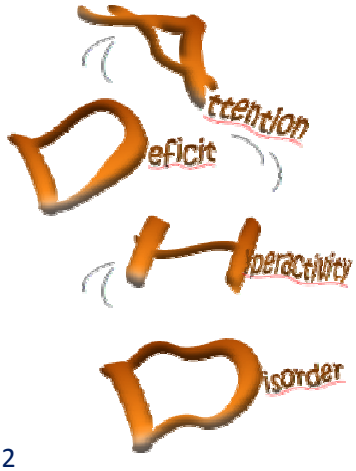
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD NOVEMBRE 2013

Acta Neuropsychol. 2013;11:181-91.

EMOTIONAL TENSION IN STRESSFUL SITUATIONS AS A MEDIATOR OF THE COMORBIDITY OF CONDUCT DISORDER IN YOUTH WITH ADHD.

Marcinkowska J, Lipowska M, Szczuka Z.

Background: Research has shown that ADHD often co-occurs with ODD and CD, especially the impulsive subtype of ADHD. Excessive impulsiveness involves not only disordered inhibition, but also difficulties with emotional control. Situations with increased emotional tension provoke behaviors intended to reduce the tension, such as aggressiveness, which can be interpreted as CD. Our research was intended to examine the specific characteristics of how youth with ADHD react to stressful situations and their emotional consequences.

Material/Methods: We examined 31 subjects, 16 to 19 years of age, diagnosed with full ADHD, using self-report questionnaires: the EAS-D and the Stress Questionnaire. This data was supplemented with the results of the Structured Diagnostic Interview for ADHD according to ICD-10 and DSM-IV-TR, which was filled out by parents or teachers.

Results: Our subjects showed an increased level of discontent, understood as a dimension of emotionality, along with a reduced level of fear. The level of discontent significantly affects emotional tension, while impulsiveness, a diagnostic criterion for ADHD, has no direct effect on the level of emotional tension in stressful situations.

Conclusions: Youth with ADHD experience a high level of generalized discontent, the cause of which is often difficult to determine. The declared mental discomfort, given high lability, may be the cause of socially undesirable behavior. A combination of factors mediates the comorbidity of behaviors from the ODD/CD spectrum in youth with ADHD.

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

Acta Paediatr Int J Paediatr. 2013.

THE IMPORTANCE OF EARLY SCREENING AND TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN ORDER TO AVOID MORBID OBESITY IN CHILDREN.

Dahlgren J, Bjork A.

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Am J Med Genet Part B Neuropsychiatr Genet. 2013;162:855-63.

HAPLOTYPE CO-SEGREGATION WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER IN UNRELATED GERMAN MULTI-GENERATION FAMILIES.

Lin MK, Freitag CM, Schote AB, et al.

Complex disorders have proved to be elusive in the search for underlying genetic causes. In the presence of large multi-generation pedigrees with multiple affected individuals, heritable familial forms of the disorders can be postulated. Observations of particular chromosomal haplotypes shared among all affected individuals within pedigrees may reveal chromosomal regions, in which the disease-related genes may be located. Hence, the biochemical pathways involved in pathogenesis can be exposed. We have recruited eight large Attention Deficit-Hyperactivity Disorder (ADHD, OMIM: #143465) families of German descent. Densely spaced informative microsatellite markers with high heterozygosity rates were used to fine-map and haplotype chromosomal regions of interest in these families. In three subsets and one full family of the eight ADHD families, haplotypes co-segregating with ADHD-affected individuals were identified at chromosomes 1q25, 5q11-5q13, 9q31-9q32, and 18q11-18q21. Positive LOD scores supported these co-segregations. The existence of haplotypes co-segregating among affected individuals in large ADHD pedigrees suggests the existence of Mendelian forms of the disorder and that ADHD-related genes are located within these haplotypes. In depth sequencing of these haplotype regions can identify causative genetic mechanisms and will allow further insights into the clinico-genetics of this complex disorder.

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Anadolu Psikiyatr Derg. 2013;14:362-68.

TEMPERAMENT AND CHARACTER DIMENSIONS OF ADOLESCENTS AND YOUNG ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Guney E, Senses Dinc G, Iseri E, et al.

Objective: Temperament and character is central to social behavioral development. It has been shown that various temperament and character dimensions are related with developmental pathologies in children and adolescents. It has been suggested that there is a complex and multi-dimensional interaction between attention deficit hyperactivity disorder (ADHD) and temperament and character. In this study it was aimed to investigate the relationship of the ADHD, a developmental psychopathology with temperament and character properties in adolescence and young adulthood in a Turkish sample.
Methods: The study included 37 adolescents and young adults of 17-22 years of age with the diagnosis of ADHD. The control group consisted of healthy individuals with no psychiatric disorder. The patients were assessed with Temperament and Character Inventory (TCI) following the diagnosis-oriented interview.
Results: ADHD group had significantly higher points for novelty seeking, and significantly lower points for persistence, self-directedness, cooperativeness, and self-transcendence. Harm avoidance points were not significantly different except for points for fear of uncertainty.
Conclusion: The results of this study in the direction of a higher novelty seeking detected in individuals with ADHD supports the literature on adults. Lower persistence, self-directedness, and cooperativeness properties, on the other hand, are consistent with previous literature on children and adolescents. The results of this study support the notion that certain temperament and character properties interact with ADHD.

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Ann Acad Med Singapore. 2013;42:S259.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMATOLOGY IN PATIENTS WITH AUTISM SPECTRUM DISORDERS.

Lai WW, Rozen SG, Sung M, et al.

Introduction: Past studies have commonly observed attention/hyperactivity problems in children/ adolescents with autism spectrum disorders (ASD). In this study, we explored the presence of AD/HD symptomatology in child/adolescent Asian individuals with ASD and hypothesised that they similarly have a high degree of AD/HD symptoms.

Methods: Parents of 60 individuals (6 to 18 years of age) diagnosed with ASD at a child and adolescent psychiatric clinic in Singapore completed the Conners 3rd EditionnullParent Form. The standardised symptomatology T-scores (age and gender specific) and the AD/HD Probability Score was computed.

Results: The mean age (SD) was 11.8 (3.5) years old. Among them, 88% were males and 12% were females. Diagnoses include Autistic Disorder (42%), PDD-NOS (31%), and Aspergernulls Disorder (27%). The mean AD/HD Probability Score is 65. Sixty-two percent of the study sample had High Average T-scores (>60) for inattention symptomatology and 57% had High Average T-score for hyperactivity/impulsivity symptomatology. Age or gender did not have significant effects on AD/HD symptomatology.

Discussion & Conclusion: Our findings are consistent with worldwide studies that reported high degree of AD/HD symptoms in individuals with ASD, with possibly about half of them meeting diagnostic criteria for AD/HD. In our ASD sample, they presented with high degree of both inattention and hyperactivity/impulsivity symptoms. These significant symptoms may approximate a diagnosis of AD/HD, although current DSM-IV-TR diagnostic criteria preclude a comorbid diagnosis of AD/HD in patients with ASD. This study highlights the importance of considering comorbid conditions such as AD/HD in the diagnosis and management of ASD, especially in light of DSM-V, which allows for comorbid diagnoses.

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Ann Acad Med Singapore. 2013;42:S306.

FAMILY ADVERSITY RISK FACTORS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ASSOCIATED DISRUPTIVE BEHAVIOUR DISORDERS IN SINGAPORE.

Chua J, Lim-Ashworth NSJ, Ooi YP, et al.

Introduction: In view of the imperative role that genes play in disruptive behavioural disorders (DBD), researchers have highlighted that more emphasis should be placed on identifying and understanding family factors that may contribute to the manifestation of this genetic predisposition. The study aims to provide supporting evidence for the role that family adversity plays in predicting DBD in a sample of clinically referred children in Singapore. This study hypothesises that a higher family adversity index increases the risk of a positive DBD diagnosis.

Methods: A total of 178 children, aged between 9 and 17 years, who attended a local outpatient psychiatric clinic were included in this study. Participants have to satisfy DSM-IV-TR criteria for ADHD, CD and/or ODD. Parents of participants to complete a parent intake interview form and a computerised structured diagnostic interview. A family adversity index was summed using six items from the parent intake interview form. Index used in our study includes socio-economic status, status of family structure, family size, stressful events in the past 12 months, and prior psychiatric consultation.

Results: Logistic regression analysis indicated that the family adversity index significantly predicted DBD, with 3.3% of the variance accounted for by the index. Odds ratio for each adversity factor ranged from 1.21 to 11.59.

Discussion & Conclusion: Our findings are congruent with previous studies which reported that a high adversity score increases the risk of a DBD. Additionally, our results demonstrated that within an Asian context, child mental health concerns, especially disruptive behaviour problems, are still positively connected to demographic adversity.

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Ann Acad Med Singapore. 2013;42:S169.

EFFECT OF TRADITIONAL CHINESE MEDICATION ON SINGAPOREAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Liang W, Ong SH, Xie Y.

Introduction: The side effects of methylphenidate have led clinicians to explore alternative treatments for attention deficit hyperactivity disorder (ADHD). This ongoing observational study examines the effect of a traditional Chinese medicine (TCM) herbal formula on ADHD and related behaviours.

Methods: One-hundred participants aged 6 to 12 who meet the diagnostic criteria for ADHD and agree to initiate TCM treatment will be recruited. Participants will consume the herbal mixture twice daily for 3 months and undergo assessments at months 0, 3 and 6. Behavioural changes will be detected using the Childrennulls Global Assessment Scale (CGAS), Clinical Global Impressions-Severity (CGI-S) and Improvement (CGI-I) scales as well as the Child Behavior Checklist (CBCL) and ADHD Rating Scale-IV (ADHD-RS-IV). Currently, 17 participants have completed the study.

Results: Preliminary analyses revealed significant differences in mean scores across all time points on the CGAS (P <0.001), CGI-S (P <0.001), ADHD-RS-IV Inattention subscale (P = 0.001), ADHD-RS-IV Hyperactivity-Impulsivity subscale (P <0.001) and all CBCL scales (P <0.001). No significant differences were found in the CGI-I scores. Pairwise comparisons between months 0 and 3 as well as months 0 and 6 indicated significant improvements in mean scores on all scales except the CBCL Withdrawn/Depressed subscale. Scores did not differ significantly for all scales between months 3 and 6.

Discussion & Conclusion: Preliminary results suggest that the TCM formula reduces ADHD symptoms and related behaviours. Furthermore, its effects are sustained for 3 months after discontinuation. TCM may prove to be an effective alternative to stimulant medication. Future studies could involve more rigorous designs and other TCM interventions as possible treatment modalities for ADHD.

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Ann Acad Med Singapore. 2013;42:S162.

PRELIMINARY FINDINGS ON THE EFFECTS OF NUTRITIONAL AND SOCIAL SKILLS INTERVENTION AMONG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lim-Ashworth N, Ooi YP, Weng SJ, et al.

Introduction: Standard treatments such as psychostimulants and psychosocial therapies for ADHD often have side effects and/or are resource intensive. This prompted families to consider alternative intervention. The effectiveness of Omega-3 supplementation and social skills training in reducing attention problems among ADHD children is assessed through a randomised, double-blind, place-controlled trial. It is hypothesised that children who received Omega-3 supplementation, social skills training, or both Omega-3 supplementation and social skills training would show greater reductions in attention problems than those who received Omega-3 placebo only.

Methods: A total of 39 participants (aged 9 to 16 years) diagnosed with ADHD only were included in our current analyses. They were randomly assigned to one of the following groups: (i) omega-3 only (n = 15); (ii) social skills + omega-3 placebo (n = 8); (iii) omega-3 + social skills (n = 9); or 4) omega-3 placebo only (n = 4). Parents of children in all groups also received standard treatment which consists of 7 lessons of behaviour management training. Parent report questionnaires such as the CBCL and the CPRS were administered at pretreatment (0-month), midtreatment (3-month), and post-treatment (6-month).

Results: Contrary to our hypotheses, the groups did not differ significantly on parent-rated attention problems. However, all groups showed a greater trend toward improvement on parent-rated attention problems at post-treatment (6-month).

Discussion & Conclusion: Findings of this subset of participants showed preliminary support for the use of omega-3 and social skills training in treating attention problems although not superior to the other treatment groups. Implications of the findings will be discussed and limitations of the study will be presented.

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Arch Dis Child Educ Pract Ed. 2013;98:A92-A93.

IS THERE A LINK BETWEEN ADHD AND SOCIAL DEPRIVATION?

Apperley L, Mittal R.

Aim: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that affects approximately 4-6% of schoolaged children. Research into the aetiology of ADHD has focussed on genetic and biological factors, with much less information on environment and social aspects. There is a general perception that ADHD is linked to deprivation, but there are not enough studies in literature to prove or disprove this assumption. The aim of this study was to investigate the relationship between social deprivation and ADHD.

Method: We included all patients diagnosed with ADHD by the community paediatric department (only those on medications). Postcodes of these patients were used to produce deprivation scores, which included overall deprivation and sub-scores for income, social and housing factors. Indices of Deprivation 2010 are available for 32,482 small geographical areas (Lower Super Output Areas, LSOAs) in England, ranked from 1 (most deprived) to 32,482 (least deprived). These are further divided into fifths to produce English deprivation quintiles. Each postcode was then allocated to a quintile based on their deprivation score, where quintile 1 represents the most deprived.

Results: A total of 144 patients diagnosed with ADHD were being treated with medication. The male to female ratio was 4.5:1 (M: F). The deprivation scores were calculated and it showed that 64 patients (44.4%) were in the most deprived quintile (quintile 1), and followed in a relatively linear pattern. A similar pattern was seen for income, crime, employment, education, skills and training domain and health deprivation and disability, where 69, 57, 74, 69 and 59 patients were placed in quintile 1, respectively.

Conclusion: Our study shows an association between the prevalence of ADHD in children and deprivation index. Also there is clear link between sub scores for income, crime, employment, education, skills and training domain and health deprivation and disability and prevalence of ADHD. Indices of deprivation could be used to predict the expected prevalence of ADHD within the community and thus plan allocation of resources. Ours is a small sample size, but results support further investigation with a larger study.

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Arch Neurocienc. 2012;17:8-13.

SCHOOL STRESS PERCEPTION AND CIRCADIAN RHYTHM OF CORTISOL IN CHILDREN WITH ADHD.

Bakker L, Rubiales J, Lopez M.

Disorder attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in childhood, clinical symptoms includes inattention, hyperactivity and impulsivity. Symptomatology is usually chronic, causing a strong impact on the family, social and academic life of the children. The beginning of schooling and its fur ther course tend to be stressful events, placing them in a vulnerable position in the perception of stress. The hypothalamic-hypothalamic-adrenal system is the physiological response to stress, the negative consequences of abnormal per formance may be higher during childhood. The aim of this study was to evaluate possible associations between the degree of perceived stress at school and disturbances in the circadian rhythm of cor tisol. An ex post facto, retrospective study was conducted. The clinical sample consisted of 10 children diagnosed with ADHD and the control sample consisted of 10 children without a diagnosis of ADHD, both aged 8 to 14 years in Mar del Plata city, Argentine. To evaluate the degree of perceived stress at school School stress questionnaire adapted (QSS-adapted) was applied, to evaluate cor tisol circadian rhythm a determination of its concentration in saliva secretion was conducted. The results obtained show that clinical sample children perceive the educational environment as a stressor being also obser ved a positive association between degree of perceived stress and circadian rhythm of cortisol disruption.

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Asian J Psychiatry. 2013.

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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Biol Psychiatry. 2013.

EFFECTS OF METHYLPHENIDATE ON COGNITIVE FUNCTIONS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EVIDENCE FROM A SYSTEMATIC REVIEW AND A META-ANALYSIS.

Coghill DR, Seth S, Pedroso S, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is associated with a broad range of neuropsychological impairments. The relationship between these neuropsychological deficits and the defining symptoms of ADHD seems more complex than originally thought. Methylphenidate (MPH) is an effective treatment for ADHD symptoms, but its impact on cognition is less clearly understood.

Methods: With a common systematic search strategy and a rigorous coding and data extraction strategy across domains, we searched electronic databases to identify published placebo controlled trials that compared MPH and placebo on executive and nonexecutive memory, reaction time, reaction time variability and response inhibition in children and adolescents (5-18 years) with a formal diagnosis of ADHD.

Results: Sixty studies were included in the review, of which 36 contained sufficient data for meta-analysis. Methylphenidate was superior to placebo in all five meta-analyses: executive memory, standardized mean difference (SMD) .26, 95% confidence interval (CI): -.39 to -.13; non-executive memory, SMD .60, 95% CI: -.79 to -.41; reaction time, SMD .24, 95% CI: -.33 to -.15; reaction time variability, SMD .62, 95% CI: -.90 to -.34; response inhibition, SMD .41, 95% CI: -.55 to -.27.

Conclusions: These data support the potentially important effects of MPH on various aspects of cognition known to be associated with ADHD. Consideration should be given to adding cognitive outcomes to the assessment of treatment outcome in ADHD, considering the complexity of the relationship between ADHD symptoms and cognition.

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Boll Lega Ital Epilessia. 2011;127-29.

XP22.31 DELETION IN A PATIENT WITH EPILEPSY, MENTAL RETARDATION AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Santulli L, Coppola A, Paravidino R, et al.

We describe a 10-year-old female patient with epilepsy, mild mental retardation and attention deficit hyperactivity disorder. Family history was remarkable for ichthyosis in the maternal line and for autism and epilepsy in the paternal line. Microarray comparative genomic hybridization (a-CGH) showed a 1.2 Mb deletion on Xp 22. 31, with a loss of function of STS, a gene causing ichthyosis

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Brain Dev. 2013.

A FEMALE CARRIER OF ORNITHINE CARBAMOYLTRANSFERASE DEFICIENCY MASQUERADING AS ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Kim SH, Lee JS, Lim BC, et al.

Many females who are heterozygous for ornithine carbamoyltransferase (OTC) deficiency are asymptomatic or intermittently symptomatic with great phenotypic variability. Therefore, the diagnosis of this condition is occasionally a challenge and is often delayed. A 12-year-old girl who was initially diagnosed as having attention deficit-hyperactivity disorder (ADHD) became comatose and developed right-sided hemiparesis during her psychiatric admission. Brain magnetic resonance imaging indicated diffuse but extensive swelling in the left hemisphere with multiple lesions suggestive of an old infarction. Repeated evaluations revealed hyperammonemia and orotic aciduria, and she was diagnosed as having an OTC deficiency. Genetic analysis revealed a heterozygous mutation of N47I in the X-linked OTC gene. Her mental status and hemiparesis improved after hyperammonemia treatment. Here, we report a rare case of a manifestating female carrier with severe symptoms of OTC deficiency masquerading as ADHD.

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Bull Exp Biol Med. 2013;1-4.

SACCADIC MOVEMENTS OF THE EYES IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY SYNDROME.

Damyanovich EV, Baziyan BK, Sagalov MV, et al.

Saccadic movements of the eyes were analyzed in children with the attention deficit and hyperactivity syndrome. Saccadic movements of the eyes were recorded by a special method for their isolated registration without involvement of the head and in coordination tests (eye-head, eye-hand, and eye-head-hand). Comparative analysis of saccadic movements in children with attention deficit and hyperactivity and in normal subjects was carried out. Saccades recorded in each participant in complex tests with one or two additional motor acts, such as movements of the head and hand, were compared and the changes were analyzed for the group. Children with attention deficit and hyperactivity syndrome had problem with gaze fixation on the peripheral target after the end of the saccade and these changes augmented in more complex tasks with one or two additional acts. This could be due to discrepancy between the difficulty of the task and the potentialities of the frontal cortex, more immature in these patients than in healthy children. The changes could form the objective base for disorders in the formation of reading and writing habits, often observed in children with attention deficit and hyperactivity syndrome.

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Can J Psychiatry. 2013;58:632-39.

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

Grizenko N, Cai E, Jolicoeur C, et al.

Objective: Examine the short-term (acute) effects of methylphenidate (MPH) on math performance in children with attention-deficit hyperactivity disorder (ADHD) and what factors predict improvement in math performance.

Method: One hundred ninety-eight children with ADHD participated in a double-blind, placebo-controlled, randomized crossover MPH trial. Math response to MPH was determined through administration of math problems adjusted to their academic level during the Restricted Academic Situation Scale (RASS). Student t tests were conducted to assess change in math performance with psychostimulants. Correlation between change on the RASS and change on the math performance was also examined. Linear regression was performed to determine predictor variables.

