abnormalities were evident early in the course of epilepsy suggesting the presence of antecedent neurodevelopmental changes, the course of which remains to be determined.

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PLoS ONE. 2014;9.

FACIAL MIMICRY IN 6-7 YEAR OLD CHILDREN WITH DISRUPTIVE BEHAVIOR DISORDER AND ADHD.

Deschamps P, Munsters N, Kenemans L, et al.

Background: Impairments in facial mimicry are considered a proxy for deficits in affective empathy and have been demonstrated in 10 year old children and in adolescents with disruptive behavior disorder (DBD). However, it is not known whether these impairments are already present at an earlier age. Emotional deficits have also been shown in children with attention-deficit/hyperactivity disorder (ADHD).

Aims: To examine facial mimicry in younger, 6-7 year old children with DBD and with ADHD.

Methods: Electromyographic (EMG) activity in response to emotional facial expressions was recorded in 47 children with DBD, 18 children with ADHD and 35 healthy developing children.

Results: All groups displayed significant facial mimicry to the emotional expressions of other children. No group differences between children with DBD, children with ADHD and healthy developing children were found. In addition, no differences in facial mimicry were found between the clinical group (i.e., all children with a diagnosis) and the typically developing group in an analysis with ADHD symptoms as a covariate, and no differences were found between the clinical children and the typically developing children with DBD symptoms as a covariate.

Conclusion: Facial mimicry in children with DBD and ADHD throughout the first primary school years was unimpaired, in line with studies on empathy using other paradigms.

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PLoS ONE. 2014;9:e88297.

STRUCTURAL AND FUNCTIONAL RICH CLUB ORGANIZATION OF THE BRAIN IN CHILDREN AND ADULTS.

Grayson DS, Ray S, Carpenter S, et al.

Recent studies using Magnetic Resonance Imaging (MRI) have proposed that the brain's white matter is organized as a rich club, whereby the most highly connected regions of the brain are also highly connected to each other. Here we use both functional and diffusion-weighted MRI in the human brain to investigate whether the rich club phenomena is present with functional connectivity, and how this organization relates to the structural phenomena. We also examine whether rich club regions serve to integrate information between distinct brain systems, and conclude with a brief investigation of the developmental trajectory of rich-club phenomena. In agreement with prior work, both adults and children showed robust structural rich club organization, comprising regions of the superior medial frontal/dACC, medial parietal/PCC, insula, and inferior temporal cortex. We also show that these regions were highly integrated across the brain's major networks. Functional brain networks were found to have rich club phenomena in a similar spatial layout, but a high level of segregation between systems. While no significant differences between adults and children were found structurally, adults showed significantly greater functional rich club organization. This difference appeared to be driven by a specific set of connections between superior parietal, insula, and supramarginal cortex. In sum, this work highlights the existence of both a structural and functional rich club in adult and child populations with some functional changes over development. It also offers a potential target in examining atypical network organization in common developmental brain disorders, such as ADHD and Autism.

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Prev Sci. 2014 Apr.

EFFECTIVENESS OF A TEACHER-BASED INDICATED PREVENTION PROGRAM FOR PRESCHOOL CHILDREN WITH EXTERNALIZING PROBLEM BEHAVIOR.

Plueck J, Eichelberger I, Hautmann C, et al.

Externalizing behavior is common in preschool children and shows stability over the lifespan implying that strategies for early intervention and prevention are needed. Improving parenting reduces child behavior problems but it is unproven whether the effects transfer to kindergarten. Strategies implemented directly by teachers in the kindergarten may be a promising approach. The effectiveness of the teacher's module of the Prevention Program for Externalizing Problem Behavior (PEP-TE) was investigated in a study using a within-subject control group design. Each of the 144 teachers enrolled identified one child with externalizing problem behavior (aged 3-6 years) and rated that child's behavior problems [broadband externalizing, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder] as well as their own behavior (attending skills) and burden by the child. Changes in child symptoms and teacher behavior or burden during the 3-month waiting period (control) and 3-month treatment period were compared. Stability of treatment effects at both 3- and 12-months follow-up after treatment was examined. Multilevel modeling analyses showed that, despite a reduction in externalizing behavior and ADHD scores during the waiting period, all child problem behavior scores decreased during the treatment period compared with the waiting period. The teacher's behavior also improved and their burden decreased. These treatment effects were stable during follow-up for the subsample remaining in the kindergarten for up to 1 year. This study shows that a teacher-based intervention alone is associated with improvements in both the externalizing behavior of preschoolers and teacher behavior and burden. Indications of long-term stability of effects were found.

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Psychiatr Serv. 2014 Mar;65:395-98.

HEALTH CARE EXPERIENCES AND PERCEIVED FINANCIAL IMPACT AMONG FAMILIES OF CHILDREN WITH AN AUTISM SPECTRUM DISORDER.

Zablotsky B, Kalb LG, Freedman B, et al.

OBJECTIVE: The authors compared the health care experiences of families raising a child with autism spectrum disorder (ASD), an intellectual disability disorder (IDD), or attention-deficit hyperactivity disorder (ADHD).
METHODS: Children with a current diagnosis of ASD (N=3,005), ADHD (N=9,662), or IDD (N=949) were identified in the 2009-2010 National Survey of Children With Special Health Care Needs. Weighted structural equation modeling was used to determine the association between family satisfaction with medical care, timeliness of care, and medical insurance coverage and the impact of the child's condition on the family's financial situation.
RESULTS: Families of children diagnosed as having ASD comorbid with either ADHD or IDD or comorbid with both conditions reported the highest levels of dissatisfaction across all health care quality variables and experienced the greatest impact on the family's financial situation.
CONCLUSIONS: The findings underscore the need for comprehensive and accessible health care services for children with ASD, particularly those with comorbid conditions.

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Psychiatry Investig. 2014 Jan;11:24-31.

PREVALENCE AND CORRELATES OF PROBLEMATIC INTERNET EXPERIENCES AND COMPUTER-USING TIME: A TWO-YEAR LONGITUDINAL STUDY IN KOREAN SCHOOL CHILDREN.

Yang SJ, Stewart R, Lee JY, et al.

OBJECTIVE: To measure the prevalence of and factors associated with online inappropriate sexual exposure, cyber-bullying victimisation, and computer-using time in early adolescence.
METHODS: A two-year, prospective school survey was performed with 1,173 children aged 13 at baseline. Data collected included demographic factors, bullying experience, depression, anxiety, coping strategies, self-esteem, psychopathology, attention-deficit hyperactivity disorder symptoms, and school performance. These factors were investigated in relation to problematic Internet experiences and computer-using time at age 15.
RESULTS: The prevalence of online inappropriate sexual exposure, cyber-bullying victimisation, academic-purpose computer overuse, and game-purpose computer overuse was 31.6%, 19.2%, 8.5%, and 21.8%, respectively, at age 15. Having older siblings, more weekly pocket money, depressive symptoms, anxiety symptoms, and passive coping strategy were associated with reported online sexual harassment. Male gender, depressive symptoms, and anxiety symptoms were associated with reported cyber-bullying victimisation. Female gender was associated with academic-purpose computer overuse, while male gender, lower academic level, increased height, and having older siblings were associated with game-purpose computer-overuse.
CONCLUSION: Different environmental and psychological factors predicted different aspects of problematic Internet experiences and computer-using time. This knowledge is important for framing public health interventions to educate adolescents about, and prevent, internet-derived problems.

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Psychiatry Res. 2014 Apr;222:75-83.

PREFRONTAL GREY AND WHITE MATTER NEUROMETABOLITE CHANGES AFTER ATOMOXETINE AND METHYLPHENIDATE IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A (1)H MAGNETIC RESONANCE SPECTROSCOPY STUDY.

Husarova V, Bittsansky M, Ondrejka I, et al.

Attention deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral childhood disorder. Dysfunction of prefrontal neural circuits which are responsible for executive and attentional functions has been previously shown in ADHD. We investigated the neurometablite changes in areas included in dorsolateral prefrontal neural circuits after 2 months of long-acting methylphenidate or atomoxetine medication in children with ADHD who were responders to treatment. Twenty-one ADHD children were examined by single voxel (1)H-magnetic resonance spectroscopy (MRS) before and after 2 months of medication with OROS methylphenidate (n=10) or atomoxetine (n=11). The spectra were taken from the

dorsolateral prefrontal cortex (DLPFC, 8ml) and white matter behind the DLPFC (anterior semioval center, 7.5ml), bilaterally. NAA and NAA/Cr (N-acetylaspartate/creatine) decreased in the left DLPFC and Cho/Cr (choline/creatine) increased in the right DLPFC after atomoxetine medication. Glu+Gln and Glu+Gln/Cr (glutamate/glutamine) increased in the left white matter after methylphenidate medication. We hypothesize that atomoxetine could decrease hyperactivation of DLPFC neurons and methylphenidate could lead to increased activation of cortical glutamatergic projections with the consequences of increased tonic dopamine release in the mesocortical system.

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Psychiatry Res. 2014 Feb.

SLUGGISH COGNITIVE TEMPO AND PEER FUNCTIONING IN SCHOOL-AGED CHILDREN: A SIX-MONTH LONGITUDINAL STUDY.

Becker SP.

Although research demonstrates sluggish cognitive tempo (SCT) symptoms to be statistically distinct from other child psychopathologies (including attention-deficit/hyperactivity disorder [ADHD], anxiety, depression, and oppositionality) and associated with social impairment, all studies conducted to date have been cross-sectional. Thus, while extant research demonstrates an association between SCT and social functioning, it is entirely unknown whether or not SCT longitudinally predicts increases in social impairment. This study provides an initial examination of the prospective association between SCT symptoms and childrens peer functioning. Teachers of 176 children in 1st-6th grades (ages 6-13; 47% boys) provided ratings of childrens psychopathology (i.e., SCT, ADHD, anxious/depressive, and oppositional/conduct problems) and peer functioning (i.e., popularity, negative social preference, peer impairment), and peer functioning was assessed again 6 months later. Multilevel modeling analyses indicated that, above and beyond child demographics, other psychopathologies, and baseline peer functioning, SCT symptoms were significantly associated with poorer peer functioning at the 6-month follow-up. In addition, 75% of children with high levels of SCT were rated as functionally impaired in the peer domain, in contrast to only 8% of children with low SCT. Further research is needed with larger samples to examine SCT over a longer developmental period and with other domains of adjustment.

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Psychiatry Res. 2014.

SEX-SPECIFIC ASSOCIATION OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) VAL66MET POLYMORPHISM AND PLASMA BDNF WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A DRUG-NAIVE HAN CHINESE SAMPLE.

Li H, Liu L, Tang Y, et al.

A functional polymorphism of the brain derived neurotrophic factor gene (BDNF) (Val66Met) has been suggested to be involved in the pathogenesis of attention-deficit/hyperactivity disorder (ADHD). It also has an impact on peripheral BDNF levels in psychiatric disorders. This study examined the association of Val66Met with plasma BDNF level of ADHD in Han Chinese children (170 medication - naive ADHD patients and 155 unaffected controls, aged 6-16 years). The Val allele was showed a higher frequency in females with ADHD (n=84) than controls (P=0.029) from the case-control association study. The analysis of covariance (ANCOVA) indicated that the mean plasma BDNF levels of ADHD patients were significantly higher than that of controls (P=0.001). We performed both total sample and sex stratified analyses to investigate the effect of Val66Met genotype on the plasma BDNF levels, but only a trend of association was found in females with ADHD (n=84), with a tendency of lower plasma BDNF level in Val allele carriers than Met/Met genotype carriers (P=0.071). Our results suggested a sex-specific association between BDNF and ADHD. Furthermore, there was a possible sex-specific relationship between the BDNF Val66Met genotype and plasma BDNF levels. However, further studies are required to elucidate the role of BDNF in ADHD.

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Psychol Med. 2014 Jan;1-12.

DSM-5 DISRUPTIVE MOOD DYSREGULATION DISORDER: CORRELATES AND PREDICTORS IN YOUNG CHILDREN.

Dougherty LR, Smith VC, Bufferd SJ, et al.

BACKGROUND: Despite the inclusion of disruptive mood dysregulation disorder (DMDD) in DSM-5, little empirical data exist on the disorder. We estimated rates, co-morbidity, correlates and early childhood predictors of DMDD in a community sample of 6-year-olds.

METHOD: DMDD was assessed in 6-year-old children (n = 462) using a parent-reported structured clinical interview. Age 6 years correlates and age 3 years predictors were drawn from six domains: demographics; child psychopathology, functioning, and temperament; parental psychopathology; and the psychosocial environment.

RESULTS: The 3-month prevalence rate for DMDD was 8.2% (n=38). DMDD occurred with an emotional or behavioral disorder in 60.5% of these children. At age 6 years, concurrent bivariate analyses revealed associations between DMDD and depression, oppositional defiant disorder, the Child Behavior Checklist - Dysregulation Profile, functional impairment, poorer peer functioning, child temperament (higher surgency and negative emotional intensity and lower effortful control), and lower parental support and marital satisfaction. The age 3 years predictors of DMDD at age 6 years included child attention deficit hyperactivity disorder, oppositional defiant disorder, the Child Behavior Checklist - Dysregulation Profile, poorer peer functioning, child temperament (higher child surgency and negative emotional intensity and lower effortful control), parental lifetime substance use disorder and higher parental hostility.

CONCLUSIONS: A number of children met DSM-5 criteria for DMDD, and the diagnosis was associated with numerous concurrent and predictive indicators of emotional and behavioral dysregulation and poor functioning.

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Psychol Med. 2014 Mar;44:881-92.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND EXECUTIVE FUNCTIONING IN AFFECTED AND UNAFFECTED ADOLESCENTS AND THEIR PARENTS: CHALLENGING THE ENDOPHENOTYPE CONSTRUCT.

Thissen AJAM, Rommelse NNJ, Hoekstra PJ, et al.

Background: The results of twin and sibling studies suggest that executive functioning is a prime candidate endophenotype in attention deficit hyperactivity disorder (ADHD). However, studies have not assessed the co-segregation of executive function (EF) deficits from parents to offspring directly, and it is unclear whether executive functioning is an ADHD endophenotype in adolescents, given the substantial changes in prefrontal lobe functioning, EF and ADHD symptoms during adolescence.

Method: We recruited 259 ADHD and 98 control families with an offspring average age of 17.3 years. All participants were assessed for ADHD and EF [inhibition, verbal (VWM) and visuospatial working memory (VsWM)]. Data were analysed using generalized estimating equations (GEEs).

Results: Parental ADHD was associated with offspring ADHD and parental EF was associated with offspring EF but there were no cross-associations (parental ADHD was not associated with offspring EF or vice versa). Similar results were found when siblings were compared. EF deficits were only found in affected adolescents and not in their unaffected siblings or (un)affected parents.

Conclusions: The core EFs proposed to be aetiologically related to ADHD, that is working memory and inhibition, seem to be aetiologically independent of ADHD in adolescence. EF deficits documented in childhood in unaffected siblings were no longer present in adolescence, suggesting that children 'grow out' of early EF deficits. This is the first study to document ADHD and EF in a large family sample with adolescent offspring. The results suggest that, after childhood, the majority of influences on ADHD are independent from those on EF. This has potential implications for current aetiological models of causality in ADHD.

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Psychol Addict Behav. 2014;28:238-46.

A LONGITUDINAL STUDY OF CHILDHOOD ADHD AND SUBSTANCE DEPENDENCE DISORDERS IN EARLY ADULTHOOD.

Breyer JL, Lee S, Winters KC, et al .

Attention deficit hyperactivity disorder (ADHD) is a childhood disorder that is associated with many behavioral and social problems. These problems may continue when an individual continues to meet criteria for ADHD as an adult. In this study, we describe the outcome patterns for three different groups: individuals who had ADHD as children, but no longer meet criteria as adults (Childhood-Limited ADHD, n=71); individuals who met ADHD criteria as children and continue to meet criteria as young adults (Persistent ADHD n=79); and a control group of individuals who did not meet ADHD diagnostic criteria in childhood or adulthood (n=69). Groups were compared with examine differences in change in rates of alcohol, marijuana, and nicotine dependence over 3 time points in young adulthood (mean ages 18, 20, and 22 years). The method used is notable as this longitudinal study followed participants from childhood into young adulthood instead of relying on retrospective self-reports from adult participants. Results indicated that there were no significant group differences in change in rates of substance dependence over time. However, individuals whose ADHD persisted into adulthood were significantly more likely to meet DSM-IV criteria for alcohol, marijuana, and nicotine dependence across the 3 time points after controlling for age, sex, childhood stimulant medication use, and childhood conduct problems. Implications of these findings, as well as recommendations for future research, are discussed.

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Psychoterapia. 2014;47-57.

THE USE OF ELEMENTS OF AGGRESSION REPLACEMENT TRAINING IN THE TREATMENT OF A BOY WITH BEHAVIORAL AND EMOTIONAL DISORDERS AND ADHD.

Piskor-Swierad B.

The study presents methods of work with a 10 year-old boy causing significant educational problems. He was diagnosed with the micro damages in left temporal lobe, as well as ADHD and oppositional defiant disorders. The boy is under a constant neurological and psychiatric care and is taking medication. In the therapeutic process elements of Aggression Replacement Training was used. This is a cognitive-behavioral intervention for aggressive people. It has been discussed as a functioning model of his family and particular influences. The results can indicate for a long-term improvement of the boy's cognitive and emotional abilities.

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Res Dev Disabil. 2013 Sep;34:2543-50.

PREVALENCE OF ADHD IN A SAMPLE OF ITALIAN STUDENTS: A POPULATION-BASED STUDY.

Bianchini R, Postorino V, Grasso R, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common diagnosis for children and adolescents, although the reported estimates for prevalence are extremely variable worldwide. In the present work we investigate the prevalence of ADHD in a sample of Italian students in a study divided in two phases. In Phase I, a total of 6183 schoolchildren (3178 males and 3005 females, aged range 5-15 years) were screened using the SDAI rating scale for teachers. In Phase II, the parents of children and adolescents who met high screen criteria according to SDAI (cut-off>14; n=471, 7.3%) were invited to complete a specific clinical-diagnostic assessment for ADHD with the help of an experienced clinician. Within the entire sample, 107 children dropped out and 12 had mental retardation, whereas 332 subjects (278 males and 54 females, age range 5-14 years) completed the Phase II of the study. One hundred ninety subjects (163 males and 27 females, male: female ratio 6:1, mean age 8 years) were diagnosed with ADHD, indicating a prevalence of 3%. ADHD subtypes included the following: combined (n=108; 56.8%), inattentive (n=48; 25.2%) and hyperactive/impulsive (n=33; 17.3%). Our findings are in line with other reports of ADHD prevalence in the European Countries, and may contribute to underline the impact of this

phenomenon in the population, and the need of achieving an improvement in the quality of the public health mental service for the prevention and treatment of ADHD.

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Res Dev Disabil. 2014 Apr;35:1588-98.

RELIABILITY AND VALIDITY OF THE PRAGMATICS OBSERVATIONAL MEASURE (POM): A NEW OBSERVATIONAL MEASURE OF PRAGMATIC LANGUAGE FOR CHILDREN.

Cordier R, Munro N, Wilkes-Gillan S, et al.

There is a need for a reliable and valid assessment of childhood pragmatic language skills during peer-peer interactions. This study aimed to evaluate the psychometric properties of a newly developed pragmatic assessment, the Pragmatic Observational Measure (POM). The psychometric properties of the POM were investigated from observational data of two studies - study 1 involved 342 children aged 5-11 years (108 children with ADHD; 108 typically developing playmates; 126 children in the control group), and study 2 involved 9 children with ADHD who attended a 7-week play-based intervention. The psychometric properties of the POM were determined based on the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) taxonomy of psychometric properties and definitions for health-related outcomes; the Pragmatic Protocol was used as the reference tool against which the POM was evaluated. The POM demonstrated sound psychometric properties in all the reliability, validity and interpretability criteria against which it was assessed. The findings showed that the POM is a reliable and valid measure of pragmatic language skills of children with ADHD between the age of 5 and 11 years and has clinical utility in identifying children with pragmatic language difficulty.

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Res Dev Disabil. 2014 Jun;35:1364-74.

RESILIENT PARENTING OF CHILDREN AT DEVELOPMENTAL RISK ACROSS MIDDLE CHILDHOOD.

Ellingsen R, Baker BL, Blacher J, et al.

This paper focuses on factors that might influence positive parenting during middle childhood when a parent faces formidable challenges defined herein as "resilient parenting." Data were obtained from 162 families at child age 5 and 8 years. Using an adapted ABCX model, we examined three risk domains (child developmental delay, child ADHD/ODD diagnosis, and low family income) and three protective factors (mother's education, health, and optimism). The outcome of interest was positive parenting as coded from mother-child interactions. We hypothesized that each of the risk factors would predict poorer parenting and that higher levels of each protective factor would buffer the risk-parenting relationship. Positive parenting scores decreased across levels of increasing risk. Maternal optimism appeared to be a protective factor for resilient parenting concurrently at age 5 and predictively to age 8, as well as a predictor of positive change in parenting from age 5 to age 8, above and beyond level of risk. Maternal education and health were not significantly protective for positive parenting. Limitations, future directions, and implications for intervention are discussed.

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Res Dev Disabil. 2014;35:1252-58.

BALANCE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER-COMBINED TYPE.

Mao H-Y, Kuo L-C, Yang A-L, et al.

The balance ability in children with attention deficit hyperactivity disorder-combined type (ADHD-C) has not been fully examined, particularly dynamic sitting balance. Moreover, the findings of some published studies are contradictory. We examined the static and dynamic sitting balance ability in 20 children with ADHD-C (mean age: 9 years 3 months; 18 boys, 2 girls) and 20 age-, sex-, height-, weight-, and IQ-matched healthy and typically developing controls (mean age: 9 years 2 months; 18 boys, 2 girls). The balance subtests of the Movement Assessment Battery for Children (MABC) and the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) were used to compare the two groups, and a mechanical horseback riding test was

recorded using a motion-capture system. Compared with the controls, children with ADHD-C had less-consistent patterns of movement, more deviation of movement area, and less-effective balance strategies during mechanical horseback riding. In addition, their performance on the balance subtests of the MABC and BOTMP were not as well as those of the controls. Our findings suggest that balance ability skill levels in children with ADHD-C were generally not as high as those of the controls in various aspects, including static and dynamic balance.

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Res Dev Disabil. 2014;35:963-72.

IMPACT OF EXECUTIVE FUNCTIONS ON SCHOOL AND PEER FUNCTIONS IN YOUTHS WITH ADHD.

Chiang H-L, Gau SSF.

Youths with attention-deficit/hyperactivity disorder (ADHD) are more likely to have social dysfunction at school. The authors explored the role of key executive functions (EF, i.e., spatial working memory and spatial planning) on school and peer functions in 511 youths with persistent ADHD according to the DSM-IV diagnostic criteria and 124 non-ADHD controls without any EF deficits. All the participants were assessed by a semi-structured psychiatric interview to confirm their previous and current diagnosis of ADHD and other psychiatric disorders and by the Spatial Working Memory (SWM) and Stocking of Cambridge (SOC) tasks. The participants and their parents reported the participants' school functions and peer relationships. There were three ADHD subgroups: (1) ADHD with deficits in both SWM and SOC tasks (n=121); (2) ADHD with deficit in either SWM or SOC task (n=185); (3) ADHD without deficits in SWM or SOC task (n=205). All the three ADHD groups, regardless of EF deficits, had lower school grade, poorer attitude toward school work, poorer school interactions, more behavioral problems at school, and more severe problems in peer relationships than non-ADHD controls. Multivariate analyses revealed positive associations between deficit in the SWM task and school and peer dysfunctions, and between deficits in the SOC task and impaired peer interactions. Older age and psychiatric comorbidity also contributed to increased risk of school and peer dysfunctions. Our findings suggest that deficits in EF, such as spatial working memory and planning, might be associated with school and peer dysfunctions.

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Res Dev Disabil. 2014;35:1292-300.

EFFECT OF VISUAL ATTENTION ON POSTURAL CONTROL IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bucci MP, Seassau M, Larger S, et al.

We compared the effect of oculomotor tasks on postural sway in two groups of ADHD children with and without methylphenidate (MPH) treatment against a group of control age-matched children. Fourteen MPH-untreated ADHD children, fourteen MPH-treated ADHD children and a group of control children participated to the study. Eye movements were recorded using a video-oculography system and postural sway measured with a force platform simultaneously. Children performed fixation, pursuits, pro- and anti-saccades. We analyzed the number of saccades during fixation, the number of catch-up saccades during pursuits, the latency of pro- and anti-saccades; the occurrence of errors in the anti-saccade task and the surface and mean velocity of the center of pressure (CoP). During the postural task, the quality of fixation was significantly worse in both groups of ADHD children with respect to control children; in contrast, the number of catch-up saccades during pursuits, the latency of pro-/anti-saccades and the rate of errors in the anti-saccade task did not differ in the three groups of children. The surface of the CoP in MPH-treated children was similar to that of control children, while MPH-untreated children showed larger postural sway. When performing any saccades, the surface of the CoP improved with respect to fixation or pursuits tasks. This study provides evidence of poor postural control in ADHD children, probably due to cerebellar deficiencies. Our study is also the first to show an improvement on postural sway in ADHD children performing saccadic eye movements.

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Rev Bras Psiquiatr. 2013 Oct;35:393-405.

PHARMACOTHERAPY OF BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS: AN UPDATE.

Peruzzolo TL, Tramontina S, Rohde LA, et al.

OBJECTIVE: To review the options for acute and maintenance pharmacological treatment of bipolar disorder in children and adolescents, including the treatment of bipolar depression and comorbid attention deficit/hyperactivity disorder (ADHD).

METHODS: Narrative review of randomized clinical trials and open-label studies published from 2000 to 2012. The PubMed and PsycINFO websites were queried. Case series were included when a higher level of evidence was not available.

RESULTS: Published data from randomized controlled trials (RCTs) in acute mania/hypomania with significant responses are available for lithium, topiramate, risperidone, olanzapine, and aripiprazole. Open trials of lithium and lamotrigine show that these drugs may be effective in the treatment of depressive episodes. No trials of selective serotonin reuptake inhibitors (SSRIs) have been conducted. In the treatment of comorbid ADHD, there are encouraging findings with mixed amphetamine salts and atomoxetine; conflicting results are observed with methylphenidate.

CONCLUSIONS: Published RCTs of traditional mood stabilizers are scarce, but the best available evidence (results from meta-analytic regression) suggests that second-generation antipsychotics (SGAs) as a group are more effective in reducing manic symptoms. Risperidone was the only one included in head-to-head comparisons (vs. lithium and divalproex), showing superiority in terms of efficacy, but with more metabolic side effects, which were also more common in most of the SGAs. There are few studies addressing the treatment of ADHD and depression. Brazilian guidelines for the treatment of pediatric bipolar disorder should also include some SGAs (especially risperidone and aripiprazole) as first-line treatment, and these drugs should be provided by the public health services.

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Rev Med Chir Soc Med Nat Iasi. 2013 Jan;117:88-94.

CELIAC DISEASE WITH NEUROLOGIC MANIFESTATIONS IN CHILDREN.

Diaconu G, Burlea M, Grigore I, et al.

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals and neurologic manifestations may be one of the presentations form. The aim of this study was to report the incidence of neurologic manifestations in children with CD.

MATERIAL AND METHODS: Between 2000-2010, 48 children aged 2-18 years diagnosed with CD have been monitored. The diagnosis of CD was made by serological tests and intestinal biopsy. The study protocol included: measurement of weight and height, biological and immunological tests, histological examination, questionnaires filled out by parents about their child motor development and some neurologic signs, psychological exam, electroencephalogram, and brain CT-scan.

RESULTS: 16 of the 48 children presented one or more neurologic symptoms as the onset manifestation of CD. The neurologic signs in order of frequency were: headache/migraine, attention-deficit/hyperactivity disorder, epileptic seizures, mental retardation, cerebellar ataxia and behavior disorders. Brain CT-scan showed cerebral calcifications in 3 patients with epilepsy, and atrophy in 2 cases with cerebellar ataxia. All children received gluten free diet, but a favorable course was noticed only in the children with migraine and epilepsy, in the other patients this diet having no influence on neurologic symptoms.

CONCLUSIONS: This study proved the variety of neurologic symptoms that can be included in the clinical signs of celiac disease in pediatric patients. That is why in the presence of different neurologic symptoms of unknown etiology and resistant to treatment, celiac disease must be taken into account and laboratory investigations have to include intestinal biopsy and immunological test.

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Rev Med Inst Mex Seguro Soc. 2014 Jan;52:20-27.

BLOOD AND URINE LEAD LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sanchez-Villegas MC, Cortes-Vargas A, Hidalgo-Luna RG, et al.

BACKGROUND: Attention deficit hyperactivity disorder is the most common neuropsychiatric disorder in children; symptoms can persist into adult life by 60 %. Our objective was to quantify the levels of lead in blood and urine in pediatric patients with attention deficit hyperactivity disorder.

METHODS: We did an observational study which included a captive population of children diagnosed with attention deficit hyperactivity disorder in the mental health service of Hospital General, from Centro Medico Nacional La Raza. Lead levels were determined in blood and urine by atomic absorption technique.

RESULTS: We included 39 patients, 932 % male, with a mean age of 9.2 +/- 2.16 years. The deficit and hyperactivity disorder combined type was the most frequent (69.2 %); 49 % of patients were found with toxic lead levels in blood (above 10 mg/dL); 17.9 % with stage III and 5.12 % with stage IV, according to the Mexican Official Standard (NOM-199-SSA-2000). Significant association was found between blood lead levels and the clinical expression of attention deficit hyperactivity disorder.

CONCLUSIONS: Levels of lead exposure during early childhood have been shown to be inversely proportional to neurological development in the first seven years of life. Data results are insufficient to relate them with causality.

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Rev Neurol. 2014;58:S57-S63.

THETA/BETA RATIO (NEBA) IN THE DIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Delgado-Mejia ID, Palencia-Avendano ML, Mogollon-Rincon C, et al.

Introduction. In July 2013, the US Food and Drug Administration approved the use of NEBA as the first device for the complementary evaluation of attention deficit hyperactivity disorder (ADHD). It is based on quantitative electroencephalogram (qEEG) and includes the standardised theta/beta ratio, the results of which were consistent with both the medical and psychological clinical evaluation. Likewise, it has proved to be a useful tool for determining whether the ADHD is primary, secondary or comorbid to another pathology. Yet, to date no publications have specified whether it is a total theta/beta ratio or theta/beta-1 and theta/beta-2. Additionally, no data are provided to be able to discriminate between diagnostic subtypes of ADHD. Aims. To quantify the theta/beta ratios, by means of qEEG, in a sample of patients from the Rio de la Plata area with a main confirmed diagnosis of ADHD, in order to compare the neurophysiological patterns according to the diagnostic subtypes.

Patients and methods. We used a randomised stratified sample of 62 subjects of both sexes, with ages between 8 and 17 years, distributed into two groups, depending on the diagnostic subtype: attention deficit subtype of ADHD (n = 31) and the combined subtype of ADHD (n = 31).

Results. High theta/beta-1 and theta/beta-2 ratios were confirmed in the Cz region, being higher than the ratios in the C3 and C4 areas. Moderate and statistically significant differences were found between the two subtypes only in the beta-1 band in the occipital regions. The analysis of the interhemispheric coherence suggests an association of the power peak crossed with the diagnostic subtype, which is the fastest peak (10 Hz) for the combined subtype. No important differences are found on analysing the phase spectra or the theta/beta ratios.

Conclusions. Although the scientific literature, especially the NEBA system, highlights the importance of the theta/beta ratio in the differential diagnosis of ADHD in control samples and other neurodevelopmental disorders, a distinction must be made between beta-1 and beta-2.

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S D Med. 2013 Dec;66:511, 513.

ADHD: MONITORING FOR AND MANAGING STIMULANT ADVERSE EFFECTS.

Mercer M, Farver D.

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Scand J Occup Ther. 2014 May;21:181-90.

EVALUATING INTERVENTION USING TIME AIDS IN CHILDREN WITH DISABILITIES.

Janeslatt G, Kottorp A, Granlund M.

Abstract

Objective: The aim of this study was to evaluate complex intervention using time aids for children with intellectual and developmental disabilities who exhibit limitations in daily time management.

Methods: Participating children (n=47) (F17/M30) were aged 6-11 with ADHD, autism spectrum disorders, mild or moderate intellectual disability, spina bifida, and cerebral palsy. This study used a Randomized Block and Waiting List control group design, with 25 children allocated to control and 22 to intervention group. In total 10 children (21.3%), five from each group, dropped out, leaving 37 children in the data analysis.

Results: Children in both groups gained significantly in time-processing ability between the first and second data collection, but the children in the intervention group improved time-processing ability significantly more than controls. The control group also displayed significant changes after receiving intervention between the second and third data collection. The intervention had a large effect (ES Cohen's d = 0.81) on time-processing ability and a medium effect (ES Cohen's d = 0.68) on managing one's time.

Conclusions: This study provides preliminary evidence that time-processing ability and managing one's time can be improved by intervention using time aids in children with intellectual and developmental disabilities, supporting the need to consider time aids in intervention in these children.

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Sleep. 2014;37:901-09.

ASSOCIATIONS OF CHILD INSOMNIA, SLEEP MOVEMENT, AND THEIR PERSISTENCE WITH MENTAL HEALTH SYMPTOMS IN CHILDHOOD AND ADOLESCENCE.

Armstrong JM, Ruttle PL, Klein MH, et al.

STUDY OBJECTIVES: To examine the patterns of insomnia and sleep-related movement from ages 4.5 to 9 years, their concurrent associations with mental health symptoms in childhood, and the longitudinal associations of sleep-problem persistence with mental health symptoms at ages 9 and 18 years.

DESIGN: A 14-year prospective follow-up study. Assessments included maternal report on the Children's Sleep Habits Questionnaire at ages 4.5 and 9, and child mental health symptoms via maternal report at age 4.5, multi-informant (child, teacher, mother) report at age 9, and adolescent report at age 18.

SETTING: Community.

PARTICIPANTS: A total of 396 children (51% female).

INTERVENTIONS: N/A.

MEASUREMENTS AND RESULTS: Sleep problems were more common at age 4.5 than 9; symptoms of insomnia and abnormal sleep movement both had persistence rates of 9-10%. At age 4.5, insomnia was associated with hostile-aggressive and hyperactive-distractible behavior, but there were no significant associations for sleep movement. At age 9, both insomnia and sleep movement were associated with symptoms of depression, externalizing, and attention deficit hyperactivity disorder (ADHD). Insomnia persistence was associated with symptoms of depression, externalizing, and ADHD at age 9 and anxiety and externalizing at age 18; sleep- movement persistence was associated with externalizing and ADHD at age 9, and ADHD at age 18. The age 18 persistence effects for insomnia and anxiety and for sleep movement and ADHD were significant when controlling for earlier mental health.

CONCLUSIONS: Childhood insomnia and sleep movement are common and associated with mental health symptoms. Their persistence from middle to late childhood predicts associations with specific types of mental health symptoms at age 18.

CITATION: Armstrong JM, Ruttle PL, Klein MH, Essex MJ, Benca RM. Associations of child insomnia, sleep movement, and their persistence with mental health symptoms in childhood and adolescence.

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Sleep Med. 2014;15:472-75.

USE OF SLEEP MEDICATION IN CHILDREN WITH ADHD.

Efron D, Lycett K, Sciberras E.

Objective: Sleep problems are common in children with attention-deficit/hyperactivity disorder (ADHD), yet little is known about sleep medication use in this population. The aim of this study was to describe sleep medication use, as well as associated child and family characteristics in school-aged children with ADHD.

Method: Sleep medication use was ascertained using a prospective parent-completed seven-night sleep and medication log. Exposure variables included socio-demographic characteristics, total sleep problem severity (Children's Sleep Habits Questionnaire), ADHD severity and subtype (ADHD Rating Scale IV), ADHD medication use, internalising and externalising co-morbidities (Anxiety Disorders Interview Schedule for Children/Parent version IV) and parent mental health (Depression Anxiety Stress Scale).

Results: Two hundred and fifty-seven children with ADHD participated and of these 57 (22%) were taking sleep medication (melatonin 14% and clonidine 9%). Sleep medication use was associated with combined-type ADHD and ADHD medication use. The presence of co-occurring internalising and externalising co-morbidities was also associated with sleep medication use in ad hoc analyses.

Conclusion: Sleep medication use is common in children with ADHD and is associated with combined-type ADHD and use of ADHD medication. Further research is needed on the broad functional benefits and long-term safety of sleep medication in this population.

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Soc Psychiatry Psychiatr Epidemiol. 2014 Feb.

PREVALENCE AND COMORBIDITY OF PSYCHIATRIC DISORDERS AMONG 6-YEAR-OLD CHILDREN: 2004 PELOTAS BIRTH COHORT.

Petresco S, Anselmi L, Santos IS, et al.

PURPOSE: Most studies published on the prevalence of psychiatric disorders in children were conducted in high-income countries despite the fact that nearly 90 % of the world's population aged under 18 live in low- and middle-income countries. The study aimed to assess the prevalence of psychiatric disorders among children of 6 years of age, to examine the distribution of psychiatric disorders by gender and socioeconomic status and to evaluate the occurrence of psychiatric comorbidities.

METHODS: The 2004 Pelotas Birth Cohort originally comprised 4,231 live births from Pelotas, southern Brazil. A total of 3,585 (84.7 % of 4,231 births) children aged 6 years were assessed using the Development and Well-Being Assessment (DAWBA).

RESULTS: Nearly 13 % of the children presented a psychiatric diagnosis according to DSM-IV, being more prevalent among males than females (14.7 and 11.7 %, respectively, p = 0.009). Anxiety disorders were the most prevalent of all disorders (8.8 %) and specific phobias (5.4 %) and separation anxiety disorder (3.2 %) were the most common subtypes. Attention deficit hyperactivity disorder (2.6 %), oppositional defiant disorder/conduct disorder (2.6 %), and depression (1.3 %) were also diagnosed. More than one psychiatric disorder was presented by 17 % of children. Socioeconomically disadvantaged children had a higher prevalence of psychiatric disorders.

CONCLUSION: Our findings underline the early onset of psychiatric disorders among children and the frequent occurrence of psychiatric comorbidity. Early prevention is needed in the field of mental health in Brazil and should start during infancy.

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The International Journal of Psychoanalysis. 2014 Feb;95:43-66.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): AN AFFECT-PROCESSING AND THOUGHT DISORDER?

Günter M.

In the literature on child and adolescent psychoanalysis attention deficit hyperactivity disorder (ADHD) is described as complex syndrome with wide-ranging psychodynamic features. Broadly speaking, the disorder is divided into three categories: 1. a disorder in early object relations leading to the development of a maniform defence organization in which object-loss anxieties and depressed affects are not worked

through via symbolization but are organized in a body-near manner; 2. a triangulation disorder in which the cathexis of the paternal position is not stable; structures providing little support alternate with excessive arousal, affect regulation is restricted; 3. current emotional stress or a traumatic experience. I suggest taking a fresh look at ADHD from a psychoanalytic vantage point. With respect to the phenomenology of the disorder, the conflict–dynamic approach should be supplemented by a perspective regarding deficits in a-function as constitutive for ADHD. These deficits cause affect-processing and thought disorders compensated for (though not fully) by the symptomatology. At a secondary level, a vicious circle develops through the mutual reinforcement of defective processing of sense data and affects into potential thought content, on the one hand, and secondary, largely narcissistic defence processes on the other. These considerations have major relevance for the improved understanding of ADHD and for psychoanalytic technique.

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The New England Journal of Medicine. 2014 Feb;370:838-46.

ATTENTION DEFICIT–HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.

Feldman HM, Reiff MI.

A 9-year-old boy who received a diagnosis of attention deficit–hyperactivity disorder (ADHD) at 7 years of age is brought to your office by his parents for a follow-up visit. He had had behavioral problems since preschool, including excessive fidgeting and difficulty following directions and taking turns with peers. Parent and teacher ratings of behavior confirmed elevated levels of inattention, hyperactivity, and impulsivity that were associated with poor grades, disruptions of classroom activities, and poor peer relationships. He was treated with sustained-release methylphenidate. Although parent and teacher rating scales after treatment showed reduced symptoms, he still makes many careless mistakes and has poor grades and no friends. What would you advise?

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Tidsskr Nor Laegeforen. 2014 Apr;134:710-14.

CARDIOVASCULAR RISK ASSESSMENT FOR THE USE OF ADHD DRUGS IN CHILDREN.

Berg A, Bratane E, Odland HH, et al.

BACKGROUND Drug therapy for ADHD (Attention Deficit Hyperactivity Disorder) has generally been regarded as safe. ECG screening of healthy children and adolescents before initiating this type of treatment appears to be usual in Norway, despite recommendations that ECGs should only be undertaken in individuals who are at risk. The purpose of this article is to clarify relevant guidelines for cardiovascular risk assessment for the use of ADHD drugs in children and adolescents, as well as to propose practical recommendations.

METHOD The article is based on a literature search in PubMed completed on 1 October 2013, and on the author's own clinical experience and discretionary assessments.

RESULTS The use of CNS stimulants and atomoxetine is associated with a slight rise in blood pressure and pulse rate, as well as small changes in QT interval. A small percentage of patients (5-10 %) experience a clinically significant rise in blood pressure and pulse rate. Sudden death does not appear to occur more frequently in children and adolescents taking ADHD drugs in therapeutic doses than in children and adolescents who do not use such drugs. There is little knowledge available on the long-term effects of ADHD drugs on the cardiovascular system of otherwise healthy individuals, or on the risk related to the use of ADHD drugs in children and adolescents with cardiac disease. The drugs are thought to increase the risk of sudden cardiac death in some arrhythmia syndromes.

INTERPRETATION Our assessment is that caution should be exercised in the use of ADHD drugs in children with potentially dangerous cardiac arrhythmias. We recommend clinical examination and a thorough medical history review in order to identify individuals at risk before initiating drug therapy, and also suggest that it is not necessary for healthy children to be given an ECG examination before introducing ADHD drugs. In children with known cardiac disease, arrhythmia or risk factors for cardiac disease, ADHD

treatment should be undertaken in consultation with a medical specialist with competence in pediatric cardiology.

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Time. 2013 Dec;182:18.
ADHD RISING.
Park A.

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Turk J Pediatr. 2014;56:11-22.
CHILD MALTREATMENT AND ASSOCIATED FACTORS AMONG CHILDREN WITH ADHD: A COMPARATIVE STUDY.
Evinc SG, Gencoz T, Foto-Ozdemir D, et al.
This study aimed to compare the mothers of children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and the mothers of children with no psychiatric diagnosis with respect to abusive discipline attitudes. One hundred children with ADHD, 25 children with no psychiatric diagnosis, and their mothers answered the questionnaires and open-ended standard questions about the type and frequency of parental abusive discipline. Conners scores of the children were associated with characteristics of the children, maternal characteristics, and maternal use of verbal discipline. Maternal approval scores on verbally abusive disciplinary acts were predicted by maternal past experiences, maternal characteristics and Conners scores of children. Similarly, characteristics of the children and the mothers predicted maternal approval scores on physical disciplinary acts. ADHD symptoms increase the risk of parental verbally and physically abusive discipline. Vice versa, verbal discipline also predicts increased ADHD symptoms. Understanding the risk factors may help in developing more effective intervention and prevention programs.

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Vital Health Stat 10. 2013 Dec;1-81.
SUMMARY HEALTH STATISTICS FOR U.S. CHILDREN: NATIONAL HEALTH INTERVIEW SURVEY, 2012.
Bloom B, Jones LI, Freeman G.
Objectives This report presents both age-adjusted and unadjusted statistics from the 2012 National Health Interview Survey (NHIS) on selected health measures for children under age 18 years, classified by sex, age, race, Hispanic origin, family structure, parent's education, family income, poverty status, health insurance coverage, place of residence, region, and current health status. Topics included are asthma, allergies, learning disability, attention deficit hyperactivity disorder (ADHD), prescription medication use for at least 3 months, respondent-assessed health status, school days missed due to illness or injury, usual place of health care, time since last contact with a health care professional, selected measures of health care access, emergency room (ER) visits, dental care, and special education or early intervention services. Data Source NHIS is a multistage probability sample survey conducted annually by interviewers of the U.S. Census Bureau for the Centers for Disease Control and Prevention's National Center for Health Statistics and is representative of the civilian noninstitutionalized population of the United States. This report analyzes data from two of the main components of NHIS: the Family Core, in which data are collected for all family members by interviewing an adult family respondent, and the Sample Child Core, in which additional health information is collected about a randomly selected child (the sample child) from an adult familiar with the child's health. Selected Highlights In 2012, most U.S. children under age 18 years had excellent or very good health (83%). However, 7% of children had no health insurance coverage, and 4% of children had no usual place of health care. Six percent of children had unmet dental need because their families could not afford dental care. Twelve percent of children had one ER visit and 6% had two or more visits. Ten percent of children aged 3-17 years had ADHD.

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Zhongguo Dang Dai Er Ke Za Zhi. 2014 Feb;16:185-89.

EFFECT OF PARENT TRAINING IN COMBINATION WITH METHYLPHENIDATE TREATMENT ON FAMILY RELATIONSHIPS FOR CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Zhang Y, Kang CY, Zhao XR, et al.

OBJECTIVE: To investigate the effect of parent training combined with methylphenidate treatment on family relationships in children with attention deficit/hyperactivity disorder (ADHD).

METHODS: Fifty-nine parents of children with ADHD under methylphenidate treatment participated in a modified 5-week training program. The intervention effect was evaluated using the Conners Parent Symptom Questionnaire, ADHD Rating Scale-IV Home Version (ADHD-RS-IV Home Version), Caregiver Strain Questionnaire, Parent-Child Relationship Self-rating Scale and Piers-Harris Children's Self-Concept Scale. Parents also completed the training satisfaction survey before and after the intervention.

RESULTS: After the 5-week parent training, compared with the baseline values, total scores of Conners Parent Symptom Questionnaire and scores of conduct problems and anxiety significantly decreased, and scores of attention deficit, hyperactivity, impulsivity and oppositional defiant behaviors of ADHD-RS-IV Home Version, and Caregiver Strain Questionnaire total scores were all significantly decreased ($P<0.05$), while total scores of the Parent-Child Relationship Self-Rating Scale and Piers-Harris Children's Self-Concept Scale were significantly increased ($P<0.05$).

CONCLUSIONS: Modified 5-week parent training program may improve parent-child relationship and reduce parenting stress in ADHD families.

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Review

Safety of medicines used for ADHD in children: a review of published prospective clinical trials

Antonio Clavenna, Maurizio Bonati

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ABSTRACT

Objective To assess the long-term safety of drugs for attention deficit hyperactivity disorder (ADHD).

Methods A bibliographic search was performed in the MEDLINE, EMBASE and PsycINFO databases for prospective studies evaluating the incidence of adverse events (AEs) in children and adolescents treated for ADHD.

Results A total of six prospective studies that monitored drug safety during therapy for at least 12 weeks were retrieved. The drugs studied were atomoxetine (two studies, 802 patients), osmotic-controlled released oral methylphenidate formulation (two studies, 512 patients), extended release formulation of mixed amphetamine salts (one study, 568 patients) and transdermal methylphenidate (one study, 326 patients). Heterogeneity was found in the duration of follow-up (ranging between 1 and 4 years) and in the way data were reported.

The rate of treatment-related AEs ranged from 58% to 78%, and the rate of discontinuation due to AEs ranged from 8% to 25% of the children.

Decreased appetite, insomnia, headache and abdominal pain were the most common AEs observed.

Most AEs and cases of discontinuation occurred during the first few months of treatment.

Conclusions Few studies evaluated the long-term safety of drugs for ADHD. Heterogeneity in follow-up duration and in data reporting made comparing different studies and drugs difficult. A systematic monitoring of long-term safety is needed.

What is already known on this topic?

- Several short-term clinical studies have reported that drugs for attention deficit hyperactivity disorders are generally well tolerated.
- Most of their adverse effects are mild and/or temporary, but scant information exists regarding long-term safety.

What this study adds?

- Findings from long-term prospective studies on attention deficit hyperactivity disorder drug safety resemble those of short-term trials.
- Many adverse events (AEs) occur during the first year of therapy and are mild or moderate in severity.
- The most common AEs are decreased appetite, insomnia, headache and abdominal pain.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children and adolescents that comprises core symptoms of developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity.[1] Recommendations in the international guidelines on the treatment of ADHD vary. There is a general consensus on recommending psychostimulant drugs as first-line treatment, however, because of their documented efficacy in about 80% of children.[2 3] In particular, methylphenidate is preferred over amphetamines, which are generally less used in Europe. Atomoxetine, although generally less effective than stimulants, is also widely available and may be recommended as an alternative to methylphenidate.[2 3] Since their approval, several issues have affected the use of ADHD medications, such as tolerability, comorbidity, potential substance abuse risk and lack of efficacy.[4]

Hundreds of clinical studies have reported that ADHD drugs are generally well tolerated and that most of their adverse effects are mild and/or temporary.[5] Several reviews have addressed the safety of methylphenidate, amphetamines and atomoxetine in children with ADHD.[5–9] However, concerns were raised by the regulatory authorities, in particular regarding cardiovascular and psychiatric adverse drug reactions.[10] The Food and Drug Administration (FDA) requested the addition of a black box warning to the labelling of atomoxetine to alert healthcare professionals of an increased risk of suicidal thinking and behaviour. In December 2013, the FDA issued a Drug Safety Communication regarding the risk of long-lasting erection in people treated with methylphenidate.[11] According to the FDA statement, this risk is shared also by atomoxetine and amphetamine.

In 2011 the European Network for Hyperkinetic Disorders published guidelines on managing adverse effects of ADHD medication. These covered cardiac adverse events (AEs), growth, sleep disturbance, psychotic symptoms, tics, seizures and, in particular, the risk of substance abuse.[8]

The main findings of a 2001 meta-analysis by Schachter *et al* on the short-term effects of immediate-release methylphenidate (62 trials) confirmed significantly higher rates, versus placebo, of decreased appetite (Number Needed to Harm, NNH=4), insomnia (NNH=7) and stomach ache (NNH=9).[9]

Although atomoxetine is a non-stimulant, it shares several of the stimulants' properties, such as appetite suppression and increased heart rate (HR) and blood pressure (BP). Several placebo-controlled

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trials on atomoxetine exist[12] and estimated the approximate incidence of various adverse effects. Overall, these estimations were: loss of appetite, 20%, nausea and/or vomiting, 10%, dyspepsia, 10%, and fatigue and/or weakness, 10%.[7] Compared to placebo, atomoxetine significantly decreased appetite (NNH=9) and increased somnolence (NNH=19), abdominal pain (NNH=23) and vomiting (NNH=30).[12]

However, the main limitation of the available reviews was that most of the studies taken into account were short term. No randomised controlled trials (RCTs) with a duration of over 1 year regarding atomoxetine are available.

In the meta-analysis by Schachter *et al*, the average duration of intervention was 3 weeks and no studies lasted longer than 28 weeks.[9] Aagard *et al* reviewed the ADRs reported in 43 studies, with a treatment duration of no longer than 32 weeks.[6]

Multimodal treatment study of children with ADHD was the randomised clinical trial that monitored the use of stimulants for the longest time period. At the end of the 14-month follow-up 50% of children receiving stimulants reported mild, 11%, moderate and 3%, severe adverse effects. At 3-year follow-up a decreased height (on average 2 cm lower) and weight (on average 2.7 kg) were reported in children consistently medicated compared with children never medicated. No differences were found between groups concerning the incidence of substance abuse or delinquency.[13 14] At 8 years psychiatric hospitalisations occurred more often for children in multimodal treatment arm than for standard care arm, but diagnoses of psychosis, mania or hypomania were uncommon for both groups. Eight children with multimodal treatment had developed one of these disorders versus only one child in control group (1.8% vs 0.4%). Tic (4.4% vs 1.7%) and elimination disorders (0.7% and 0.0%) were also infrequent for multimodal and control groups, respectively, by 8 years.[15]

To the best of our knowledge no articles have reviewed long-term studies focused on ADRs following the use of ADHD medications in the paediatric population.

BIBLIOGRAPHIC SEARCH

A bibliographic search was performed using the MEDLINE (1950–August 2013), EMBASE (1974–August 2013) and PsycINFO (1967–August 2013) databases with the aim to retrieve prospective studies that monitored the incidence of AEs in children receiving drug therapy for ADHD (methylphenidate, amphetamine or atomoxetine) for at least 12 weeks.