Results: Children with ADHD improved significantly in their math with MPH ($P < 0.001$). The degree of improvement on the RASS (which evaluates motor activity and orientation to task) and on math performance on MPH was highly correlated. A child's age at baseline and Wechsler Individual Achievement

Test (WIAT)-Numerical Operations standard scores at baseline accounted for 15% of variances for acute math improvement.
Conclusions: MPH improves acute math performance in children with ADHD. Younger children with lower math scores (as assessed by the WIAT) improved most on math scores when given psychostimulants.

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Child Adolesc Psychiatry Ment Health. 2013;7.
THE PREVALENCE AND INCIDENCE, RESOURCE USE AND FINANCIAL COSTS OF TREATING PEOPLE WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN THE UNITED KINGDOM (1998 TO 2010).
***Holden SE, Jenkins-Jones S, Poole CD, et al*.**
Background: Attention deficit/hyperactivity disorder (ADHD) is a common disorder that often presents in childhood and is associated with increased healthcare resource use. The aims of this study were to characterise the epidemiology of diagnosed ADHD in the UK and determine the resource use and financial costs of care.
Methods: For this retrospective, observational cohort study, patients newly diagnosed with ADHD between 1998 and 2010 were identified from the UK Clinical Practice Research Datalink (CPRD) and matched to a randomly drawn control group without a diagnosis of ADHD. The prevalence and incidence of diagnosed ADHD were calculated. Resource utilisation and corresponding financial costs post-diagnosis were estimated for general practice contacts, investigations, prescriptions, outpatient appointments, and inpatient admissions.
Results: Incidence of diagnosed ADHD (and percentage change using 1998 as a reference) increased from 6.9 per 100,000 population in 1998 to 12.2 per 100,000 (78%) in 2007 and then fell to 9.9 per 100,000 (44%) by 2009. The corresponding prevalence figures were 30.5, 88.9 (192%) and 81.5 (167%) per 100,000. Incidence and prevalence were higher in males than females. Mean annual total healthcare costs were higher for ADHD cases than controls ((pounds)1,327 versus (pounds)328 for year 1, (pounds)1,196 vs. (pounds)337 for year 2, (pounds)1,148 vs. (pounds)316 for year 3, (pounds)1,126 vs. (pounds)325 for year 4, and (pounds)1,112 vs. (pounds)361 for year 5).
Conclusions: The prevalence of diagnosed ADHD in routine practice in the UK was notably lower than in previous reports, and both prevalence and incidence of diagnosed ADHD in primary care have fallen since 2007. Financial costs were more than four times higher in those with ADHD than in those without ADHD.

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Clin Child Psychol Psychiatry. 2013 Oct;18:483-503.
IT IS TIME FOR A MORE INTEGRATED BIO-PSYCHO-SOCIAL APPROACH TO ADHD.
***Richards LM-E*.**
The role of psychosocial factors in perpetuating and predisposing towards the development of attention deficit hyperactivity disorder (ADHD) symptoms has been neglected within the field of child mental health. Clinicians, when told that a child had a diagnosis of ADHD, have been found to underestimate the presence of psychosocial factors, and are less likely to ask about the possibility of neglect or abuse. This article details the considerable research showing links between ADHD symptoms and parental mental illness, child maltreatment, post-traumatic stress disorder (PTSD), attachment disorders and other environmental factors. Recent neuro-biological findings showing the impact on brain development of early abuse and attachment concerns are cited. The implications of these findings both for clinicians, and at policy level, are discussed, and the reasons underlying the need for a more integrated Bio-Psycho-Social approach to ADHD are outlined.

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Clin EEG Neurosci. 2013;44:169-70.

CLINICAL OUTCOME OF EEG-NEUROFEEDBACK IN A SINGLE-BLIND RANDOMIZED PLACEBO-CONTROLLED TREATMENT STUDY IN ADHD CHILDREN.

Van Dongen-Boomsma M, Vollebregt M, Slaats-Willemse D, et al.

Currently, children with ADHD are worldwide treated with EEG-neurofeedback. Still, solid evidence of efficacy and safety of this treatment method by methodologically sound studies is still lacking, although recently the amount of studies with a better methodological approach is rising (Gevensleben et al., 2012; Arns et al., 2009). This study addressed both the efficacy and the safety of EEG-neurofeedback for children with ADHD. On the basis of the experiences with and results of a pilot-study (Lansbergen et al., 2010), we conducted the present study. Forty-one children with ADHD underwent 30 sessions of EEG-neurofeedback, twice weekly (22 in the active feedback condition (8 in the pilot study, 14 postpilot study), and 19 in the sham feedback condition (no differences with pilot)). Our goal is to answer the question whether EEGneurofeedback in children with ADHD is both an effective and safe treatment method. A broad range of electrophysiological, cognitive, and behavioral measures were tested in advance, straight after, and 6 months after treatment. Results are currently analyzed and will be presented. This methodologically sound study will add-together with the current literature- arguments in the long-lasting discussion about the efficacy of EEG-neurofeedback, specifically for children with ADHD. Possible explanations and implications of the results will be discussed.

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Clin EEG Neurosci. 2013;44:168.

NEUROFEEDBACK IN ADHD: NEW RESEARCH DEVELOPMENTS.

Brandeis D.

Recent controlled EEG neurofeedback studies indicate sizeable clinical effects on ADHD (attention-deficit/hyperactivity disorder) symptoms. However, unspecific effects are often underestimated due to the study designs, and usually it remains unclear which specific neurophysiological networks and processes are regulated and altered with training. New studies and meta-analyses are briefly reviewed, and neurophysiologically and topographically specific results and approaches like tomographic EEG-based neurofeedback, and hemodynamic approaches like NIRS- based and fMRIbased neurofeedback (e.g. real-time fMRI) are presented. The first results from these new approaches suggest that their increased spatial resolution may not only allow one to target more circumscribed brain functions and networks, but also to develop improved control conditions. The findings also suggest that delayed and integrated feedback can be quite effective. Most approaches are still under development, however, and assumptions that a better trainability of specific regional activity translates into larger and more specific clinical effects must be critically evaluated for children and adults suffering from ADHD.

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Clin EEG Neurosci. 2013;44:168.

EFFECTIVENESS OF NEUROFEEDBACK IN ADOLESCENTS WITH ADHD FEATURES AND COMORBID DISORDERS: A RANDOMIZED CONTROLLED TRIAL.

Bink M, Bongers L, Popma A, et al.

Attention deficit/hyperactivity disorders (ADHD) is the most common neurodevelopment disorder. Best practice at this moment consists of medication and behavioral interventions. However, this best practice seems to be less effective for youngsters with ADHD-features and comorbid disorders. Neurofeedback intends to improve behavior by giving feedback of brain activity to the patient. The aim of this study is to investigate the additional value of neurofeedback for behavior and cognition relative to the current treatment as usual (TAU) with a multicenter parallel randomized controlled trial design. Adolescents with ADHD features, between age 12 and 24, were randomized to receive either a combination of TAU and neurofeedback (NFB+; N = 45) or TAU only (N = 26). Neurofeedback treatment consisted of approximately 37 sessions of theta/sensorimotor rhythm (SMR)-training on the vertex (Cz). Primary behavioral outcome

measures included the ADHDrating scale, Youth Self Report and Child Behavior Checklist; all assessed pre- and post-intervention. In the presentation, preliminary pre- and direct postmeasurements of behavior and cognition were presented. In conclusion, the hypothesis is that neurofeedback will reduce inattention, hyperactivity and impulsivity symptoms.

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Clin EEG Neurosci. 2013;44:167.

A MULTICENTERED RANDOMIZED CONTROLLED CLINICAL TRIAL: NEUROFEEDBACK FOR CHILDREN WITH ADHD-AIMS, STUDY DESIGN, LEARNING THEORY CONSIDERATIONS AND CURRENT SITUATION.

Strehl U.

Until the end of the last century neurofeedback studies were criticized because of methodological shortcomings. In the meantime, although many of the reservations have been resolved by studies in the last 10 years, there is still a debate about the placebo issue. The main points are ethical considerations and feasibility. In addition, specific and unspecific mechanisms of effect in treatments and treatment fidelity have to be taken into consideration. The clinical study "Neurofeedback for children with ADHD" compares two different treatments: EEG (Slow cortical potential feedback) or EMG (musculus supraspinatus) feedback. Both treatments are carried out in an identical fashion, but neither therapists nor subjects are blinded. A superiority of SCPFeedback is expected because of the pathology of ADHD and the results of neurofeedback studies in the past. It is not denied that EMG-Feedback may result in positive, yet smaller effects. In 2013 the last out of 144 participants will have finished the treatment and results will be available shortly thereafter. In designing neurofeedback protocols basics of learning have to be adhered to and self-regulation learning should be related to treatment outcome. By doing so, treatment fidelity as well as the placebo issue might be better considered than sham treatments.

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CMAJ. 2013;185:1333-35.

A 7-YEAR-OLD BOY EXPERIENCING DIFFICULTY AT SCHOOL.

Jimenez ME, Guevara JP.

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Environ Res. 2013.

ASSOCIATION BETWEEN PHTHALATES AND ATTENTION DEFICIT DISORDER AND LEARNING DISABILITY IN U.S. CHILDREN, 6-15 YEARS.

Chopra V, Harley K, Lahiff M, et al.

Objective: This study investigates the association between urinary phthalate metabolite levels and attention deficit disorder (ADD), learning disability (LD), and co-occurrence of ADD and LD in 6-15-year-old children.

Methods: We used cross-sectional data from the National Health and Nutrition Examination Survey (NHANES, 2001-2004). Phthalate metabolites with (greater-than or equal to)75% detection in urine samples were examined. The study population comprised 1493 children with parent-reported information on ADD or LD diagnosis and phthalate concentrations in urine. Phthalate concentrations were creatinine-adjusted and log10-transformed for analysis. All models controlled for child sex, age, race, household income, blood lead, and maternal smoking during pregnancy.

Results: There were 112 ADD cases, 173 LD cases, and 56 ADD and LD cases in the sample. After adjusting for potential confounders, we found increased odds of ADD with increasing urinary concentration of di-2-ethylhexyl phthalates (OR: 2.1; 95% CI: 1.1, 3.9) and high molecular weight phthalates (OR: 2.7; 95% CI: 1.2, 6.1). In addition, dibutyl phthalates (OR: 3.3; 95% CI: 0.9, 12.7) and high molecular weight phthalates (OR: 3.7; 95% CI: 0.9, 14.8) were marginally associated with increased odds of co-occurring

ADD and LD. We did not find associations for any phthalate and LD alone. We observed stronger associations between phthalates and ADD and both ADD and LD in girls than boys in some models. **Conclusions:** We found cross-sectional evidence that certain phthalates are associated with increased odds of ADD and both ADD and LD. Further investigations with longitudinal data are needed to confirm these results.

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Eur Child Adolesc Psychiatry. 2013;1-7.

ON THE LINK BETWEEN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND OBESITY: DO COMORBID OPPOSITIONAL DEFIANT AND CONDUCT DISORDER MATTER?

Pauli-Pott U, Neidhard J, Heinzel-Gutenbrunner M, et al.

The link between attention deficit/hyperactivity disorder (ADHD) and elevated body weight/obesity can be regarded as well established. Because oppositional defiant disorder (ODD)/conduct disorder (CD) has also been found to be associated with these characteristics and ADHD and ODD/CD often occur comorbidly, we investigated whether ODD/CD and ADHD are independently linked with body weight and obesity. The clinical records of 360 children, 257 (6-12 years) with diagnoses of ADHD, ODD/CD, or comorbid ADHD and ODD/CD and 103 children with adjustment disorder (as a control group) constituted the database. All children were seen for the first time in two outpatient psychiatric clinics. Associations of the psychiatric diagnoses (ADHD present vs. not present; ODD/CD present vs. not present) with the standard deviation scores (according to German reference data) of the child's body mass index (BMI-SDS) and presence of obesity were analyzed by ANCOVA and hierarchical logistic regression analysis, respectively. Children with ODD/CD showed higher BMI-SDS ($F = 7.67$, $p < 0.006$) and rate of obesity (Wald = 4.12, $p < 0.05$, OR = 2.43) while controlling for ADHD comorbidity. While adjusting for ODD/CD comorbidity, the links between ADHD and BMI-SDS or obesity did not reach statistical significance. Given a cross validation of these findings, future (preferably prospective longitudinal) research should analyze the mediating mechanism between the psychiatric conditions and obesity.

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Eur J Health Econ. 2013;1-11.

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

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

Background: The aim of our study is to compare the validity of a generic preference-based Quality of Life (QoL) instrument for adults to that of a generic child-specific QoL instrument in children and adolescents with attention deficit hyperactivity disorder (ADHD).

Methods: EQ-5D and KIDSCREEN-10 data were collected using a questionnaire survey performed among parents with a child or adolescent diagnosed with ADHD. The measurements were compared to assess (dis)similarities of the instruments' constructs and responsiveness to different health states. Principal component analysis (PCA) with varimax rotation was used to identify factors underlying the constructs of both instruments. Instruments' index scores of respondents with different treatment and comorbidity profiles were compared using Student's t tests. Cohen's effect sizes were calculated for an indirect comparison of the instruments' responsiveness and discriminating ability. Separate analyses were performed in children aged 8-12 and 13-18 years.

Results: A strong relation was found between the EQ-5D and KIDSCREEN-10 index scores. However correlations between EQ-5D and KIDSCREEN-10 items were moderate or low. The PCA identified five separate factors of quality of life. A physical and a mental factor included a combination of three EQ-5D dimensions and six KIDSCREEN-10 items; the remaining EQ-5D and KIDSCREEN-10 items constituted complementary factors without any overlap between the separate instruments. Scores of both instruments differed significantly according to respondents' response to treatment and comorbidity profile. Cohen's effect sizes indicated comparable results of the instruments' responsiveness and discriminative ability.

Conclusions: The results highlight that the instruments measure different constructs of QoL in children

with ADHD. Despite this, the analyses showed comparable responsiveness and discriminative ability of the instruments. These results suggest that for economic evaluations, the EQ-5D is an appropriate and valid instrument for measuring QoL in children.

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Eur J Paediatr Neurol. 2013.

ENVIRONMENTAL CIRCUMSTANCES INFLUENCING TIC EXPRESSION IN CHILDREN.

Caurin B, Serrano M, Fernandez-Alvarez E, et al.

Aim: To assess the clinical features and severity of tics and environmental factors influencing tic expression in a cohort of children with tic disorders.

Methods: We performed a cross-sectional study in a cohort of children and adolescents (N = 92) with tic disorders referred to the outpatient clinic of a tertiary-level paediatric centre in Barcelona. The severity of tics was evaluated using the Yale Global Tic Severity Scale (YGTSS). A questionnaire including a list of environmental factors and common daily activities that might influence tic occurrence was completed for patients greater than 5 years old.

Results: Children were classified as having Tourette syndrome (TS) (52 patients), chronic motor or phonic tics (22 patients) and tics of less than 12 months' duration (18 patients). Tics worsened with stressful situations, activities related to school, playing video games and watching TV. A significant proportion of children reported a reduction in tics while they were concentrating on artistic or creative activities or when playing sports and participating in outdoor activities. The YGTSS scores were higher for TS patients (P < .001) and correlated positively with the time of evolution of tics (r = .273, P = .026). Poor school performance was associated with TS (p = .043) and higher scores on the YGTSS (P = .018), as well as attention deficit/hyperactivity disorder (P = .007).

Conclusions: Several activities of daily living were identified as modifying tic severity in children and may be important clues for tic management. In a subgroup of children with TS, tics were associated with significant morbidity and poor academic performance. Our results emphasise the importance of developing specific school programmes and tailored recommendations in patients with TS.

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Eur J Pediatr. 2013;1-2.

REPLY TO L. REALE ET AL. "MORE AND BETTER SHOULD BE DONE TO GUARANTEE EVIDENCE-BASED MANAGEMENT OF ADHD IN CHILDREN ACROSS EUROPE".

Hodgkins P, Setyawan J, Mitra D, et al.

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Eur Neuropsychopharmacol. 2013;23:S598-S599.

HEALTH-RELATED QUALITY OF LIFE OUTCOMES IN A LONG-TERM STUDY OF LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AND ADOLESCENTS WITH ADHD.

Coghill D, Banaschewski T, Zuddas A, et al.

Background and Objectives: Optimal management of patients with attention deficit/hyperactivity disorder (ADHD) aims not only to relieve symptoms, but to improve health-related quality of life (HRQoL). The long-acting prodrug stimulant, lisdexamfetamine dimesylate (LDX) is an effective once-daily treatment for the symptoms of ADHD, as confirmed in a long-term ((greater-than or equal to)6-month) efficacy and safety study (SPD489-326). In this study, HRQoL was assessed using the Child Health and Illness Profile - Child Edition: Parent Report Form (CHIP-CE:PRF), a generic (i.e. not disease-specific) paediatric instrument with demonstrated reliability and validity.

Methods: Study participants were aged 6-17 years with ADHD and a baseline ADHD Rating Scale IV (ADHD-RS-IV) total score (greater-than or equal to)28. European patients had participated in a previous

study; additional US patients were enrolled directly. Patients who completed a (greater-than or equal to)26-week open-label period (OLP) of LDX treatment were randomized (1:1) to continue on LDX or to switch to placebo, for a 6-week, double-blind, randomized-withdrawal period (RWP). Parents completed CHIP-CE:PRF questionnaires at weeks 0, 8 and (greater-than or equal to)26 of the OLP and weeks 0 and 6 of the RWP, or at early termination. Scores in the five domains were standardized to T-scores (mean = 50, standard deviation [SD] = 10) based on (Table Presented) US community samples. Higher T-scores indicate better HRQoL. Endpoint was defined as the last visit of the OLP or RWP with valid data ((less-than or equal to)30% missing items).
Results: At OLP baseline, mean CHIP-CE:PRF T-scores were lowest in the Achievement domain and were also (greater-than or equal to)1 SD below the normative mean (i.e., below 40) in three of the four remaining domains (Table 1). T-scores in all domains improved from OLP baseline to endpoint, with the largest changes in the Achievement and Risk Avoidance domains (Table 1). Mean T-scores in all five domains were above 40 in participants who completed (greater-than or equal to)26 weeks on LDX and entered the subsequent RWP (Table 1). From baseline to endpoint of the 6-week RWP, CHIP-CE:PRF T-scores in the LDX group continued to improve in the Satisfaction domain and were stable in the four other domains, but deteriorated in all domains in the placebo group. These changes were statistically significantly different for LDX compared with placebo in the Risk Avoidance (effect size, 0.829; p<0.001), Achievement (0.696; p<0.001) and Satisfaction (0.636; p<0.001) domains.
Conclusion: The burden of illness in children and adolescents with ADHD was reflected in baseline CHIP-CE:PRF T-scores (greater-than or equal to)1 SD below 50 in four of five CHIP-CE:PRF domains. Treatment with LDX led to improved HRQoL scores in these four domains, with the greatest effects in Achievement and Risk Avoidance. These benefits were maintained with continued LDX treatment, but HRQoL scores deteriorated following treatment withdrawal.

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Eur Neuropsychopharmacol. 2013;23:S599-S600.

IMPACT OF PREVIOUS ADHD MEDICATION ON THE EFFICACY OF LISDEXAMFETAMINE DIMESYLATE IN THE TREATMENT OF ADHD: POST HOC ANALYSES.

Coghill D, Banaschewski T, Lecendreux M, et al.

Background and Objectives: Amfetamine- and methylphenidate (MPH)-based psychostimulants are effective treatments for attention-deficit/hyperactivity disorder (ADHD). The prodrug lisdexamfetamine dimesylate (LDX) is the first long-acting amfetamine-based ADHD medication to be licensed in Europe, where it is approved for the treatment of children and adolescents who have experienced an inadequate response to previous MPH therapy. These post hoc analyses examine the impact of previous ADHD medication on the efficacy of LDX in a European study (SPD489-325), with the aim of aiding clinicians when developing individualized, patient-centred treatment strategies for the management of ADHD.
Methods: SPD489-325 was a phase 3, double-blind, randomized controlled trial in children and adolescents (aged 6-17 years) with ADHD. Patients were randomized (1:1:1) to receive once-daily LDX, placebo or osmotic-release oral system methylphenidate (OROSMPH; included as a reference arm) for a 7-week, dose-optimized evaluation period. Patients were excluded if they had previously failed to respond, based on the investigators' judgement, to an adequate course (dose and duration) of OROS-MPH therapy, or if their current ADHD medication provided effective control of symptoms with acceptable tolerability. Individuals with documented allergy, hypersensitivity or intolerance to amfetamine or MPH were also excluded. Efficacy outcomes included the change from baseline in ADHD Rating Scale version IV (ADHD-RS-IV) total score and Clinical Global Impressions-Improvement (CGI-I) scores.
Results: Of 336 patients enrolled, 317 comprised the full analysis set (FAS). Among the patients included in the FAS who had previously received any ADHD medication (n = 170), the most commonly prescribed was MPH (n = 146). Baseline ADHD-RS-IV total scores were similar across treatment groups and subgroups. The difference between active drug and placebo in LS mean change (95% confidence interval [CI]) from baseline to endpoint in ADHD-RS-IV total score in the overall study population (LDX, -18.6 [-21.5, -15.7]; OROSMPH, -13.0 [-15.9, -10.2]) was similar to that observed in treatment-naive individuals (n = 147; LDX, -15.1 [-19.4, -10.9]; OROS-MPH, -12.7 [-16.8, -8.5]), patients previously treated with any ADHD

medication (n = 170; LDX, -21.5 [-25.5, -17.6]; OROS-MPH, -14.2 [-18.1, -10.3]), patients treated with MPH at any time before the study (n = 146; LDX, -21.8 [-26.0, -17.5]; OROS-MPH, -15.1 [-19.4, -10.9]) and patients receiving MPH immediately (up to 30 days) prior to randomization (n = 77; LDX, -20.1 [-26.5, -13.7]; OROS-MPH, -14.3 [-21.2, -7.4]). Similarly, the proportions of patients (95% CI) who were improved at endpoint based on CGI-I (CGI-I score of 1 or 2) among treatment-naive individuals (LDX, 80.4% [69.0, 91.9]; placebo, 19.6% [8.7, 30.5]; OROS-MPH, 63.8% [50.1, 77.6]) and those previously treated with any ADHD medication (LDX, 75.9% [64.5, 87.3]; placebo, 9.4% [1.6, 17.3]; OROS-MPH, 57.9% [45.1, 70.7]) were similar to that of the overall study population (LDX, 78.0% [69.9, 86.1]; placebo, 14.4% [7.7, 21.2]; OROSMPH, 60.6% [51.2, 70.0]).
Conclusion: LDX and the reference treatment OROS-MPH were associated with clinically significant reductions in ADHDrelated symptoms and behaviours in children and adolescents, irrespective of their ADHD medication history

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Eur Neuropsychopharmacol. 2013;23:S119.
PERSISTENCE OF BRAIN DEFICITS IN ADULT ADHD.
Cubillo A, Rubia K.
Attention Deficit Hyperactivity Disorder (ADHD) was traditionally conceptualized as a childhood disorder however, the evidence shows that it persists into adulthood in 65% of cases with a prevalence of 3-4% of the adult population. Functional and structural brain imaging studies in adult ADHD by and large suggest similar deficits both in adults and children with the disorder with however some exceptions. Thus, structural imaging studies in adult ADHD show deficits in similar brain regions as those found to be abnormal in childhood ADHD such as in several frontal lobe structures, in temporal and parietal lobes, and the cerebellum, with evidence for abnormal inter-regional structural white matter connectivity in these regions [1]. An exception, however are deficits in the basal ganglia, where a meta-regression analysis has shown that structural gray matter abnormalities appear to be normal in adulthood but not childhood [2]. Similarly, while our fMRI studies in medication-naive adults with ADHD show strikingly similar brain dysfunctions in frontostriatal and parietal regions during the same cognitive tasks as we have previously observed in medication-naive children with ADHD [1], our recent meta-regression analysis of all published whole-brain fMRI studies shows more pronounced basal ganglia dysfunction in children, whereas adult ADHD patients show more pronounced frontal deficits [3]. Overall, the evidence suggests that adult ADHD is characterized by similar structural and functional brain abnormalities as childhood ADHD with the exception of the basal ganglia deficits, which seem to become less pronounced or may normalize with age.

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Eur Neuropsychopharmacol. 2013;23:S584.
PHARMACOLOGICAL TREATMENT VERSUS NEUROFEEDBACK IN TYPICAL SYMPTOMATOLOGY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Cardo E, Servera M, Bernad M, et al.
Neurofeedback emerged more than 30 years ago in the area of Child and Adolescent Psychiatry, and has been studied extensively as a treatment for attention deficit hyperactivity disorder (ADHD). Previous studies have reported a decrease of behavioral problems and improved cognitive performance in ADHD children after theta/beta training. Purpose: The objective of the present study is to analyze, in a randomized controlled trial, the effectiveness of neurofeedback (NFB) compared to standard pharmacological intervention (FAR) in the treatment of the typical symptoms of ADHD.
Method: The study population consisted of 63 children aged 7-14 years, diagnosed with ADHD, with normal IQ, excluding oppositional defiant disorder (ODD) and other comorbid disorders. Subjects were randomly assigned to one of two treatment arms: NFB or FAR. Parents of 14 children refused participation, and 19 other children were excluded because they did not meet all inclusion criteria. The final population consisted of 12 children in the NFB arm and 11 children in the FAR arm. They were evaluated pre-

treatment, post-treatment, at two-month follow-up (FU1) and at six-month follow-up (FU2) using several scales: Du- Paul ADHD-IV (parent and teacher inattention and impulsivity/ hyperactivity measure), and an ODD scale (parent and teacher ODD measure). Once the treatment was finished, the NFB children were eligible for pharmacological treatment. The NFB treatment consisted of 40 sessions of one hour each, twice a week, focused on the improvement of theta/beta ratio.
Results: Both groups showed significant improvements based on effect size. Post-treatment, a medium effect size in all measures was apparent in mothers of the NFB group (0.75); effect size was 0.34 in fathers, and 0.49 in teachers. In the FAR group, these rates were 0.77, 0.90 and 0.79. At FU1, a medium effect size was apparent in mothers of the NFB group (1.05); effect size was 0.26 in fathers, and 0.91 in teachers. In the FAR group, these values were 0.68, 0.90 and 0.79. Finally, at FU2 a medium size effect was apparent in mothers of the NBF group (80.749); effect size was 0.37 in fathers, and 0.84 in teachers. In the FAR group, these values were 0.75, 0.98 and 1.00.
Conclusions: In general, the results were quite similar for both treatments, but different longitudinal tendencies were observed, as well as important differences between evaluators. Post-treatment, FAR scores were better in fathers and teachers, but not in mothers. At FU1 this tendency was partially reversed and NFB showed better results in mothers and teachers but worse in fathers. At FU2 the post-treatment situation appeared again, but at that time 67% of the NFB participants were already taking medication. Overall, the two clearest conclusions are that pharmacological treatment provides more important short-term improvements and that NFB treatment can show short-term improvements. On the other hand, the observed results are much more consistent for mothers and teachers than for fathers.

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Eur Neuropsychopharmacol. 2013;23:S605.
GROWTH ON STIMULANT MEDICATION: EFFECTS IN CHILDREN WITH ADHD.
Carucci S, Usala T, Granitzio F, et al.
Background: Stimulant medications represent the main effective treatment in improving the core symptoms of ADHD. However, in the last 30 years, there has been increasing concern about the risks associated with these medications in particular with respect possible growth deficits, due to their impact on weight, height and BMI. This has highlighted the need for long-term studies.
Objectives: The purpose of this study was to evaluate, within a systematic review and a prospective study, whether methylphenidate interferes with growth in children affected by ADHD and to assess whether the effects on growth are related to length of treatment or dose/kg/day or are more evident during the early stages of therapy.
Methods: For the systematic review a Pubmed search and a centralized search using Ovid Medline, Embase and PsychInfo was carried out up to January 2013. The systematic review was centered on human studies focusing on the impact of chronic methylphenidate and stimulants exposure on growth in children and adolescents affected by ADHD diagnosed according to DSM criteria. Within the prospective study growth parameters were collected from 89 ADHD, aged 6-14, enrolled into the Italian ADHD Registry. Sixty five were Drug Naive (DN), 24 had been on MPH for 1-3 years prior to enrollment into the registry (PR). Weight, height and BMI and Z-scores of height and BMI, growth velocity SDS, height deficit and BMI deficit were assessed at baseline, 6, 12, 18, 24 months.
Results: In the systematic review 15 eligable studies were identified covering a total of 2668 children and adolescents. Analysis of the impact of methylphenidate was performed in 1511 subjects. Six studies did not support the hypothesis of a correlation between a growth deficit and treatment. Nine studies (n =1003) found significant changes on height, weight and BMI z scores. Height deficit appeared more evident during the first 6-12 months with a subsequent normalization. 4 studies revealed a dose dependent effect. In the prospective study at the 24 month observation, absolute values of height and weight continued to increase in all subjects. BMI Z-score decreased significantly at T12 ($p<0.001$) with no further at T24. Height Z-score showed a slight decrease only from T12 to T24 ($p = 0.062$). Growth velocity SDS at T12 was not significantly different when compared to T24. Height deficit compared to expected height was -1.26(plus or minus)4.61 at 24 months. Height deficit appeared significantly related to dosage pro/kg/day ($p = 0.02$). No significant difference was found regarding absolute values of height, weight, BMI and BMI Z-score at

baseline between DN and PR. Both groups had a significant decrease in BMI Z-score at T12 (p<0.001). Height deficit appeared related to dosage for DN at T12 (p = 0.02) and for PR at baseline (p = 0.05). **Discussion:** These studies indicate that long-term treatment with methylphenidate might result in a slight growth deficit, in particular with respect to height. Further larger studies are needed to confirm that this slight growth deficit may be dependent on the maximum dose taken pro die rather than on the length of treatment.

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Eur Neuropsychopharmacol. 2013;23:S603-S604.

EFFICACY OF LISDEXAMFETAMINE DIMESYLATE AND ATOMOXETINE IN CHILDREN AND ADOLESCENTS WITH ADHD: HEAD-TO-HEAD RESPONDER ANALYSES.

Cardo E, Coghill D, Nagy P, et al.

Background and Objectives: The long-acting prodrug psychostimulant lisdexamfetamine dimesylate (LDX) has recently been approved in several European countries for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents who have experienced a previous inadequate response to methylphenidate treatment. The head-to-head study SPD489-317 compared the efficacy and safety of LDX and the non-stimulant, noradrenergic compound atomoxetine (ATX) in children and adolescents with ADHD who had previously responded inadequately to methylphenidate. The primary analysis demonstrated that the time to clinical response was significantly faster for LDX than for ATX. Response was defined as a Clinical Global Impression-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved). The objective of the responder analyses was to evaluate the proportions of patients who sustained improvements in core symptoms and clinical global impressions, as assessed using the investigator-rated ADHD Rating Scale Version IV (ADHD-RS-IV) and CGI-I scale, respectively. **Methods:** This phase 3b, multicentre, parallel-group, activecontrolled study enrolled patients (aged 6-17 years) with ADHD. Patients were required to have a baseline ADHD-RS-IV total score of at least 28. Patients were randomized (1:1) to a once-daily, optimized dose of LDX (30, 50 or 70 mg) or ATX (patients <70 kg, 0.5-1.2 mg/kg with total daily dose not to exceed 1.4 mg/kg; patients (greater-than or equal to)70 kg, 40, 80 or 100 mg). The 9-week double-blind treatment period comprised 4 weeks of dose optimization (visits 0-3) followed by 5 weeks of dose maintenance (visits 4-9). CGI-I sustained responders were defined as those patients with a CGI-I of 1 or 2 at visits 4-9. ADHD-RS-IV sustained responders were those patients achieving the following prespecified thresholds at visits 4-9; (greater-than or equal to)25%, (greater-than or equal to)30% or (greater-than or equal to)50% reductions from baseline in ADHD-RS-IV total score. Efficacy outcomes were assessed for the full analysis set (FAS), defined as all patients who were randomized and took at least one dose of study drug.
Results: Of 267 patients randomized (LDX, n = 133; ATX, n = 134), 200 (LDX, n = 99; ATX, n = 101) completed the study. The FAS comprised 262 patients (LDX, n = 127; ATX, n = 135). At baseline, the mean (standard deviation) ADHD-RS-IV total score was 42.6 (6.17) for LDX and 41.9 (6.68) for ATX (FAS). The percentage of patients (95% confidence intervals [CI]) categorized as CGI-I sustained responders was significantly greater for LDX (52.0% [43.3, 60.7]) than for ATX (39.3% [31.0, 47.5]; p <0.05). For each of the thresholds analysed, the percentage of ADHDRS- IV sustained responders (95% CI) was significantly greater for LDX than for ATX ((greater-than or equal to)25% reduction, LDX, 66.1% [57.9, 74.4], ATX, 51.1% [42.7, 59.5], p<0.05; (greater-than or equal to)30% reduction, LDX, 61.4% [53.0, 69.9], ATX, 47.4% [39.0, 55.8], p<0.05; (greater-than or equal to)50% reduction, LDX, 41.7% [33.2, 50.3]), ATX, 23.7% [16.5, 30.9], p<0.01).
Conclusions: In children and adolescents with ADHD and an inadequate response to previous methylphenidate therapy, significantly greater proportions of patients treated with LDX maintained improvements in investigator-rated core symptoms and clinical global impressions throughout the 5-week dose maintenance period compared with those who received ATX. (Table Presented)

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Eur Neuropsychopharmacol. 2013;23:S586-S587.

CAN AUTISTIC TRAITS BE IDENTIFIED IN CHILDREN WITH ADHD? A CONTROLLED STUDY.

Biederman J.

Background: Twin, family and linkage studies indicate that attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs) share a portion of their heritable etiology [1,2]. These findings raise the possibility that some children with ADHD may manifest symptoms of autism even in the absence of a fullfledged disorder. This study sought to address the implications of autistic traits (ATs) in ADHD youth without a diagnosis of autism by providing a comprehensive comparison of clinical and neuropsychological correlates of children with and without ATs across multiple non-overlapping domains of functioning. To this end we used data from an existing, large scale, sample of pediatrically and psychiatrically referred youth with and without ADHD of both sexes in which the diagnosis of autism was specifically exclusionary. Based on our literature review, we hypothesized that ATs would be prevalent in children with ADHD and that their presence would be associated with higher levels of morbidity and disability in general, and with interpersonal deficits, in particular.

Methods: Participants were 242 youth with ADHD and 227 controls without ADHD of both sexes. Participants completed a large battery of measures designed to assess psychiatric comorbidity, psychosocial, educational, and cognitive parameters. A diagnosis of autism was exclusionary. ATs were operationalized using a unique profile from the CBCL consisting of 3 subscales (Withdrawn + Social + Thought Problems T-scores), which had been previously linked with autism spectrum disorders.

Results: A positive AT profile was significantly overrepresented among ADHD children (18% vs. 0.87%, $p<0.01$) when compared with Controls. While ADHD children with and without a positive AT profile did not differ in the core symptoms of ADHD, ADHD children with a positive AT profile were significantly more impaired as indexed by additional psychopathology and functioning in the interpersonal, school, family and cognitive domains.

Conclusions: In this large, controlled study of youth with and without ADHD of both sexes ascertained from pediatric and psychiatric sources in which a diagnosis of autism was exclusionary, we found that ATs are prevalent in children with ADHD and that their presence heralds a significantly more compromised clinical presentation characterized by higher rates of psychopathological, neuropsychological and interpersonal deficits. A substantial minority of ADHD children manifests autistic traits. Additionally, we observed that although ADHD children with ATs do not differ from ADHD-only children in the core symptoms of ADHD, they face a set of challenges characterized by more severe psychopathology, neuropsychological functioning, emotional dysregulation, and interpersonal deficits. The identification of ADHD-AT children in those already diagnosed with ADHD and evaluated for the absence of ASDs heralds the opportunity for early recognition of these highly impairing features and for individualized, targeted treatment. Scientifically, our improved ability to recognize impairment related to traits of autism in children with ADHD will help inform future work targeted at identifying biomarkers - neurobiological and genetic - and the environmental factors associated with this potentially distinct subtype of ADHD.

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Eur Neuropsychopharmacol. 2013;23:S600.

ASSESSMENT OF EFFECTS OF ATOMOXETINE IN ADULT PATIENTS WITH ADHD: CONSISTENCY AMONG 3 GEOGRAPHIC REGIONS IN A RESPONSE MAINTENANCE STUDY.

Tanaka Y, Upadhyaya H.

Purpose: Atomoxetine has been approved as a treatment for attention-deficit/hyperactivity disorder (ADHD) for adults (as well as children and adolescents) in many countries around the world. The purpose of this analysis was to assess the consistency of treatment effect and tolerability of atomoxetine in adults with ADHD across 3 regions (Europe, United States/Canada [US/Can], and Latin America [LA]).

Methods: This study was a Phase 3, multicenter, randomized, double-blind, maintenance of response (randomized withdrawal) trial of atomoxetine (80 or 100 mg/day) versus placebo in adult outpatients with ADHD. The study consisted of 3 study periods: screening/washout, open-label acute treatment (approximately 3 months), and double-blind maintenance/randomized withdrawal (approximately 9 months). Results are from the double-blind randomization phase (approximately 6 months duration after

the double-blind maintenance phase). Satisfactory response to treatment was defined as a (greater-than or equal to)30% reduction in Conners' Adult ADHD Rating Scale Investigator-Rated: Screening Version 18-Item (CAARS-Inv:SV) total score and a score of (less-than or equal to)3 on the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S). Consistency across the 3 regions, based on response rate, was assessed using Higgins's I2 and Guidance Methods 1 and 2 from the Japanese regulatory guidance document for global trials. Other tests of consistency (the interaction test, t-tests, and tests of noninferiority) were based on change from baseline to endpoint (last observation carried forward) on the CAARS-Inv:SV total score.
Results: A total of 524 patients were randomized (atomoxetine N= 266, placebo N= 258). Patient demographics were similar across regions with respect to gender, age, ADHD subtype, and cytochrome P450 2D6 status; however, the percentage of stimulantna ive patients varied significantly across regions (P = 0.002). The percentage of patients completing the study was similar among the 3 regions. The percentages of patients experiencing nasopharyngitis [P = 0.039] and upper respiratory tract infection [P = 0.042]) differed significantly among regions. During the randomized withdrawal period, atomoxetine maintained improved ADHD symptoms relative to placebo on the CAARS-Inv:SV total score in all 3 regions, though the magnitude was minimal in both the atomoxetine and placebo groups for patients in the LA region. The results were similar for the CAARS-Inv:SV hyperactive/ impulsive and inattention subscale scores, except that, on the hyperactive/impulsive subscale, the LA region placebo group actually improved. For the consistency analysis of efficacy among 3 regions, the interaction test was not significant at the 0.10 level (P = 0.111) and Higgins's I2 indicated very low heterogeneity. Japanese Guidance Method 2 indicated consistent treatment effects for all studies, but results for the LA region were barely in the improved direction. For the consistency of treatment effects in 1 region versus the others, several differences were found. T-tests were significant for Europe and LA regions (both P <0.001). Using the method of noninferiority, only Europe met the criteria (using a margin of 1.87 [1/2 of total treatment effect]). Finally, Japanese Guidance Method 1 indicated inconsistent treatment effects for LA region.
Conclusions: Atomoxetine was shown to be an effective and generally well-tolerated treatment of ADHD in the maintenance of response for each of the 3 regions, though the effect of treatment may differ among the regions studied.

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Eur Neuropsychopharmacol. 2013;23:S588-S589.

THE ASSOCIATION BETWEEN GENE POLYMORPHISMS AND VISUAL-SPATIAL FUNCTIONS AND ORGANISATION OF GRAPHOMOTOR ACTIONS IN ADHD PATIENTS.

Slopien A, Borkowska AR, Dmitrzak-Weglarz M, et al.