The search strategy involved terms present either in the title/abstract or in the subject headings, that is, Medical Subject Headings (MeSH) for MEDLINE, Emtree for EMBASE and thesaurus for PsycINFO.

The search terms used were: (Attention Deficit Disorder with Hyperactivity OR attention deficit disorder OR ADHD OR attention deficit hyperactivity disorder) AND (methylphenidate OR atomoxetine OR amphetamines OR stimulant*) AND (children OR adolescents) AND (adverse drug reactions OR adverse drug events OR adverse effect* OR side effect* OR drug toxicity) AND (cohort studies OR prospective study OR longitudinal study OR surveillance).

Studies that not addressed drug safety as one of their main objectives were not considered for inclusion.

Two assessors (AC, LR) independently screened the title, abstract and keywords of each citation to determine its relevance. In case of disagreement, the opinion of a third assessor (FF) was sought.

A manual search of the bibliographies of the selected article was also carried out to identify additional pertinent studies.

For each relevant study the following data, if available, were extracted: incidence of AEs (percentage of children with at least one AE), incidence of treatment-related AEs (percentage of children with at least one AE considered by the physicians as possibly or probably related to the drug therapy) and percentage of children who discontinued the treatment due to an adverse drug event. Information concerning the most common AEs was also collected.

RESULTS

After a preliminary evaluation of the abstracts of the articles found by the electronic search strategy, 312 potentially relevant published studies were identified. Sixty-eight of these were duplicate titles indexed in multiple databases and were excluded. Of the 244 resulting studies, 95 were excluded because not pertinent, 38 because they were short-term RCTs and 34 because they were focused only on monitoring growth (19) or cardiovascular (12) or psychiatric (3) AEs.

Only 16 of the remaining 77 studies lasted at least 12 weeks.[16–31] After excluding three studies that did not report any data concerning AEs,[17 27 31] one interim analysis[29] and one study presented as an abstract in a congress,[24] 11 studies were evaluated.[16 18–23 25 26 28 30]

Three studies were retrospective chart reviews,[16 21 25] two analysed data collected prospectively in an Italian register[18 28] and six were prospective trials.[19 20 22 23 26 30]

Only prospective studies were considered in the analysis (table 1).

The prospective studies concerned atomoxetine (two studies, 802 patients), the osmotic-controlled released oral formulation of methylphenidate (two studies, 512 patients), the extended release formulation of mixed amphetamine salts (one study, 568 patients) and transdermal methylphenidate (one study, 326 patients).

All studies were open-label extension that followed patients previously enrolled in a total of 24 short-term randomised clinical trials, with a duration of treatment ranging from 1 to 18 weeks.

Hoare *et al* and Hafterkamp *et al* were long-term extension of one RCT each, while the study by Donnelly *et al* followed patients previously enrolled in 13 short-term RCTs.

Four studies evaluated long-term effectiveness and safety,[22 23 26 30] while only two studies focused mainly on safety evaluation.[19 20]

Vital signs (eg, HR, BP), weight and height were monitored in four studies.[19 20 26 30]

AEs were collected mainly through spontaneous reporting by patients and/or caregivers, and in one study in combination with investigator queries.[26] Two studies did not clarify how the AEs were collected.[20 23] The Children's Sleep Habits Questionnaire was used in one study to monitor the effect of the treatment on sleep.[20]

In four studies investigators evaluated the severity of AEs and their relationship to drug treatment.[20 23 26 30]

Heterogeneity was found in the duration of follow-up (ranging between 1 and 4 years) and in the way data were reported. Only two studies reported all the safety measures: the incidence of AEs, treatment-related AEs and discontinuation due to AEs.[26 30] The rate of discontinuation due to AEs was the only measure reported in all six studies (table 1).

According to the long-term open-label extension studies the rate of treatment-related AEs ranged from 58% to 78%, and most of the AEs were mild or moderate in severity, with a range

Table 1 No of subjects (%) with at least one adverse event (AE)

References	Drug	No short-term controlled trial*	No children†	Age (years)	Duration (years)	% Cut-off for AE reporting Any	AEs Serious	AEs Any	Treatment-related AEs Serious	Discontinuation due to AEs
Hafterkamp *et al*[22]	Atomoxetine	1	88	6–17	12 weeks	≥1	n.r.	2 (2)	n.r.	0 11 (25)
Donnelly *et al*[19]	Atomoxetine	13	1533 (508)‡	6–17	≥4	≥10	n.r.	78 (15)‡	n.r.	n.r. 71 (9)‡
	Atomoxetine	14	596	6–17		–				82 (14)
McGough *et al*[26]	Extended release amphetamine	2	568 (284)	6–17	2	≥5	525 (92)	18 (3)	440 (78)	2 (<1) 84 (15)
Wilens *et al*[30]	Osmotic-controlled released methylphenidate	3	407 (229)	6–13	2	≥5	363 (89)	n.r.	282 (69)	n.r. 31 (8)
Hoare *et al*[23]	Osmotic-controlled released methylphenidate	1	101 (56)	6–16	1	≥2	76 (72)	n.r.	61 (58)	4 (4) 16 (15)
	Osmotic-controlled released methylphenidate	4	508	6–16	1–2	–	439 (86)	–	343 (68)	– 47 (9)
Findling *et al*[20]	Transdermal methylphenidate	4	326	6–15	1	≥5	265 (81)	3 (1)	n.r.	0 29 (9)

*Number of short-term clinical trials that originally enrolled children followed up by each open-label extension study.
†Number of children followed up; number of children who were still on drug treatment at the end of the study period are reported under brackets.
‡Number of children treated for at least 4 years were considered as the denominator, with the exception of discontinuation, which was calculated using the 1533 patients initially enrolled and treated for less than 3 years. n.r., not reported.

of 86–98%. The rate of discontinuation due to AEs ranged from 8% to 25% of the children (table 1).

AEs most commonly associated with therapy discontinuation were reported in five out of six studies. None of these AEs were reported in all the studies. Insomnia and abdominal pain were among the most common AEs leading to discontinuation in four studies. Weight loss (32% of the children who discontinued) and decreased appetite (26%) were the most common reasons for suspending extended release amphetamine,[26] tics (24%) and decreased appetite (24%) were the most common for discontinuing osmotic-controlled released oral formulation of methylphenidate,[30] and upper abdominal pain (21%) and emotional lability (17%) were the most common AEs for atomoxetine discontinuation.[19]

Most of the discontinuation occurred during the first year of treatment. The rate of discontinuation in patients treated with extended release amphetamine was 7% in the first quarter and 6% in the second quarter. In the third and fourth quarters it decreased to 2%, after which it was <1%.[26] The discontinuation rate with osmotic-controlled released oral formulation of methylphenidate was 7% in the first 12 months and 8% after 24 months.[29 30] A total of 71 (4%) out of 1553 children receiving atomoxetine interrupted the therapy before 3 years had elapsed. The subsequent rate of discontinuation in those treated for ≥3 years and ≥4 years was 2%.[19]

In order to evaluate whether a different safety profile was observed during long, versus short, observation periods, data reported in long-term open-label extension studies were compared with those presented in the publications of original RCTs. Data concerning AEs were available for 17 out of 24 short-term RCTs.

Only for a few studies was it possible to compare the incidence of AEs over time.

Table 2 Comparison of the incidence (%) of all cause adverse events (AEs) in the experimental versus open-label extension phases in studies concerning atomoxetine[19]

	Experimental phase		Open-label extension
	No studies reporting AE	Mean (range)	Mean
No *(total; range)*		2361 (30–1326)	714
Duration (weeks)		6–18	≥3 years
Any AEs (%)	0	n.r.	n.r.
Discontinuation due to AEs (%)	8	4 (2–6)	9
AE (%)			
Headache	9	20 (7–30)	54
Abdominal pain/ upper abdominal pain	8	13 (9–31)	33*
Decreased appetite/ anorexia	9	12 (8–22)	21
Irritability/ nervousness	5	10 (6–16)	15
Somnolence	8	9 (6–14)	<10
Vomiting	8	9 (6.0–16)	37
Nausea	8	8 (4–16)	27
Fatigue	7	6 (5–12)	18
Insomnia	4	6 (3–9)	13
Diarrhoea	5	4 (2–7)	18

*Figure regards upper abdominal pain.

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Table 3 Comparison of the incidence of adverse events (AEs) in the experimental versus open-label extension phases in studies concerning extended release mixed amphetamine salts[26 32 33]

	Experimental phase	Open-label extension	
	Mean (range)	Mean	Mean
No *(total; range)*	423 (49–374)	568	284
Duration (weeks)	1–3	1–6 months	18–24+ months
Any AEs (%)	7*	92	
Discontinuation due to AEs (%)	2*	15	
AE (%)			
Anorexia	24 (22–40)	37	4
Anxiety	22*	n.r.	n.r.
Headache	19 (18–27)	27	18
Insomnia	18 (17–25)	26	4
Abdominal pain	17 (14–33)	18	7
Depression	13	5	2
Nervousness	11 (6–51)	17	3
Emotional lability	10 (9–19)	14	2
Twitching	5*	5	1
Weight loss	n.r.	17	1
Abnormal thinking	n.r.	4	<1

*Reported only in one short-term randomised controlled trial.

Hafterkamp *et al* compared the rate of AEs during the first 8 weeks of treatment with atomoxetine (experimental phase) with the rate during the subsequent 12 weeks of treatment.

A decrease in the rate across time was observed for all the AEs. In particular, a statistically significant reduction was found for nausea (from 13.6% to 1.1%, p=0.003) and fatigue (from 18.2% to 6.8%, p=0.04).[22]

The comparison between short-term and long-term AEs reported by Donnelly *et al* regarding atomoxetine should be met with caution since all the AEs were considered independently of the evaluation of the causal relationship with the drug therapy (table 2). In all 9 short-term clinical trials among the 13 that enrolled children followed by Donnelly *et al* reported AEs in a comparable manner.[19] Only headache and decreased appetite/anorexia were reported in all 9 RCTs. Abdominal pain, somnolence, nausea and vomiting were observed in eight studies. For all the AEs an increase in the percentage of affected children was observed, with the exclusion of somnolence, which was not reported among children treated for 3 or more years.

McGough *et al* compared the percentage of the AEs reported with extended release amphetamine in four periods, from months 1–6 to months 18–24. For all the AEs, the percentage of cases was highest in the first 6 months and decreased with time. In all, 58% of the AEs were recorded during the first 4 months of therapy. However, the incidence during the first 6 months of the open-label extension was higher than the pooled rate obtained from the two short-term RCTs (table 3).[32 33]

Moreover, weight loss and abnormal thinking were not reported during the short-term RCTs.

Wilens *et al* reported the cumulative incidence of AEs during 12 months[29] and 24 months of treatment with osmotic-controlled released oral formulation of methylphenidate.[30] Table 4 compares the rate observed in the RCTs with those reported in the open-label extension study at 12 and 24 months. The incidence of AEs increased from 42% to 89%. No children had tics in the experimental phase, and no psychiatric AEs (eg, aggravation reaction, anxiety, emotional lability and hostility) were reported in the short-term RCTs.[34 35]

Table 4 Comparison between the incidence (%) of treatment-related adverse events (AEs) in the experimental versus open-label extension phases in the studies concerning osmotic-controlled released methylphenidate[29 30 34 35]

	Experimental phase	Open-label extension	
	Mean (range)	Mean	Mean
No *(total; range)*	164 (70–94)	407/289	407/240
Duration (weeks)	1–4	12 months	24 months
Any AEs (%)	42*	85	89
Discontinuation due to AEs (%)	1 (0–1)	7	8
AE (%)			
Loss of appetite	20 (18–23)	14	19
Poor sleep	16*	15	20
Headache	14 (12–14)	25	30
Abdominal pain	9 (7–13)	8	11
Vomiting	3*	2	n.r.
Dizziness	3*	2	n.r.
Tics	0*	7	10
Aggravation reaction	n.r.	3	n.r.
Somnolence	n.r.	3	n.r.
Anxiety	n.r.	2	n.r.
Weight loss	n.r.	2	n.r.
Emotional lability	n.r.	2	n.r.
Hostility	n.r.	2	n.r.
Nervousness	n.r.	2	n.r.
Depression	n.r.	2	n.r.

*Reported only in one short-term randomised controlled trial.

Comparing the two studies by Hoare *et al* and Remschmidt *et al* (12 months vs 3 weeks), a similar incidence of abdominal pain (4% in both studies) and headache (10% vs 8%) was reported, while the incidence of tics doubled (8% vs 4%).[23 36]

Table 5 Comparison of the incidence (%) of all cause adverse events (AEs) in the experimental versus open-label extension phases in studies concerning transdermal methylphenidate[20 37 38]

	Experimental phase	Open-label extension
	Mean (range)	Mean
No *(total; range)*	178 (80–98)	326
Duration	7 weeks	12 months
Any AEs (%)	55 (30–76)	81
Discontinuation due to AEs (%)	7	9
AE (%)		
Decreased appetite	26*	25
Insomnia	13*	9
Vomiting	10*	7
Decreased weight	9*	10
Nausea	8 (4–12)	6
Tics	7*	3
Affect lability	6*	n.r.
Anorexia	4 (3–5)	n.r.
Headache	4*	17
Abdominal pain	n.r.	8
Irritability	n.r.	6

*Reported only in one short-term randomised controlled trial.

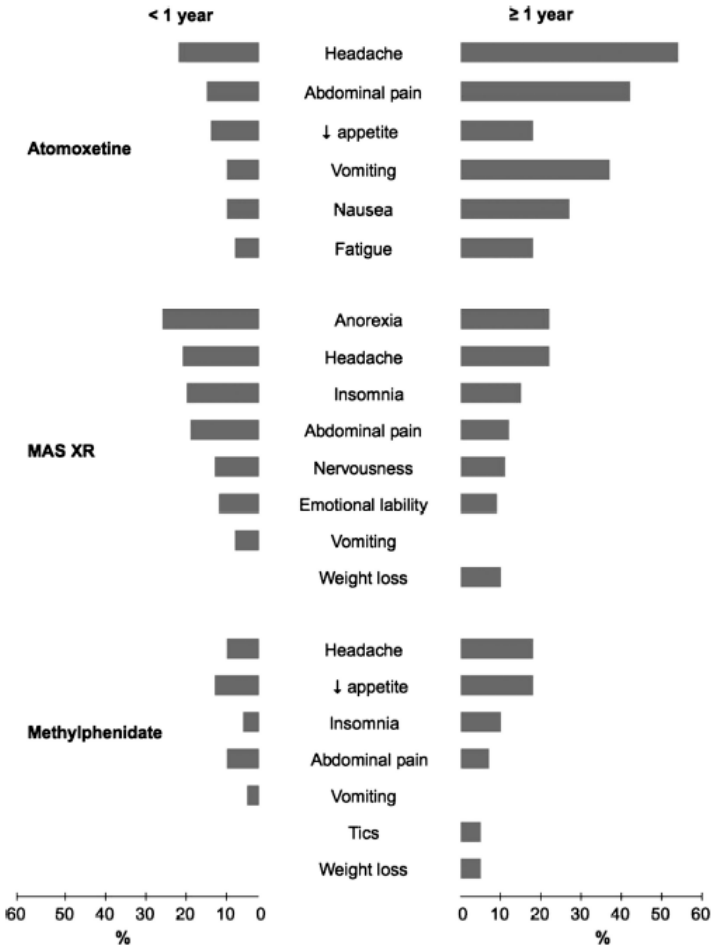

Figure 1 Incidence (%) of the most common adverse events (AEs) in short versus long periods by drug. Incidence was calculated using all the monitored children as denominator.

An increase in the incidence of AEs was observed comparing short-term RCTs with the prospective open-label extension trial concerning transdermal methylphenidate (from 55% to 81%). The percentage of children with decreased appetite was similar, the incidence of headache increased from 4% to 17%, while the incidence of insomnia, vomiting and nausea decreased (table 5). Tics, affect lability and anorexia were reported only during short-term trials, while abdominal pain and irritability only during the open-label extension phase.[20 37 38]

The incidence of the most common AEs observed in the short-term and long-term periods is summarised in figure 1.

DISCUSSION

This is the first review of prospective studies evaluating long-term safety of ADHD medications.

In this regard, few studies were found, monitoring a total of 3000 children, nearly half of whom were taking atomoxetine.

Only for atomoxetine were data regarding treatments lasting longer than 3 years available. On the contrary, for transdermal methylphenidate, the follow-up lasted less than 1 year.

Wide heterogeneity was found regarding the way information concerning AEs was reported, making the comparison between studies not possible.

The rate of discontinuation due to AEs was the only measure reported in all the studies, but with different treatment duration, and three studies did not report the overall incidence of treatment-related AEs.

Different criteria were used in reporting the most common AEs. First of all, the threshold varied between 1% and 10%, which means that only AEs classified as 'common' (frequency >1/100) were described in the papers, or 'very common' (frequency >1/10) in the case of atomoxetine.

Moreover, it is possible that differences exist in the way AE are classified. For example, decrease or loss of appetite was the most common AE with stimulant treatment.

Anorexia occurred very frequently with extended release, but was reported with a lower frequency in the RCTs investigating transdermal methylphenidate, not reported in the subsequent open-label extension period, and, surprisingly, never reported with osmotic-controlled released oral formulation of methylphenidate, despite the fact that, in the 12-month open-label extension, all the treatment-related AEs with an incidence >1% were reported.

Review

When monitoring the long-term safety of extended release amphetamine McGough *et al* used the term anorexia to group loss of appetite and decreased appetite.[26] On the contrary, in short-term RCTs regarding transdermal methylphenidate McGough *et al* and Findling *et al* discriminated between anorexia and decreased appetite.[37 38]

In studies concerning osmotic-controlled released oral formulation of methylphenidate the following terms were used: loss of appetite, appetite suppression and decreased appetite.[29 30 34 35] Paradoxically, in the paper reporting on a 24-month follow-up period the term used was decreased appetite,[30] while in the previous analysis of the first 12 month the same AE was reported as appetite loss.[29]

The reporting of AEs in clinical trials seems therefore unsatisfactory, as highlighted by other researchers, and more should be done to improve the evaluation of drug safety.[39–42]

Despite some limitations, the results of this study confirm findings from previous reviews.

Drugs for ADHD seem to be safe and well tolerated. Decreased appetite, insomnia, headache and abdominal pain are the most common AEs observed in the long-term prospective trials (figure 1). Tics were reported in all long-term studies regarding methylphenidate, while emotional lability was reported only with mixed amphetamine salts.

Many AEs are mild or moderate in severity, and the incidence of serious AEs was low. Despite these reassuring results, it should be underlined that lack of tolerability caused the discontinuation of treatment in a proportion of children ranging from one-tenth to one-fourth.

Most of the AEs and discontinuation cases occurred in the first few months of drug treatment.

Given the small sample and the threshold chosen to report the results, few data are available concerning events that occur with a frequency less than 1%. Many psychiatric AEs may be missed or underestimated, in particular the more severe ones (eg, suicide attempts).

Retrieved studies provided scant information concerning the effect of treatments on growth and on the cardiovascular system. However, several ad hoc studies and reviews are available regarding these topics.[5 8 43 44]

Although the medications for ADHD are generally well tolerated, with only mild or minor adverse effects in most cases, their rational use can be guaranteed by implementing and monitoring evidence-based practices, that is, by monitoring the safety and efficacy of treatments in the short and long terms with adequate and appropriate tools and approaches.[18 45]

Taking into account the wide heterogeneity between studies in the follow-up duration, and the AE reporting criteria, any consideration on which treatment has the least AEs is currently questionable.

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On the relationship between retrospective childhood ADHD symptoms and adult BPD features: The mediating role of action-oriented personality traits

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Abstract

A number of studies have reported data suggestive of a significant association between ADHD and BPD, nevertheless, the nature of this relation has not been fully understood yet. In our study, we tried to evaluate if the relationship between retrospectively assessed ADHD symptoms and adult BPD features could mediated by selected temperament/personality traits. Four hundred forty-seven in- and outpatients consecutively admitted to the Clinical Psychology and Psychotherapy Unit of the Scientific Institute H San Raffaele of Milan, Italy, were administered the Italian versions of the following instruments: Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II), Wender Utah Rating Scale (WURS), Temperament and Character Inventory-Revised (TCI-R), Barratt Impulsiveness Scale-11 (BIS-11), and Aggression Questionnaire (AQ). Our mediation analyses showed that the combination of impulsivity, aggression, novelty seeking, and juvenile conduct problems completely mediate the relationship between retrospectively assessed ADHD symptoms and current BPD features.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by a persistent and developmentally inappropriate pattern of inattention, impulsivity, and hyperactivity [1]. ADHD is thought to affect 3–7% of school-age children, albeit prevalence estimates vary predictably depending on sampling strategies and methods of ascertainment [1]. Although ADHD symptoms, especially restlessness, tend to diminish with age [1,2], it has been consistently reported that ADHD tend to persist into adolescence in 30–80% of affected subjects [3–5], and into adulthood in up to nearly 50% of childhood cases [6–8]. Biederman et al. [9] also found that, in adult life, a large proportion of subjects who had previously received a diagnosis of ADHD, although no longer meeting criteria for the disorder, continue to show residual symptoms or fail to attain a functional remission. As in the case of childhood ADHD, adult ADHD is associated with an increased risk for comorbid psychopathology. Data collected from a substantial sample of adult respondents ($N = 3199$) in the National Comorbidity Survey Replication [10] indicated that adult ADHD is highly comorbid with many other Axis I DSM-IV disorders (i.e., mood disorders, anxiety disorders, substance use disorders and intermittent explosive disorder) [11]. Moreover, long-term longitudinal studies consistently evidenced a significant association between childhood ADHD and antisocial personality disorder in adulthood [12–14].

The relationships between ADHD and another cluster B personality disorder, namely borderline personality disorder (BPD), have been investigated less thoroughly, this in spite of the several similarities that can be found in the clinical presentation of the two disorders. Indeed, though ADHD patients are not characterized by the intense suicidal preoccupations, self-mutilating behavior or feelings of abandonment often seen in those with BPD, the two disorders share other prominent symptoms, such as impulsivity, affective instability, and difficulty in controlling anger

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[15]. The high degree of similarity between ADHD and BPD may even represent a risk factor for misdiagnosing ADHD patients as if they suffered from BPD (and vice versa). Herpertz [16], for instance, suggested that diagnostic procedure should be supplemented by neuropsychological assessment which includes, in particular, testing of inhibitory functioning. Otherwise, it has to be highlighted that similarities between the disorders also extend to their neuropsychological profile.

In ADHD research, meta-analytic [17,18] reviews have found that deficits in executive functioning, especially in motor inhibition, are among the most robust neuropsychological findings. Since impulsivity is a core aspect of BPD [19], not surprisingly poor inhibitory functioning, particularly poor executive response inhibition [20], has also been consistently found in BPD subjects [21]. However, it has been pointed out that BPD patients generally perform more poorly than control across a wide range of cognitive domains [22,23]. Notably, BPD also shares with ADHD significant impairments in attention [23]. Various studies [24] found significant differences between BPD samples and controls in the performance on the Digit Symbol subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) [25], which is considered a test of attention and visual motor coordination [26]. Carpenter and colleagues [27] reported that individuals with BPD performed poorer than controls on the Trail Making Test A and B [28]. Similar results have been found by Monarch et al. [23], who additionally demonstrated that BPD patients also had worse results than controls on the Continuous Performance Task (CPT) [29]. Posner et al. [30] showed that BPD patients performed worse than controls in the conflict module of the Attentional Network Task (ANT) [31], but displayed no deficit in other attentional networks. More specifically, individuals with BPD exhibited significant difficulties in correctly indicate the direction of a target arrow surrounded by flanker arrows pointed in the opposite direction (incongruent trials). Similar results have also been found with children scoring high on BPD precursors [32] (e.g., emotional lability/negativity, diminished effortful control, interpersonal difficulties, etc.). Notably, Rogosch and Cicchetti [32] found inefficient processing in the conflict attentional network to be relatively unrelated to other forms of childhood disturbance. This result led the authors to suggest it may represent a risk factor for BPD that is less affected by experience, probably linked to neuronal loss in the anterior cingulated cortex (ACC). ACC is a brain region which is essential to executive control [33,34], particularly to conflict monitoring [35], and attention [36], but also plays an important role in emotional processing [37]. Interestingly, functional and volumetric abnormalities of the ACC have been found in both ADHD [38] and BPD [39,40] patients. More generally, ADHD and BPD have been associated with dysfunctions in various prefrontal areas [38,40] related to attentional mechanisms, decision-making, impulse control, etc.

These similarities in the neuropsychology of the disorders could maybe explain the high rates of comorbidity between them. A recent cross-sectional study [41] reports that of 181 participants who were diagnosed as BPD, 69 (38.1%) were diagnosed as suffering a comorbid adult ADHD. Moreover, the BPD-ADHD group was found to be associated with higher rate of substance abuse disorder and suicidal behavior and to score higher on self-reported impulsivity, showing a more impulsive profile than BPD patients without ADHD comorbidity, which, by contrast, reports more anxiety and depressive disorders. Another study [42], examining a group of women with BPD, found a prevalence of adult ADHD of approximately 16%, a value significantly lower than that reported by Ferrer and colleagues [41]. However, as argued by these last authors [41], this difference may be explained by the fact that, in Philipsen et al.'s study [42], men were not included in the sample (ADHD is more common among males than females [1]) and that only the combined ADHD type was studied, which could have led to an underestimation of comorbidity rates. Various studies also examined the prevalence of BPD among adults with ADHD: comorbidity rates ranged from 19% to 37% [43–45,20]. Miller et al. [43], in particular, subdivided a group of older adolescents/young adults (aged 16–26 years) previously diagnosed with childhood ADHD into those who continued to meet diagnostic criteria for ADHD ("persisters") and those that did not ("remitters") and compared them to a never-ADHD comparison group. Interestingly, although persisters were significantly more likely than controls to be diagnosed with paranoid, narcissistic, borderline and antisocial personality disorders, they were separable from remitters only for antisocial personality disorder and paranoid personality disorder.

With regard to the relationship between childhood ADHD and BPD, retrospective studies report prevalence estimates of childhood ADHD in adult BPD patients ranging from 25.5% up to 59.5% [42,46–51]. In particular, Philipsen et al. [42] found that, among women with BPD, childhood ADHD was associated with greater emotional abuse in childhood as well as more severe BPD psychopathology in adulthood. Among the major controlled prospective studies on childhood ADHD, only the Milwaukee follow-up study [52] reported data regarding BPD. Its results indicated that 14% of the hyperactive children met the criteria for BPD diagnosis as adults, and that the presence of adolescence CD increased the likelihood of BPD diagnosis in adulthood. Using a prospective follow-up design, Miller et al. [43] found a similar percentage (13.5%) of childhood ADHD-diagnosed subjects with BPD but it did not confirm Fischer et al.'s evidence [52] on the relationship between ADHD, CD and BPD. In fact, Miller et al.'s results [43] showed that externalizing childhood comorbidity marginally predicted antisocial personality disorder but not BPD. In a recent prospective longitudinal study [53], Stepp and colleagues examined ADHD and Oppositional Defiant Disorder (ODD) severity as childhood psychopathology precursors of BPD

symptoms in adolescence. The authors used data collected in a large sample of girls, followed annually from late childhood to early adolescence, finding that ADHD and ODD at age 8 predicted BPD symptoms at age 14. Furthermore, the effects of ADHD and ODD were independent from Conduct Disorder (CD) and depression at baseline. Similar evidences were found in another prospective study [54] conducted on a clinical sample of males, initially aged between 7 and 12, and reassessed on multiple occasions through to age 24. Again, ADHD and ODD were the only childhood psychiatric disorders to predict BPD symptoms.

Although various studies have reported data suggestive of a significant association between ADHD and BPD, this relation has not been fully understood yet. One hypothesis is that the overlap of phenomenological features between ADHD and BPD may indicate that the two disorders belong to a common liability spectrum [55]. In particular, following Hollander's [55] suggestion, ADHD, BPD and other psychiatric disorders (e.g., impulse control disorders, cluster B personality disorders, substance use, etc.) may belong to a shared group lying at one end of a spectrum of compulsive-impulsive disorders related to risk taking or avoidance. Other researchers have proposed that ADHD could be a childhood precursor of BPD [43,56]. For example, it has been suggested that impulsivity and impulse control disorders, such as ADHD, may predispose individuals to the development of BPD [57]. In particular, Crowell et al. [56,57], extending Linehan's biosocial theory of BPD [58] suggested that impulsivity is among the earliest emerging traits among those who later receive a BPD diagnosis. According to Linehan [58], BPD's core problem is emotion dysregulation, resulting from the interaction between biological vulnerabilities and an invalidating developmental context. Crowell et al.'s model [57] posit that impulsivity has a primary role in generating escalating transactions between the child and the caregiver which increase risk for emotion dysregulation. According to another hypothesis [59], ADHD may represent a risk factor that may interact with the social environment of the child so as to aggravate and amplify his/her neurobehavioral vulnerabilities through poor affective fit and/or maltreatment. These transactions may contribute to an insecure/disorganized attachment model and dissociation, which, in turn, would contribute to impaired metacognition and difficulties in the cognitive processing of interpersonal information. This would lead to various manifestations of BPD, including splitting, paranoia, transient psychoses, etc.

In this study, we tried to evaluate if the relationship between retrospectively assessed childhood history of ADHD symptoms and adult BPD features could be mediated by selected temperament/personality traits. In particular, we focused our attention on the mediating role of action-oriented personality traits [60,61], a cluster of personality features (including extraversion, sensation seeking, and lack of inhibition) considered orthogonal to anxiety proneness and associated to risk taking, acting without thinking, and lack of planning.

2. Method

2.1. Participants

The subjects in this study were 447 in- and outpatients (193 [43.2%] males, 254 [56.8%] females; mean age = 39.21 years [SD = 11.41]) consecutively admitted, from January 2008 to May 2011, to the Clinical Psychology and Psychotherapy Unit of the Scientific Institute H San Raffaele of Milan, Italy. None of the subjects met any of the following exclusion criteria: (1) age less than 18 years; (2) IQ less than 75; (3) diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder according to DSM-IV diagnostic criteria; (4) diagnosis of dementia or organic mental disorder according to DSM-IV diagnostic criteria; and (5) education level lower than elementary school. Subjects with Axis I diagnoses were administered the SCID-II at acute symptom remission, according to the judgment of the clinicians who were following them in treatment, by expert trained raters to avoid confounding effects of Axis I disorders on Axis II diagnoses [62]. The absence of acute symptom remission was considered an exclusion criterion from the study.

2.2. Measures

Participants were administered the Italian versions of the following instruments: a) Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II) [63]; b) Wender Utah Rating Scale (WURS) [64]; Temperament and Character Inventory-Revised (TCI-R) [65]; Barratt Impulsiveness Scale-11 (BIS-11) [66]; Aggression Questionnaire (AQ) [67].

2.2.1. SCID-II

The SCID-II [63] is a semi structured interview of 140 items organized by diagnosis, which provides both a categorical and a dimensional (i.e., the number of criteria found) assessment of ten DSM-IV axis II personality disorders as well as depressive personality disorder, passive-aggressive personality disorder, and personality disorder not otherwise specified (NOS). The SCID-II was administered approximately one week after questionnaire completion by trained raters who were blind to the aims of the study and also to the personality traits data. Although DSM-IV conceptualizes mental disorders as distinct categories, several studies have provided data suggesting that personality disorders can be best described as dimensional constructs, rather than as discrete categories [68–74]. The DSM-IV's categorical approach to diagnosis has been criticized for inadequate coverage and for the use of arbitrary diagnostic thresholds [75], whereas dimensional scores are thought to approximate more closely the continuous distribution of cognitive and social features associated with

personality disorders [76]. In light of these considerations, we used dimensional scores of personality disorders (i.e., the number of criteria rated as present for each disorder) in most of our analyses; a categorical measure of BPD was used only to provide a prevalence rate of childhood ADHD comparable to those reported in prior studies.

In the current study, the inter-rater reliability of the SCID-II diagnoses was assessed in the first 67 consecutively admitted outpatients, using a pairwise interview design. Interclass correlation coefficients (ICCs), based on a one-way random effects ANOVA, were computed to evaluate the inter-rater reliability of dimensionally assessed SCID-II personality disorders. As a whole, the inter-rater reliability of the dimensional SCID-II diagnoses was acceptable, median ICC value = .84, SD = .15; in particular, the ICC value for the dimensional BPD diagnosis was .88. The inter-rater reliability of the number of personality disorder diagnoses based on SCID-II was adequate, ICC = .88. The inter-rater reliability of the categorical SCID-II personality disorder diagnoses was assessed computing Cohen κ coefficient. The Cohen κ value for BPD diagnosis was .90; the inter-rater reliability of any PD diagnosis was adequate, κ = .88.

2.2.2. WURS

The WURS [64] is a self-report questionnaire designed to retrospectively assess the severity of ADHD symptoms during childhood. Ward et al. [64] reported adequate split-half reliability of the WURS; the scale also showed a moderate convergence with parent retrospective reports and demonstrated to efficiently discriminate subjects with adult ADHD from controls. Moreover, the WURS significantly predicted the treatment outcome of subjects with adult ADHD. In Ward et al.'s study [64], a cut-off score of 46 was proposed. A recent review of the currently available adult ADHD rating scales cited the WURS, together with the CAARS, as having the best psychometric properties among the fourteen scales identified; it also reported for the WURS a 85% sensitivity and a >90% specificity at its given cut off [77]. The Italian translation of the WURS showed adequate reliability and validity [78]. In the present study, the Cronbach α value of the WURS total score was .89.

2.2.3. TCI-R

The TCI-R [65] is a 240-item self-report questionnaire, with responses in a five point Likert-type scale questionnaire, measuring the four dimensions of temperament (novelty seeking, harm avoidance, reward dependence, and persistence) and three dimensions of character (self-directedness, cooperativeness, and self-transcendence). The scales of the Italian version of the TCI-R showed adequate internal consistency and 1-month test-retest reliability [79]; moreover, the factor analysis results have been found to be consistent with the 7-factor structure of the TCI-R scales. In the present study, the Cronbach α values of the TCI scales were .69, .87, .78, .89, .87, .85 and .85, respectively.

2.2.4. BIS-11

The BIS-11 [66] is a 30-item self-report questionnaire with responses in a four point Likert-type scale. It measures three subtypes of impulsivity: motor impulsivity, attention impulsivity, and nonplanning impulsivity. The three scores are summed to produce a total impulsivity score. The Italian version showed internal consistency reliability, test-retest reliability, and construct validity data almost identical to those reported for the English version in both nonclinical [80] and clinical samples [81]. In the present study, we have taken into account only the BIS-11 total score, the Cronbach α value was .69.

2.2.5. AQ

The AQ [67] is a 29-item, Likert type, self-report questionnaire, which measures four components of aggression: physical aggression, verbal aggression, anger, and hostility. The four components are summed to produce a total aggression score. Evidence of reliability and construct validity for both English [67] and Italian [82] versions of the scale was reported in previous studies. In the present study, we have taken into account only the AQ total score, the Cronbach α value was .90.

2.3. Mediation analyses

Mediation models of psychological processes are popular because they allow interesting associations to be decomposed into components that may be useful for theory development and identification of possible points of intervention in applied work [83].

Fig. 1 shows the elements of the mediation analysis. Part 1 of Fig. 1 implies that a unit change in X is associated with a change of c units in Y, when only X and Y are considered (i.e., c represents the ordinary least square regression coefficient). Part 2 of Fig. 1 shows a model that includes variable I, the proposed mediator. The mediation model assumes that I is affected by changes in X; one unit change in X is associated with a change of a units in I. The model also assumes that changes in I are associated with changes in Y, above and beyond the direct affect of X on Y. A unit change of I is associated with a change of b units in Y, when X is held constant. As a result, X is said to have an indirect effect on Y through the mediator I [83].

In order to assess the intervening variable effect, we estimated, following Shrout and Bolger's [83] recommendations, indirect path coefficients ($a \times b$ coefficients). In the case of multiple intervening variables, the method of $a \times b$ products provides both an overall significance test and separate significance tests for the individual mediating variables, it allows also to statistically evaluate the existence of significant differences between the mediating variables [83]. In order to evaluate not only the significance of the mediation effect, but also the strength of mediation, we computed the effect proportion mediated measure (P_M) [83]. P_M is the ratio of the indirect effect to the total effect of the independent variable in predicting the dependent variable.

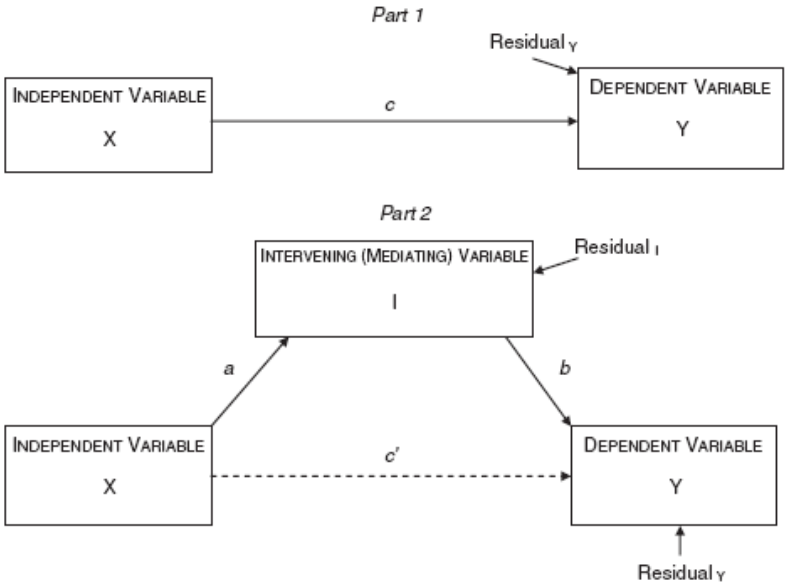

Fig. 1. Path diagrams showing total effect (Part 1) and mediated effect (Part 2) of the independent variable (*X*) on the dependent variable (*Y*).

Normal-theory significance tests were used to test the significance of all path coefficients, with the exception of indirect effect (*ab*) path coefficients. Following recommendations by Bollen and Stine [84] and Shrout and Bolger [83], the significance of indirect effect coefficients was tested by computing confidence intervals (CIs) using bootstrap simulations; in particular, 95% bias corrected accelerated CIs were computed based on 5,000 bootstrap replications. Mediation and bootstrap analyses were carried out using Preacher and Hayes's [85] computer program. In all regression models collinearity diagnostics were based on condition index values and on regression coefficient variance decomposition [86].

3. Results

Roughly 75% of the participants (74.9%, $n = 335$) had a personality disorder (PD); the most frequently diagnosed personality disorders were narcissistic PD (21.5%, $n = 96$), PD NOS (17.7%, $n = 79$) and BPD (14.5%, $n = 65$). In this sample, gender was not significantly associated with both categorical, $\chi^2 = .19$, $p > .50$, and dimensional, $t\ (445) = .64$, $p > .50$, BPD diagnoses. With regard to Axis I diagnoses, 162 (36.2%) of participants had an Axis I disorder; the most frequently diagnosed Axis I disorders were mood disorders (22.0%, $n = 105$).

Descriptive statistics and gender comparisons for all measures used in this study are listed in Table 1. Participants' gender showed a significant correlation only with novelty seeking scores, $r_{p\text{-}b} = .14$, $p < .005$, with males reporting higher levels of novelty seeking than females. The percentage of participants scoring over the WURS cut-off point of 46 was 12.8% ($n = 57$). Among BPD participants, the percentage of subjects scoring 46 or more on the WURS (30.8%, $n = 20$) was significantly higher than that of non-BPD participants (9.7%), $\chi^2 = 20.34$, $p < .001$, $\phi = .22$.

In Table 2 are listed the correlation coefficients of the WURS scores and the SCID-II BPD dimensional scores with the other measures used in this study. As regards the correlations with other dimensionally assessed psychopa-

Table 1
Wender Utah Rating Scale, Temperament and Character Inventory-Revised, Barratt Impulsiveness Scale-11, and Aggression Questionnaire descriptive statistics and gender comparisons.

	Whole sample ($N = 447$)		Male participants ($N = 193$)		Female participants ($N = 254$)	
	M	SD	M	SD	M	SD
WURS	23.15	18.63	24.93	19.34	21.83	18.02
NS	102.08	13.61	104.24	13.64	100.47	13.41
HA	103.94	19.39	102.25	18.91	105.33	19.56
RD	98.12	14.48	95.97	13.75	99.61	14.80
P	108.31	19.75	107.73	18.55	108.60	20.55
SD	122.68	22.09	121.93	22.36	123.07	21.81
C	122.41	18.50	119.89	17.83	124.12	18.72
ST	66.25	15.61	65.20	15.02	66.98	16.03
BIST	66.62	11.46	66.75	11.16	66.55	11.71
AQT	76.50	19.92	78.36	19.66	75.15	20.06

WURS: Wender Utah Rating Scale; NS: Novelty Seeking; HA: Harm Avoidance; RD: Reward Dependence; P: Persistence; SD: Self-Directedness; C: Cooperativeness; ST: Self-Transcendence; BIST: Barratt Impulsiveness Scale-11 Total score; AQT: Aggression Questionnaire Total score.

Table 2
Correlations of Wender Utah Rating Scale scores and SCID-II BPD dimensional scores with Temperament and Character Inventory-Revised, Barratt Impulsiveness Scale-11, and Aggression Questionnaire Scores (N = 447).

	NS	HA	RD	P	SD	C	ST	BIST	AQT
WURS	.32*	.20*	−.00	−.09	−.21*	−.17*	.23*	.46*	.52*
BPD	.31*	.06	.05	−.09	−.14*	−.13	.12	.39*	.37*

BPD: SCID-II BPD Dimensional Score. * Significant after Bonferroni correction ($p < .004$).

thology, even after Bonferroni correction for multiple testing (Bonferroni-corrected significance level: $p = .004$), BPD diagnosis correlated significantly with histrionic PD, $r = .30$, $p < .001$, antisocial PD, $r = .21$, $p < .001$, and dimensionally assessed CD – i.e., the number of DSM-IV criteria for conduct disorder based on SCID-II interview – $r = .38$, $p < .001$. After Bonferroni correction (Bonferroni-corrected significance level: $p = .004$), the WURS correlated significantly with dimensionally assessed BPD, $r = .35$, $p < .001$, CD, $r = .31$, $p < .001$, antisocial PD, $r = .21$, $p < .001$, narcissistic PD, $r = .19$, $p < .001$, and passive-aggressive PD, $r = .14$, $p < .004$. However, no significant association was observed between the WURS and antisocial PD when the effect of CD was held constant, partial $r = .07$, $p > 0$.

Participant's gender did not show a significant moderator effect on the association between WURS and BPD, gender-by-WURS $\beta = -.12$, $p > .10$ (Bonferroni-corrected significance level: $p = .017$), but it has been found to moderate the relationships between the WURS and CD, gender-by-WURS $\beta = -.36$, $p < .001$, and adult antisocial PD, gender-by-WURS $\beta = -.36$, $p < .001$. Interestingly, the WURS significantly predicted the number of adult antisocial PD traits only in male participants, $\beta = .32$, $p < .001$ (female participants: $\beta = .01$, $p > .90$). On the other hand, despite the gender-by-WURS effect, the WURS significantly predicted CD both in men, $\beta = .39$, $p < 001$, and women, $\beta = .19$, $p < .005$.

The variables we have chosen as possible mediators in the relation between childhood ADHD symptoms and adult BPD features were those which showed significant correlation with both WURS scores and SCID-II BPD dimensional scores (namely, CD, novelty seeking, self-directedness, BIS-11 total score, and AQ total score). In all mediation models participants' gender were entered as control variable.

For the first five models, The Bonferroni-corrected significance threshold was set to $p = .017$. In the first mediation model, we tested the mediation effect of CD on the relation between WURS scores and BPD dimensional scores. The WURS significantly predicted conduct disorder, standardized path coefficient = .31, $p < .001$; in turn, the conduct disorder significantly predicted BPD, standardized path coefficient = .30, $p < .001$. The total standardized effect of the WURS on BPD was .35, $p < .001$. Conduct disorder significantly mediated the relationship between WURS scores and BPD dimensional scores, $a \times b = .09$, 95% CI: .05–.14, although the direct effect of the WURS remained significant, standardized path coefficient = .26, $p < .001$. The P_M effect size measure for this partial mediation effect was .26, i.e., 26% of the association between WURS scores and SCID-II BPD dimensional scores was mediated by conduct disorder.

In the second mediation model, WURS scores significantly predicted the mediator, that is, novelty seeking scores, standardized path coefficient = .32, $p < .001$; in turn, novelty seeking scores significantly predicted BPD dimensional scores, standardized path coefficient = .21, $p < .001$. The total standardized effect of the WURS on BPD was .36, $p < .001$. The mediator effect was significant, $a \times b = .07$, 95% CI: .03–.12, nevertheless, as above, the direct effect of the WURS remained significant, standardized path coefficient = .29, $p < .001$. The P_M effect size measure for this mediation model was .19.

In the third model, the mediator role of self-directedness was tested. WURS scores significantly predicted self-directedness scores, standardized path coefficient = −.21, $p < .001$; on the contrary, self-directedness scores did not significantly predict BPD, standardized path coefficient = −.07, $p > .05$. The total standardized effect of the WURS on BPD dimensional scores was .36, $p < .001$. The mediator effect was not significant, $a \times b = .01$, 95% CI: −.00–.04; the direct effect of the WURS total score remained significant, standardized path coefficient = .35, $p < .001$. The P_M effect size measure was .03.

In the fourth mediation model, we tested the mediation effect of BIS-11 total scores. The WURS significantly predicted the mediator, standardized path coefficient = .46, $p < .001$; in turn, the BIS-11 significantly predicted BPD, standardized path coefficient = .29, $p < .001$. The total standardized effect of the WURS on BPD was .35, $p < .001$. BIS-11 total scores significantly mediated the relationship between WURS scores and BPD dimensional scores, $a \times b = .14$, 95% CI: .09–.19, but the direct effect of the WURS remained significant, standardized path coefficient = .21, $p < .001$. The P_M effect size measure for this partial mediation effect was .40.

In the fifth model, the mediator role of AQ total scores was analyzed. The WURS significantly predicted AQ total scores, standardized path coefficient = .52, $p < .001$; in turn, the AQ significantly predicted BPD, standardized path coefficient = .27, $p < .001$. The total standardized effect of the WURS on BPD dimensional scores was .34, $p < .001$. The mediator effect was significant, $a \times b = .14$, 95% CI: .08–.20; also the direct effect of the WURS total score remained significant, standardized path coefficient = .20, $p < .001$. The P_M effect size measure for this mediation model was .40.

Lastly, we tested the combined mediation effect of CD, novelty seeking, BIS-11, and AQ; self-directedness was excluded from the model because, as indicated by the previous mediation analysis, it did not result a significant mediator of the relation between the WURS and BPD. In this last model, the significance level, according to Bonferroni

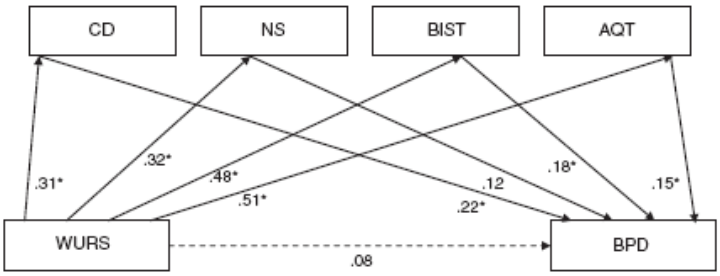

Fig. 2. Path diagram showing mediated effect (through Conduct Disorder, Novelty Seeking, Barratt Impulsiveness Scale-11, and Aggression Questionnaire) and direct effect of the Wender Utah Rating Scale on SCID-II BPD Dimensional Scores. The model included participants' gender as control variable. For ease of presentation residual terms were omitted. Note. *Significant after Bonferroni correction ($p < .008$).

correction, was set to $p = .008$. Standardized path coefficients for this model are presented in Fig. 2. The total mediation effect was significant, $a \times b = .27$, 95% CI: .18–.36, while the direct effect of the WURS resulted no longer significant, standardized path coefficient = .08, $p > .05$, suggesting complete mediation. The P_M effect size measure for this mediation model was .76.

4. Discussion

The relationship between ADHD and BPD has been documented by a number of studies, however has not yet been fully understood. The two disorder share diverse clinical features [15] and show several overlapping functional and structural neuroanatomical abnormalities [87]. Further, cross-sectional and longitudinal studies (for references, see Introduction) reported evidences suggesting that childhood ADHD may be a serious risk factor for adult BPD. However, as discussed by Philipsen [87], BPD patients present some symptoms, such as suicidal and self-injurious behaviors, which are not characteristic of ADHD. Moreover, the interpersonal correlates of the two disorders are quite different. Therefore, the emergence of BPD symptoms in ADHD individuals might depend on additional developmental antecedents. Following Philipsen's suggestions, the present study investigated if temperament/personality traits could mediate the relation between childhood ADHD symptoms and adult BPD features.

The main finding of our study is that this relation seems to be mediated by action-oriented personality traits. Indeed, impulsivity, aggression, novelty seeking, and juvenile conduct problems altogether completely mediated the relationship between retrospective ADHD symptoms and current BPD features. These evidences suggest that the developmental relationships between ADHD and BPD are likely to be complex and to involve the impact of childhood ADHD on extreme manifestations of a selected personality profile. Following Judd's [59] hypothesis, it could be argued that the early parent–child relationship may be negatively influenced by transactions between neurocognitive difficulties associated to ADHD and an extreme temperament profile, leading to insecure attachment patterns, which are thought to play a role in BPD development [88]. However, our results also support alternative propositions within the literature on BPD and its developmental antecedents. Hollander [55], for example, formulated the hypothesis of common neurobiological liability factors underlying ADHD and BPD. According to the author, ADHD and BPD share structural and neurotransmitter alterations in the brain which result into impulsive decision-making and risky behaviors. Action-oriented personality traits have been similarly linked to risk taking and impulse control/dyscontrol [60,61], thus our results could suggest a possible overlap in the neurobiological substrates underlying ADHD and BPD.

The results of our mediation analyses show that, taken individually, impulsivity and aggression explain about 40% of the association between ADHD and BPD. This results are consistent with the notion of impulsivity and impulsive aggression as major underlying dimensions of BPD [19,89] and provide support to the biosocial developmental model proposed by Crowell and colleagues [57]. According to this model, early biological vulnerabilities, initially expressed as impulsivity, affects nurturing contexts, which in turn affect the child's biological functioning, in an escalating process. These transactions would lead to emotional, behavioral, and cognitive dysregulation, and thereby contribute to the genesis of a borderline personality. Starting from this theory, the developmental link between ADHD and BPD could be explained as primarily due to the child's impulsivity and its interaction with an invalidating family environment. The results of the present study do highlight the prominent role of impulsivity in mediating the relation between ADHD and BPD, but also draw attention to the contribution of other personality features, particularly aggression.

The main limitation of the present study is that it is retrospective in nature. Following Brewin et al.'s [90] recommendations, we used a structured method of assessment that could enhance recall of childhood ADHD symptoms (i.e., the WURS). However, the risk of a memory bias cannot be completely ruled out, and our results should be considered in the light of the questions raised about the accuracy of adult

recall of childhood ADHD symptoms [91]. A second major limitation of this study is its cross-sectional design. In this case, mediation analyses need to be considered with caution, because alternative directions of causality cannot be exclude. Although it was based on a large number of participants, our sample was not actually randomly selected. In other words, it represented a convenient study group of clinical adults rather than a representative sample. This sampling procedure raises questions about the generalizability of our findings to different clinical samples, and to nonreferred samples; we emphasize the need for further studies that replicate our findings. Finally, no measures of general psychiatric severity were gathered, hence our analyses could not be controlled for the potential confounding effect of this variable.

Even with these limitations, the present study contributes to increase the existing body of evidences regarding the developmental antecedents of BPD and, in particular, offers insights on the role played by action-oriented personality traits. Otherwise, further studies, especially prospective ones, are needed to elucidate the association between ADHD in childhood and later BPD, and the effect of temperament/personality traits on this relation. Indeed, although recent longitudinal studies [53,54] have provided initial support for the notion that BPD symptoms may emerge as the result of previous ADHD symptoms, little is known about the process (or processes) underlying this progression.