Attention-Deficit Hyperactivity Disorder (ADHD) is a complex neurodevelopmental condition. The cluster of symptoms that define disorder likely represents the final common behavioral pathway of diverse underlying problems. Neuropsychological studies in ADHD are devoted to executive function, but rarely visual or visual-spatial functions [1]. ADHD etiology and deficits of cognitive functions are related to genetic background (dopaminergic, noradrenergic activity) and maturation of central nervous system [2].
Aim: The aim of study was an evaluation of association between deficits in visual-spatial, visual memory, planning, organization of the visual-motor functions and trait of reflectionimpulsivity and polymorphisms of studied genes. Study group: We studied 360 people both sexes aged 7-17 years. The study group was 205 unrelated ADHD patients fulfilling ICD-10 and DSM-IV diagnostic criteria. The mean age of the study group was 10.88 years (SD = 2.67). Controls consisted of 155 healthy subjects (mean age: 10.31 years; SD = 2.28). They were not relatives of patients, had no psychiatric diagnosis, had no I grade relatives with a psychiatric disorder. All studied children were Polish. Legal guardians, patients and controls gave a written consent to take part in the study. The study obtained the positive opinion of Bioethics Committee of Poznan Medical University.
Methods: We used two tests: Rey-Osterrieth Complex Figure Test (ROCF) and Matching Familiar Figures Test (MFFT). We analyzed a possible relationship between their results and 14 polymorphisms of 8 genes of catecholaminergic system (DRD2, DRD3, DRD4, DAT, COMT, SNAP-25), serotoninergic system (5-HTR2A) and important in central nervous system maturation (BDNF). Genomic DNA of patients was isolated from peripheral blood leucocytes and of controls from saliva with the use of Oragene system

(Genotek). Polymorphism rs1800955 of DRD4 gene was analyzed with the use of PCR-RLFP, and polymorphism VNTR of DAT and DRD4 genes with the use of PCR-VNTR. Other 11 polymorphisms SNP type were evaluated with the use of iPLEX Gold method (Sequenom system). Statistical analysis was done with the use of Statistica v 8 and GraphPad Instant v 3.06. Genotypes frequency was analyzed with the use of c2 Pears test and allele frequency with the use of Fisher test.
Results: Relationship of neuropsychological tests and genes polymorphism was analyzed separately in the study and control group. In the study group there was a correlation between the type of reproduce the figure from memory in ROCF test with SNAP25 rs363039 (p = 0.015). There was no association between MFFT and polymorphisms of studied genes. In the control group there was a correlation between the number of errors in MFFT test with 5-HT2A rs17288723 (p = 0.038), SNAP25 rs363043 (p = 0.028) and COMT rs4680 (p = 0.003) and impulsiveness index with SNAP25 rs363043 (p = 0.010). There was also an association between the total numbers of points during reproduce the figure and DAT rs463379 (p = 0.042), time of reproduce the figure from memory and DAT rs27072 (p = 0.038) and the type of reproduce the figure with SNAP25 rs363039 (p = 0.047).
Conclusions: Obtained results suggest a possible role of biogenic amines in visual-spatial functions, visual memoryand and impulsivity and to the lesser degree cognitive functions impairment.

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Eur Neuropsychopharmacol. 2013;23:S118-S119.

QUANTITATIVE ELECTROENCEPHALOGRAPHIC ASSESSMENT OF ADHD.

Simon V.

Quantitative electroencephalogram (QEEG) with modern statistical and digital technology provides a uniquely high temporal resolution in studying the details of cortical functions and related neuronal activity. Although QEEG studies have a long history in investigating ADHD in children, adult studies emerged only in the last 2 decades. In children, increased frontocentral theta band activity and increased theta/beta ratio during rest were consistently detected. Adult studies show inconsistent results with regard to relative and absolute power of the high frequency and delta bands, while majority of the studies detected increased frontal theta band activity. In the background of these observed changes developmental factors and methodological issues are both suggested by the literature. A broad range of methodology and theoretical models have been tested in QEEG research during cognitive performance from which, for example arousal models and hemispheric assymetry were predominantly associated with alpha band variances in rest, during engagement to and performing cognitive tasks, between adults with ADHD and controls, while based on assessing very low frequency oscillations, different pattern of deactivation of the default mode network was suggested between individuals with high and low ADHD symptom frequency [1]. Multiple studies found event related potential differences associated with attentional control-, error detection-, reward sensitivity-, and inhibition features of ADHD. Although QEEG constantly adds to the understanding of the neurobiological background of ADHD and considered as a useful and promising tool for targeting the identification of objective indices for the diagnosis of ADHD, current markers are not yet specific enough for diagnostic purposes[2,3].

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Eur Neuropsychopharmacol. 2013;23:S590-S591.

REDUCED SEROTONIN TRANSPORTER BINDING IN ADULT ADHD INVESTIGATED BY PET AND [11C]DASB.

Kranz G, Mitterhauser M, Kutzelnigg A, et al.

Introduction and Purpose of the study: Attention deficit hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in children and adolescents, which often persists into adulthood [1]. Several lines of evidence indicate that serotonergic neurotransmission may, in addition to dopamine, play an important role in the aetiology of ADHD. Reduced central serotonergic activity has been associated with poor impulse regulation, hyperactivity and aggressive behavior [2], while early biochemical studies suggest low serotonin levels and reduced serotonergic uptake in platelets of ADHD patients [3]. The aim of the

present study was to investigate serotonin transporter (SERT) binding using positron emission tomography (PET) and the selective radioligand [11C]DASB in adult ADHD patients and healthy control subjects. **Methods**: Study population: 21 medication-free ADHD patients (aged 33.2(plus or minus)10.9, nine females) without any psychiatric comorbidity, and 21 age and sex matched healthy controls (aged 32.6(plus or minus)10.7, nine females) were included in this study. Measurements and SERT quantification: Each subject underwent a [11C]DASB PET scan using an advance full-ring scanner (General Electric Medical Systems, Milwaukee, WI, USA) in 3D mode. PET scans were corrected for head motion and spatially normalized in SPM8. The SERT binding potential (BPND) was quantified via a voxelwise whole-brain and a regions of interest (ROI) approach using Ichise's multilinear reference tissue model 2 (MRTM2). Data analysis: BPND maps and ten a priori defined ROIs of patients were compared to those of healthy control subjects by means of independent samples-t-test. SPM8 and SPSS were used for statistical assessment of voxel-wise and ROI-based analyses, respectively.
Results: Compared to healthy control subjects, patients with ADHD tended to have reduced SERT binding within the right thalamus, right caudate and pallidum, left putamen and left amygdala ($p<0.005$ uncorrected) as well as in the subgenual anterior cingulate and the ventromedial orbitofrontal cortex, right putamen, left thalamus and bilateral nucleus accumbens ($p<0.01$ uncorrected) within the voxel-wise analysis. These findings in the basal ganglia were in accord with the ROI-based approach showing reduced SERT binding in ROIs for the left putamen and left striatum ($p<0.03$, uncorrected). None of the clusters or ROIs survived correction for multiple comparisons. Including age as covariate did not change the main findings.
Conclusions: Our findings may indicate reduced SERT binding in several cortical and subcortical sites. These sites are located within brain structures that process cognitive and motivational functions that are known to be impaired in ADHD. Thus, the observed regional specificity may support the hypothesis of a serotonergic mediation of ADHD symptomatology. As previous studies indicate reduced serotonin levels and serotonin uptake in ADHD patients, our findings suggest a compensatory down regulation of SERT expression. Since all of the presented findings are uncorrected for multiple comparisons, interpretations and conclusions must be preliminary in nature. Nevertheless, the observed reductions in SERT binding are located in regions that exhibit relatively high signal-to-noise ratio in SERT binding potential, which deems our results reliable and promising.

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Eur Neuropsychopharmacol. 2013;23:S604-S605.

METHYLPHENIDATE HYDROCHLORIDE MODIFIED RELEASE IMPROVED INATTENTION AND HYPERACTIVITY/IMPULSIVITY SCORES IN ADULT ADHD PATIENTS.

Huss M, Ginsberg Y, Tvedten T, et al.

Purpose of the study: Globally, about 2 to 5% of adults are estimated to have ADHD. Many adults remain undiagnosed and/or untreated due to poor awareness of the diagnosis in adults and suboptimal transition of patients from pediatric/adolescent to adult medical services. ADHD symptoms differ in adults compared with children and this may contribute to under-diagnosis of ADHD in adults. Hyperactivity and impulsivity may become less evident with age, but inattention and impaired executive function tend to continue. Treatment options for adult ADHD patients are limited. This study evaluated effective and safe dose range of Methylphenidate hydrochloride modified release (MPH-LA) in adults with ADHD. (Table Presented)
Methods: This 40-week, double-blind, randomized, placebocontrolled study consisted of three Treatment Periods (TPs). (TP1): Patients were randomized to either MPH-LA 40, 60 or 80 mg/day (3-week titration, starting dose 20 mg/day, followed by 6-week fixed-dose) or matching placebo in a 1:1:1:1 ratio. (TP2): 5-week titration to individual optimal dose, wherein all patients, including those treated with placebo in TP1, were titrated starting from 20 mg/day in increments of 20 mg/week to their optimal dose (dose at which the investigator considered an optimal symptom was maintained for a period of at least one week) of MPH-LA (40, 60 or 80 mg/day). (TP3): Patients were rerandomized (3:1) to their optimal dose or placebo for 6 months double-blind follow up to evaluate maintenance of effect. Improvement from baseline to the end of TP1 in DSM-IV ADHD RS total score, inattention and hyperactivity sub scores were evaluated using an analysis of covariance (ANCOVA) model with treatment group and center as factors, and baseline score as covariate. Adult patients (18-60 years) with ADHD according to DSM-IV diagnostic criteria and a DSM-IV

ADHD RS total score of (greater-than or equal to)30 at screening and baseline were included in the study.
Results: Out of totally 863 patients screened, 725 were randomized to 40 (N = 181), 60 (N = 182), or 80 mg (N = 181) MPH-LA or Placebo (N = 181). Overall, 584 (80.6%) patients completed TP1. All three doses significantly improved measures of both inattention and hyperactivity/impulsivity as evaluated by sub-scores of the DSM-IV ADHD RS at the end of the 9-week double-blind dose confirmation phase (table). Safety results were consistent with the established safety profile for MPH-LA in children.
Conclusions: MPH-LA at dose levels of 40 to 80 mg/day significantly improved inattention and hyperactivity/impulsivity compared to placebo at the end of the 9-week double-blind dose confirmation study phase. No new unexpected adverse events (AEs) or serious adverse events (SAEs) were observed.

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Eur Neuropsychopharmacol. 2013;23:S595-S596.

CONNECTOMIC DISTURBANCES IN ADHD COMBINED VERSUS PREDOMINANTLY INATTENTIVE TYPE.

Hong S, Zalesky A, Fornito A, et al.

Objective: Consistent evidence from diffusion tensor imaging (DTI) studies points to abnormal white matter as an important pathophysiological characteristic of attention-deficit/hyperactivity disorder (ADHD). To the best of our knowledge, however, there has been no study attempting to identify, in a regionally unbiased way, distributed sub-networks of brain regions showing altered connectivity between different types of this disorder. This study aimed to derive a relatively comprehensive, whole-brain characterization of connectomic disturbances in ADHD combined type compared to ADHD predominantly inattentive type.
Method: Using DTI, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in children and adolescents with ADHD combined type (N = 39; age range 72-177 months) compared to those with ADHD predominantly inattentive type (N = 26; age range 75-188 months). The study protocol was approved by the institutional review board for human subjects at the Seoul National University Hospital. Detailed information about the study was given to parents and children, and written informed consents were obtained prior to study entry.
Results: Participants in the two groups were not significantly different regarding any of the demographic and social variables tested (i.e., age, gender, intelligence quotient, handedness, parental education level, familial socioeconomic status, maternal age at pregnancy, and child's birth weight). A single network was identified, characterized by decreased connectivity in the combined type patients (P = 0.052, FWEcorrected). The network comprised 17 links connecting 17 different brain regions (threshold of t = 2.1). No significant betweengroup difference was found in mean FA value of the fiber bundles. The subsequent correlation analysis performed in combined type patients revealed multiple significant associations between FA and the continuous performance test (CPT) scores, involving superior frontal gyrus, anterior cingulate gyrus, and supplementary motor area (Table 1). No significant positive correlation was found between FA and the CPT scores.
Conclusions: Using an unbiased, whole-brain, data-driven approach, we demonstrated that abnormal white matter connectivity in ADHD combined type is largely focused on superior frontal gyrus, anterior cingulate gyrus, and supplementary motor area. The correlations observed with measures of attentional performance underscore the functional importance of these connectomic disturbances for the clinical phenotype of ADHD combined type.

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Front Human Neurosci. 2013.

MATURATIONAL DELAY IN ADHD: EVIDENCE FROM CPT.

Berger I, Slobodin O, Aboud M, et al.

While data from behavioral, neuropsychological, and brain studies suggested that Attention-Deficit/Hyperactivity Disorder (ADHD) is related to a developmental lag that reduces with age, other studies have proposed that ADHD represents a deviant brain function. The present study used a cross-sectional approach to examine whether ADHD children show a developmental delay in cognitive performance

measured by continuous performance test (CPT). We thus, compared six age groups of ADHD children (N = 559) and their unaffected peers (N = 365), aged 6-11, in four parameters of MOXO-CPT performance: Attention, Timing, Hyperactivity and Impulsivity. Results have shown that despite improvement in CPT performance with age, ADHD children continued to demonstrate impaired performance as compared to controls. In most parameters, CPT performance of ADHD children matched that of 1-3 years younger normal controls, with a delay most prominent in older children. However, in the Hyperactivity parameter, ADHD children's performance resembled that of much younger healthy children, with almost no evidence for a developmental catch up. This study suggests that while some cognitive functions develop slower but normally, other functions (e.g., inhibitory control) show a different trajectory.

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Health Qual Life Outcomes. 2013;11.

COMPARISON OF CHILD SELF-REPORTS AND PARENT PROXY-REPORTS ON QUALITY OF LIFE OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Marques JCB, Oliveira JA, Goulardins JB, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a neurobiological condition that affects 3%-7% of the pediatric population and significantly compromises the quality of life (QoL) of these individuals. The aim of the current study was to compare child self-reports and parent proxy reports on the QoL of children with ADHD.Methods: Forty-five children with ADHD, combined type, aged 8-12 years without comorbidities, were compared with 43 typically developing children. PedsQL(trademark) 4.0 (Pediatric QoL Inventory(trademark)) Generic Core Scales (physical, emotional, social, and school functioning) were completed by families and children self-reporting their health-related QoL.

Results: Children with ADHD reported themselves significantly lowered their PedsQL(trademark) scores on all dimensions in comparison to typically developing children. Statistically significant differences were observed in social functioning ($p = 0.010$), school functioning ($p < 0.001$), psychosocial health ($p < 0.001$), and total score ($p = 0.002$). The physical functioning and emotional functioning dimensions did not differ significantly between groups, with $p = 0.841$ and $p = 0.070$, respectively. Parents of children with ADHD also reported lower PedsQL(trademark) scores, with statistically significant differences in all dimensions. The relationship between child self-reports and parent proxy reports indicated that there is greater agreement among children with ADHD, except for the school functioning.

Conclusions: This suggests that children with the disorder and their parents have a perception of the functional limitations the disorder brings. It is therefore important to undertake studies to verify the QoL in children with ADHD that aim to provide and measure the scope of the well-being of these children.

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Hum Psychopharmacol. 2013;28:600-07.

METHYLPHENIDATE-OSMOTIC-CONTROLLED RELEASE ORAL DELIVERY SYSTEM TREATMENT REDUCES PARENTING STRESS IN PARENTS OF CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hwang JW, Kim B, Kim Y, et al.

Objective: The aim of the current study was to investigate the effect of methylphenidate-osmotic release oral delivery system (MPH-OROS) treatment on parenting stress in parents of children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

Methods: Four hundred and ninety-five children and adolescents (391 boys and 104 girls), aged 7 to 18 years who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria for ADHD, were recruited at 48 psychiatric outpatient clinics across South Korea. Children's symptoms, parenting stress, and parental depression were assessed at baseline, week 4, and week 8 of MPH-OROS treatment using the Korean version of the DuPaul's ADHD Rating Scale (ARS), the Beck's Depression Inventory (BDI), and the Parenting Stress Index, Short Form (PSI-SF).

Results: We found significantly decreased scores of ARS, parental BDI, and PSI-SF from baseline to week 4 and from week 4 to week 8. Also, there were positive correlations among baseline PSI-SF, ARS, and BDI

scores. The changes in BDI and ARS scores were significantly associated with the PSI score changes, accounting for 20.1% and 10.0%, respectively.
Conclusions: We suggest that the increased parenting stress and depression in parents of children and adolescents with ADHD can be improved following the treatment with MPH-OROS.

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J AAPOS. 2013;17:507-11.

THE POSSIBLE ASSOCIATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH UNDIAGNOSED REFRACTIVE ERRORS.

Fabian ID, Kinori M, Ancri O, et al.

Purpose: To evaluate whether attention deficit disorder (ADD) or attention deficit with hyperactivity disorder (ADHD) is associated with undiagnosed refractive errors or binocular function difficulties.
Methods: In this case-control study, ADD/ADHD children diagnosed according to criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR), along with age-matched controls, were examined at the ADD clinic at the Sheba Medical Center. For children in both groups the following data were recorded: uncorrected visual acuity for distance and near, cycloplegic refraction, ocular motility, and binocular function.
Results: A total of 56 children (12 girls; mean subject age, 9.5 years) were included in the ADD/ADHD group. The control group comprised 66 patients (29 girls; mean subject age, 9 years). Mean uncorrected visual acuity was nearly 20/20 for distance and J1 for near in both groups. Cycloplegic spherical equivalent was +0.89 (plus or minus) 1.1 D for the control group and +0.63 (plus or minus) 0.89 D for the ADD/ADHD group (P = 0.16). Binocular function and accommodation were similar in both groups, except for a significant difference between the near point of convergence of the controls versus the ADD/ADHD group (5.3 (plus or minus) 2.3 cm versus 4.1 (plus or minus) 1.8 cm, respectively; P = 0.002).
Conclusions: ADD/ADHD children had similar visual acuity at distance and near and refractive errors as normal subjects. Binocular function and accommodation were also found to be similar in both groups and thus might not contribute to ADD/ADHD.

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J Affective Disord. 2013.

HIGHER RISK OF MOOD DISORDERS AMONG ADOLESCENTS WITH ADHD AND ASTHMA: A NATIONWIDE PROSPECTIVE STUDY.

Chen MH, Su TP, Chen YS, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) and asthma are commonly comorbid together, and are associated with an increased risk of development of mood disorders separately. However, there has been no study investigating the comorbid effect of these two disorders on developing mood disorder.
Methods: Using the National Health Insurance Research Database, adolescents with ADHD-alone, asthma-alone, ADHD comorbid with asthma, and age-/gender-matched (1:4) controls were recruited in 2003. Subjects who developed major depression, any depressive disorder, or bipolar disorder during the follow-up period (2003-2010) were identified.
Results: In all, 1172 adolescents with ADHD-alone, 487 with asthma-alone, 238 with ADHD+asthma, and 7552 controls were recruited in 2003. Adolescents with ADHD+asthma and those with ADHD-alone, but not those with asthma-alone, had an elevated risk of developing major depression (hazard ratio [HR]: 10.25, 95% confidence interval [CI]: 3.86-27.19; HR: 8.64, 95%CI: 5.00-14.93; HR: 2.11, 95%CI: 0.71-6.23) and bipolar disorder (HR: 31.25, 95%CI: 8.87-110.12; HR: 10.42, 95%CI: 4.60-23.63; HR: 1.91, 95%CI: 0.24-15.32) compared to the control group.
Discussion: Our results showed that ADHD adolescents had an increased risk of developing both unipolar depression and bipolar depression in their later life, and that the comorbidity of asthma with a synergistic

effect increased this risk further. The underlying pathophysiology among ADHD, asthma, and mood disorders needs further investigation.

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J Affective Disord. 2013.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND SUICIDALITY IN A TREATMENT NAIVE SAMPLE OF CHILDREN AND ADOLESCENTS.

Bals J, Miklosi M, Kereszteny A, et al.

Background: The aim of the present study was to investigate the possible association between attention-deficit/hyperactivity disorder (ADHD) and suicidality.

Methods: Using a structured interview (Mini International Neuropsychiatric Interview Kid), the authors examined 418 treatment naive children/adolescents (aged: 3-18 years). Suicidality was defined by the M.I.N.I. Kid as having any current suicidal ideations and/or suicide attempts.

Results: Two hundred and eleven children/adolescents fulfilled the DSM-IV diagnosis of ADHD and a further 105 showed symptoms of ADHD in subthreshold level. Multiple mediation analyses resulted in a moderated meditational model in which the relationship between symptoms of ADHD and current suicidality was fully mediated by the symptoms of comorbid conditions, but this was moderated by age. In children under 12 years, significant mediators were the symptoms of specific anxiety disorders, while in the adolescent group symptoms of major depressive episode and dysthymia and symptoms of substance abuse/dependence approved as significant mediators. Limitations: As the study was cross-sectional, it did not reveal any causal relationship among the investigated factors. Furthermore, as the study population included a treatment naive clinical sample, we can assume that adolescents, who and/or whose family seek for help at the first time in this age belonged to the less sever end of the spectrum.

Conclusions: ADHD symptoms are associated with an increased risk of suicidality in treatment naive children/adolescents. The mechanisms of this relationship can be understood only when developmental factors are considered. Our findings suggest that clinicians should screen suicidality and comorbid symptoms routinely in patients with ADHD.

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J Autism Dev Disord. 2013;1-10.

ADHD SYMPTOMS MODERATE THE RELATION BETWEEN ASD STATUS AND INTERNALIZING SYMPTOMS IN 3-6-YEAR-OLD CHILDREN.

Wilson BJ, Manangan CN, Dauterman HA, et al.

The current study sought to understand the relation between diagnostic status (autism spectrum disorders [ASD] versus typically developing) and internalizing problems in children with and without co-occurring attention deficit hyperactivity disorder (ADHD) symptoms. Participants were 88 children, ages 3:0-6:11, their parents and teachers. Findings indicated that ADHD symptoms moderated the relation between diagnostic status and depressive and somatic symptoms. High ADHD symptoms in children with ASD were associated with increased depressive and somatic symptoms compared to children with typical development. Findings suggest poor prognostic outcomes for children with ASD and co-occurring ADHD symptoms and highlight the need for early identification and targeted intervention.

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J Child Adolesc Psychopharmacol. 2013 Sep;23:502-06.

A RARE CASE OF ANTI-N-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS IN AN ADOLESCENT.

Fields J, Lim T, Kolevzon A, et al.

Presents a clinical case report of a 16-year-old adolescent girl with a history of ADHD, learning disability, and anxiety treated with atomoxetine, who presented with acute and significant changes in mental status.

M. exhibited fluctuations in mental status including extremes of mood, emotional liability and bizarre thoughts. She also experienced waxing and waning of cognitive lucidity and thought disorganization. In addition, M. had intermittent neurological symptoms, including unusual arm movements, paucity of speech, headaches, left facial droop, inability to follow complex commands, and poor performance on the clock face task. Anti-NMDA receptor encephalitis is an autoimmune disease, and while autoimmune diseases can be genetically linked, there is no known history of autoimmune disease in M.'s family. This case is a dramatic example of the florid presentation of ahmbic encephalitis, illustrating the importance of early recognition and comprehensive and exhaustive medical workup, leading to timely diagnosis and early, aggressive treatment. Since these patients can present in many treatment settings, from outpatient practice to emergency departments, as illustrated here, all practitioners should have an awareness of the disorder.

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Journal of Child Psychology and Psychiatry. 2013 Nov;54:1208-14.

ASTHMA AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A NATIONWIDE POPULATION-BASED PROSPECTIVE COHORT STUDY.

Chen MH, Su TP, Chen YS, et al.

Background: Previous cross-sectional studies have suggested an association between asthma and attention-deficit/hyperactivity disorder (ADHD), but the temporal relationship was not determined. Using a nationwide population-based prospective case–control cohort study (1:4, age-/gender-matched), we hypothesized that asthma in infanthood or early childhood would increase the risk of ADHD in later life. **Methods:** In all, 2,294 children with asthma and 9,176 controls aged between 0 and 3 years in 2000 were included in our study. Cases of ADHD that occurred to the end of follow-up (31 December 2010) were identified.

Results: Children with asthma had a higher incidence of developing ADHD (7% vs. 4.6%, $p < .001$) than control cohort during the follow-up period. After adjusting for age at enrollment, gender, level of urbanization, and comorbid allergic diseases (allergic rhinitis and atopic dermatitis), children with asthma had an elevated risk (HR: 1.31, 95% CI: 1.07–1.59) of developing ADHD compared with control group. **Discussion:** Our prospective study supported a temporal relationship between asthma and ADHD. Asthma in very early life increased the risk of developing ADHD during the school years. Further studies are required to investigate whether the prompt treatment of asthma and comorbid allergic diseases could prevent the development of ADHD or decrease ADHD symptoms.

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J Cogn Dev. 2013;14:633-50.

NEONATAL INTENSIVE-CARE UNIT GRADUATES SHOW PERSISTENT DIFFICULTIES IN AN INTRADIMENSIONAL SHIFT CARD SORT.

Kittler PM, Brooks PJ, Rossi V, et al.

Neonatal intensive-care unit (NICU) graduates, a group at risk for attention problems and attention-deficit hyperactivity disorder, performed an intradimensional shift card sort at 34, 42, 51, and 60 months to assess executive function and to examine effects of individual risk factors. In the "silly" game, children sorted cards (airplanes and dogs) so they were not the same as targets. In the "same" game, they did the opposite. Performance on the "silly" game was poor, especially when it was presented first. Success in following "silly" game rules improved with age and was significantly linked to maternal education and birth weight for gestational age, a measure of intrauterine stress. Degree of central nervous system injury differentiated children who completed the task from children who did not, and it also affected the need to repeat instructions in the "same" game. These results confirm an increased likelihood of impairments in executive function during preschool years in NICU graduates.

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J Dev Behav Pediatr. 2013 Oct;34:623-25.

BULLYING AND ADHD: WHICH CAME FIRST AND DOES IT MATTER?

Keder R, Sege R, Raffalli PC, et al.

Presents a case study of 13-year-old boy (Aiden), in the sixth grade who is relatively new to the practice, is seen for follow-up after his routine physical last month when he presented concerns for possible attention-deficit hyperactivity disorder (ADHD) and gave the family Vanderbilt Scales to complete. Drs. Keder and Sege emphasize that the case illustrates the need to address individual circumstances when devising a treatment plan for a child with attention-deficit hyperactivity disorder (ADHD). Stimulant medications can decrease the risk for subsequent comorbid psychiatric disorders and academic failure in a child with ADHD. School accommodations and behavioral therapy offer important additional advantages. Although Aiden struggled more in school than had been reported, retention was not a recommended course of action. Further information is needed and meeting with his teachers is recommended. Dr. Raffalli understands that Aiden's plight is very typical for a child with attention deficit hyperactivity disorder (ADHD), particularly before the diagnosis is firmly established and adequate treatment is in place. The clinician evaluating Aiden will have to consider whether the ADHD symptoms represent ADHD or are secondary to some other condition such as a sleep disorder or other psychological condition. This case brings up a second but equally important dilemma: What to make of the teacher's behavior? Her remark is one of frustration and anger. In addition, Dr. Augustyn points out that this case brings home 2 important themes: clinicians may only hear about what we ask, and whether we call it "bullying" or "ostracism" or "mean," the teacher's behavior had an impact on Aiden's functioning and is an important aspect of his treatment plan.

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J Dev Behav Pediatr. 2013 Oct;34:566-74.

ADHD IS A RISK FACTOR FOR OVERWEIGHT AND OBESITY IN CHILDREN.

Fliers EA, Buitelaar JK, Maras A, et al.

Objective: Although hyperactivity would seem to increase energy expenditure, attention-deficit hyperactivity disorder (ADHD) appears to increase the risk for being overweight. This study examined the body mass index (BMI) in children with ADHD and its relationship with age, gender, ADHD and comorbid symptom severity, inhibitory control, developmental coordination disorder, sleep duration, and methylphenidate use.

Method: Participants were 372 Dutch children with ADHD combined type aged 5 to 17 years participating in the International Multicenter ADHD Genetics (IMAGE) study. We categorized BMI according to international age- and gender-specific reference values and calculated BMI-standard deviation scores (BMISDS). The control population was matched for age, gender, and ethnicity and originated from the same birth cohort as the ADHD group. Inhibitory control was measured by the computerized Stop-signal task. Prevalence differences of underweight, overweight, and obesity between groups were expressed in odds ratios. We used linear regression analyses with gender, age, parent- and teacher-rated ADHD and comorbid scores, inhibitory control, sleep duration, motor coordination, and methylphenidate use to predict BMI-SDS.

Results: Boys with ADHD aged 10 to 17 years and girls aged 10 to 12 years were more likely to be overweight than children in the general Dutch population. Younger girls and female teenagers, however, seemed to be at lower risk for being overweight. Higher oppositional behavior and social communication problems related to higher BMI-SDS scores, whereas more stereotyped behaviors related to lower BMI-SDS scores. We found no effects of the other examined associated risk factors on BMI-SDS.

Conclusions: Attention-deficit hyperactivity disorder in boys is a risk factor for overweight. In girls with ADHD, the prevalence of overweight is age dependent and most pronounced in girls aged 10 to 12 years. They have a 4-fold risk of being obese. Higher oppositional and social communication problems pose an increased risk for overweight, whereas sleep duration, motor coordination problems, and methylphenidate use do not.

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J Neural Transm. 2013 Nov;120:1619-21.

STIMULUS-PRECEDING NEGATIVITY IN ADHD.

Mourik R, Janssen T, Oosterlaan J.

Children with ADHD often show disrupted response preparation as indicated by attenuated stimulus-preceding negativity (SPN). This study examined response preparation in a relatively short cue–stimulus interval. No differences in SPN occurred between children with ADHD and their normal peers. A strong positive relationship was found between SPN and mean reaction time in both groups. Children with ADHD are able to mentally prepare themselves for upcoming events in short cue–stimulus intervals.

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J Neurol. 2012;259:S33-S34.

EFFECT OF TRANSDERMAL METHYLPHENIDATE WEAR TIMES ON SLEEP IN CHILDREN WITH ADHD.

Ashkenasi A.

Sleep disturbances are common among children and adolescents with attention deficit hyperactivity disorder. This study sought to evaluate the effects of individualizing wear times of the methylphenidate transdermal system on sleep parameters. In this open-label, randomized trial, 26 children with attention deficit hyperactivity disorder and sleep disturbances were randomized (after dose optimization) to one of four groups with different sequences of patch wear times (i.e., 9, 10, 11, and 12 h per day wear times each for week in different sequences). The primary endpoint comprised sleep latency. Secondary endpoints included total sleep time, sleep quality, and attention deficit hyperactivity disorder and related signs (assessed with Attention Deficit Hyperactivity Disorder Rating Scale-IV and Connor's Global Impression-Parent). A mixed-effects regression model evaluated the effects of patch wear time on sleep and symptom measures. Patch wear time exerted no significant effect on sleep latency or total sleep time, although a trend toward improved sleep quality was evident (P (registered trademark) 0.059) with longer patch wear times. Sleep parameters were not adversely affected by longer methylphenidate transdermal system patch wear times. Thus, if replicated in larger samples, the individualization of patch wear times should be considered according to the needs and responses of patients.

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J Pediatr Psychol. 2013 Nov;38:1081-90.

AN EXAMINATION OF THE SPECIFICITY OF MOTIVATION AND EXECUTIVE FUNCTIONING IN ADHD SYMPTOM-CLUSTERS IN ADOLESCENCE.

Lopez-Vergara HI, Colder CR.

Objective: Motivation and executive functioning are central to the etiology of attention-deficit/hyperactivity disorder (ADHD). Furthermore, it has been hypothesized that motivation should show specificity of association with ADHD-impulsivity/hyperactivity symptoms, whereas executive functioning should show specificity of association with ADHD-inattention symptoms. This study tests this specificity-hypothesis and extends previous research by conceptualizing motivation to include both reactivity to reward and punishment.

Methods: Executive functioning was assessed using two different laboratory measures (the Wisconsin-Card-Sort and Stop-Signal Tasks) and motivation was measured using a laboratory measure of sensitivity to reward and punishment (the Point-Scoring-Reaction-Time Task).

Results: Findings suggested specificity of association between executive functioning and symptoms of inattention, and between motivation and symptoms of impulsivity/hyperactivity. However, support varied across indices of executive functioning.

Conclusions: Results provide support for multiple component models of ADHD symptoms and extend the literature by providing a theoretically based conceptualization of motivation grounded on developmental neuroscience models of motivated behavior.

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J Psychiatr Res. 2013.

GENOME-WIDE COPY NUMBER VARIATION ANALYSIS IN ADULT ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER.

Ramos-Quiroga JA, Sanchez-Mora C, Casas M, et al.

Attention-deficit and hyperactivity disorder (ADHD) is a common psychiatric disorder with a worldwide prevalence of 5-6% in children and 4.4% in adults. Recently, copy number variations (CNVs) have been implicated in different neurodevelopmental disorders such as ADHD. Based on these previous reports that focused on pediatric cohorts, we hypothesize that structural variants may also contribute to adult ADHD and that such genomic variation may be enriched for CNVs previously identified in children with ADHD. To address this issue, we performed for the first time a whole-genome CNV study on 400 adults with ADHD and 526 screened controls. In agreement with recent reports in children with ADHD or in other psychiatric disorders, we identified a significant excess of insertions in ADHD patients compared to controls. The overall rate of CNVs >100 kb was 1.33 times higher in ADHD subjects than in controls (p = 2.4e-03), an observation mainly driven by a higher proportion of small events (from 100 kb to 500 kb; 1.35-fold; p = 1.3e-03). These differences remained significant when we considered CNVs that overlap genes or when structural variants spanning candidate genes for psychiatric disorders were evaluated, with duplications showing the greatest difference (1.41-fold, p = 0.024 and 2.85-fold, p = 8.5e-03, respectively). However, no significant enrichment was detected in our ADHD cohort for childhood ADHD-associated CNVs, CNVs previously identified in at least one ADHD patient or CNVs previously implicated in autism or schizophrenia. In conclusion, our study provides tentative evidence for a higher rate of CNVs in adults with ADHD compared to controls and contributes to the growing list of structural variants potentially involved in the etiology of the disease.

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Journal of the American Academy of Child & Adolescent Psychiatry. 2013 Nov;52:1204-12.

CANDIDATE GENETIC PATHWAYS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SHOW ASSOCIATION TO HYPERACTIVE/IMPULSIVE SYMPTOMS IN CHILDREN WITH ADHD.

Bralten J, Franke B, Waldman I, et al.

Objective: Because multiple genes with small effect sizes are assumed to play a role in attention-deficit/hyperactivity disorder (ADHD) etiology, considering multiple variants within the same analysis likely increases the total explained phenotypic variance, thereby boosting the power of genetic studies. This study investigated whether pathway-based analysis could bring scientists closer to unraveling the biology of ADHD.

Method: The pathway was described as a predefined gene selection based on a well-established database or literature data. Common genetic variants in pathways involved in dopamine/norepinephrine and serotonin neurotransmission and genes involved in neuritic outgrowth were investigated in cases from the International Multicentre ADHD Genetics (IMAGE) study. Multivariable analysis was performed to combine the effects of single genetic variants within the pathway genes. Phenotypes were DSM-IV symptom counts for inattention and hyperactivity/impulsivity (n = 871) and symptom severity measured with the Conners Parent (n = 930) and Teacher (n = 916) Rating Scales.

Results: Summing genetic effects of common genetic variants within the pathways showed a significant association with hyperactive/impulsive symptoms (p[sub]empirical[/sub] = .007) but not with inattentive symptoms (p[sub]empirical[/sub] = .73). Analysis of parent-rated Conners hyperactive/impulsive symptom scores validated this result (p[sub]empirical[/sub] = .0018). Teacher-rated Conners scores were not associated. Post hoc analyses showed a significant contribution of all pathways to the hyperactive/impulsive symptom domain (dopamine/norepinephrine, p[sub]empirical[/sub] = .0004; serotonin, p[sub]empirical[/sub] = .0149; neuritic outgrowth, p[sub]empirical[/sub] = .0452).

Conclusion: The present analysis shows an association between common variants in 3 genetic pathways and the hyperactive/impulsive component of ADHD. This study demonstrates that pathway-based association analyses, using quantitative measurements of ADHD symptom domains, can increase the power of genetic analyses to identify biological risk factors involved in this disorder.

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J Am Acad Child Adolesc Psychiatry. 2013;52:1173-82.

A POTENTIAL ELECTROENCEPHALOGRAPHY AND COGNITIVE BIOSIGNATURE FOR THE CHILD BEHAVIOR CHECKLIST-DYSREGULATION PROFILE.

McGough JJ, McCracken JT, Cho AL, et al.

Objective: The Child Behavior Checklist-Dysregulation Profile (CBCL/DP) identifies youth at increased risk for significant psychopathology. Although the genetic architecture and several biological correlates of the CBCL/DP have been described, little work has elucidated its underlying neurobiology. We examined the potential utility of electroencephalography (EEG), along with behavioral and cognitive assessments, in differentiating individuals based on the CBCL/DP.

Method: Participants aged 7 to 14 years of age were categorized into 3 age- and sex-matched groups based on clinical assessment and CBCL/DP: typically developing controls without attention-deficit/hyperactivity disorder (ADHD) (n = 38), individuals with ADHD without the CBCL/DP (ADHD/DP-) (n = 38), and individuals with the CBCL/DP (CBCL/DP+) (n = 38). Groups were compared with EEG and measures of clinical phenomenology and cognition.

Results: ADHD/DP- and CBCL/DP+ groups had increased inattention, but the CBCL/DP+ group had increased hyperactive/impulsive symptoms, disruptive behavior, mood, and anxiety comorbidities compared with the group with ADHD alone. Cognitive profiles suggested that ADHD/DP-participants had fast impulsive responses, whereas CBCL/DP+ participants were slow and inattentive. On EEG, CBCL/DP+ had a distinct profile of attenuated (delta)-band and elevated (alpha)-band spectral power in the central and parietal regions compared to ADHD/DP- and controls. The low-(delta)/high-(alpha) profile was correlated with measures of emotion and behavior problems and not with inattentive symptomatology or cognitive measures. There were no EEG differences between the ADHD/DP- and control groups.

Conclusions: An EEG/cognitive profile suggests a distinct pattern of underlying neural dysfunction with the CBCL/DP that might ultimately serve as a biosignature. Further work is required to identify potential relationships with clinically defined psychiatric disorders, particularly those of dysregulated mood.

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Neurol Sci. 2013;1-4.

SEQUENCE ANALYSIS OF THE ADRA2A CODING REGION IN CHILDREN AFFECTED BY ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Castro T, Mateus HE, Fonseca DJ, et al.

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral pathology characterized by distinct degrees of inattention, hyperactivity and impulsivity. Although ADHD etiology remains elusive, the ADRA2A candidate gene underlies a particular interest, since it participates in the prefrontal cortex regulation of executive function. Three SNPs located on 5' and 3'UTR regions of the gene have been extensively explored but none of them have been definitely validated as a predisposition or a causative sequence variation. In this study, in order to determine whether ADRA2A non-synonymous sequence variants, resulting in biochemical modifications of the protein, are a common cause of the disease we sequenced the complete ADRA2A coding region in a panel of ADHD children of Colombian origin. We identified the c.1138 C>A (p.Arg380Arg) silent substitution. We conclude that ADRA2A non-synonymous sequence variants do not cause ADHD in our sample population. We cannot formerly discard a potential role of this gene during ADHD pathogenesis since only the coding region was analysed. We hope that these results will encourage further researchers to sequence the promoter and coding regions of ADRA2A in large panels of ADHD patients from distinct ethnical origins.

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Neurosci Bull. 2013;29:603-13.

LOCAL SYNCHRONIZATION AND AMPLITUDE OF THE FLUCTUATION OF SPONTANEOUS BRAIN ACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RESTING-STATE FMRI STUDY.

An L, Cao QJ, Sui MQ, et al.

Regional homogeneity (ReHo) and the amplitude of low-frequency fluctuation (ALFF) are two approaches to depicting different regional characteristics of resting-state functional magnetic resonance imaging (RS-fMRI) data. Whether they can complementarily reveal brain regional functional abnormalities in attention-deficit/hyperactivity disorder (ADHD) remains unknown. In this study, we applied ReHo and ALFF to 23 medication-naive boys diagnosed with ADHD and 25 age-matched healthy male controls using whole-brain voxel-wise analysis. Correlation analyses were conducted in the ADHD group to investigate the relationship between the regional spontaneous brain activity measured by the two approaches and the clinical symptoms of ADHD. We found that the ReHo method showed widely-distributed differences between the two groups in the fronto-cingulo-occipito-cerebellar circuitry, while the ALFF method showed a difference only in the right occipital area. When a larger smoothing kernel and a more lenient threshold were used for ALFF, more overlapped regions were found between ALFF and ReHo, and ALFF even found some new regions with group differences. The ADHD symptom scores were correlated with the ReHo values in the right cerebellum, dorsal anterior cingulate cortex and left lingual gyrus in the ADHD group, while no correlation was detected between ALFF and ADHD symptoms. In conclusion, ReHo may be more sensitive to regional abnormalities, at least in boys with ADHD, than ALFF. And ALFF may be complementary to ReHo in measuring local spontaneous activity. Combination of the two may yield a more comprehensive pathophy-siological framework for ADHD.