A promising research line is that concerning the role of the interaction between the child's personality profile and his/her family environment in the transition from ADHD to BPD. In the present study, we focused primarily on the part played by personality features, but other researchers have highlighted the critical role of the parent–child relationship in the genesis of BPD (e.g., Crowell et al. [57]; Judd [59]). It would be of great interest to conduct longitudinal studies following ADHD children into adulthood, evaluating the different contribution of individual temperamental characteristics and parent's rearing attitudes to the later emergence of PDs, particularly BPD. Considering the importance ascribed to attachment relations in the development of BPD [88], longitudinal studies could also provide data on how ADHD symptomatology and extreme temperamental traits impact on attachment patterns, and whether, and in what ways, this influence may account for the development of BPD features. An alternative approach might be to specifically select "at-risk" samples on the basis of extreme temperamental characteristics. These subjects may be followed longitudinally and compared with "normal" controls in respect to rates of ADHD and BPD symptoms, testing the possible differences in the correlations between the two disorders. The results from such studies may help to confirm and to extent our findings, shedding light on the developmental pathways linking childhood ADHD to later BPD.

From a clinical perspective, our results lend support to the utility of a temperament/personality testing in the assessment of ADHD in children, in order to identify potential risk factors for developing later personality problems and to arrange early preventive interventions. In addition, evaluating the presence of childhood and adult ADHD in BPD patients could aid case formulation, informing clinical decisions on choice and course of treatment. Moreover, the integration of neurobehavioral testing into ADHD and BPD assessment procedures might help to identify potential targets of preventive interventions and could serve to improve diagnostic accuracy, to guide prognostic judgments and to suggest intervention priorities.

Taking into account the overlapping clinical features of adult ADHD and BPD, Hesslinger et al. [92] have presented a structured skills training program for adult patients with ADHD based on the principles of Dialectical Behavioral Therapy (DBT) for BPD developed by Linehan [58]. This treatment resulted in positive outcomes, with patients significantly improving on measures of ADHD and depressive symptoms, and overall personal health status. However, the current literature on psychotherapy research lacks empirical data on the effect of psychotherapy in BPD patients with current or childhood ADHD. Hence, in line with Philipsen's suggestions [42], we recommend further research to evaluate whether these subgroups of patients would benefit from specific interventions.

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This Section of *Epidemiology and Psychiatric Sciences* appears in each issue of the Journal to stress the role of the epidemiological approach to promote advances in the field of clinical psychopharmacology, with a particular attention to controversial findings. The ultimate aims are to help develop a more critical attitude towards the results of research studies published in the international literature, to promote original research projects with higher methodological standards, and to implement the most relevant results of research in every-day clinical practice. These contributions are written in house by the journal's editorial team or commissioned by the Section Editor (no more than 1000 words, short unstructured abstract, four key-words, one Table or Figure and up to ten references).

Corrado Barbui, *Section Editor*

Does psychostimulant treatment in children with ADHD increase later risk of substance use disorder?

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Psychostimulants are the first choice medication in children with attention-deficit/hyperactivity disorder (ADHD). Despite the proven high efficacy of psychostimulants, at least in the short term, for ADHD core symptoms, concerns continue to be raised on their adverse effects, including putative increased risk of substance use disorders (SUDs). A recent multicentre, case–control, longitudinal, prospective, European study by Groenman and colleagues found that treatment with psychostimulants in children with ADHD lowered the risk of SUDs in adolescence. However, this finding is at odds with other recent evidence concluding that ADHD children with and without medication treatment history did not significantly differ on any subsequent SUDs rates. In the present paper, we discuss the study by Groenman and colleagues in view of its methodological strengths and limitations, and we suggest possible implications for day-to-day clinical practice.

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Psychostimulants (including methylphenidate and amphetamines) are indicated by several guidelines (e.g., Pliszka, 2007; NICE, 2008) as first choice medication for children with attention-deficit/hyperactivity disorder (ADHD). Whereas a large body of randomised controlled trials supports the high efficacy of psychostimulants on ADHD core symptoms (at least in the short-term), concerns continue to be raised regarding their adverse effects, including possible increased risk of substance use disorders (SUDs) (Cortese *et al.* 2013).

To address the effects of psychostimulant treatment in childhood on later risk for SUDs, Groenman *et al.* (2013) analysed data from the International Multicenter ADHD Genetics study (IMAGE), a multi-site longitudinal, prospective study including probands with ADHD and healthy controls (HC). The authors assessed the relation between exposure to psychostimulants in childhood (age range: 5–17 years) and rates of SUDs (including nicotine dependence) at follow-up, on average 4.4 (±0.7) years after study entry. Baseline assessment included categorical measures of ADHD, oppositional defiant disorder (ODD) and conduct disorder (CD), as well as measures of ADHD symptoms severity. At follow-up, analysable

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data were available for 388 probands with ADHD and 211 HC. Among the participants with ADHD, 327 had been treated for at least 12 months with psychostimulants (ADHD-T) and 61 were either psychostimulants-naïve or had received a short or inconsistent treatment for <12 months (ADHD-NT). Follow-up assessment included indicators of SUDs/nicotine dependence, obtained combining self-rated and parent-reported measures, as well as data on medication history (current use, age at treatment initiation, age-adjusted duration use and cumulative dosage of psychostimulants) as per parents report and pharmacy records.

Results showed that ADHD-NT participants had a 2.6 times higher risk (hazard ratio (HR)) to develop any SUDs at follow-up compared to HC (95% confidence interval [CI]: 1.35–4.99) and two times higher risk in relation to ADHD-T participants (95% CI: 1.11–3.63); no statistically significant differences were found between ADHD-T and HC. However, both the ADHD-T and the ADHD-NT participants had an increased risk of developing nicotine dependence compared with HC (HR = 3.56, 95% CI: 1.28–9.88 and HR = 3.83, 95% CI: 1.11–13.28, respectively), whereas no differences were detected between ADHD-T and ADHD-NT participants for this outcome. These results remained substantially unchanged after adjusting for ODD, CD and ADHD severity at baseline. Among the possible moderators, earlier age at treatment initiation was associated with significantly lower risk of SUDs at follow-up; however, this effect diminished with age, and reversed around the age of 18.

The authors concluded that psychostimulant treatment in childhood has a protective effect on the risk of SUDs (except nicotine dependence) in adolescence. This finding is at odds with a recent meta-analysis of 15 longitudinal studies reporting that ADHD-T children did not differ from ADHD-NT on any subsequent SUD outcome (Humphreys *et al.* 2013).

However, before drawing any clinical conclusion, it is important to consider the methodological strengths and limitations of Groenman *et al.* study. This study has several remarkable strengths. The psychiatric assessment of ADHD and comorbid disorders was based on state-of-the-art tools and diagnostic algorithms. The authors controlled for the effect of comorbid disorders, such as ODD and CD, which have been shown to increase SUDs risk. They also explored possible moderators that have been overlooked in previous studies, such as age at treatment initiation, duration of treatment use and cumulative dosage. These variables were evaluated not only with parental reports, but also with pharmacy records, likely less prone to recall bias than retrospective information provided by parents.

Some limitations of the study should also be noted. As acknowledged by the authors, an important limitation is related to the naturalistic design of the study. It is well known that in naturalistic studies, greater treatment intensity may paradoxically be associated with worse outcome, since individuals with more severe disorders tend to be treated with more intense treatment and may have worse outcome. In this regard, it is worth noting that the ADHD-NT group had fewer symptoms than the ADHD-T group, so that the study findings cannot be ascribed to the difference in symptoms severity between the two ADHD groups. However, other possible differences between the two groups might have introduced important bias. For example, information on some key family characteristics is not provided in the paper. Families who seek medication treatment for their youths might be more invested in their children's success and in parenting, which, in turn, is a protective factor for the risk of SUDs (Wilens *et al.* 2003). The uneven distribution of this confounding factor between ADHD-T and ADHD-NT would be reduced *a priori* using a randomised design (Cipriani & Geddes, 2009). However, given the well-established effectiveness of psychostimulants for ADHD core symptoms and the population of interest (children with mental illness), such design would be difficult to apply (Adams, 2013). It would anyway be recommended to control for this possible confounding factor *a posteriori*, during the statistical analyses. Another limitation of the study pertains to the duration of follow-up (about 4 years). In general, follow-up studies in adolescence have shown a greater protective effect of psychostimulants for risk of SUDs (average odd ratio, OR: 5.8) compared with those in adulthood, where the OR (average: 1.4), despite being still statistical significant, may be less relevant clinically (Wilens *et al.* 2003). Therefore, it is possible that psychostimulant use delays the occurrence of SUDs, rather than protecting from it. As such, follow-up studies in adulthood are more suited to address the relationship between psychostimulants and SUDs risk. A further limitation is related to the outcome. Groenman *et al.* (2013) used measures of SUDs either from parents or from adolescents and this may have introduced heterogeneity. Additionally, they considered categorical outcomes for SUDs. No information is provided on clinically relevant features such as frequency and amount of substance use. Finally, ADHD participants were considered as a homogenous group. Given the phenotypical heterogeneity of ADHD, analyses considering the moderating role of ADHD subtypes (i.e., inattentive and hyperactive/impulsive) and of related personality traits that have been shown to impact on SUDs risk (such as high levels of *sensation seeking*) would provide clinically meaningful information.

Therefore, further research addressing the limitations of the Groenman *et al.* study, building on its strengths, seems necessary to address the question:

'Does psychostimulant treatment in children with ADHD increase later risk of SUD?' An additional and perhaps more relevant question would be 'In which patients and to which extent do psychostimulants in childhood increase or decrease the risk for later SUD?' Addressing these questions with methodologically sound trials will provide meaningful information to support the clinician in daily practice.

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Conflict of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Review

Headache and attention deficit and hyperactivity disorder in children: Common condition with complex relation and disabling consequences

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ABSTRACT

The aim of this review was to analyze literature data on the complex association between headache and attention deficit and hyperactivity disorder (ADHD) in children, in order to explore its possible consequences on child neurological development.

Headache and ADHD are two common conditions in the pediatric population. They both are disabling diseases that impact the child's quality of life and are associated with severe cognitive, emotional, and behavioral impairments. To assess and analyze literature data about the association of ADHD and headache in children and possible physiopathogenesis relationships, we searched for the following terms: headache, migraine, tension-type headache, ADHD, and children (MESH or text words).

We found different studies that assess the clinical, epidemiological, and physiopathogenetic overlap between these two diseases, with contrasting results and unresolved questions. Structural and functional abnormalities in brain networks have been found to be central in both headache and ADHD pathophysiology. It will be crucial to gain a better understanding of how subcortical–cortical and corticocortical network development is altered during the onset of the disorders.

1. Introduction

Headache is a common disease in the pediatric population [1]; it may become a disabling condition for both children and families, impacting the child's quality of life and leading to worry in parents and caregivers [2,3]. Recurrent, episodic, and paroxysmal attacks are suggestive of primary headache disorders, subdivided into migraine, tension-type headaches (TTHs), cluster headaches, and other (uncommon) types in children. Migraine is among the most common chronic conditions with an estimated prevalence of 10–28% among children and adolescents [2]. It is a painful and disabling condition, particularly in childhood, often accompanied by severe impairments, including low quality of life, low emotional functioning [4,5], absenteeism from school, and poor academic performance [6,7], as well as poor cognitive functioning [8,9], motor coordination, sleep habits [10,11], and high maternal stress. Several studies have focused on the impact of headaches on school performance and on the association between primary headaches and attention deficit, hyperactivity, and emotional and behavioral problems, raising a number of controversial points.

Attention deficit and hyperactivity disorder (ADHD) is also common among the pediatric population, with a worldwide prevalence of 5.3% [12], and is considered to be an important factor leading to poor academic performance. It is one of the most common childhood-onset neuropsychiatric conditions characterized by developmentally inappropriate behavioral symptoms categorized into three subtypes: inattentive, impulsive and hyperactive, and combined type. It has been associated with epilepsy [13], learning disability [14], and behavioral problems [15,16].

The prevalence of ADHD among children with headaches as well as its association with headache duration and frequency are still contradictory. The two diseases may influence each other simultaneously; concentration difficulties, hyperactivity, inappropriate behavioral symptoms, as well as stress among the family or at school are psychological predictors of headaches [17]. On the other hand, frequent headaches may increase distractibility and further impair learning.

Literature data suggest that pediatric migraine is associated with impaired attention span [18] and hyperactivity–impulsivity [19] but not with fully developed ADHD [19]. However, it is interesting to

Abbreviations: ADHD, attention deficit and hyperactivity disorder; TTHs, tension-type headaches; PAG, periaqueductal gray matter; SDB, sleep-disordered breathing; RLS, restless leg syndrome; PLMs, periodic limb movements; ID, iron deficiency.

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observe that both ADHD and migraine have well-established comorbid connections with mood and anxiety disorders. This has been shown both in clinical [20,21] and epidemiological [22] studies. There is also evidence for the involvement of dopaminergic systems in the pathophysiology of all three categories of disorders [23], which is one of the possible attractive pathophysiological ways to explain linkage between headaches and ADHD. Other possible explanations have focused on dysfunctional brain iron metabolism, possible genetic linkage, and an underlining common sleep disturbance [24].

2. Epidemiological data

Arruda et al. in a cross-sectional study on 1856 participants aged 5 to 11 years demonstrated that migraine and TTH are not comorbid to ADHD overall but are comorbid to hyperactive–impulsive behavior [19]. Leviton reported in a study on 150 elementary school children with recurrent headaches that about 40% had academic difficulties. These results are also in accordance with other recent studies that found a significantly high incidence of hyperactivity and impulsivity symptoms in children with headaches compared with healthy controls [25]. Strine et al. [26] demonstrated in a population of 4- to 17-year-old children that the ones who were referred for neurological assessment for frequent headaches were 2.6 times more likely to have inattention and hyperactivity. Genizi et al. in a recent retrospective study on 243 children and adolescents aged 6–18 years showed that learning disabilities and ADHD are more common in children and adolescents who are referred for neurological assessment for primary headaches compared with the general pediatric population [6].

However, the association between attention deficit and hyperactivity disorder and headache type remains controversial. Villa described impaired visual attention in children with migraine and suggested that impaired attention depends on neurotransmitters such as dopamine and noradrenalin. These same neurochemical aspects involved in the pathophysiology of migraine, therefore, may dispose those children to attention deficit and hyperactivity disorder [27].

In a recent study, Riva et al. compared 62 children with headaches (14 patients with migraine headaches with aura, 29 patients without aura, and 19 patients with tension-type headaches) with 52 controls using Conners' Continuous Performance Test. They found that patients with headaches had mean scores in hit reaction time significantly different from those of controls and also had a higher percentage of atypical scores in 2 indices of Conners' Continuous Performance Test (faster mean reaction time and more commissions) [28]. They found no differences between migraine and tension-type headache. Therefore, they suggested that these two conditions form a continuum that may share the same pathophysiological mechanisms [29] and that the same cerebral circuits underlining headache, personality profile, and attention overlap.

3. Pathophysiology

Several studies tried to identify alterations of neuronal circuits and cerebral regions which could explain the comorbidity between migraine and ADHD and clarify the association between the two conditions and between them and the different diseases often associated with them.

The pathophysiology of primary headaches involves the neurovascular system with cortical spreading depression and trigeminovascular activation, followed by transmission through the thalamus to higher cortical structures [30,31].

Despite extensive research, the pathophysiological mechanisms underlying ADHD are not completely understood [32]. Neuronal deficits in attention and executive function processing networks have been frequently reported in ADHD using structural and functional neuroimaging approaches [33,34]. Neuroimaging studies have demonstrated global cortical maturation delay based on reduced cortical thickness and reduced GM and WM volumes, specifically in the frontal lobe [35], regional WM microstructural abnormalities in the frontal, temporal, and parietal lobes [36–38], and aberrant neuronal activations in the interregional functional connectivity of these cortical areas [39,40].

All these structural and functional abnormalities in the brain have been associated with impaired cognitive, affective, and motor behaviors seen in ADHD.

3.1. Sleep disorders and dopaminergic dysfunction

The analysis of the associations between sleep disorders and both migraine and ADHD could help to better understand the complex relationship between headaches and ADHD. It is known that sleep is related to the occurrence of some headache syndromes while headache may cause sleep disruption and several sleep disturbances either in adults or children. Headache episodes are known to occur in relationship with various sleep stages. On the other hand, an excess or lack of sleep or bad quality or inadequate duration of sleep can trigger headache [10,11].

The trigeminal nucleus caudalis in the pons and midbrain is considered to be the migraine generator, and the hypothalamus is involved in the prodromal symptoms of migraine, such as hunger, fatigue, mood changes, and sensory and visual distortions, that are commonly considered as dopaminergic premonitory symptoms [41,42]. The hypothalamus is connected with anatomical structures involved in the control of the sleep–wake cycle as well as in the modulation of pain [43] (limbic system, pineal gland, noradrenergic locus coeruleus, and serotonergic dorsal raphe), with the serotonergic system playing an important role in the relationship between headache and sleep.

The role of dopamine in the pathogenesis of migraine has been evaluated by different studies: individuals susceptible to migraine appear to have genetic polymorphisms in the dopamine D2 gene, which increase responsiveness to dopamine, or defects in tyrosine hydroxylase, which inhibit dopamine metabolism, and an imbalance of the dopaminergic system is responsible for some premonitory symptoms of migraine, such as nausea, yawning, and dizziness [44,45]. Finally, melatonin is a chronobiotic substance that has demonstrated therapeutic efficacy in some forms of migraine and headache [46,47].

An imbalance between neurotransmitters, with damaged serotonergic and dopaminergic pathways, which characterizes both migraine and sleep disorders, could begin in the early period of life and tend to persist during childhood and adolescence, leading to disorders of the sleep–wake rhythm in infancy and determining the comorbidity between altered neurodevelopment and headache disorder [48]. An altered modulation of synaptic potentiation and pruning by dopamine during development, which results in altered patterns of corticocortical connectivity, has been linked to the structural and functional connectivity deficits of the ADHD [49].

One important anatomical region for the connectivity of headache and sleep is the ventrolateral part of the periaqueductal gray matter (PAG), which is responsible for "rapid-eye-movement sleep-off" when activated by orexin. On the other hand, orexin can stimulate neurons in the ventrolateral part of the PAG, inhibiting antinociceptive activity in the trigeminal nucleus caudalis, thus facilitating trigeminal nociception and triggering a migraine attack. Dysfunctional hypothalamic activity might contribute to both altered sleep–wake function and altered pain processing via its orexinergic neurons [50].

It is, therefore, very likely that pain processing can be modulated via these circuits by vegetative/autonomic symptoms and reflex mechanisms: sleep can trigger a migraine attack, and on the other hand, through changes of the autonomic homoeostasis, it can facilitate or suppress pain processing.

Subcortical regions may also significantly contribute to the pathophysiology of ADHD [51]. Neuroimaging studies have demonstrated regional structural and functional deficits of the basal ganglia, especially in the striatum; as mentioned, disturbed WM structural connectivity and atypical functional connectivity have been shown in the frontal–

striatal network in both adults and children with ADHD [52]. However, very recently, investigation with high resolution structural magnetic resonance imaging (MRI) has highlighted the role of the thalamus and its mediating role in corticostriatal and corticocortical pathways in ADHD. New evidence has revealed reduced bilateral thalamic volumes, as well as regional surface atrophy in the pulvinar nucleus of the left side thalamus in children with ADHD [53]. In the same study, disturbed frontal-thalamo and thalamostriatal WM connectivity has also been demonstrated in the children with ADHD. Furthermore, significantly reduced pulvinar activations and abnormal pulvinar–frontal and occipital–pulvinar functional connectivity have been shown in children with ADHD during a visual sustained attention task, which were also significantly correlated with their inattentiveness indices for clinical diagnoses [72]. About 25–50% of children and adolescents with ADHD experience sleep problems. An appropriate assessment and treatment of such problems might improve the quality of life in such patients and reduce both the severity of ADHD and the impairment it causes. According to data in the literature, five sleep phenotypes may be identified in ADHD: (1) one characterized by a hypoarousal state, resembling narcolepsy, which may be considered a "primary" form of ADHD; (2) a phenotype associated with delayed sleep-onset latency and with a higher risk of bipolar disorder; (3) a phenotype associated with sleep-disordered breathing (SDB); (4) another phenotype related to restless legs syndrome (RLS) and/or periodic limb movements (PLMs); and (5) a phenotype related to epilepsy and/or EEG interictal discharges [52,54,55]. Each sleep phenotype is characterized by sleep alterations expressed by either an increased or a decreased level of arousal during sleep. Both an increase and a decrease in arousal are linked to executive dysfunctions controlled by prefrontal cortical regions and the arousal system, which may be hyperactivated or hypoactivated depending on the form of ADHD/sleep phenotype [54–56].

In conclusion, headaches, ADHD, and sleep disorders seem to be related to dysfunction in the same brain structures involved in the control of the sleep–wake cycle as well as in the arousal generation during sleep and modulation of pain.

3.2. Brain iron metabolism

Impaired brain iron homeostasis could be one of the possible pathogenetic links between headache and ADHD. It has been proposed that either a deficiency of peripheral iron or a dysfunction of the blood–brain barrier, in the presence of normal peripheral iron levels, may contribute to low brain iron levels, which, in turn, would increase the risk of ADHD symptoms in a subgroup of individuals with this disorder [57]. The iron deficiency (ID) hypothesis of ADHD is grounded on several lines of evidence. First, iron is a coenzyme necessary for the synthesis and catabolism of monoaminergic neurotransmitters, which are implicated in ADHD pathophysiology [58]. Second, ID is associated with decreased dopamine transporter expression [59]; variation in the corresponding dopamine transporter gene has been linked to genetic vulnerability for ADHD [60]. Third, ID may lead to dysfunction in the basal ganglia [61], which have been implicated in the pathophysiology of ADHD [62]. Fourth, ID has been reported in children with cognitive and behavioral impairments that include poor attention and hyperactivity.

Since brain iron impacts on neurotransmitter levels, whose dysregulation is supposed to underpin ADHD symptoms, Cortese et al. [63] suggested that low brain iron, not necessarily peripheral iron, increases the risk of ADHD due to dysfunction in the blood–brain barrier, which regulates the entry of iron into the brain. Periodic movement disorders, and especially restless legs syndrome (RLS), can profoundly disrupt sleep macrostructure and therefore impact the restorative function of sleep. Periodic limb movement has also been associated with both headache and ADHD. A dopaminergic dysfunction and ID may be the neuroanatomical substrate linking migraine, ADHD, and RLS [64,65].

Iron is essential in oxygen carrier proteins and in many metabolic enzymes. Up to 25% of the total oxygen consumption of the body is by brain metabolic processes, which implicates a relatively high utilization of iron. Nonheme iron is primarily stored inside the nontoxic ferritin protein but can also be present in an unshielded, soluble form. This iron can become toxic since it can catalyze the formation of free radicals, which can lead to DNA, protein, and neuronal cell damage [66,67].

In normal aging, iron accumulates throughout the brain, particularly in the basal ganglia [68].

Magnetic resonance imaging study showed increased iron depositions in the periaqueductal gray matter in patients with migraine headaches, suggestive of a disturbed central antinociceptive neuronal network [69,70]. Repeated migraine attacks are associated with increased iron concentration/accumulation in multiple deep nuclei that are involved in central pain processing and migraine pathophysiology [73]. It remains unclear whether iron accumulation in the antinociceptive network has a causative role in the development of (chronic) migraine headache [69].

An important factor for interpreting the findings in migraine is the fact that transferrin receptor binding is proportional to the metabolic activity of the neuron and, in turn, may be influenced by nociceptive function [70]. Some of the reasons for high iron in brainstem structures include overproduction of transferrin, increased iron uptake reflecting increased activity, and iron sequestered after cellular damage. By whatever mechanism, abnormally high or low iron in these structures affects homeostasis and is a marker of altered function; increased iron might reflect free radical damage in repeatedly activated networks involved in nociception [71].

4. Conclusion

Structural and functional abnormalities in brain networks have been found to be central in both headache and ADHD pathophysiology. It is important to gain a better understanding of how subcortical–cortical and cortical–cortical network development is altered during the onset and course of these disorders. Future research studies are needed to explore this association and better understand its clinical implication in altering neurocognitive and behavioral child development.

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ORIGINAL CONTRIBUTION

Serum brain-derived neurotrophic factor (BDNF) levels in attention deficit–hyperactivity disorder (ADHD)

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Abstract It has been proposed that the neurotrophin brain-derived neurotrophic factor (BDNF) may be involved in attention deficit–hyperactivity disorder (ADHD) etiopathogenesis. Alterations in BDNF serum levels have been observed in childhood/adulthood neurodevelopmental pathologies, but no evidence is available for BDNF serum concentrations in ADHD. The study includes 45 drug-naïve ADHD children and 45 age–sex matched healthy subjects. Concentration of serum BDNF was determined by the ELISA method. BDNF serum levels in patients with ADHD were not different from those of controls (mean ± SD; ADHD: 39.33 ± 10.41 ng/ml; controls: 38.82 ± 8.29 ng/ml, $t = -0.26$, $p = 0.80$). Our findings indicate no alteration of serum BDNF levels in untreated patients with ADHD. A further stratification for cognitive, neuropsychological and psychopathological assessment in a larger sample could be useful to clarify the role of BDNF in the endophenotype characterization of ADHD.

Keywords BDNF · Attention deficit–hyperactivity disorder · Serum

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Introduction

Attention deficit–hyperactivity disorder (ADHD) is a common childhood and adolescence syndrome characterized by behavioral and cognitive alterations such as inattention, impulsivity and hyperactivity. The worldwide prevalence of ADHD is approximately 5.3 % in children and adolescents [1].

To date, diagnostic biological and genetic markers are lacking. Following Schmidt et al. [2], a biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of a normal biological process, a pathogenic process or a response to a therapeutic intervention. Recent review and meta-analyses [3] provide support to monoaminergic systems as well as HPA axis being dysregulated in ADHD and that exposure to lead and zinc may be risk factors. These peripheral measures could be identified as biomarkers for diagnosis and, though more work is needed, they could be used for diagnostic purposes in clinical practice.

Convergent data from neuroimaging, neuropsychological, genetics and neurochemical studies in ADHD patients have evidenced functional and structural alterations in development in several areas of the brain [4]. Molecules implicated in neuroplasticity changes in these areas may potentially contribute to the pathogenetic mechanisms.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely expressed in the brain that plays a key role

in the regulation of neurogenesis and in the differentiation of neural pathways during neurodevelopment as well as in the modulation of synaptic plasticity and dendritic growth in the adult brain [5–8]. BDNF gene expression is reduced in the frontal cortex of dopamine transporter knockout mice, which is considered an animal model for ADHD [9], and BDNF conditional knockout mice exhibit learning deficiencies, aggressiveness, anxiety and hyperactive locomotor behavior, which mimic the fundamental behavioral characteristics of ADHD [10, 11]. Moreover, central BDNF expression is modulated by psychostimulant and antidepressant drugs used for ADHD treatment [12, 13] and mediates their neuroadaptative mechanisms [14]. Finally, it has been demonstrated that the BDNF gene may play a role in cognitive functions in ADHD patients [15–18].