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Pediatr Allergy Immunol. 2013.

FOOD ALLERGY AND FOOD-BASED THERAPIES IN NEURODEVELOPMENTAL DISORDERS.

De Theije CGM, Bavelaar BM, Lopes da Silva S, et al.

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders which occur in childhood and may persist into adulthood. Although the etiology of these disorders is largely unknown, genetic and environmental factors are thought to play a role in the development of ASD and ADHD. Allergic immune reactions, in prenatal and postnatal phases, are examples of these environmental factors, and adverse reactions to foods are reported in these children. In this review, we address the clinical and preclinical findings of (food) allergy in ASD and ADHD and suggest possible underlying mechanisms. Furthermore, opportunities for nutritional interventions in neurodevelopmental disorders are provided.

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Pediatr Clin North Am. 2014;61:81-90.

MANAGEMENT OF A HYPERACTIVE TEEN AND CARDIAC SAFETY.

Sowinski H, Karpawich PP.

Since the earliest descriptions of the condition, controversy has prevailed as to the existence of as well as appropriate management of attention deficit hyperactivity disorder. Often diagnosed in childhood, symptoms of attention deficit hyperactivity disorder can continue into adolescence and adulthood, requiring lifelong therapy. Effective therapeutic interventions include stimulant medications with all their respective potential side effects, including the cardiovascular system. However, although initial studies raised concerns for an increase in serious adverse cardiovascular effects among children receiving these drugs, more recent and extensive reports have failed to substantiate those findings among young patients.

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Pediatr Neonatol. 2013.

HYPERACTIVITY AND IMPULSIVITY IN CHILDREN WITH UNTREATED ALLERGIC RHINITIS: CORROBORATED BY RATING SCALE AND CONTINUOUS PERFORMANCE TEST.

Yang MT, Lee WT, Liang JS, et al.

Background: Allergic rhinitis (AR) is the most common chronic allergic disease in school-age children. An increased prevalence of attention deficit hyperactivity disorder (ADHD) in AR patients has been reported; however, inattention and hyperactivity in AR children have not been investigated using objective and scientific measurements

Methods: We used AR symptom score, ADHD symptom scale, and computerized continuous performance test (CPT) to study the attention and impulsivity in AR children, age-matched controls, and ADHD children (aged 6-15 years). Univariate and multivariate linear regression analyses were applied to identify risk factors for impulsivity and inattention in AR children.

Results: Twenty-nine controls, 10 ADHD, and 105 AR children were enrolled. There were no differences in age and gender among the three groups. The scores of Hyperactivity/Impulsivity subscales of ADHD symptoms from both parents and teachers were significantly higher in the AR children. The CPT in AR children revealed higher commission errors, shorter reaction times, and more perseveration. Risk factors for inattention and impulsivity in AR children included younger age, male gender, higher AR symptom scores, persistent AR, moderate/severe AR, multiple atopic diseases, family history of atopy, and possible comorbidity with ADHD.

Conclusion: Care for AR children should not only involve treating their allergy, but also monitoring the possible comorbidities of impulsivity and inattention. In children with impulsivity, AR should be considered in addition to ADHD.

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Perfusion. 2013;28:495.

COMMENTARY ON: ATTENTION DEFICIT/HYPERACTIVITY DISORDER AFTER NEONATAL SURGERY: REVIEW OF THE PATHOPHYSIOLOGY AND RISK FACTORS.

Sistino JJ.

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Pharmacopsychiatry. 2013;46:A57.

METHYLPHENIDATE REGULATES HEY1, SLC2A3, ATXN1, GUCY1B3 AND MAP3K8 IN LYMPHOBLASTOID CELLS FROM ADULT ADHD PATIENTS.

Schwarz R, Kittel-Schneider S, Weissflog L, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric condition of children. Up to 30% of adults with a history of childhood ADHD still display symptoms in later life. The worldwide prevalence of children is estimated about 5 - 10% and of adults up to 4%. ADHD is with a heritability of 80% one of the most heritable psychiatric disorders, but gene-environment interaction also contributes to the risk of disorder. Comorbidities in children are amongst others dyslexia and language development disorders, in adult patients major depression, bipolar disorder, alcohol and drug abuse and personality disorder can be seen. Methylphenidate (MPH) is a commonly used stimulant medication for treating ADHD. Besides inhibiting dopamine/norepinephrine reuptake, MPH is also influences gene expression levels. We investigated the impact on methylphenidate treatment of lymphoblastoid cells derived from adult ADHD patients and healthy control on gene expression levels. The results of a hypothesis-free microarray analysis and subsequent confirmation by quantitative Real Time PCR analysis showed ATXN1, MAP3K8, HEY1 and SLC2A3 expression to be influenced by methylphenidate treatment dependent on the diagnosis. GUCY1B3 expression was different between ADHD and healthy control cells. Our results demonstrate novel pathways for the mode of action of methylphenidate and molecular pathomechanism of ADHD and could point to different effects of MPH in ADHD patients compared to healthy controls.

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Pharmacopsychiatry. 2013;46:A99.

AMONG A SAMPLE OF IRANIAN STUDENTS, ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IS RELATED TO CHILDHOOD ADHD, BUT NOT TO AGE, GENDER, SOCIO-ECONOMIC STATUS OR BIRTH ORDER-AN EXPLORATORY STUDY.

Jahangard L, Haghighi M, Bajoghli H, et al.

Objective: The aim of the present study was explore the prevalence of adult attention deficit hyperactivity disorder (ADHD) in young adult Iranian students and to examine gender, birth order, socio-economic status (SES), and history of ADHD as potential predictors of adult ADHD.

Methods: A total of 387 young adult students (mean age: 19.6 years; 66.3% females) completed the Adult ADHD Self-Report-Scale-V1.1 symptom checklist to assess current symptoms of ADHD and the Wender-Utah-Rating-Scale to assess symptoms of ADHD in childhood and adolescence. Experts' ratings were based on Wender-Reimherr-Interview.

Results: Self-rated and expert-rated prevalence rates were 16.5%, and 13.4%, respectively. Past symptoms of ADHD were correlated with current symptoms. Childhood ADHD, current hyperactivity and disorganization predicted current ADHD.

Conclusions: Among a sample of Iranian students prevalence of ADHD was higher than estimated rates worldwide. Data also show child ADHD to be associated with adult ADHD; gender, age, birth order and SES did not seem to influence current symptomatology.

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Psychiatry Clin Neurosci. 2013.

ONE-WEEK TEMPORAL STABILITY OF HYPERACTIVITY IN PRESCHOOLERS WITH ADHD DURING PSYCHOMETRIC ASSESSMENT.

Miyahara M, Healey DM, Halperin JM.

Aim: To examine the usefulness of temporal measures of motor activity during psychometric assessment on two different assessment days, 1week apart with a scope to help the early identification of hyperactivity.

Methods: Actigraph measures at the ankle and the waist were compared on the first and the second days of psychometric assessment in a total of 169 children (93 children in ADHD group; 76 children in Non-ADHD group) aged 3 years and 4 years.

Results: There was a significant interaction effect between group and time on the activity level at the waist. Although the activity level of the waist in the children with ADHD did not significantly differ between Day 1 and Day 2, the activity level of the children without ADHD declined significantly from Day 1 to 2. A total of 70% of children were correctly classified into ADHD or Non-ADHD groups based only on Day 2 waist activity data.

Conclusion: The temporal consistency of hyperactivity in young children with ADHD during psychometric assessment is confirmed, indicating that objective measures of motor activity at the waist over different days of psychometric assessment can provide additional information for the stability of hyperactivity.

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Psychiatry Res. 2013.

NEGATIVE EMOTIONALITY MEDIATES THE ASSOCIATION OF 5-HTTLPR GENOTYPE AND DEPRESSION IN CHILDREN WITH AND WITHOUT ADHD.

Li JJ, Lee SS.

The 44-base-pair polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been implicated in the etiology of depression, but relatively little is known about potential mediators of this association. Although dimensions of temperament are likely to be proximal to the neurobiological and genetic factors underlying depression, studies have yet to formally evaluate temperament as a potential causal pathway. We examined individual differences in dimensions of temperament [negative emotionality (NE), prosociality (PRO), and daring (DA)] as potential mediators of 5-HTTLPR genotype and child depression. Using a multiple mediation framework, we tested the association of child 5-HTTLPR genotype

and these dimensions of temperament with multi-informant ratings of child depression in a sample of 218 children with and without attention-deficit/hyperactivity disorder (ADHD). The long allele of 5-HTTLPR was associated with higher NE and lower PRO, but not DA. High NE mediated the association of 5-HTTLPR genotype and separate parent and teacher ratings of depression. ADHD status did not moderate the mediational role of NE for 5-HTTLPR and depression. Results suggest that NE may constitute a pathway between 5-HTTLPR and child depression. The role of genetic variation and temperament dimensions as intermediate traits in the development of depression is discussed.

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Psychol Med. 2013 Sep;43:1973-84.

DIFFERENT HENTABILITIES BUT SHARED ETIOLOGICAL INFLUENCES FOR PARENT, TEACHER AND SELF-RATINGS OF ADHD SYMPTOMS: AN ADOLESCENT TWIN STUDY.

Merwood A, Greven CU, Price TS, et al.

Background: Parent and teacher ratings of attention deficit hyperactivity disorder (ADHD) symptoms yield high estimates of hentabihty whereas self-ratings typically yield lower estimates. To understand why, the present study examined the etiological overlap between parent, teacher and self-ratings of ADHD symptoms in a population-based sample of 11-12-year-old twins.

Method: Participants were from the Twins Early Development Study (TEDS). ADHD symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ) hyperactivity scale completed by parents, teachers and children. Structural equation modeling was used to examine genetic and environmental contributions to phenotypic variance/covariance.

Results: The broad-sense heritability of ADHD symptoms was 82% for parent ratings, 60% for teacher ratings and 48 % for self-ratings. Post-hoc analyses revealed significantly higher heritability for same-teacher than different-teacher ratings of ADHD (76% v. 49%). A common pathway model best explained the relationship between different informant ratings, with common genetic influences accounting for 84% of the covariance between parent, teacher and self-rated ADHD symptoms. The remaining variance was explained by rater-specific genetic and non-shared environmental influences.

Conclusions: Despite different heritabilities, there were shared genetic influences for parent, teacher and self-ratings of ADHD symptoms, indicating that different informants rated some of the same aspects of behavior. The low heritability estimated for self-ratings and different-teacher ratings may reflect increased measurement error when different informants rate each twin from a pair, and/or greater non-shared environmental influences. Future studies into the genetic influences on ADHD should incorporate informant data in addition to self-ratings to capture a pervasive, heritable component of ADHD symptomatology.

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Psychol Med. 2013 Sep;43:1997-2011.

FAMILIALITY OF NEURAL PREPARATION AND RESPONSE CONTROL IN CHILDHOOD ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Albrecht B, Brandeis D, Uebel H, et al.

Background: Patients with attention deficit-hyperactivity disorder (ADHD) exhibit difficulties in multiple attentional functions. Although high heritability rates suggest a strong genetic impact, aetiological pathways from genes and environmental factors to the ADHD phenotype are not well understood. Tracking the time course of deviant task processing using event-related electrophysiological brain activity should characterize the impact of familiality on the sequence of cognitive functions from preparation to response control in ADHD.

Method: Preparation and response control were assessed using behavioural and electrophysiological parameters of two versions of a cued continuous performance test with varying attentional load in boys with ADHD combined type (n = 97), their non-affected siblings (n = 27) and control children without a family history of ADHD (n = 43).

Results: Children with ADHD and non-affected siblings showed more variable performance and made more omission errors than controls. The preparatory Cue-P3 and contingent negative variation (CNV) following cues were reduced in both ADHD children and their non-affected siblings compared with controls. The NoGo-P3 was diminished in ADHD compared with controls whilst non-affected siblings were located intermediate but did not differ from both other groups. No clear familiality effects were found for the Go-P3. Better task performance was further associated with higher CNV and P3 amplitudes.
Conclusions: Impairments in performance and electrophysiological parameters reflecting preparatory processes and to some extend also for inhibitory response control, especially under high attentional load, appeared to be familially driven in ADHD and may thus constitute functionally relevant endophenotypes for the disorder.

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Psychopharmacology. 2013;230:69-76.

THE ASSOCIATION BETWEEN THE CATECHOL-O-METHYLTRANSFERASE VAL108/158MET POLYMORPHISM AND HYPERACTIVE-IMPULSIVE AND INATTENTIVE SYMPTOMS IN YOUTH.

Nikolac Perkovic M, Kiive E, Nedic Erjavec G, et al.

Rationale: Hyperactivity, impulsivity, and inattention are major symptoms occurring in attention-deficit/hyperactivity disorder. This disorder is highly heritable, multifactorial, polygenic, and associated primarily with dysfunctions of dopaminergic, noradrenergic, and serotonergic systems. Objectives: The present study tested the possible association of the catechol-O- methyltransferase (COMT) Val108/158Met (rs4680) polymorphism with hyperactive-impulsive and inattentive symptoms in male youth.
Method: Polymorphism COMT Val108/158Met was analyzed in 807 male unrelated Caucasian young subjects: 231 healthy controls, 195 subjects with moderate hyperactive symptoms and 254 subjects with moderate inattentive symptoms, 111 subjects with severe hyperactive symptoms and 90 subjects with severe inattentive symptoms, all evaluated using Swanson, Nolan, and Pelham Questionnaire IV criteria.
Results: The frequency of the COMT genotypes, alleles, and the homozygous Met/Met genotype versus Val carriers ((chi) 2 test with standardized residuals) differed significantly between subjects without and subjects with hyperactive-impulsive and inattentive symptoms. In addition, significantly higher hyperactive-impulsive and inattentive scores were found in subjects with the Met/Met genotype compared to carriers of other COMT genotypes. These significant results were due to the more frequent occurrence of Met/Met genotype or the Met allele in subjects with moderate and severe hyperactive-impulsive and inattentive symptoms compared to matched controls.
Conclusion: These results suggest that the Met/Met genotype or the Met allele of the COMT Val108/158Met, contributing to higher dopaminergic activity, are significantly overrepresented in subjects with moderate or severe hyperactive-impulsive and inattentive symptoms, and that this polymorphism is significantly associated with hyperactive-impulsive and inattentive symptoms in young boys and adolescents.

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Res Autism Spectr Disord. 2013 Nov;7:1339-45.

COMPARING THE RATES OF TANTRUM BEHAVIOR IN CHILDREN WITH ASD AND ADHD AS WELL AS CHILDREN WITH COMORBID ASD AND ADHD DIAGNOSES.

Konst MJ, Matson JL, Turygin N.

The current study investigated the presentation of tantrum behaviors in individuals with an autism spectrum disorder (ASD) diagnosis with and without a comorbid diagnosis of attention deficit hyperactivity disorder (ADHD). Participants included 347 children ranging in age from 2 to 18 years old. Diagnostic categories in the current study were based upon clinical diagnosis. The severity of ASD symptomology was measured by the Autism Spectrum Disorder-Diagnostic Child Version (ASD-DC). The presence and severity of tantrum behaviors were measured by the Tantrum behavior subscale of the Autism Spectrum Disorders-Comorbidity for Children (ASD-CC). The influence of diagnosis and ASD symptomology had upon the

expression of tantrum behaviors were examined, controlling for participant age. Initial analysis revealed significant differences in the expression of tantrum behavior between the ASD, ADHD and ASD/ADHD groups. However, age did not have a significant influence on the exhibition of tantrum behaviors. Follow-up analyses demonstrated that those individuals diagnosed with an ASD and a comorbid ADHD diagnosis exhibited significantly greater tantrum behavior. Post hoc analyses identified a significant positive correlation between increases in ASD symptomology and elevations of the severity of tantrum behaviors for each group. The observed correlation for the ADHD group was found to be significantly greater than the ASD group. Correlations for individual item responses of the ASD-CC were also computed and discussed for each diagnostic group.

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Res Autism Spectr Disord. 2013;7:1638-46.

A QUANTITATIVE COMPARISON OF HANDWRITING IN CHILDREN WITH HIGH-FUNCTIONING AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Johnson BP, Papadopoulos N, Fielding J, et al.

Children with high-functioning autism (HFA) and attention deficit hyperactivity disorder (ADHD) often experience significant handwriting difficulties, which can hamper their academic progress and ability to express themselves through symbols and words. Handwriting of children with HFA was compared to those with ADHD based on performance on the speed subtest of the Handwriting Performance Test. Differences in handwriting speed, size and alignment of words, and proportion of handwriting errors, such as corrections and substitutions, were assessed between groups. Results indicated distinct profiles of handwriting problems in HFA and ADHD: children with HFA demonstrated poorer spatial arrangement of words and reduced handwriting speed, and those with ADHD made more handwriting errors, such as corrections and transpositions. These findings have important implications in understanding the similarities and differences for children with HFA and ADHD and lay the groundwork for effective intervention strategies.

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Res Dev Disabil. 2014;35:87-98.

THE NEGATIVE ATTRIBUTION PROCESSES OF MOTHERS OF CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Huang HL, Li SS, Cheng CP, et al.

The objective of this study was to investigate the attribution processes of mothers regarding children's prosocial behaviors, inattention, and hyperactivity/impulsivity (symptoms of attention deficit/hyperactivity disorder, ADHD) using two paradigms. The first paradigm involved multidimensional attributions. The second paradigm concerned making attributions of children's identical behaviors based on information such as consensus, distinctiveness, and consistency. The participants were 64 mothers of children with ADHD (7-13 years old) and 64 mothers with typical/normal children (7-12 years old). The results showed that mothers of typical children exhibited positive attribution styles or person attributions whereas mothers of children with ADHD exhibited negative attribution styles. Mothers of children with ADHD tended to make personal attributions of children's negative behaviors (e.g., inattention and hyperactivity/impulsivity; HI) but made situational attributions of prosocial behaviors. The results of this study can be used in future studies of the effects of intervention on children with ADHD or in studies related to neurophysiology.

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Value Health. 2013;16:A549-A550.

COMPARISON OF HEALTH CARE RESOURCE UTILIZATION AND COSTS AMONG CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN GERMANY WHO INITIATED TREATMENT WITH ATOMOXETINE OR LONG-AC TING METHYLPHENIDATE.

Curtice TG, Greven P, Yeaw J, et al.

Objectives: This study compared health care resource utilization (HRU) and costs among children/adolescents with attention deficit/hyperactivity disorder (ADHD) in Germany who initiated treatment with atomoxetine (ATX) or long-acting methylphenidate (LA-MPH).

Methods: A retrospective propensity score matched cohort analysis was conducted using the IMS electronic medical record database comprising > 15 million patient records from -3,000 German physicians. Included patients were aged 6-17 years, with a first (index) ATX or LA-MPH prescription in 2006-2010; = 1 ADHD diagnoses 12-month before (pre-index) and after (post-index) index; and = 1 index medication prescription post-index. Patients in the ATX and LA-MPH sympcohorts were matched 1:1 using nullnearest neighbornull greedy match propensity score method. HRU (inpatient, outpatient, and medications) and costs were compared between the two cohorts. Unit costs were identified from German Diagnosis-related Group for inpatient, Einheitlicher Bewertungsmassstab doctor fee scale for outpatient and Rote Liste(registered trademark)for medication costs. Direct medical costs over the postindex period were reported in 2011 Euros. Chi-square for categorical variables and t-test or Wilcoxon-Mann-Whitney for continuous variables were used to test for differences between cohorts (alpha= 0.05). Generalized linear models with negative binomial (for HRU) and gamma (for cost) distributions were used to address residual differences between matched cohorts.

Results: Of 4705 eligible patients 737 with ATX (mean age= 10.9 years, 20.8% female) were identified and matched 1:1 with LA-MPH patients (mean age= 11.2 years, 18.6% female). Patients initiating ATX had higher HRU and spending per-patient than patients initiating LA-MPH over the post-index: 20.9 (SD= 11.5) vs. 15.7 (SD= 9.0) outpatient prescriptions, 10.1 (SD= 6.3) vs. 8.3 (SD= 5.3) outpatient visits, (euro) 1029 (SD= 574) vs. (euro) 496 (SD= 334) in retail pharmacy costs, and (euro) 1,258 (SD= 739) vs. (euro) 684 (SD= 515) in total all-cause costs (all p= < .0001).

Conclusions: Among children/adolescents with ADHD in Germany ATX initiators consumed significantly more health care resources and were associated with significantly higher direct medical costs compared with LA-MPH initiators.

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Article

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Iron and ADHD: Time to Move Beyond Serum Ferritin Levels

Renato Donfrancesco[1], Pasquale Parisi[2], Nicola Vanacore[3], Francesca Martines[1], Vittorio Sargentini[4], and Samuele Cortese[5,6,7]

Abstract

Objective: (a) To compare serum ferritin levels in a sample of stimulant-naïve children with ADHD and matched controls and (b) to assess the association of serum ferritin to ADHD symptoms severity, ADHD subtypes, and IQ. **Method:** The ADHD and the control groups included 101 and 93 children, respectively. Serum ferritin levels were determined with the enzyme-linked immunosorbent assay method. **Results:** Serum ferritin did not significantly differ between children with ADHD and controls, as well as among ADHD subtypes. Correlations between serum ferritin levels and measures related to IQ or ADHD severity were not significant. **Conclusion:** This is the largest controlled study that assessed ferritin levels in stimulant-naïve ADHD children. The findings of this study do not support a significant relationship between serum ferritin levels and ADHD. However, the authors' results based on peripheral measures of iron do not rule out a possible implication of brain iron deficiency in ADHD, grounded on neurobiological hypotheses and preliminary empirical evidence. *(J. of Att. Dis. 2013; 17(4) 347-357)*

Keywords

ADHD, iron, ferritin

With an estimated worldwide-pooled prevalence of approximately 5% in children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007), ADHD is one of the most common childhood neuropsychiatric conditions. According to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. text rev.; *DSM-IV-TR*; American Psychiatric Association [APA], 2000), ADHD is defined by a pervasive and age-inappropriate pattern of inattention, hyperactivity-impulsivity, or both. Despite an extensive worldwide literature (Wolraich, 1999), the genetic (Mick & Faraone, 2008) and environmental etiological factors (Millichap, 2008), as well as the exact pathophysiology underlying ADHD, are not well understood.

Intriguing albeit preliminary observations suggest that iron deficiency may be involved in the pathophysiology of ADHD, at least in a subset of patients (Cortese et al., 2008; Konofal, Lecendreux, Arnulf, & Mouren, 2004). Iron is an essential trace metal, which plays a central role in a multitude of biological processes, including many essential brain functions (Andrews, 1999). The iron deficiency hypothesis of ADHD is grounded on several lines of evidence. First, iron is a cofactor of enzymes necessary for the synthesis and catabolism of the monoaminergic neurotransmitters (Youdim, 2000), which are implicated in the pathophysiology of ADHD. Second, iron deficiency is associated with decreased dopamine transporter expression (Beard, Connor, & Jones, 1993); variation in the dopamine transporter gene has been linked to genetic vulnerability for ADHD (Mick & Faraone, 2008). Third, iron deficiency may lead to dysfunction in the basal ganglia (Youdim, Ben-Shachar, & Yehuda, 1989), which are believed to play a significant role in the pathophysiology of ADHD (Biederman & Faraone, 2005). Fourth, iron deficiency has been reported in children with cognitive and behavioral impairments that prominently include poor attention and hyperactivity (Lozoff et al., 2006).

Peripheral (i.e., in the body) iron status may be estimated by serum ferritin levels. To date, 14 studies assessing serum

[1]S. Pertini Hospital, ASL RM/B, Rome, Italy
[2]Sapienza University of Rome, Italy
[3]National Centre of Epidemiology, Surveillance and Health Promotion, National Health Institute, Rome, Italy
[4]ASL RM/A, Rome, Italy
[5]New York University Child Study Center, USA
[6]UMR_S INSERM U 930, CNRS ERL 3106, François-Rabelais University, Child Psychiatry Centre, University Hospital, Tours, France
[7]Verona University, Italy

Corresponding Author:
Samuele Cortese, Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, New York University Child Study Center, 215 Lexington Ave, 14th Floor, New York, NY 10016, USA.
Email: samuele.cortese@gmail.com

ferritin levels in children with ADHD have been published (Calarge, Farmer, DiSilvestro, & Arnold, 2010; Cortese et al., 2011; Cortese, Konofal, Bernardina, Mouren, & Lecendreux, 2009; Juneja, Jain, Singh, & Mallika, 2010; Kiddie, Weiss, Kitts, Levy-Milne, & Wasdell, 2010; Konofal et al., 2004, 2007; Menegassi et al., 2010; Millichap, Yee, & Davidson, 2006; O. Oner, Alkar, & Oner, 2008; O. Oner et al., 2010; P. Oner, Dirik, Taner, Caykoylu, & Anlar, 2007; P. Oner & Oner, 2008; Sever, Ashkenazi, Tyano, & Weizman, 1997). The main characteristics of these studies are summarized in Table 1, reporting demographic information of the participants, tools used to diagnose ADHD, prevalence of ADHD subtypes and psychiatric comorbidities, inclusion/exclusion criteria, data on pharmacological treatment, mean value of serum ferritin, and key findings for each study. We excluded from this table one case report (Konofal, Cortese, Lecendreux, Arnulf, & Mouren, 2005) and one trial (Konofal et al., 2008) that assessed only participants with selected values of serum ferritin (i.e., <30 ng/mL).

Most of the studies included in Table 1 have been correlational because they have explored the relationship between serum ferritin levels and ADHD symptoms severity within the ADHD group, without specifically assessing and including a comparison group. Findings from these correlational studies have been mixed: Whereas seven studies (Calarge et al., 2010; Cortese et al., 2009; Konofal et al., 2004, 2007; O. Oner, et al., 2008; O. Oner et al., 2010; P. Oner & Oner, 2008) found an inverse significant relationship between serum ferritin levels and ADHD symptoms severity, three other studies (Corteseet al., 2011; Juneja et al., 2010; Menegassi et al., 2010) failed to confirm a significant relationship. Also, the only three studies that included a control group have yield mixed findings: Whereas Konofal et al. (2004) and Juneja et al. (2010) reported significantly lower serum ferritin levels in ADHD versus controls, Menegassi et al. (2010) failed to replicate this finding.

All available studies on iron deficiency in ADHD have included school-age children. Most of the studies have used semistructured interviews according to formal criteria to confirm the diagnosis of ADHD. Most of the studies have included children with all the three subtypes of ADHD (i.e., combined, predominantly inattentive, and predominantly hyperactive-impulsive types) although some articles did not specify the ADHD subtype (Kiddie et al., 2010; Konofal et al., 2004, 2007; Millichap et al., 2006; P. Oner & Oner, 2008; Sever et al., 1997) or included only children with the combined subtype (O. Oner et al., 2010). Although most of the studies included all the three ADHD subtypes, none of them reported serum ferritin levels in relation to the subtype. This likely reflects the lack of statistical power for this analysis because the reviewed studies included small or relatively small sample (mean number of participants with ADHD across studies was approximately 48). This is unfortunate because there is a growing interest to better characterize the ADHD subtypes in terms of clinical phenotype, underlying neurobiology, and response to treatment, and it is not clear to which extent the current *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; APA, 1994) subtypes reflect different underlying neurobiological pathways (for a critical review, see Nigg, Tannock, & Rohde, 2010). Therefore, an exploratory investigation of a possible relationship of iron status to *DSM-IV* ADHD subtypes is warranted. With regard to inclusion and exclusion criteria, most of available studies excluded medical/neurological conditions affecting serum ferritin levels. However, studies are heterogeneous with respect to medication status of the participants. Whereas five studies (Cortese et al., 2009; Menegassi et al., 2010; O. Oner, et al., 2008, 2010; P. Oner et al., 2007) included stimulant-naïve participants, all the other studies reported data on children with current or previous history of pharmacological treatment with stimulants or other ADHD drugs. One of the well-known adverse effects of stimulant treatment (although generally manageable in the clinical practice) is appetite reduction (Graham et al., 2011). As pointed out (D'Amato, 2005), appetite reduction may lead to decreased oral intake of iron-rich foods, with consequent decrease in serum ferritin levels. Therefore, assessing iron status in stimulant-naïve individuals may avoid a possibly relevant bias. Very few studies have explored the relationship between serum ferritin levels and factors other than ADHD symptoms severity in individuals with ADHD. Cortese et al. (2009) found a significant inverse relationship between serum ferritin levels and severity of sleep-wake transition disorders. Calarge et al. (2010) reported evidence suggesting that serum ferritin levels are directly related to response to stimulant treatment. Only one study (O. Oner, et al., 2008) assessed the relationship between serum ferritin levels and cognitive/neuropsychological measures, reporting negative results.

Given the limitations and mixed findings in previous studies, further research in larger stimulant-naïve samples including a control group is warranted. Moreover, some underexplored aspects in this field of research, such as the degree of association between serum ferritin levels and ADHD severity, ADHD subtypes, or measures of cognitive functioning, deserve investigation. The main aim of this study was to overcome limitations and unresolved issues of previous research by comparing serum ferritin levels in a larger sample of 101 stimulant-naïve children with ADHD and 93 matched controls. The secondary aim was to assess the association of serum ferritin levels to measures of ADHD symptoms severity, ADHD subtypes, and IQ.

Table 1. Characteristics of Studies Assessing Serum Ferritin Levels in Individuals With ADHD.

	ADHD		Controls							SF (ng/mL)	
Reference	*n* (*M*)	Age (*SD*)	*n* (*M*)	Age (*SD*)	Diagnostic tool(s)	ADHD subtype	Psychiatric comorbid disorders	Inclusion criteria	Exclusion criteria	Pharmacological treatment	*M* (*SD*)	Key finding(s)
Cortese et al. (2011)	18 (16)	9.8 (1.4)	9 (5)	10 (2.1)	K-SADS-PL	*n* = 13: C; *n* = 4: I; *n* = 1: HI	No comorbid disorders (except *n* = 2: ODD)	ADHD according to *DSM-IV* criteria	Other comorbid psychiatric disorders (except ODD), IQ < 70, any neurological disease, any medical condition or drug affecting SF	All stimulant naïve except *n* = 3	ADHD: 32.4 (13.4); controls: 51.6 (16.4)	Significantly lower SF in ADHD vs. controls. Significantly lower thalamic iron levels in ADHD vs. controls. No significant relationship between SF and brain iron levels
Calarge, Farmer, DiSilvestro, and Arnold (2010)	52 (43)	10.0 (2.6)	NA	NA	P-chips	*n* = 38: C; *n* = 14: I	*n* = 34: ODD; *n* = 10: LD; *n* = 9: AD; *n* = 5: PD; *n* = 4: ED	ADHD C or ADHD I; ADHD scores > 1.5 (more than 3)	Comorbid psychiatric disorders requiring pharmacotherapy other than psychostimulants, serious medical disorders, zinc supplementation, current infection/ inflammation, contraindications to zinc or amphetamine	*n* = 22: previous treatment with psychostimulant, α-2-agonists, or ATMX	18.4 (11.4; total); stimulant naïve: 18.7 (12.1); stimulant treated: 18.0 (10.6)	At baseline, 83% of participants had SF < 30 ng/mL; 23% had SF < 7 ng/mL. SF inversely correlated with ADHD symptoms severity. No significant differences in SF concentration between previously treated and medication-naïve participants
Kiddie, Weiss, Kitts, D. Levy-Milne, and Wasdell (2010)	44 (37)	8.5 (NS)	NA	NA	K-SADS-E	NS	NS	ADHD according to *DSM-IV*	Any medical conditions and drugs (except stimulants and atomoxetine) altering nutritional status	*n* = 18: stimulant treated; *n* = 9: ATMX treated; *n* = 17: ADHD drugs-naïve	6-8 years: 36.9 (19.7); 9-11 years: 39.7 (17.2)	Mean SF in ADHD not significantly different compared with mean SF in national population norms
Menegassi et al. (2010)	41 (31)	8.8 (2.4) 9.0 (2.6)	21 (15)	8.9 (2.7)	K-SADS-E	*n* = 27: C; *n* = 10: I; *n* = 4: HI	*n* = 21: ODD; *n* = 2: CD	ADHD according to *DSM-IV* criteria	IQ < 70, psychiatric disorders other than ODD or CD, and medical conditions interfering with serum iron levels	2 groups (*n* = 19: current stimulant treatment; *n* = 22: stimulant naïve)	Stimulant treated 59.3 (21.0); stimulant naïve: 54.2 (17.2)	No significant differences in mean SF between ADHD (treated or stimulant naïve) and controls; no significant correlation between SF and ADHD severity

(continued)

Table 1. (continued)

Reference	ADHD *n* (*M*)	ADHD Age (*SD*)	Controls *n* (*M*)	Controls Age (*SD*)	Diagnostic tool(s)	ADHD subtype	Psychiatric comorbid disorders	Inclusion criteria	Exclusion criteria	Pharmacological treatment	SF (ng/mL) *M* (*SD*)	Key finding(s)
O. Oner et al. (2010)	118 (97)	9.8 (2.3)	NA	NA	K-SADS-PL	All: C	*n* = 50: ODD; *n* = 32: AD or DD	ADHD according to *DSM-IV* criteria	Medical conditions, psychosis, EaD, SUD, PDD	All: naïve	NS	CPRS hyperactivity scores significantly correlated with SF
Juneja, Jain, Singh, and Mallika (2010)	25 (21)	8.4 (1.7)	25 (21)	7.9 (1.5)	Clinical interview (*DSM-IV-TR* criteria)	*n* = 23: C; *n* = 2: HI	*n* = 11: ODD; *n* = 2: CD	ADHD according to *DSM-IV-TR*; hemoglobin > 10 g/dL; CPRS and CTRS *T*-scores > 65	Iron therapy, IQ < 85, any chronic illness, any severe illness in the past 2 weeks, autism	NS	6.04 (3.85)	SF < 12 ng/mL in 92% of participants with ADHD; SF significantly lower in participants with ADHD than controls. SF inversely correlated with oppositional subscore of the CPRS, not with I or HI subscales
Cortese, Konofal, Bernardina, Mouren, and Lecendreux (2009)	68 (56)	9.1 (2.4)	NA	NA	K-SADS-PL	*n* = 40: C; *n* = 9: HI	*n* = 20: ODD, GAD, P, DYS, SAD, OCD, TS, CD, MDD, TIC (total *n* = 43)	ADHD according to *DSM-IV*	NA (naturalistic study) but no patients with anemia or infection; all stimulant naïve	All: ADHD treatment-naïve	38.5 (26.7)	SF < 45 ng/mL in 41 participants; SF inversely correlated with CPRS-ADHD index scores. SF < 45 ng/mL associated with risk for sleep-wake transition disorders
Oner et al. (2008)	52 (42)	9.9 (2.1)	NA	NA	K-SADS-PL	*n* = 47: C; *n* = 4: I; *n* = 1: HI	*n* = 9: ODD; *n* = 1: C; *n* = 6: A; *n* = 1: DD; *n* = 2: ED	ADHD according to *DSM-IV*	Any medical condition, psychosis, eating disorders, SUD, PDD, MR	All: stimulant naïve	30.6 (15.4)	CPRS hyperactivity score significantly correlated with SF; no significant correlation between SF and neuropsychological tests scores
Oner et al. (2008)	151 (127)	9.9 (2.8)	NA	NA	K-SADS-PL	NS	LD, AD, Tic, ED, DD, CD (total: *n* = 45)	ADHD according to *DSM-IV*	Any medical condition, psychosis, eating disorders, SUD, PDD, MR	All: stimulant naïve	ADHD without comorbid disorders: 30.3 (14.3); ADHD with comorbid disorders: 33.1	CPRS and CTRS total scores inversely correlated with SF in the total ADHD group and in the subgroup with, but not in the subgroup without, comorbid disorders

Konofal et al. (2007)	22 (17)	ADHD without RLS: 6.7 (0.9); ADHD with RLS: 7.3 (1.2)	10 (7)	7.0 (0.9)	Clinic interview (*DSM-IV-TR* criteria)	NS	NA	ADHD according to *DSM-IV*	Additional behavioral, mood and anxiety disorders, physical diseases and malnutrition	All drug free when 21 (11) evaluated		Mean SF significantly lower in ADHD vs. controls; ADHD symptom severity higher in ADHD with RLS; Mean SF < in ADHD + RLS vs. ADHD
P. Oner, Dirik, Taner, Caykoylu, and Anlar (2007)	87 (79)	9.3 (2.5)	NA	NA	K-SADS-PL	*n* = 80: C; *n* = 7:1	*n* = 8: ODD; *n* = 10: AD; *n* = 1: DD; *n* = 9: ED; *n* = 3: SD; *n* = 16: LD	ADHD according to *DSM-IV*	Sleep disorders, epilepsy, peripheral neuropathy, radiculopathy, psychosis, mental retardation, and any acute medical conditions affecting iron	All: stimulant naïve	NS	Rates of iron deficiency (SF < 12 ng/mL) was significantly higher in ADHD + RLS children compared with ADHD-RLS children
Millichap, Yee, and Davidson (2006)	68 (54)	5-16	NA	NA	Clinical interview	NS	NS	NS	NS	NS	39.9 (40.6)	Mean SF compared with mean SF in national population norms. Clinical characteristics of children with SF > 20 ng/mL and < 20 ng/mL were not significantly different
Konofal, Lecendreux, Arnulf, and Mouren (2004)	53 (45)	9.2 (2.2)	27 (20)	9.5 (2.8)	Clinical interview (*DSM-IV-TR* criteria)	NS	NA	ADHD according to *DSM-IV*	Mental retardation, mood, anxiety disorders, physical diseases, malnutrition	All: drug free for at least 2 months	23 (13)	Mean SF significantly lower in children with ADHD vs. controls; 84% of ADHD children: SF < 30 ng/mL; 32%: SF < 15 ng/mL. In ADHD, SF significantly correlated with CPRS total score and CPRS inattentive score
Sever, Ashkenazi, Tyano, and Weizman (1997)	14 (14)	8.9 (1.4)	NA	NA	Clinical interview	NS	NS	ADHD according to *DSM-III-R* criteria	IQ < 80, any medical or neurological disease, CD, PDD	Drug free for at least 3 months	25.9 (9.3)	Significant increase in SF and decrease in CPRS scores after 30 days oral iron supplementation. No significant changes in CTRS

Note: ATMX = atomoxetine; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic; DYS: dysthimic disorder; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*–4th ed.; SF = serum ferritin; ADHD subtypes: C = combined subtype; I = predominantly inattentive; HI = predominantly hyperactive-inattentive subtype; ODD = oppositional defiant disorder; LD = learning disorders; AD = anxiety disorders; PD = phonological disorder; ED = elimination disorder; SAD = separation anxiety disorder; DD = depressive disorders; EaD = eating disorders; SUD = substance use disorders; PDD = pervasive developmental disorders; *DSM-IV-TR* = *Diagnostic and Statistical Manual of Mental Disorders*–4th ed.. text rev.; NS = not specified; CPRS = Conners' Parent Rating Scale; CTRS =Conners' Teacher Rating Scale; GAD = generalized anxiety disorder; P = simple phobias; OCD = obsessive compulsive disorder; TS = Tourette syndrome; MDD = major depressive disorder; MR = mental retardation; SD = speech disorder; RLS = restless legs syndrome; *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders*–3rd ed., revised (American Psychiatric Association, 1987).

Method

The present study was conducted at the Child Neuropsychiatry Outpatient Service of "Azienda Sanitaria Locale (ASL) Roma A," Rome (Italy). This was a joint collaborative project with the chair of pediatrics at Second Faculty of Medicine, "Sapienza" University of Rome. Children were referred to the Child Neuropsychiatry Outpatient Service following parent complaints of restlessness and/or inattention and/or "school problems."