BDNF is also present at high levels in the blood, where it is mostly stored in platelets [19]. Several evidences indicated that the neurotrophin serum levels might reflect the brain content and be associated to markers of neuronal integrity [20–22]. In recent years, the involvement of BDNF in the pathogenesis of several mental disorders has been corroborated by a series of biochemical studies. In particular, reduced BDNF serum concentrations were consistently observed in several adulthood psychiatric pathologies such as major depression disorder [23], bipolar disorder [24], schizophrenia [25, 26], eating disorders [27] and obsessive–compulsive disorder [28]. Similarly, also in childhood neurodevelopment disorders such as autism, alterations in serum BDNF levels were found [29–34]. A recent study reported an increase of plasma BDNF levels in untreated child ADHD patients [18]. Since methodological investigations indicated that plasma BDNF dosage might be affected by the handling of the blood sample (temperature, anticoagulant, time before centrifugation) while the measure of BDNF in serum is more stable [35], the aim of this study was to analyze serum BDNF in drug-naïve child ADHD patients compared to a control group.

Methods

Subjects

Drug-naïve ADHD patients were enrolled by a network of clinical centers (Department of Childhood and Adolescent Neuropsychiatry, Spedali Civili Brescia; Childhood and Adolescent Neuropsychiatry (UONPIA), Spedali Riuniti, Bergamo and Adolescent Neuropsychiatry Unit of Fatebenefratelli and Oftalmico, Milan). Patients were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) [36] and the guidelines of the Italian Institute of Health (ISS). Moreover, revised Touwen neurological tests were performed. Exclusion criteria included diagnosis of childhood schizophrenia, autism, epilepsy, encephalitis, Tourette syndrome, conduct disorder and IQ $\leq$70 (Wechsler Intelligence Scale for Children, WISC). Psychopathological features were assessed by specific questionnaires for parents and teachers (Conner's Rating Scale Revised). Depressive and anxious symptoms were addressed by using CDI [37].

The control group consisted of unrelated volunteers not affected by mental retardation, chronic and medical diseases, inflammatory diseases and allergies, undergoing blood tests for a pre-surgical screening. All the subjects enrolled in this study were Caucasoid and living in Northern Italy.

The study protocol was approved by the local ethics committee and, since the participants were all under-age youths, also their parents were requested to give written informed consent to the study as indicated on the approval note by the local ethics committee. It was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

BDNF determination

Venous blood samples of patients and controls were collected in anticoagulant-free tubes (for serum preparation) in the morning after an overnight fast (between 08:00 and 09:00 h). Serum tubes were kept at room temperature for 2 h followed by 1 h at 4 °C before serum separation by centrifugation (1,620×*g* for 15 min). Serum samples were stored at −80 °C till the time of assay. BDNF levels were measured by an ELISA method using the human BDNF Kit (R&D System, MN, USA), according to the manufacturer's instructions. Serum samples were diluted 1:100 for BDNF measurement. All BDNF measurements were performed in duplicate. Patient and control samples were run together in the same plates. The intra-assay coefficient of variation was <8 %. The BDNF content was expressed as ng of human recombinant BDNF protein/ml of serum.

Statistical analysis

Fisher's exact test was used for the gender analysis differences. After checking for normality with Shapiro–Wilk test, two-tailed student *t* tests were used to evaluate differences in quantitative variables. Statistical analyses were performed using SPSS, version 13.0 (website: http://www.spss.com).

Results

Forty-five ADHD patients participated in the study. The age at data collection was 10.71 ± 2.48 years and the

Table 1 Morphometrical and demographic characteristics of the patient and control samples

	ADHD ($N = 45$)	Controls ($N = 45$)
Age in years, mean (SD)	10.71 (2.48)	10.31 (2.04)
Gender, boys *N* (%)	42 (93 %)	41 (91 %)
BMI, mean (SD)	18.12 (3.49)	18.04 (3.16)
BDNF, mean (SD)	39.33 ± 10.41	38.82 ± 8.29
ADHD rating scale:		
Combined type	30 (67 %)	
Predominantly inattentive type	12 (27 %)	
Predominantly hyperactive–impulsive type	1 (2 %)	
Presence of depressive symptoms (CDI scale)	17 (38 %)	

proportion of males was 93 %. The mean of BMI was 18.12 ± 3.49. Stratification according to diagnostic subtypes evidenced 67 % for the ADHD combined type, 27 % for predominantly inattentive type and 2 % for predominantly hyperactive–impulsive type.

From a sample of 78 healthy subjects recruited, 45 were selected for the study since this group showed similar morphometric and demographic characteristics as compared to the patients (Table 1). No differences in mean age ($p = 0.41$), gender (Fisher's exact test $p = 1$) and BMI ($p = 0.90$) were evidenced among the groups.

Mean serum BNDF levels in patients with ADHD were not significantly different from those of controls (mean ± SD; ADHD: 39.33 ± 10.41 ng/ml; controls: 38.82 ± 8.29 ng/ml, $t = -0.26$, $p = 0.80$, Table 1). Also, serum BNDF levels in the patients were not different on comparing the more represented diagnostic subtypes (combined and predominantly inattentive) with controls. Similarly, no associations were observed between BDNF serum levels and the presence of depressive symptomatology in patients ($p = 0.76$), as well as no correlations between BMI and peripheral BDNF concentration ($p = 0.41$).

Discussion

BDNF is a member of the nerve growth factor family that plays pivotal roles in neurodevelopment and in the maintenance of adult brain homeostasis through the regulation of neurogenesis and neuronal plasticity [38]. Biochemical studies have reported reduction of serum BDNF levels in many childhood [31, 32] and adulthood [23, 24, 26–28] mental disorders, suggesting a common etiopathogenetic mechanism for these pathologies.

In this work, we intended to verify for the first time whether serum BDNF could be a potential biomarker for ADHD diagnosis in childhood and adolescence. The results obtained indicated no significant alterations of serum BDNF levels in ADHD patients or in the diagnostic subtypes, combined and predominantly inattentive. Our negative findings are in accordance with the recent genetic studies where both the genome-wide association studies (GWAS) and meta-analyses (see http://adhd.psych.ac.cn/ [39]) supported no preferential associations between BDNF gene and ADHD pathology.

A recent paper analyzed the BDNF concentration in plasma from ADHD patients [18]. The results indicated higher BDNF levels in ADHD patients as compared to healthy subjects, in contrast to our findings. The discrepancies could be due to the fact that serum and plasma BDNF are two different compartments (serum is about 20-fold more concentrated than plasma) and they are not correlated [23, 40]. We chose to analyze BDNF in serum since methodological investigations indicate that plasma BDNF dosage may be affected by the differences in blood sample processing (temperature, anticoagulant, time before centrifugation), while the measure in serum seems more stable [35]. More recently, D'sa et al. [40] reported also a lower analytical variance and higher day-to-day within-individual stability of serum BDNF levels compared with plasma measures. The contrasting finding between the studies could be due to the different characteristics of the samples, in particular demographic features. Our patient sample was composed almost entirely of males and was matched with the control group, whereas in Shim et al. [18] the sample was not balanced according to gender. More recently, Corominas-Roso et al. [41] reported a decrease in the serum levels of BDNF in adult ADHD patients. This supports that the unchanged levels found in our ADHD children sample could decrease in adulthood, on the basis that the BDNF levels change throughout life [42].

The study presents some limitations: (1) the sample is not representative of the predominantly hyperactive–impulsive type subgroup; thus, we cannot exclude differences in BDNF levels for this diagnostic subtype; (2) in this study we have not evaluated some possible confounding factors in BDNF measures, such as motor activity, exercise or diet.

In conclusion, our findings indicate no alteration of serum BDNF levels in untreated patients with ADHD. A further stratification for cognitive, neuropsychological and psychopathological assessment in a larger sample could be useful to clarify the involvement of BDNF in the endophenotype characterization of ADHD.

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Conflict of interest The authors declare that they have no conflict of interest and have no financial interests of any kind in publishing the results of this study.

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CLINICAL PRACTICE

Effect of Osteopathic Manipulative Therapy in the Attentive Performance of Children With Attention-Deficit/Hyperactivity Disorder

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Context: Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder most commonly affecting children and teenagers. It is characterized by the coexistence of attention problems and impulsivity and hyperactivity. Although several studies have been conducted on the efficacy of conventional and alternative therapies in children with ADHD, few studies have specifically investigated the efficacy of osteopathic manipulative therapy (OMTh).

Objective: To evaluate the efficacy of OMTh in the treatment of children with ADHD.

Methods: Children aged 5 to 15 years with a primary diagnosis of ADHD who were admitted to a single neuropsychiatry unit from November 2008 to September 2009 were randomly assigned to an intervention group (OMTh + conventional care) or a control group (conventional care only). Biancardi-Stroppa Modified Bell Cancellation Test accuracy and rapidity scores were recorded for both groups at baseline and after 10 weeks. Statistical analyses included univariate tests and multivariate linear regressions.

Results: A total of 28 participants were included in the study: 14 in the OMTh group and 14 in the control group. Univariate statistical analysis showed no statistically significant differences between the intervention and control groups in terms of characteristics measured at baseline, except for psychosocial intervention (P=.05). Multivariate linear regression showed that OMTh was positively associated with changes in the Biancardi-Stroppa Test accuracy (β=7.948 points; P=.04) and rapidity (β=9.089 points; P=.03) scores.

Conclusion: Participants who received OMTh had greater improvement in Biancardi-Stroppa Test scores than participants who received conventional care only, suggesting that OMTh can potentially increase performances of selective and sustained attention in children with ADHD. To confirm these findings, studies of larger and more diverse populations are warranted.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder most commonly affecting children and teenagers that is characterized by deficit of attention associated with impulsivity and hyperactivity.[1] Attention-deficit/hyperactivity disorder is typically diagnosed in children before age 7 years, with symptoms being present for at least 6 months before diagnosis.[1-3] In 2007, a systematic review reported that the worldwide prevalence of children affected by ADHD was 5%.[4] Another multicenter study showed that the prevalence of ADHD is 3 times higher in males than in females.[5] Current advances in neurobiology have led to research on the multifactoral etiologic processes of ADHD; the evidence concludes that genetic, traumatic, neurologic, and environmental components are the most likely causes of the disorder.[6-10] Although pharmacokinetic drugs targeted at the central nervous system and behavioral therapy are standard treatments for patients with ADHD, results are discordant in terms of long-term efficacy and effectiveness.[11] Furthermore, adverse effects have been associated with long-term use of pharmacokinetic drugs.[12]

The use of complementary and alternative medicine for the management of ADHD in children has been investigated.[13-15] This area of research, however, still lacks robust evidence. Similarly, few studies have been conducted on the use of osteopathic manipulative treatment (OMT) for ADHD. Frymann and colleagues have investigated the application of osteopathic care for children with learning problems,[16] psychological deficiencies,[17] and seizure disorders.[18] This research highlighted the clinical association between newborns' traumas, somatic dysfunction, and physiologic development of the central nervous system.[16-18] Lassovetskaia[19] carried out a study on children with language and learning problems. Among 96 children with delayed academic performance, children who received OMT scored significantly higher in almost all categories of academic performance after 6 to 12 weeks compared with children who did not receive OMT.

Several tools have been widely used to evaluate attention performance in children with ADHD. However, differences in applicability, interrater reliability, ease of use, and validity exist. Among those clinical tests, the Biancardi-Stroppa Modified Bell Cancellation Test was introduced in late 1989 to evaluate the performance of sustained and selective attention in visual neglect,[20] incident stroke,[21] and children with ADHD.[22]

The primary objective of the present study was to determine the effect of osteopathic manipulative therapy (OMTh) on attention tasks in children with ADHD. Specifically, we aimed to detect differences in Biancardi-Stroppa Test scores between children who received OMTh plus conventional care and children who received conventional care only.

Methods

Setting and Participants

The present randomized controlled trial was approved by the Accademia Italiana Osteopatia Tradizionale institutional review board and was conducted at the Center for Pediatric Neuropsychiatry at the Macerata Public Hospital in Italy from November 2008 to September 2009. Male and female children aged 5 to 15 years with a primary diagnosis of ADHD who presented to the Center for Pediatric Neuropsychiatry during the study period were recruited to participate in the study. Participants were excluded if they had a secondary diagnosis of ADHD or a diagnosis of mental retardation, anxiety disorder, pervasive development disorder, diphasic disorder, childhood schizophrenia, manic episode, underdevelopment of a special learning skill, overactive symptoms caused by organic disorders, or adverse drug reactions. All participants needed informed consent from their parent or legal guardian to be included in the study. Parents and participants were given information regarding the study design and protocols.

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At enrollment, participants were examined by a neuropsychiatrist (M.P.), who confirmed the ADHD diagnosis according to criteria in the 4th edition of *Diagnostic and Statistical Manual of Mental Disorders*.[1] The neuropsychiatrist (M.P.) and the psychologist (F.F.) entered the following clinical data for each participant into a computer-based spreadsheet at enrollment: age, sex, date of birth, duration of labor, route of delivery, gestational age at birth, body mass index, psychomotor development (ie, time to crawling, walking, and verbalization), drug therapy, psychosocial intervention, and history of sleep disorder, physical or psychological trauma, physical activity, menarche, gastrointestinal disorders, and visual, dental, and otolaryngologic disorders. Moreover, data on adverse effects and adverse events were collected at each session by the neuropsychiatrist (M.P.).

At entry, participants were randomly assigned to either an intervention group (OMTh + conventional care) or a control group (conventional care only). The randomization was based on permuted-block process (ratio 1:1) and was generated using R statistical program (v.2.12.0, R Foundation for Statistical Computing). Both the neuropsychiatrist and the psychologist were blinded to the allocation of participants. The participants and their parents were not blinded to group placement, but they did not receive information about the outcomes of the study.

Conventional Care

Participants in both groups were receiving drug therapy and psychosocial intervention before enrollment in the study, if indicated, and continued to receive these therapies for the duration of the study. First-line drug therapy involved the use of psychostimulants (methylphenidate or atomoxetine), with posology following national guidelines defined by the Italian Ministry of Health.[23] The psychosocial intervention was part of a cognitive-behavioral program that was led by a specialized psychologist (F.F.). Participants in the program underwent weekly group and individual sessions aimed at promoting and strengthening the use of self-control strategies (cognitive-behavioral program).[24] The psychosocial therapy was performed weekly by the same psychologist and in different days with respect to OMTh.

Osteopathic Manipulative Therapy

In addition to conventional care, children from the intervention group received OMTh for the entire period of the study. The OMTh techniques were chosen according to each participant's needs, as well as the physical condition and age of the participant. Manipulative techniques used included myofascial release, craniosacral, balanced ligamentous tension, and balanced membranous tension.[25-27] At enrollment, each participant was randomly assigned to 1 of 4 osteopaths (A.A., C.L., L.D.M., or C.G.) certified by the Registro Osteopati d'Italia. Osteopaths included in the study obtained the same osteopathic education at Accademia Italiana Osteopatia Tradizionale and underwent 8 hours of prestudy training that defined a standardized evaluation procedure on the basis of Johnston's functional tests.[28] Osteopaths remained with their assigned participants for the duration of the study.

The sequence and dose of OMTh techniques were left to the discretion of the osteopaths and not based on a predetermined protocol. Participants allocated to the intervention group received six 40-minute OMTh sessions. The first 2 sessions occurred weekly and the last 4 sessions biweekly, for a total of 10 weeks. Sessions occurred on the same day of the week to reduce performance bias, increase adherence rates, and reduce the risk of overlapping treatments. For each session, the treating osteopath collected data on somatic dysfunction found.

Biancardi-Stroppa Modified Bell Cancellation Test

All participants took the Biancardi-Stroppa Modified Bell Cancellation Test (*Figure*)[22] at enrollment and after 10 weeks; participants in the intervention group took the test the day after their last OMTh session. The Biancardi-

Stroppa Test, used to measure visual-spatial attention, is a modified version of the traditional paper-and-pencil test called the Bell Cancellation Test.[21] The test consists of 4 different sheets, each of which contains 35 bells among other confounding stimuli (such as icons of houses, trees, fish, and horses) of the same size and orientation in space. Participants are asked to find and tick only the bells within a fixed time (2 minutes) for each sheet. The examiner (F.F.) recorded the total number of bells found on all 4 sheets after 8 minutes (ie, the accuracy score) and the total number of bells identified in the first 30 seconds per sheet (ie, the rapidity score) for each participant. Four rapidity scores were recorded for each participant (ie, 1 per sheet), and the mean score was used for analysis.

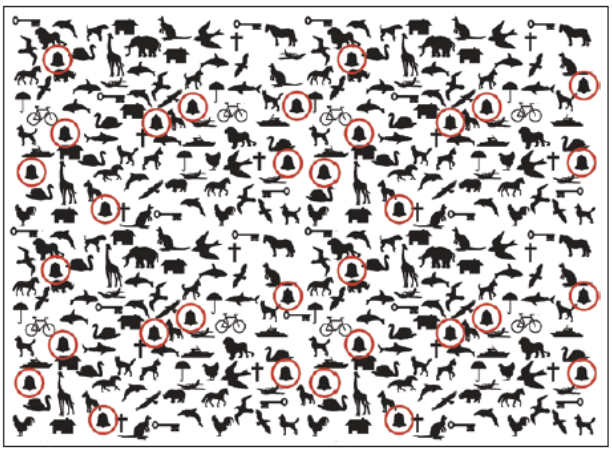

Figure.
Biancardi-Stroppa Modified Bell Cancellation Test.[22]
Red circles highlight all bells in the chart. Reprinted with permission from Andrea Biancardi.

Statistical Analyses

Descriptive analysis was performed on continuous data using arithmetic mean, median, and standard deviation (SD) and on categorical data using frequency and percentage. The Shapiro-Wilk test was used to assess the normality of the sample. Univariate statistical tests (student t and χ^2) were performed to explore the differences in Biancardi-Stroppa Test scores between intervention and control groups at baseline and at the end of the study period. Multivariate linear regression was used to evaluate differences in Biancardi-Stroppa Test accuracy and rapidity scores and independent variables including age, sex, drug therapy, psychosocial intervention, OMTh, and the other Biancardi-Stroppa Test score (ie, the rapidity score for the accuracy score and vice versa). Results were expressed in point estimates (β) and 95% confidence intervals (CIs).

Period prevalence was used as an epidemiologic measure to detect the proportion of the population with a given SD over the entire study period. Alpha values less than .05 were considered statistically significant. To compute post hoc power analysis, regression model values were used. The following parameters were taken into account: numerator degree of freedom equal to 6, denominator degree of freedom equal to 27, and effect size equal to 2.44. The effect size was calculated using the following formula: $R^2/1\text{-}R^2$, where R^2 is the population squared multiple correlation. All analyses were performed using R statistical program (v.2.12.0, R Foundation for Statistical Computing). The R package used for post hoc power calculation was "pwr."

Results

Forty consecutive outpatients entered the study, 28 of whom met the study criteria and were included in the study. Of those, 14 participants were randomly assigned to the intervention group and 14 to the control group. No dropouts were recorded throughout the study period. At enrollment, the study sample was normally distributed (Shapiro-Wilk normality test for age, W=0.97; P=.58) and univariate statistical analysis showed no significant

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Table 1.
Baseline Characteristics and Outcome Measures of Children With Attention-Deficit/Hyperactivity Disorder (N=28)

Characteristic, No. (%)[a]	Study Group (n=14)	Control Group (n=14)	*P* Value[b]
Sex			>.99
Male	11	12	
Female	3	2	
Age, Mean (SD)	7.8	8.6	.24
Drug Therapy			>.99
Yes	4	5	
No	10	9	
Psychosocial Intervention			.05
Yes	6	12	
No	8	2	
Biancardi-Stroppa Modified Bell Cancellation Test Score, Mean (SD)			
Rapidity	44.1	42.9	.81
Accuracy	104.1	112.7	.24

[a] Data presented as No. (%) unless otherwise indicated.
[b] For data presented as No. (%), *P* value is from χ^2; for data presented as mean (standard deviation [SD]), *P* value is from *t* test.

differences between the 2 groups for any characteristic except for psychosocial intervention (*Table 1*). No statistically significant differences were found between groups for any clinical data.

At the end of the study period, there was a statistically significant difference between the intervention group and the control group on Biancardi-Stroppa Test scores for rapidity (mean [SD] score, 59.2 [17.6] vs 42.2 [7.4]; *P*<.01) but not for accuracy (mean [SD] score, 116.4 [24.3] vs 110.5 [10.5]; *P*=.14).

Multivariate linear regression showed that OMTh was positively associated with a change in the Biancardi-Stroppa Test accuracy score (β=7.948 points; 95% CI, 0.181-15.714; *P*=.04). Similarly, the Biancardi-Stroppa Test rapidity score was associated with a positive change for the Biancardi-Stroppa Test accuracy score (β=0.387 points; 95% CI, 0.006-0.769; *P*=.04) (*Table 2*). Multivariate linear regression also revealed that OMTh and the Biancardi-Stroppa Test accuracy score were positively associated with a change in the Biancardi-Stroppa Test rapidity score (β=9.090 points; 95% CI, 0.821-17.358; *P*=.03 and β=0.451 points; 95% CI, 0.007-0.896; *P*=.05; respectively) (*Table 3*).

Post hoc power analysis was computed and the final result was 0.99. No adverse effects were recorded in the study and control groups during the investigation.

In the intervention group, baseline prevalence of somatic dysfunction was as follows: L5-S1, 9; sphenobasilar synchondrosis, 7; left sacroiliac, 6; occipital condylar, 5; visceral fascia, 4; left ilium, 3; diaphragm, 2; and metopic

suture, 2. At the end of the study period, somatic dysfunction prevalence was as follows: L5-S1, 9; left sacroiliac, 3; diaphragm, 3; visceral fascia, 2; and sphenobasilar synchondrosis, 2 (*Table 4*).

During the study, the period prevalence for the following somatic dysfunctions were as follows: L5 through S1, 14; sphenobasilar synchondrosis, 11; left sacroiliac, 10; occiput-mastoid suture, 9; left ilium, 9; diaphragm, 9; interparietal suture, 7; viscera fascia, 6; occiput condyles left, 7, and right, 5; and T12 through L1, 6.

Discussion

The present study demonstrated beneficial effects of OMTh in children with ADHD. The use of OMTh as an adjunct to conventional care was associated with a statistically significant improvement of selective and sustained attentive performances, as measured using the Biancardi-Stroppa Test. On the basis of these results, it is possible to speculate that OMTh might have positive effects on short- and long-term attention in this patient population. These findings are particularly noteworthy considering that the number of participants who were undergoing psychosocial intervention was lower in the intervention group than in the control group, suggesting that the intervention group may have been in less favorable conditions than the control group at baseline. Drug therapy was not associated with changes in Biancardi-Stroppa Test scores.

Because the Biancardi-Stroppa Test was administered the day after the last OMTh session, OMTh could have more than just immediate effects on attentive performances. Limited ADHD research has been conducted in the field of osteopathic medicine; it is therefore difficult to interpret and compare our findings to those of other researchers.

In the last few years, it has been demonstrated that the endocannabinoid system is a key element in the neurophysiologic management of ADHD and that rebalancing the function of the endocannabinoid system should be the target of all therapeutic approaches.[29] McPartland et al[30] proposed that OMT produces a cannabinoid effect. Although McPartland et al studied the use of OMT in an adult population, their results raise the question of a possible cannabimimetic mechanism of the OMTh used in the current study's pediatric population. Additional research is needed to corroborate an endogenous action of OMTh.

Table 2.
Multivariate Linear Regression for Biancardi-Stroppa Modified Bell Cancellation Test—Accuracy

Characteristic	β	95% CI	*P* Value
Age	−0.714	−1.967 to 0.538	.25
Sex	2.689	−2.532 to 7.929	.30
Treatment			
Drug therapy	−0.861	−5.794 to 0.538	.72
Psychosocial intervention	−0.090	−5.860 to 5.680	.97
OMTh	7.948	0.181 to 15.714	.04
Biancardi-Stroppa Modified Bell Cancellation Test—Rapidity	0.387	0.006 to 0.769	.04

Abbreviations: CI, confidence interval; OMTh, osteopathic manipulative therapy.

Table 3.
Multivariate Linear Regression for Biancardi-Stroppa Modified Bell Cancellation Test—Rapidity

Characteristic	β	95% CI	*P* Value
Age	0.652	−0.712 to 2.017	.33
Sex	−0.495	−6.288 to 5.297	.86
Treatment			
Drug therapy	−0.176	−5.516 to 5.163	.95
Psychosocial intervention	−0.992	−7.202 to 5.218	.74
OMTh	9.090	0.821 to 17.358	.03
Biancardi-Stroppa Modified Bell Cancellation Test—Accuracy	0.452	0.007 to 0.896	.05

Abbreviations: CI, confidence interval; OMTh, osteopathic manipulative therapy.

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Table 4.
Somatic Dysfunction Prevalence in Children With Attention-Deficit/Hyperactivity Disorder Before and After Osteopathic Manipulative Therapy (N=14)

Anatomic Region With Somatic Dysfunction	Positive Findings, No.	
	Baseline	End Point
Cranium		
Sphenobasilar synchondrosis	7	2
Occipitomastoid suture	1	1
Lambdoid suture	0	1
Sphenoparietal suture	1	1
Frontal suture	2	0
Left frontozygomatic suture	1	0
Left orbit	1	1
Intersquamous occiput	1	0
Left occipital condyle	3	0
Right occipital condyle	2	0
Ilium		
Left	3	1
Right	1	0
Sacrum		
S4-S5 region	0	1
Lumbosacral spine	9	9
Left sacroiliac joint	6	3
Cervical Region	1	0
Thoracic Region		
T1-T4	0	1
T5-T8	1	1
T9-T12	0	2
T12-L1	1	2
Rib/sternum	1	1
Lumbar Region	1	0
Diaphragm	2	3
Visceral Fascia	4	2

It is interesting to highlight that all participants were found to have L5-S1 dysfunction at least once during the study period. Moreover, sphenobasilar synchondrosis dysfunction was diagnosed in 79% of participants. Regarding the cranial region, the highest period prevalence was for the occiput mastoid suture (64%), the interparietal suture (50%), and occiput condyles (left, 46%; right, 29%). These results seem to confirm data from previous studies,[31] although the heterogeneity of the current study sample limits further comparisons.

Finally, the current study had several limitations. The sample size was small, and because of the lack of previous ADHD studies, we were unable to estimate a sample size based on expected effect before initiating the study. In addition, participants were not blinded and not controlled for other psychosocial and drug treatments. Thus, no detailed data on drug posology and psychosocial intervention were collected. Interexaminer reliability was not formally tested before the start of the investigation. Moreover, the lack of a predetermined treatment protocol reduces the generalizability of the results. Furthermore, the Biancardi-Stroppa Modified Bell Cancellation Test is only validated and used in children in Italy with ADHD; thus, results may not be reproducible in study populations outside of Italy.

Conclusion

Results from the present randomized controlled trial suggest that OMTh can improve selective and sustained attention performances in children with ADHD. Additional explanatory research is needed to confirm and clarify the role of OMTh in the management of ADHD.

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Planning Deficit in Children With Neurofibromatosis Type 1: A Neurocognitive Trait Independent From Attention-Deficit Hyperactivity Disorder (ADHD)?

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Abstract

Neurofibromatosis type 1 is associated with executive dysfunctions and comorbidity with attention-deficit hyperactivity disorder (ADHD) in 30% to 50% of children. This study was designed to clarify the neurocognitive phenotype observed in neurofibromatosis type 1 by testing the hypothesis that children with neurofibromatosis type 1 have specific planning deficits independently from intellectual level and ADHD comorbidity. Eighteen children with neurofibromatosis type 1 were pair-matched to 18 children with ADHD and 18 healthy controls. All groups were assessed on the presence of ADHD symptoms (Conners Scales) and planning deficits (Tower of London). Compared with control group, groups with neurofibromatosis type 1 and ADHD demonstrated significant impairment of planning and problem solving. The lack of correlation between Tower of London results and Conners subscale scores in neurofibromatosis type 1 group confirmed that the planning and problem-solving deficit is not directly related to inattention level. These findings suggested that the executive impairment probably represents a peculiar trait of neurofibromatosis type 1 neurocognitive phenotype.

Keywords

neurofibromatosis type 1, attention-deficit hyperactivity disorder (ADHD), executive functions, planning, Tower of London

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Neurofibromatosis type 1 is an autosomal dominant disorder caused by mutations in the *NF1* gene, characterized by café-au-lait macules, neurofibromas, freckling in the axillary or inguinal regions, optic glioma, Lisch nodules (iris hamartomas), and distinctive osseous lesions.[1] In about 40% to 90% of children with neurofibromatosis type 1, lesions of the brain recognized as unidentified bright objects are commonly observed as areas of increased T2-weighted signal intensity on magnetic resonance imaging (MRI).[2-4] Identification of these lesions is not currently encompassed in the National Institutes of Health (NIH) diagnostic criteria for neurofibromatosis type 1, but their presence has been related to different cognitive and neurobehavioral alterations in these patients.[4-8]

Functional executive deficits and comorbidity with attention-deficit hyperactivity disorder (ADHD), prevalently of the inattentive type, are present in 30% to 50% of neurofibromatosis type 1 children.[5,7-13] In neurofibromatosis type 1, the executive dysfunctions are not necessarily associated with ADHD comorbidity; nevertheless, their role in the pathophysiology of the disorder is still poorly understood.[5,10,12,13]

The majority of studies reported in the literature have compared children with neurofibromatosis type 1 and children with neurofibromatosis type 1 and a *comorbid* diagnosis of ADHD.[5,10,12,13] To our knowledge, no comparison studies between subjects with neurofibromatosis type 1 and subjects with ADHD with no other comorbid diagnoses have been published to date in the scientific literature. To highlight the similarities and differences between executive dysfunctions in

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Table 1. Results of Kruskal-Wallis Test.

	NF1 group (n = 18)	ADHD group (n = 18)	Control group (n = 18)	χ^2	*P*
Age	11.00 ± 2.87	11.17 ± 2.92	11.22 ± 2.80	0.076	.963
IQ	101.61 ± 12.19	104.72 ± 12.47	100.89 ± 8.66	1.157	.561
ToL total score	24.50 ± 3.07	28.39 ± 1.09	31.56 ± 2.41	41.436	.001*
ToL total time	329.22 ± 73.60	250.22 ± 121.91	190.89 ± 35.87	23.226	.001*
Oppositional	53.00 ± 4.16	66.89 ± 7.51	47.44 ± 2.95	42.171	.001*
Inattention	56.83 ± 7.40	74.94 ± 7.22	49.33 ± 3.63	40.041	.001*
Hyperactivity	54.78 ± 3.87	78.39 ± 8.85	48.72 ± 3.41	41.976	.001*
Conners ADHD index	56.33 ± 3.93	81.61 ± 7.08	50.72 ± 2.47	42.942	.001*

Abbreviations: ADHD, attention-deficit hyperactivity disorder; IQ, intelligence quotient; NF1, neurofibromatosis type 1; ToL, Tower of London.
Level of significance *$P < .05$.

neurofibromatosis type 1 and ADHD, we have assessed neurofibromatosis type 1 children *without* ADHD, children with ADHD, and healthy controls, matched for age and sex.

Subjects

The target samples consisted of 18 children with a clinical diagnosis of neurofibromatosis type 1 without ADHD comorbidity (7 males, 11 females; mean age: 11.00 ± 2.87) and 18 children with a diagnosis of ADHD (according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*, criteria, 13 males, 5 females; mean age: 11.17 ± 2.92;) who had been referred to our Neuropsychiatric Unit in the "Tor Vergata" Hospital of Rome for clinical management, and 18 controls matched for age (mean age: 11.22 ± 2.80) and sex (10 males and 8 females). All subjects with neurofibromatosis type 1 and ADHD and their parents have been carefully evaluated by a clinical workup in order to confirm the diagnosis and to exclude differential diagnosis. All neurofibromatosis type 1 patients have been referred to our Unit to take part in a clinical neurofibromatosis type 1 protocol to screen out neurologic and psychiatric involvement, and all included subjects met the diagnostic criteria for the disease (based on criteria of the National Institutes of Health 1988). They did not perform the genetic confirmatory test, which is indicated for individuals in whom Neurofibromatosis type 1 is suspected but do not fulfill the National Institutes of Health criteria.[1]

Selected neurofibromatosis type 1 patients had undergone an accurate neurologic examination, electroencephalographic registrations, and brain magnetic resonance study, and children with central nervous system pathology (ie, optic nerve glioma, brain tumors, epilepsy) and ADHD comorbidity were excluded. Brain magnetic resonance studies revealed the presence of unidentified bright objects in all children with neurofibromatosis type 1 (100%), with different size, number, and brain localization of the lesions. In particular, unidentified bright objects were present in the basal nuclei (88%, 16/18 of neurofibromatosis type 1 patients), thalamus (44%, 8/18 of neurofibromatosis type 1 patients), cerebellum (44%, 8/18 of neurofibromatosis type 1 patients), cerebral peduncles (33%, 6/18 of neurofibromatosis type 1 patients), brain stem (28%, 5/18 of neurofibromatosis type 1 patients), internal capsule (22%, 4/18 of neurofibromatosis type 1 patients), and corpus callosum (11%, 2/18 of neurofibromatosis type 1 patients).

Healthy controls were selected from a pool of volunteers from the local community with a negative familiar history for major psychiatric disorders, according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*, criteria.[14] Those who were not able to complete the tasks because of cognitive or language barriers were not included in this study. Participants of all groups had a total intelligence quotient score in the normal range (mean intelligence quotients: neurofibromatosis type 1 group = 101.61 ± 12.9; ADHD group = 104.72 ± 12.47; control group = 100.89 ± 8.66; see Table 1). All participants have been also selected from families with medium to high level of education, in order to exclude potential influences in the cognitive development of children, and in particular on their executive functions tasks.[15]

All parents and participants were informed of the aim and nature of the study and gave their written consent.

Materials and Procedures

Participants of all groups had a total Intelligence Quotient assessment (Wechsler Intelligence Scales, Italian version WISC-III).[16] The Conners ratings scale for parents (CPRS-R: L) was completed by parents of all 3 groups.[17] The Conners questionnaire contained a subset of questions covering the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*, ADHD symptoms.[14] This subset was used as a symptom checklist in the diagnostic procedure of the disorder. The questionnaire consisted of 3 empirically derived scales: the Inattentive scale, the Hyperactive/Impulsive scale and the Oppositional scale. In addition to these 3 scales, the Conners ADHD Index is included. A *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*, diagnosis was made by combining the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*, symptoms with the Conners scales (T score > 65 in Inattentive and/or Hyperactivity Scales, as well as Conners ADHD Index).[17] According to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised*, criteria, the diagnosis of ADHD would be confirmed if 6 or more symptoms of

Table 2. Results of Mann-Whitney *U* Test for Neurofibromatosis Type 1 and Attention-Deficit Hyperactivity Disorder (ADHD) Groups.

	NF1 group (n = 18)	ADHD group (n = 18)	z	P	d
Age	11.00 ± 2.87	11.17 ± 2.92	−0.113	.910	0.000
IQ	101.61 ± 12.19	104.72 ± 12.47	−0.777	.437	0.250
ToL total score	24.50 ± 3.07	28.39 ± 1.09	−4.622	.001*	2.000
ToL total time	329.22 ± 73.60	250.22 ± 121.91	−3.054	.002*	0.814
Oppositional	53.00 ± 4.16	66.89 ± 7.51	−5.063	.001*	2.364
Inattention	56.83 ± 7.40	74.94 ± 7.22	−4.629	.001*	2.571
Hyperactivity	54.78 ± 3.87	78.39 ± 8.85	−5.135	.001*	4.364
ADHD index	56.33 ± 3.93	81.61 ± 7.08	−5.134	.001*	5.000

Abbreviations: ADHD, attention-deficit hyperactivity disorder; IQ, intelligence quotient; NF1, neurofibromatosis type 1; ToL, Tower of London.
Level of significance (*) $P < .05$.

inattention or hyperactivity-impulsivity were present for at least 6 months with an onset before age 7, and if there was a clear evidence of significant impairment in at least 2 settings (home and school functioning).[14] Only neurofibromatosis type 1 subjects without ADHD comorbid diagnosis (negative Conners scales and psychiatric evaluation) have been enrolled in this study, in order to exclude an influence of ADHD on Tower of London performance.[18,19]

The Tower of London task was administered to all participants of the study. Subjects were required to move beads of different colors between 3 vertical rods of distinct lengths, matching a displayed goal arrangement. Before moving the balls, subjects needed to plan the sequences of moves. An impairment in Tower of London performance could occur either because of the inability to successfully inhibit inappropriate move selections at a specific point of the decisional pathway, or because of a deficit of visuospatial working memory, or a planning deficit.[20] Two different scores have been considered: (1) total score (number of correct responses), a measure of global planning efficiency; (2) total time (elapsed from the first move to the final one), a measure of psychomotor speed. Testing was conducted on an individual basis in a quiet room. On the basis of questionnaire and Tower of London results, all patients with neurofibromatosis type 1 and ADHD and their parents were evaluated by a trained and expert child psychiatrist to confirm the symptomatology.

Statistical Analysis

For statistical analysis, an α level of 0.05 was applied. All analyses were performed using the Statistical Package for Social Sciences (SPSS 14 Inc, Chicago, IL, USA). Data were examined using Kruskal-Wallis test to determine whether significant differences were present among the 3 groups (neurofibromatosis type 1 group, ADHD group, and control group) for 6 variables (Tower of London total score, Tower of London total time, oppositional, inattention, hyperactivity and ConnersADHD index). The Kruskal-Wallis test is a nonparametric method for analysis of variance. When the Kruskal-Wallis test leads to significant results, then at least one of the samples is different from the other samples. Post hoc comparisons of independent samples was performed with Mann-Whitney *U* test. Effect sizes for differences between paired observations were computed. Cohen's *d* was used to calculate the effect size. Cohen's *d* is defined as the difference between 2 means divided by a standard deviation for the data, and is frequently used in estimating sample sizes. Following Cohen's guidelines for interpreting effect sizes, small effects ($d \geq 0.20$), medium effects ($d \geq 0.50$), and large effects ($d \geq 0.8$) were distinguished.[21]

The Kendall rank correlation coefficient, Kendall τ is used to find a correlation between the independent variables (oppositional, inattention, hyperactivity, and Conners ADHD index) and dependent variables (Tower of London total score and Tower of London total time) in the neurofibromatosis type 1 and ADHD groups. The Kendall τ is a nonparametric measure of the statistical dependence among various variables and it is indicative of the strength and direction of the association among various variables measured on at least an ordinal scale.

Results

The comparison of 3 groups using the Kruskal-Wallis test revealed a significant difference among patients with neurofibromatosis type 1, patients with ADHD, and healthy children for Tower of London total score ($\chi^2 = 41.436$; $P = .001$), Tower of London total time ($\chi^2 = 23.226$; $P = .001$), oppositional ($\chi^2 = 42.171$; $P = .001$), inattention ($\chi^2 = 40.041$; $P = .001$), hyperactivity ($\chi^2 = 41.976$; $P = .001$), and Conners ADHD index ($\chi^2 = 42.942$; $P = .001$), but not for age ($\chi^2 = 0.076$; $P = .963$) and intelligence quotient ($\chi^2 = 1.157$; $P = .561$) (see Table 1).

Neurofibromatosis Type 1 Group Versus ADHD Group

We found no significant differences between neurofibromatosis type 1 group and ADHD group matched for age ($z = -0.113$, $P = .910$) and intelligence quotient ($z = -0.777$, $P = .437$). When neurofibromatosis type 1 and ADHD groups were compared using Mann-Whitney test, a significant difference emerged with regard to Tower of London total score ($z = -4.622$, $P = .001$), Tower of London total time ($z = -3.054$, $P = .002$), oppositional ($z = -5.063$, $P = .001$), inattention ($z = -4.629$, $P = .000$), hyperactivity ($z = -5.135$, $P = .001$), and ADHD index ($z = -5.134$, $P = .001$) (see Table 2).

Table 3. Results of Mann-Whitney *U* Test for Neurofibromatosis Type I and Control Groups.

	NFI group (n = 18)	HC group (n = 18)	z	P	d
Age	11.00 ± 2.87	11.22 ± 2.80	−0.276	.782	0.000
IQ	101.61 ± 12.19	100.89 ± 8.66	−0.206	.873	0.100
ToL total score	24.50 ± 3.07	31.56 ± 2.41	−5.155	.001*	2.800
ToL total time	329.22 ± 73.60	190.89 ± 35.87	−4.714	.001*	2.574
Oppositional	53.00 ± 4.16	47.44 ± 2.95	−3.980	.001*	2.000
Inattention	56.83 ± 7.40	49.33 ± 3.61	−3.982	.001*	1.400
Hyperactivity	54.78 ± 3.87	48.72 ± 3.41	−3.826	.001*	2.000
ADHD index	56.33 ± 3.93	50.72 ± 2.47	−4.098	.001*	0.857

Abbreviations: HC, control group; IQ, intelligence quotient; NFI, neurofibromatosis type I; ToL: Tower of London.
Level of significance (*) $P < .05$.

Table 4. Results of Mann-Whitney *U* Test for Attention-Deficit Hyperactivity Disorder (ADHD) and Control Groups.

	ADHD group (n = 18)	HC group (n = 18)	z	P	d
Age	11.17 ± 2.92	11.22 ± 2.80	−0.160	.873	0.000
IQ	104.72 ± 12.47	100.89 ± 8.66	−1.077	.282	0.400
ToL total score	28.39 ± 1.09	31.56 ± 2.41	−4.336	.001*	2.000
ToL total time	250.22 ± 121.91	190.89 ± 35.87	−1.725	.085	0.769
Oppositional	66.89 ± 7.51	47.44 ± 2.95	−5.137	.001*	4.200
Inattention	74.94 ± 7.22	49.33 ± 3.61	−5.137	.001*	5.000
Hyperactivity	78.39 ± 8.85	48.72 ± 3.41	−5.134	.001*	5.455
ADHD index	81.61 ± 7.08	50.72 ± 2.47	−5.139	.001*	6.889

Abbreviations: ADHD, attention-deficit hyperactivity disorder; HC, control group; IQ, intelligence quotient; ToL, Tower of London.
*$P < .05$.

Neurofibromatosis Type I Group Versus Control Group

We also found no significant differences between neurofibromatosis type 1 group and control group matched for age ($z = -0.113$, $P = .910$) and intelligence quotient ($z = -0.276$, $P = .782$). When neurofibromatosis type 1 and control groups were compared using the Mann-Whitney test, a significant difference emerged with regard to Tower of London total score ($z = -5.155$, $P = .001$), Tower of London total time ($z = -4.714$, $P = .002$), oppositional ($z = -3.980$, $P = .001$), inattention ($z = -3.982$, $P = .001$), hyperactivity ($z = -3.826$, $P = .001$), and ADHD index ($z = -4.098$, $P = .001$) (see Table 3).

ADHD Group Versus Control Group

We found no significant differences between ADHD group and control group matched for age ($z = -0.160$, $P = .873$) and intelligence quotient ($z = -1.077$, $P = .282$). When ADHD and control groups were compared using the Mann-Whitney test, a significant difference emerged with regard to Tower of London total score ($z = -4.336$, $P = .001$), oppositional ($z = -5.137$, $P = .001$), inattention ($z = -5.137$, $P = .001$), hyperactivity ($z = -5.134$, $P = .001$) and ADHD index ($z = -5.139$, $P = .001$), but not with regard to Tower of London total time ($z = -1.725$, $P = .085$) (see Table 4).

Neurofibromatosis Type I Group

The correlation analysis according to Kendall did not show a significant correlation between oppositional and Tower of London total score ($\tau = -0.111$, $P = .552$), between inattention and Tower of London total score ($\tau = 0.118$, $P = .526$), between hyperactivity and Tower of London total score ($\tau = 0.030$, $P = .874$), and between Conners ADHD index and Tower of London total score ($\tau = 0.118$, $P = .527$). The Kendall test did not show a significant correlation between oppositional and Tower of London total time ($\tau = 0.410$, $P = .818$), between inattention and Tower of London total time ($\tau = -0.074$, $P = .674$), between hyperactivity and Tower of London total time ($\tau = -0.082$, $P = .646$), and between Conners ADHD index and Tower of London total time ($\tau = -0.081$, $P = .647$) (see Table 5).

ADHD Group

The correlation analysis according to Kendall did not show a significant correlation between oppositional and Tower of London total score ($\tau = 0.321$, $P = .950$), between inattention and Tower of London total score ($\tau = -0.198$, $P = .309$), between hyperactivity and Tower of London total score ($\tau = -0.062$, $P = .746$) and between Conners ADHD index and Tower of London total score ($\tau = -0.156$, $P = .417$). The Kendall test showed a significant correlation between inattention and

Table 5. Results of Correlation Analysis According to Kendall for Neurofibromatosis type 1Group.

	ToL total score *T*	*P*	ToL total time τ	*P*
Oppositional	−0.111	.552	0.410	.818
Inattention	0.118	.526	−0.074	.674
Hyperactivity	0.030	.874	−0.082	.646
Conners ADHD index	0.118	.527	−0.081	.647

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ToL, Tower of London.
Correlation is significant at the 0.05 level.

Table 6. Results of Correlation Analysis According to Kendall for Attention-Deficit Hyperactivity Disorder (ADHD) Group.

	ToL total score *T*	*P*	ToL total time τ	*P*
Oppositional	0.321	.950	−0.293	.099
Inattention	−0.198	.309	0.454*	.011*
Hyperactivity	−0.062	.746	0.109	.540
Conners ADHD index	−0.156	.417	0.176	.320

Abbreviation: ADHD, attention-deficit hyperactivity disorder; ToL, Tower of London.
Correlation is significant at the 0.05 level.
*$P < .05$.

Tower of London total time ($\tau = 0.454, P = .011$) but not between oppositional and Tower of London total time ($\tau = -0.293$, $P = .099$), between hyperactivity and Tower of London total time ($\tau = 0.109$, $P = .540$), and between Conners ADHD index and Tower of London total time ($\tau = 0.176, P = .320$) (see Table 6).

Discussion

Executive functions refer to a number of interrelated cognitive and behavioral skills that are responsible for purposeful, goal-directed behaviors, including planning/organization, cognitive flexibility, abstract concept formation, and impulse control.[22]

Difficulty in executive functions is a core symptom of ADHD, a neurobehavioral condition characterized by nonadaptive levels of sustained attention, impulsiveness, and hyperactivity. In particular, the Tower of London task, a measure of executive planning and problem solving, has been showed to be impaired in ADHD children.[18,19]

ADHD, prevalently of inattentive type, has a significantly higher prevalence in neurofibromatosis type 1 patients (30%-50%)[11] compared to worldwide children (about 3%-8%).[23] In a recent study, spatial working and response inhibition tasks have been administered to children with neurofibromatosis type 1 with or without comorbid ADHD and typically developing controls. The results show that executive dysfunction can represent a "core feature" of neurofibromatosis type 1 phenotype and that a comorbid diagnosis of ADHD does not exacerbate its severity.[5]

However, to our knowledge, the presence of ADHD symptoms has been prevalently investigated in subjects with neurofibromatosis type 1 without comparison with other populations of patients. Moreover, in a large percentage of studies, patients with neurofibromatosis type 1 *also* had a comorbid diagnosis of ADHD, and their neurocognitive features have been compared with children with a diagnosis of neurofibromatosis type 1 without ADHD.[5,6,10,12,24] An empirical demonstration of the ways in which different aspects of executive performances correlate in neurofibromatosis type 1, in ADHD and in normal population, should be of additional benefit. In order to define the characteristics of planning/organization impairments in these samples, we have compared neurofibromatosis type 1 children *without* ADHD, children with "pure" ADHD (without neurofibromatosis type 1 or other comorbidities) and healthy controls, matched for age and sex. No noteworthy differences in intellectual function have been observed among all groups. Interestingly, in our neurofibromatosis type 1 group, the mean intelligence quotient value was higher than reported in the literature.[8] These data could hypothetically relate to the absence of neurologic and psychiatric comorbidities in our neurofibromatosis type 1 sample, or to the medium-high parental-level education.[15,25]

We have found higher scores of ADHD symptoms on Conners subscales in both neurofibromatosis type 1 and ADHD groups than controls. Moreover, both neurofibromatosis type 1 and ADHD groups performed a poor Tower of London task compared to their peers. In ADHD children, in whom the Tower of London task was very compromised, we also found a significant correlation between Tower of London total time and Inattention scores of Conners scale.[17] On the other hand, these findings have not been observed in our neurofibromatosis type 1 sample, suggesting that the poor performance obtained by neurofibromatosis type 1 children on the Tower of London task is not directly related to inattention or intelligence quotient level but can represent an intrinsic and specific neurocognitive feature of neurofibromatosis type 1. However, neurofibromatosis type 1 group's Conners scores appear to be mildly higher than controls (but not significantly so), demonstrating that a slight quota of inattention is typical of neurofibromatosis type 1 phenotype.

The cause of this neurofibromatosis type 1 cognitive phenotype is still unknown. It should be directly related to *NF1* gene dysfunctions, as suggested in a recent study.[25] Neurofibromin regulates prefrontal and striatal inhibitory networks, specifically activity-dependent γ-aminobutyric acid (GABA) release, and is required for working memory performances. $NF1^{+/-}$ mice displayed inhibition-dependent working memory deficits, and brain functional magnetic resonance studies in humans with neurofibromatosis type 1 revealed hypoactivation of corticostriatal networks.[6,26] On the other hand, all our neurofibromatosis type 1 sample showed the presence of unidentified bright objects in different brain areas. It has been demonstrated that neurofibromatosis type 1 children carrying unidentified bright objects in the thalamic-striatal pathway showed significantly lower intelligence quotients and visuospatial deficits than neurofibromatosis type 1 patients without unidentified bright objects in this location.[4] Moreover, diffusion tensor magnetic resonance imaging confirms the influence of unidentified bright objects in the decreased white matter fractional anisotropy values in these patients,[27] which persisted over time despite the disappearance or reduction of unidentified bright objects.[28] These microstructural abnormalities in white matter tracts should result in a "cerebral disconnection" even in some of the brain regions that appear normal in conventional magnetic resonance sequences. This can justify the planning deficits observed in our neurofibromatosis type 1 patients.

A limitation of our study is the small neurofibromatosis type 1 sample size, because of the restricted selection criteria in comparison with other published studies (ie, exclusion of ADHD, normal intelligence quotient, absence of neurologic impairment). Aside from this limitation, the severity of inclusion criteria assures the reliability of our findings. Further studies are needed to confirm our results; however, some clinical implications can already be drawn from our work. Our findings confirm the necessity of executive functions investigation in pediatric patients with neurofibromatosis type 1, also when ADHD has been excluded, emphasizing the need for a precocious, patient-specific neurocognitive counseling and/or management in this population.

Author Contributions

CG and AP evaluated the neurologic and psychiatric aspects of all participants. PC proposed and designed the study and revised the final draft. AL-C drew the first draft and reviewed relevant articles on the literature with the assistance and contribution of LDC, EDA, and MBP. All authors contributed to the intellectual content and approved the final version.

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Prevalence of ADHD in a sample of Italian students: A population-based study

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common diagnosis for children and adolescents, although the reported estimates for prevalence are extremely variable worldwide. In the present work we investigate the prevalence of ADHD in a sample of Italian students in a study divided in two phases. In Phase I, a total of 6183 schoolchildren (3178 males and 3005 females, aged range 5–15 years) were screened using the SDAI rating scale for teachers. In Phase II, the parents of children and adolescents who met high screen criteria according to SDAI (cut-off > 14; $n = 471$, 7.3%) were invited to complete a specific clinical-diagnostic assessment for ADHD with the help of an experienced clinician. Within the entire sample, 107 children dropped out and 12 had mental retardation, whereas 332 subjects (278 males and 54 females, age range 5–14 years) completed the Phase II of the study. One hundred ninety subjects (163 males and 27 females, male: female ratio 6:1, mean age 8 years) were diagnosed with ADHD, indicating a prevalence of 3%. ADHD subtypes included the following: combined ($n = 108$; 56.8%), inattentive ($n = 48$; 25.2%) and hyperactive/impulsive ($n = 33$; 17.3%).

Our findings are in line with other reports of ADHD prevalence in the European Countries, and may contribute to underline the impact of this phenomenon in the population, and the need of achieving an improvement in the quality of the public health mental service for the prevention and treatment of ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common diagnosis worldwide for children and adolescents and, according to DSM-IV-TR, it is characterized by pervasive and impairing symptoms of inattention, hyperactivity and impulsivity (APA, 2000; Biederman & Faraone, 2005; Swanson et al., 1998). ADHD comprises a broad spectrum of clinical manifestations highly heterogeneous in terms of presence and level of symptoms. Longitudinal studies showed that ADHD is not restricted to childhood and adolescence, but it tends to persist also in adulthood, although with

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variable rates across the lifespan (Biederman et al., 2000, 2006; Cahill et al., 2012; Hill & Schoener, 1996; Simon, Czobor, & Bitter, 2012).

Studies published so far, have reported highly variable rates for ADHD prevalence worldwide during childhood and adolescence, ranging from 0.9% to 20%, raising concerns about the consistency of estimates and the validity of diagnoses (Bener, Qahtani, & Abdelaal, 2006; Cardo, Servera, & Llobera-Canaves, 2007; Cornejo et al., 2005; de la Barra, Vicente, Saldivia, & Melipillan, 2012; Goodman et al., 2005; Harzke et al., 2012; Montiel, Pen, Montiel-Barbero, & Polanczyk, 2008; Skounti, Philalithis, & Galanakis, 2007; Skounti, Philalithis, Mpitzaraki, Vamvoukas, & Galanakis, 2006; Wolraich et al., 2012). Overall, the reported rates for ADHD prevalence are lower for Europe as compared to North America, and this brought many authors to hypothesize that the ADHD may be typical of the western countries as a result of some demographic characteristics (Anderson, 1996; Bird, 2002; Timimi & Taylor, 2004). However, it has to be pointed out that all the studies have applied different methodologies, including rating scales and checklists, as well as diagnostic interviews, and this may represent another possible explanation for these discrepancies (Faraone, Sergeant, Gillberg, & Biederman, 2003; Swanson et al., 1998; Timimi, 2005). Indeed, this variability would likely disappear by applying similar instruments, as suggested by a review study on epidemiology of ADHD across the lifespan showing similar estimates for North America and Europe upon adjustment for methodological issues (5.29%) (Polanczyk & Rohde, 2007). From other studies, an incidence of ADHD, ranging from 5.29% to 7.5%, was found in different socio-cultural settings, such as Switzerland, Brazil, England, Holland, Venezuela, Taiwan, and Congo (Ford, Goodman, & Meltzer, 2003; Gau, Chong, Chen, & Cheng, 2005; Kashala, Tylleskar, Elgen, Kayembe, & Sommerfelt, 2005; Rohde et al., 1999; Steinhausen, Metzke, Meier, & Kannenberg, 1998).

To our knowledge, only three studies so far were conducted in Italy, reporting variable prevalence rates (Frigerio et al., 2009, 2006; Mugnaini et al., 2006). Specifically, Mugnaini et al. (2006), evaluating 1891 first-graders, aged 6.6–7.4 years, throughout teacher rating scales and without a specific clinical-diagnostic assessment for ADHD, reported an ADHD rate of 7.1%. On the other hand, Frigerio et al. (2009), in the preadolescent mental health project (PrISMA), evaluated 3418 adolescents, aged 10–14 years, throughout parents rating scales for the prevalence of mental disorders at large, and estimated a much lower rate of externalizing disorders (1.2%).

Studies in children consistently suggest that the ADHD prevalence is higher in boys than in girls with a male to female ratio from 3:1 to 9:1, depending on the origin of the sample ascertainment: indeed, the prevalence in girls seems to be higher in community samples than in clinical samples (Staller & Faraone, 2006). The impact of ethnic and socio-economic issues on the ADHD prevalence rates has not been extensively addressed.

ADHD can often be found in comorbidity with other psychiatric disorders. Indeed, a recent study on the prevalence of psychiatric disorders in young children, showed that 12.5% of 4-years-olds had at least one psychiatric disorder, and that when a child had an ADHD, an oppositional defiant disorder, a conduct disorder or a depressive disorder, it was more likely than not that she or he had another emotional or behavioral disorder in comorbidity (Wichstrom et al., 2011).

Finally, an epidemiological study on pharmacologically treated ADHD children, adolescents and adults in the UK, revealed a trend of increasing prescription of ADHD treatment drugs over the period 2003–2008 for all age groups, further highlighting the urgent need to deeply investigate the prevalence of this disorder in order to plan appropriate treatment strategies (McCarthy et al., 2012).

The aim of the present study was to investigate ADHD prevalence in a sample of Italian students, at first, by using a screening for attention deficit and hyperactivity/impulsivity symptoms completed by teachers, and afterwards, by applying a more specific clinical-diagnostic assessment for ADHD, completed by children, parents and teachers with the help of an experienced clinician.

2. Materials and methods

2.1. Sampling population of Phase I

During Phase I of the study, children attending primary and middle schools were submitted to a screening for attention deficit and hyperactivity/impulsivity symptoms. All elementary and middle schools (36 schools for 9151 children) in the urban area of Syracuse (Italy) were asked to participate. Out of them, 24 schools agreed to the study, whereas 12 schools (6 elementary and 6 middle) did not participate: a total of 6183 schoolchildren (3178 males and 3005 females, age range 5–15 years) were, therefore, included in the study. The informed consent, during Phase I, was not required because the primary aim of this phase was to assess the health status of the population.

2.2. Phase I: screening for attention deficit and hyperactivity/impulsivity symptoms

For every schoolchild, the teachers were asked to fill out the "*SDAI*" *Rating Scale* (*ADHD Rating Scale for Teachers* [*Scala per i Disturbi di Attenzione/Iperattività per Insegnanti*]), for the presence of ADHD symptoms (Cornoldi, Gardinale, Masi, & Pattenò, 1996; Cornoldi & Marzocchi, 2000). The *SDAI* is a 18-item four-point Likert scale, requiring the teacher to rate the child frequency/intensity of symptoms (from 0 = no problem to 3 = severe problem). The *SDAI* includes three subscales: one for Inattentive symptoms, one for Hyperactive/Impulsive symptoms, and one for Inattention and Hyperactive Combined symptoms. Conventionally, a score above 14, with a mean score of 1.5, for the three subscales, indicates a high presence of symptoms. The *SDAI* scale has been validated and standardized for the Italian population and shows an interrater reliability

of 0.80 and 0.74, for the Inattentive subscale and the Hyperactive/Impulsive subscale, respectively. The test–retest reliability is 0.83 and 0.81, for Inattentive and Hyperactive/Impulsive, respectively (Comoldi & Marzocchi, 2000).

Data from teachers were used to identify the subjects eligible for Phase II of the study: children resulting above the cut-off (>14) for ADHD symptoms, as evaluated by *SDAI*, were classified as "high screen" and included in Phase II.

2.3. Sampling procedure of Phase II

The school staff contacted the families whose children were categorized as "high screen" (*SDAI* cut-off >14), and requested a written informed consent to participate in the study. Families who returned their permission to participate in the study ($n = 451$) were invited to take part into the clinical-diagnostic phase (Phase II) at the Child and Adolescent Psychiatric Unit of Syracuse, where children, parents and teachers completed a clinical-diagnostic assessment for ADHD symptoms with an experienced clinician. This assessment started on September 2010 and ended on December 2011. A total of 332 children (73.6% of those invited) participated in Phase II. A flow-chart describing the recruitment procedure and the participation rates is depicted in Fig. 1.

2.4. Phase II: clinical-diagnostic assessment to evaluate the presence of Attention-deficit/hyperactivity disorder (ADHD)

The Schedule for Affective Disorders and Schizophrenia for School-Age Children/Present and Lifetime Version (*K-SADS-PL*) was completed by all the children and parents included in the study with an experienced trained clinician (Kaufman et al., 1997). The *K-SADS-PL* is a semi-structured psychiatric interview that ascertains both lifetime and current diagnostic status based on DSM-IV-TR criteria (APA, 2000). The *K-SADS-PL* includes three components: introductory interview (demographic, health, and other background information), screen interview (82 symptoms related to 20 diagnostic areas), and five diagnostic supplements including affective disorders (major depression, dysthymia, mania, hypomania), psychotic disorders, anxiety disorders (social phobia, agoraphobia, specific phobia, obsessive-compulsive disorder, separation anxiety disorder, generalized anxiety disorder, panic disorder, post-traumatic stress disorder), disruptive behavioral disorders (attention deficit and hyperactivity disorder, conduct disorder, oppositional defiant disorder),substance abuse, and other disorders (tic disorders, eating disorders, and elimination disorders). The skip-out criteria in the screen interview specify which sections of the supplements, if any, should be completed. The Italian version of this tool has been shown to have good psychometric properties, as demonstrated by an excellent interrater reliability of 0.80, for the age group between 6 and 17 years. Indeed, a recent study (Birmaher et al., 2009) have established the psychometric properties of the *K-SADS-PL* in preschool children (aged 2–5 years,) reporting an excellent discriminant validity (a p-value ≤ 0.02 for ADHD), and an excellent internal consistency of Cronbach's α ranging between 0.80 and 0.90.

The Swanson, Nolan and Pelham Scale-Version IV (*SNAP-IV*) was completed by teachers and parents (Bussing et al., 2008; Swanson et al., 2001). This is a 26-item questionnaire, in a 4-point Likert scale, that is used to evaluate ADHD symptoms and severity. The 26 items include 18 items for ADHD symptoms (9 for Inattentive, 9 for Hyperactive/Impulsive), and 8 items for

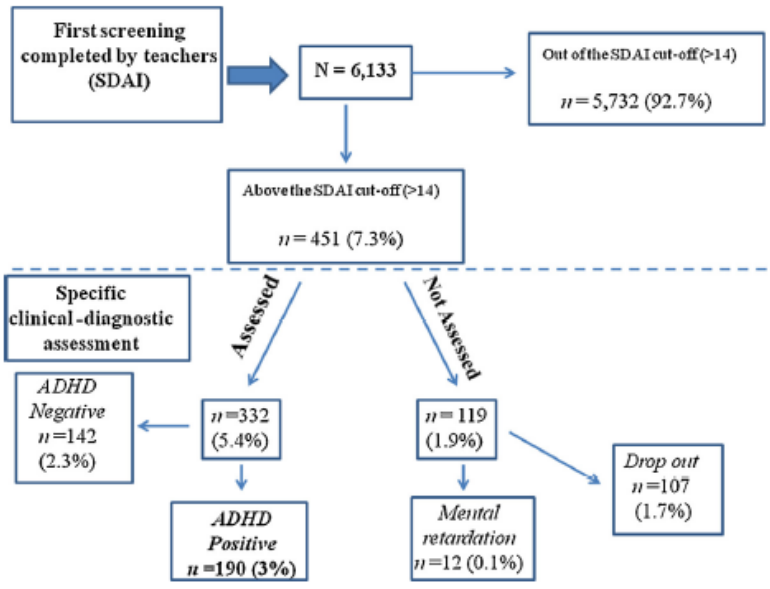

Fig. 1. Recruitment procedure and participation rates.

oppositional defiant disorder (ODD) symptoms, as defined in the DSM-IV-TR. Each item is rated on a 0–3 score scale (0 = not at all, 1 = just a little, 2 = quite a bit and 3 = very much). The *SNAP-IV* consists of the Inattention, Hyperactive/Impulsive, Inattention and Hyperactive/Impulsive Combined, and Oppositional subscales. Each subscale has a different cut-off score that can be considered indicative of clinical impairment: 1.78 for Inattention subscale, 1.44 for Hyperactive/Impulsive subscale, 1.67 for Inattention and Hyperactive/Impulsive Combined, and 1.88 for Oppositional Defiant Disorder. The *SNAP-IV* has been shown to have a good internal consistency for all domains (Inattentive: $\alpha = 0.88–0.89$, Hyperactive/Impulsive: $\alpha = 0.76–0.80$, and Oppositional Defiant Disorder: $\alpha = 0.87–0.90$) (Bussing et al., 2008).

All the subjects were examined by an experienced clinician, and the diagnoses of ADHD were established following the three different definitions of impairment, as stated in the DSM-IV-TR criteria (APA, 2000).

Moreover, all the children were assessed for cognitive function by the Italian validated version of *Wechsler Intelligence Scale for Children-III* (*WISC-III*) (Orsini & Picone, 1995; Wechsler, Golombok, & Rust, 1992). The *WISC–III* comprises 10 subtests (5 verbal and 5 performance subtests) that sum to the Verbal Intelligence Quotient and Performance Intelligence Quotient, and produce a Full-Scale Intelligence Quotient. Scores were age standardized according to the Italian validated version of the *WISC-III* manual.

Finally, to evaluate the presence of comorbidity with a Specific Learning Disorder, the children were assessed with the *Battery for Evaluating Dyslexia and Dysorthography* (*DDE*), and the *M.T. reading test* (Cornoldi & Colpo, 1998; Sartori, Job, & Tressoldi, 1995). The *DDE* comprises 12 tests (9 to evaluate reading abilities and 3 to assess writings abilities). On each test, the examiner should note reading accuracy, determined by the number of correctly decoded words, and test execution speed, measured by the relationship between the total number of syllables read and total time in seconds. The *M.T. reading test* is a text, varying for each grade and phase of the scholastic year (initial, middle and final), that the participants are asked to read. Errors made and time needed to read the entire text are taken into account. For each text, normative data, means, standard deviations, and percentiles were provided.

2.5. Data analysis

The data were analyzed using the statistical software package SPSS, Version 16.0. Descriptive analyses were used, and variables are presented as either mean ± standard deviation (SD), or frequency. Prevalence rates were calculated on the total number of children assessed. An interrater reliability analysis using the Kappa statistic was performed to determine consistency among DSM-IV-TR criteria and *K-SADS-PL* diagnoses. Group comparisons (ADHD versus non-ADHD) were conducted using chi-square test for categorical variables (gender), and analysis of covariance (ANCOVA) for continuous variables (age and IQ). For binary variables the effect size is provided as odds ratio, whereas for continuous or discrete variables as difference between means. The degree of uncertainty around each effect size is provided in terms of 95% confidence interval. Comparisons within the ADHD group for categorical variables were performed using chi-square tests. An alpha level of 0.05 was set for statistical significance.

3. Results

3.1. Phase I: screening for attention deficit and hyperactivity/impulsivity symptoms

The teachers completed the *SDAI* for a total of 6183 Caucasian schoolchildren (age range 5–15 years, mean age 8.9 years), 3178 of whom were males (51.4%) and 3005 females (48.6%). Three thousand, seven hundred and thirty-two children resulted out of the *SDAI* cut-off (>14), whereas 451 children, corresponding to 7.3% of total, were above the cut-off (mean age 8.3 years, age range from 5 to 14 years). Among them, 356 were males (78.9%), and 95 were females (21.0%), and 55 (12.7% of the 451 children) benefitted from a scholastic support. In more detail, the *SDAI* results for these 451 children showed that 248 of them (204 males and 44 females) were above the cut-off for "Inattentive and Hyperactive/Impulsive Combined symptoms" (54.9%), 162 (127 males and 35 females) for "Inattentive symptoms" (35.9%), and 41 (25 males and 16 females) for "Hyperactive/Impulsive symptoms" (9.0%). None of the participants had ever used any psychotropic medication at the time of the study. The demographic characteristics of the children included in the survey are summarized in Table 1.

Table 1
Demographic characteristics of the total sample.

Groups	Total screened schoolchildren ($N = 6183$[a])	Schoolchildren above the SDAI[b] cut-off ($N = 451$)
Gender		
Males *N* (%)	3178 (51.4)	356 (78.9)
Females *N* (%)	3005 (48.6)	95 (21.0)
Age range (mean)	5–15 (8.9)	8–14 (8.3)

[a] Number of subjects.
[b] ADHD rating scale for teachers.

Table 2
Comparisons of demographic characteristics of children with ADHD versus children without ADHD.

Groups	ADHD children (N = 190[a])	Non-ADHD children (N = 142)	p	Effect size
Gender			NS[b]	
Males N (%)	163 (85.7)	115 (80.9)		1.42 (0.79–2.54)[c]
Females N (%)	27 (14.2)	27 (19.0)		0.71 (0.39–1.27)
Age (mean ± SD[d])	8.0 ± 2.30	8.1 ± 2.14	NS	−0.10 (−0.59;0.39)[e]
IQ[f] (mean ± SD)	87.54 ± 9.59	88.16 ± 9.43	NS	−0.62 (−2.70;1.46)

[a] Number of subjects.
[b] Not significant for $p > 0.05$.
[c] For binary variables the effect size (ADHD versus non-ADHD children) is provided as odds ratio and 95% confidence interval.
[d] Standard deviation.
[e] For continuous variables the effect size is given as difference between means and 95% confidence interval of the corresponding point estimate.
[f] Intelligence quotient.

3.2. Phase II: clinical-diagnostic assessment to evaluate the presence of Attention-deficit/hyperactivity disorder (ADHD)

Among the 451 children and adolescents that scored above the cut-off for *SDAI* symptoms, 332 subjects (278 males and 54 females, age range 5–14 years, mean age 8.4 years) were submitted to the specific clinical-diagnostic assessment for ADHD, whereas 119 were excluded, either because they dropped out (n = 107), or had a mental retardation (n = 12, Full-Scale IQ <70 assessed with *WISC-III*). All the subjects were evaluated by an experienced children and adolescents psychiatrist according to DSM-IV-TR ADHD criteria. Moreover, all the parents and children completed the *K-SADS-PL* with a trained clinician. An interrater reliability analysis using the Kappa statistic was performed to determine consistency among DSM-IV-TR criteria and *K-SADS-PL* diagnoses, returning an almost perfect agreement (Kappa = 0.913, $p < 0.001$). Finally, ADHD diagnosis was considered completed by symptoms positivity in the *SNAP-IV* teachers and parents version.

One hundred ninety subjects out of the 332 tested (163 males and 27 females, with a male: female ratio of 6:1, mean age of 8 years) resulted positive for ADHD, corresponding to a prevalence of 3%. ADHD subtypes included the following: combined (n = 108; 56.8%); inattentive (n = 48; 25.2%); hyperactive/impulsive (n = 33; 17.3%).

Gender (X^2:3.742, p = 0.293), age (F: .718, p = 0.709) and IQ (F: 2.328, p = 0.554) distribution were similar between children with (n = 190) and without (n = 142) diagnosis of ADHD (Table 2). Accordingly, analysis carried out by calculating the effect size showed that the 95% confidence interval of each point estimates, crossed one for binary variables and zero for continuous or discrete variables, indicating no significant associations between gender, age, IQ, and the presence/absence of ADHD diagnosis (Table 2).

Analysis of comorbidities revealed that 143 children (75.2%) affected by ADHD had a comorbidity with one other disorder, In more detail, the following disorders were found in comorbidity: Oppositional Defiant Disorder (n = 42), Specific Learning Disorder (n = 36), Conduct Disorder (n = 22), Generalized Anxiety Disorder (n = 17), Depressive Disorder (n = 9), a different comorbid diagnosis (such as Tourette Syndrome, Tic Disorders, Eating Disorder and Enuresis) (n = 17). Moreover, of these 143 children, 47 (24.7%) had two comorbid disorders. Specifically: Oppositional Defiant Disorder (n = 20), Specific Learning Disorder (n = 10), Generalized Anxiety Disorder (n = 4), a different comorbid diagnosis (such as Tourette Syndrome, Tic Disorders, Eating Disorder and Enuresis) (n = 13).

No significant differences were found between ADHD males (n = 163) and females (n = 27) according to age, IQ, ADHD subtypes, comorbidity, *SDAI* subscales, *SNAP-IV* Parents and Teachers version. The clinical characteristics of the subjects with ADHD are shown in Table 3.

4. Discussion

Epidemiological studies on ADHD prevalence during childhood and adolescence have reported highly variable rates worldwide, ranging from 0.9% to 20% (Bener et al., 2006; Cardo et al., 2007; Cornejo et al., 2005; de la Barra et al., 2012; Goodman et al., 2005; Harzke et al., 2012; Montiel et al., 2008; Skounti et al., 2007, 2006; Wolraich et al., 2012). In our sample, 3% of the screened children and adolescents met the criteria for ADHD, indicating a slightly lower rate as compared to the ADHD worldwide pooled prevalence of 5.29% (Faraone et al., 2003; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). However, our results are in line with other epidemiological reports investigating the prevalence of ADHD in Europe, which is generally lower than in North America (Faraone et al., 2003; Polanczyk et al., 2007). The DSM-IV-TR reports that ADHD prevalence rates vary from 3% to 5%, whereas studies based on the ADHD DSM-IV-TR criteria report a proportion of children affected by ADHD ranging from 3.7% to 8.9%, with lower rates when applying a more rigorous impairment criterion (APA, 2000; Baumgaertel, Wolraich, & Dietrich, 1995; Canino et al., 2004; Wolraich, Hannah, Pinnock, Baumgaertel, & Brown, 1996). Moreover, ADHD prevalence seems to depend on the source evaluating the symptoms (Breton et al., 1999; Magnusson, Smari, Gretarsdottir, & Prandardottir, 1999; Stanger & Lewis, 1993). For instance, Breton et al. (1999) reported estimate rates varying from 3.3% to 5% and 8.9%, according to children's, parents', and teachers' reports, respectively. In our study, diagnosis of ADHD required the three different definitions of impairment, as stated in the DSM-IV-TR. Furthermore, to be in receipt of an ADHD diagnosis, different tools, such as *K-SADS-PL*, and *SNAP-IV*, completed by different sources (children,

Table 3
Distribution of ADHD subtypes, comorbidity and clinical characteristics of the ADHD group.

	Males (N = 163[a])	Females (N = 27)	Total (N = 190)
IQ[b] (mean ± SD)	87.82 ± 9.62	85.89 ± 9.44	87.54 ± 9.59
Subtypes of ADHD			
Inattentive N (%)	38 (20.0)	11 (5.8)	49 (25.8)
Hyperactive/Impulsive N (%)	27 (14.2)	6 (3.2)	33 (17.4)
Combined N (%)	98 (51.6)	10 (5.3)	108 (56.8)
SDAI[c] subscales			
Inattentive (mean ± SD)[d]	19.87 ± 5.49	18.89 ± 4.72	19.73 ± 5.39
Hyperactive/Impulsive (mean ± SD)	16.82 ± 6.92	13.67 ± 8.37	16.37 ± 7.20
Combined (mean ± SD)	36.68 ± 9.19	32.56 ± 9.27	36.09 ± 9.29
SNAP-IV-parents[e] subscales			
Inattentive (mean ± SD)	2.03 ± 0.50	2.04 ± 0.39	2.03 ± 0.49
Hyperactive/Impulsive (mean ± SD)	1.88 ± 0.62	1.67 ± 0.69	1.85 ± 0.63
Combined (mean ± SD)	3.91 ± 0.74	3.71 ± 0.68	3.88 ± 0.73
SNAP-IV-teachers[f] subscales			
Inattentive (mean ± SD)	2.48 ± 0.48	2.47 ± 0.32	2.48 ± 0.46
Hyperactive/Impulsive (mean ± SD)	1.77 ± 0.61	1.54 ± 0.72	1.74 ± 0.63
Combined (mean ± SD)	4.26 ± 9.19	4.02 ± 0.67	4.22 ± 0.72

[a] Number of subjects.
[b] Intelligence quotient.
[c] SDAI-ADHD rating scale for teachers.
[d] Standard deviation.
[e] Swanson, Nolan and Pelham Scale-Version IV for parents.
[f] Swanson, Nolan and Pelham Scale-Version IV for teachers.

parents and teachers) had to result positive for ADHD symptoms all at once. Therefore, the lower prevalence that we found in our sample could be due to the rigorous exclusionary methodology.

To our knowledge, our study is the first epidemiological survey on ADHD in a large sample of Italian children and adolescents. The preadolescent mental health project (PrISMA), described by Frigerio et al. (2009) evaluated adolescents for the prevalence of mental disorders in general, and Mugnaini et al. (2006), reporting an ADHD prevalence of 7.1%, applied only teachers' reports, without a specific clinical-diagnostic assessment for ADHD. Indeed, this percentage is similar to the rate that we found by teachers' reports in the first phase of our study (7.3%) (Frigerio et al., 2009, 2006; Mugnaini et al., 2006).

Moreover, these surveys were carried out in the North of Italy, whereas the children included in our study were attending schools in the South (Sicily), indicating that there may be dissimilarities also according to cultural and geographical differences.

The results reported in our study are in line with those by other studies, in terms of prevalence of ADHD subtypes (combined more frequent, and hyperactive/impulsive less frequent), gender ratio (6:1), and presence of a comorbid internalizing or externalizing disorder (Baumgaertel et al., 1995; Biederman et al., 2002; Ersan, Dogan, Dogan, & Somer, 2004; Frigerio et al., 2006; Gomez, Harvey, Quick, Scharer, & Harris, 1999; Graetz, Sawyer, Hazell, Arney, & Baghurst, 2001; Kashala et al., 2005; Staller & Faraone, 2006; Timimi, 2005; Wolraich et al., 1996; Wolraich, Hannah, Baumgaertel, & Feurer, 1998).

Our findings have to be interpreted in light of certain limitations. First, we did not analyze the negative predictive value of the screening test used, which could have been evaluated by including in Phase II of the study a certain number of children that had scored negatively on *SDAI* within Phase I. Second, children from only one region of the country were included. Third, participant selection was conducted throughout schools, rather than public registers, due to the Italian personal data privacy law, which not allow public registers to be viewed (DL 30 July 1999, n. 281 and 282), and fourth, socio-economic status and parental education variables were not considered, although the schools included in the study represented areas of both high and low socio-economic status.

5. Conclusion

In conclusion, besides to these limitations, our study has added a new insight into the existing knowledge on ADHD prevalence, documenting the rates of a European country for which these data were missing. Shed light on the epidemiology of ADHD is a fundamental issue for researchers in order to better define methodological and conceptual problems that need to be further addressed. Moreover, these results underline the importance of applying a screening methodology in the school context that could easily be applied to other mental disorders and the need of developing a thorough assessment. Finally, understanding the impact of ADHD in the general population, may also help the clinicians to develop an adequate service, in terms of both psychological screening, and treatment procedure, and possibly to prevent the onset of other disorders in comorbidity during lifespan.

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