Participants

ADHD participants. All 6- to 14-year-old children newly consecutively diagnosed with ADHD in the Outpatient Service of "ASL Roma A" from January 2009 to September 2010 were included in the present study. The age range was selected to include as much of the age range most representative of "classic" childhood ADHD. Exclusion criteria were as follows: (a) intellectual deficiency (Full Scale IQ < 70 on the Wechsler Intelligence Scale for Children–Third Edition [WISC-III]–Italian Version [Orsini & Picone, 2006], plus impairment in adaptive function, according to Criterion 2 of the *DSM-IV-TR* [APA, 2000]); (b) any neurological diseases—Criteria (a) and (b) were intended to reduce neurobiological heterogeneity which may affect iron status; and (c) any chronic conditions or diseases (e.g., anemia or celiac disorder) as well as acute inflammatory conditions that could affect peripheral iron status. All children with ADHD recruited in the study were stimulant naïve since at first diagnosis. We point out that in Italy, psychostimulant treatment is allowed only after an accurate diagnostic process confirming a formal diagnosis of ADHD. Following the diagnosis, children with ADHD are registered in a "National Surveillance Register" (see Panei et al., 2004), and then the treatment can be started. Therefore, it is infrequent to find children treated with psychostimulants before a formal diagnosis of ADHD.

Controls. A control group matched for age and gender was randomly recruited among the children seen by family pediatricians in routine care in the same local area. The family pediatricians collaborating with the authors were asked to refer children suitable as control participants for the study. Therefore, the pediatricians were asked to refer only healthy children, that is, children without chronic or acute medical conditions as well as without known mental disorders according to their medical records and a detailed clinical interview.

The study was conducted in accordance with the Declaration of Helsinki (International Committee of Medical Journal Editors, 1989). Written informed consent was obtained from the parents of all participants, and written assent was obtained from all children.

Procedures

Psychiatric and psychometric evaluation. Psychiatric diagnoses were established according to *DSM-IV-TR* criteria (APA, 2000) and confirmed by means of the semistructured interview Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) conducted by an experienced child psychiatrist (R. D.). The parents and schoolteachers of all the children in the ADHD group were also asked to fill out the ADHD–Rating Scale (ADHD-RS) adapted for the Italian population (Marzocchi & Cornoldi, 2000). The WISC-III–Italian Version (Orsini & Picone, 2006), was used to estimate the IQ. For logistic reasons, it was not possible to perform the assessment with the K-SADS-PL, the ADHD-RS, and the WISC-III in the control participants. However, before being referred to the study, control participants were carefully interviewed by the local pediatricians who were specifically trained in the diagnosis of ADHD according to the *DSM-IV-TR*. Therefore, ADHD in the control participants was ruled out on the basis of clinical interview.

Medical assessment. Medical history, neurological and physical examinations, and electroencephalogram during sleep were performed in all ADHD participants to exclude comorbid medical and neurological conditions. Blood samples were collected by a registered nurse in the morning from each participant to obtain serum ferritin (the main parameter of this study), as well as other measures, including serum iron, a complete blood count, globular volume, and hemoglobin values. Serum ferritin levels were determined by means of the enzyme-linked immunosorbent assay (ELISA) method (http://www.bio.davidson.edu/courses/genomics/method/ELISA.html).

Statistical Analysis

Demographic and clinical data are presented as means and standard deviation and categorical data. The ADHD-RS scores are presented as raw scores (minimum total score = 0, maximum total score = 54, minimum total score for ADHD = 12, minimum score in each of the two subscales [predominantly inattentive, predominantly hyperactive-impulsive] = 0, maximum score in each of the two subscales = 27, minimum score in each subscale for ADHD = 12). Two-tailed *t* tests for independent samples were used to compare age, serum ferritin levels, red cell number, and globular volume value in children with ADHD versus controls. One-way ANOVA was used to compare age, serum ferritin levels, red cell number, and globular volume value among children with ADHD inattentive subtype, ADHD hyperactive-impulsive subtype, combined subtype, and control group. A chi-square test and odds ratio (OR) with

Table 2. Demographic and Biochemical Data of Participants With ADHD and Controls.

	ADHD (n = 101)	Controls (n = 93)	p^a
Sex (M/F)	92/9	82/11	NS
Age (months)	107.25 ± 30.24	110.01 ± 36.92	NS
Serum ferritin (ng/mL)	33.01 ± 17.79	33.14 ± 18.73	NS
Red cells (millions)	4.89 ± 0.38	4.79 ± 0.29	.05
Globular volume (mm^3)	80.70 ± 5.87	80.21 ± 4.71	NS

[a]Chi-square or *t* test for independent samples.

Table 3. Demographic and Biochemical Data of ADHD Groups.

	Inattentive ADHD (n = 28)	Hyperactive-impulsive ADHD (n = 27)	Combined ADHD (n = 46)	Control group (n = 93)	p^a
Sex (M/F)	24/4	24/3	41/5	82/11	NS
Age (months)	117.3 ± 31.2	95.6 ± 30.9	107.6 ± 27.8	110.0 ± 36.9	NS
Serum ferritin (ng/mL)	32.9 ± 20.5	29.6 ± 15.1	34.5 ± 17.7	33.1 ± 18.7	NS
Red cells (millions)	4.9 ± 0.3	4.9 ± 0.4	4.9 ± 0.4	4.8 ± 0.3	NS
Globular volume (mm^3)	81.5 ± 4.6	79.5 ± 6.0	80.6 ± 6.5	80.2 ± 4.7	NS

[a]Chi-square or ANOVA analysis.

relative confidence intervals (CI) were used for categorical variables. A correlation analysis using Pearson's correlation was performed between serum ferritin values and behavioral data (i.e., ADHD symptoms severity, assessed with the ADHD–Rating Scale–Total score [ADHD-RS-TOT], ADHD–Rating Scale–Hyperactive Impulsive score [ADHD-RS-HI], and ADHD–Rating Scale–Inattentive score [ADHD-RS-I]) as well as cognitive scores (IQ: Full Scale IQ [FSIQ], Verbal IQ [VIQ], Performance IQ [PIQ]). A probability level of $p < .05$ was used to indicate statistical significance. Statistical analyses were performed using SPSS v15.0 (SPSS, Inc., Chicago, IL, USA).

Results

In all, 113 children were referred for ADHD symptoms evaluation, and 96 controls were assessed for inclusion criteria. A total of 7 children with ADHD-like symptoms presented with Full Scale IQ < 70 and were therefore excluded; 5 children in the ADHD group and 3 in the control group were excluded from statistical analysis due to nonavailability of ADHD-RS or refusal to give blood sample. No other children were excluded because of exclusion criteria. Therefore, analyses were conducted on a sample of 101 children with ADHD (males: n = 92) and 93 controls (males: n = 82).

Demographic and biochemical data are reported in Tables 2 and 3. Psychiatric comorbid disorders in the ADHD group were as follows: 42 ADHD children presented with oppositional defiant disorder (ODD), 16 with generalized anxiety, 4 with major depressive disorder, and 1 with dysthymic disorder. None of the participants were treated with antiepileptic or oral antipsychotic. Two-tailed *t* tests showed that age, serum ferritin, and globular volume did not significantly differ between children with ADHD and controls. Red cells number was significantly higher in children with ADHD than in controls, although marginally (p = .05). According to the cutoff used by Konofal et al. (2004) to indicate iron deficiency in children (30 ng/mL), patients with ADHD were more likely to present the lowest ferritin values, although not significantly (OR = 0.78, CI 95% = [0.44, 1.37]; p = .392). One-way ANOVA showed that age, serum ferritin, red cells, and globular volume did not significantly differ among children with ADHD inattentive subtype, ADHD hyperactive-impulsive subtype, combined subtype, and controls (Table 3).

Table 4 reports descriptive data regarding FSIQ, VIQ, PIQ, ADHD-RS-TOT, ADHD-RS-HI, and ADHD-RS-I. All correlations between serum ferritin levels and the aforementioned cognitive/behavioral data were not significant, either collapsing all the participants in one group or considering children with ADHD and controls separately (data not shown).

Discussion

To our knowledge, this is the largest study that assessed serum ferritin levels in stimulant-naïve children with ADHD and controls matched for gender and age. We found a nonsignificant difference in serum ferritin levels between children

Table 4. Descriptive Cognitive and Behavioral Data of ADHD Group.

	M	*SD*	Minimum	Maximum
FSIQ	101.0	14.1	69	134
VIQ	106.6	14.7	67	141
PIQ	97.9	15.1	58	147
ADHD-RS-TOT	36.2	8.5	16	52
ADHD-RS-HI	18.2	5.5	6	29
ADHD-RS-I	18.2	4.9	1	27

Note: FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ; ADHD-RS-TOT = ADHD–Rating Scale–Total score; ADHD-RS-HI = ADHD–Rating Scale–Hyperactive-Impulsive score; ADHD-RS-I = ADHD–Rating Scale–Inattentive score.

with ADHD and controls. Moreover, the associations between serum ferritin levels and ADHD symptoms severity, ADHD subtypes, or IQ were not significant.

Considering the other available controlled studies on iron status in ADHD, our main finding (i.e., non significant difference in serum ferritin levels between children with ADHD and comparisons) is in line with the report by Menegassi et al. (2010), but in contrast with the results by Konofal et al. (2004) and Juneja et al. (2010). Among others, two factors may explain these discordant results. First, it has been pointed out that psychostimulants or other psychotropic medications may affect appetite and, consequently, alter serum ferritin levels (D'Amato, 2005). Juneja et al. (2010), who found significantly lower serum ferritin levels in children with ADHD compared with controls, did not specify the medication status of their participants previously to the study inclusion, and, therefore, their study is not informative in this respect. Therefore, it is possible that the significant differences reported were accounted for by stimulant treatment not mentioned in the text. Konofal et al. (2004), who also found significantly lower serum ferritin levels in children with ADHD compared with controls, used a 2-month wash-out period from previous psychostimulant treatment. However, as reported by Menegassi et al. (2010), it is not clear whether this prior period of medication suspension would be sufficient to normalize possible nutritional deficiencies due to previous treatment. Whereas, Menegassi et al. reported no significant difference in serum ferritin levels between stimulant-naïve children with ADHD and controls. Indeed, they also found no significant differences between controls and children with ADHD treated with methylphenidate. However, serum ferritin levels were lower (although not significantly) in children with ADHD treated with stimulants. Because the treatment lasted only for 3 months, we cannot exclude, on a theoretical ground, that a longer period of treatment would have led to significantly lower serum ferritin values in children with ADHD treated with stimulants versus controls, although this remains speculative because there is no empirical evidence indicating to which extent and how methylphenidate affects serum ferritin levels. Second, different techniques to measure serum ferritin levels between our study (ELISA) and the study by Konofal et al. (2004; Elecsys Enzymun-Test) were used. We are not aware of a head-to-head comparison of these two techniques, so we cannot exclude different specificity and sensitivity of these two techniques, leading to possible different results in serum ferritin values. Third, our study was conducted in a different country (Italy) compared with those by Konofal et al. (2004) and Juneja et al. (2010; France and India, respectively). However, we do not think that these differences may account for the discrepancy in the results among our study and those by Konofal et al. (2004) and Juneja et al. (2010) because it is unlikely that differences in techniques or geographic location affected selectively on ADHD or controls.

We point out that the mixed findings on serum ferritin levels reported in available controlled studies (including the present one) of children with ADHD should not suggest that iron deficiency is not involved in the pathophysiology of ADHD. Indeed, serum ferritin is a marker of peripheral (i.e., not in the brain) iron status. The extent to which serum ferritin correlates with brain iron levels remains unclear (Cortese et al., 2011). In the study by Cortese et al. (2011), there was a trend, which, however, did not reach statistical significance, for correlation of serum ferritin levels with brain iron levels in most of the brain regions assessed. Previous studies of other disorders have yielded mixed findings. Whereas one study (Argyropoulou et al., 2000) found a significant relationship in beta-thalassemia major, and another (Christoforidis et al., 2007) reported only a moderate correlation (r = .56) in the same disease, other authors (Godau, Klose, Di, Schweitzer, & Berg, 2008) failed to find a significant correlation in restless legs syndrome (RLS). Therefore, there is no solid evidence to state that ferritin is a highly reliable marker of brain iron, although it may roughly estimate it. Because brain iron is what is expected to affect neuronal functions and myelination of white matter (Lozoff, 2011; Georgieff, 2008) expected to underpin ADHD symptoms, we suggest that, besides an assessment of peripheral iron markers, an estimation of brain iron levels is crucial to establish a possible role of iron deficiency in the pathophysiology of ADHD. A reduced amount of peripheral iron may have an impact on central levels of iron. However, normal peripheral ferritin levels do not always necessarily reflect normal brain iron. For instance, a dysfunction in the blood-brain barrier would lead to decreased entry of iron in the brain, and, therefore, to reduced brain iron levels in the presence of normal peripheral ferritin values. To this regard, Cortese et al. (2011) recently published a pilot study assessing brain iron levels in ADHD. They found significant lower levels of

estimated brain iron in the thalamus bilaterally in ADHD children versus controls. Although serum ferritin levels were correlated with estimated brain iron, this association failed to reach statistical significance in most of the brain regions assessed. Recently, a deficit in the entry of iron in the brain has been reported in patients with RLS (Connor et al., 2011). It has been observed that patients with RLS appear to have marginal central nervous system iron levels (Allen & Earley, 2007). These levels can become insufficient for an appropriate brain functioning even with normal peripheral iron (Allen & Earley, 2007). Interestingly, it has been reported that RLS may be comorbid with ADHD (Cortese et al., 2005), thus suggesting that these two disorders might share common underlying pathophysiological mechanisms. Accordingly, we speculate that dysfunction in the blood-brain barrier or iron transport mechanisms also in children with ADHD (with or without RLS) may account for a possible mismatch between peripheral and central iron. Unfortunately, given the unavailability of a formal Italian translation of the official RLS research criteria for RLS in children, we could not collect methodologically sound data about the prevalence of RLS in our sample.

With regard to the second aim of our study, the lack of significant association between serum ferritin levels and ADHD symptoms severity is in contrast with the results by seven studies (Calarge et al., 2010; Cortese et al., 2009; Konofal et al., 2004, 2007; O. Oner, et al., 2008, 2010; P. Oner & Oner, 2008) but in agreement with three other studies (Cortese et al., 2011; Juneja et al., 2010; Menegassi et al., 2010). As it can be the case with mixed results from small or relatively small samples, we cannot exclude that positive results were accounted for in a Type I error. Moreover, the lack of significant correlation between serum ferritin levels and measures of cognitive function confirms, in a larger sample, the results by O. Oner, et al. (2008). The same considerations on central versus peripheral iron status apply also to the results related to our second aims.

Our results should be considered in the light of some limitations. First, we did not perform a formal evaluation of the nutritional status and eating patterns of the participants. We note that, unfortunately, none of the available studies has reported a specific assessment of eating patterns. As previously stated, D'Amato (2005) pointed out that possible differences in iron status between those with ADHD and controls may be accounted for by appetite abnormalities. These might be related not only to stimulant treatment but also to other factors independent of stimulant treatment, such as, for example, putative alterations of eating patterns in ADHD (Cortese, Bernardina, & Mouren, 2007), which might, on a theoretical ground, alter iron intake. However, although the evaluation of eating patterns might have been of relevance on the case of significant differences between ADHD children and controls, to shed light on possible reasons underlying the difference, it seems less necessary given our results showing no significant differences. Second, the K-SADS-PL was not performed in the control participants. However, ADHD in the controls was ruled out by means of a clinical interview by the local pediatricians specifically trained in recognizing the symptoms of ADHD according to the *DSM-IV* criteria. Third, only White participants were included. Further studies should assess the impact of race on the relationship between ADHD and iron status because it has been reported that mean serum ferritin levels vary according to race in children (Brotanek, Gosz, Weitzman, & Flores, 2007) and adults (Zacharski, Ornstein, Woloshin, & Schwartz, 2000). Notwithstanding these limitations, we think that our study adds to the previous literature on iron status and ADHD addressing underexplored issues on the relationship between serum ferritin levels and ADHD. Our study suggests no relationship between serum ferritin levels and ADHD. However, we think that the key result of this article should not be a reason to dismiss research on the relationship between ADHD and iron status. Considering the preliminary results by Cortese et al. (2011) along with our study, the largest in the field based on serum ferritin and free of possible bias, we conclude that if we rely only on serum ferritin, we might miss the opportunity to find a true relationship between low iron status and ADHD. Therefore, we advocate a high level and methodologically sound modern investigation of the relationship between ADHD and iron status.

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Author Biographies

Renato Donfrancesco, MD, completed his training as pediatrician at Florence University (Italy) and as child neuropsychiatrist at Pisa University (Italy). He is now senior consultant at the child neuropsychiatry department, S. Pertini Hospital, Rome (Italy), where he is also the director of the Regional ADHD Center. His research areas of interest are ADHD, bipolar disorder, and the medical features of dyslexia.

Pasquale Parisi, MD, PhD, completed his training at Naples University (Italy) first as pediatrician and later as neurologist, and his PhD in child neuropsychiatry at Sapienza University, Rome (Italy). He is professor of pediatrics and child neurology at Second Faculty of Medicine at Sapienza University in Rome. His research interests include epilepsy, headache, ADHD, neurocutaneous, and other genetic syndromes. He has published more than 180 articles in pediatric and neuropediatric journals (about 100 with *impact factor* indexed in PubMed).

Nicola Vanacore, MD, PhD, is researcher at the National Centre of Epidemiology, Surveillance and Health Promotion, Italian National Institute of Health. His research activity focuses on neuroepidemiology, in particular of dementia, Parkinson's disease, and amyotrophic lateral sclerosis. He published more than 150 articles in national and international scientific journals.

Francesca Martines, PsyD, completed her training as clinical neuropsychologist at University La Sapienza, Rome (Italy), with a research project on the psychological features of bipolar disorder comorbid with ADHD. Currently, she collaborates with the Regional ADHD Center of S. Pertini Hospital in Rome. She has published in the field of dyslexia and ADHD.

Vittorio Sargentini, MD, completed his training at the University La Sapienza, Rome (Italy). He is now the codirector of the laboratory of the Italian National Health System in Rome. He collaborates with the regional ADHD Center of the Hospital La Scarpetta in Rome on projects focused on ADHD.

Samuele Cortese, MD, PhD, completed his MD, child neuropsychiatry residency, and PhD in biomedical imaging at the University of Verona (Italy). He is currently a postdoctoral research fellow at the Institute for Pediatric Neuroscience of the New York University Child Study New Center, New York City, under the mentorship of professor F. Xavier Castellanos. His main research interests focus on the neurobiology of ADHD. He is author/coauthor of 43 publications with impact factor (first author in 25 publications; total impact factor: 140; H factor: 10). Since 2009, he has been a member of the scientific committee of the European ADHD guidelines group (EUNETHYDIS).

P.7.d.010 Growth on stimulant medication: effects in children with ADHD

S. Carucci[1]*, T. Usala[2], F. Granitzio[1], C. Balia[1], D. Coghill[3], A. Zuddas[1] [1]*University of Cagliari, Biomedical Science Centre for Pharmacological Therapies in Child & Adolescent Neuropsychiatry, Cagliari, Italy;* [2]*University of Messina, Clinical and Sperimental of Medicine and Pharmacology, Messina, Italy;* [3]*University of Dundee, Division of Neuroscience Medical Research Institute, Dundee, United Kingdom*

Background: Stimulant medications represent the main effective treatment in improving the core symptoms of ADHD. However, in the last 30 years, there has been increasing concern about the risks associated with these medications in particular with respect possible growth deficits, due to their impact on weight, height and BMI. This has highlighted the need for long-term studies.

Objectives: The purpose of this study was to evaluate, within a systematic review and a prospective study, whether methylphenidate interferes with growth in children affected by ADHD and to assess whether the effects on growth are related to length of treatment or dose/kg/day or are more evident during the early stages of therapy.

Methods: For the systematic review a Pubmed search and a centralized search using Ovid Medline, Embase and PsychInfo was carried out up to January 2013. The systematic review was centered on human studies focusing on the impact of chronic methylphenidate and stimulants exposure on growth in children and adolescents affected by ADHD diagnosed according to DSM criteria.

Within the prospective study growth parameters were collected from 89 ADHD, aged 6–14, enrolled into the Italian ADHD Registry. Sixty five were Drug Naïve (DN), 24 had been on MPH for 1–3 years prior to enrollment into the registry (PR). Weight, height and BMI and Z-scores of height and BMI, growth velocity SDS, height deficit and BMI deficit were assessed at baseline, 6, 12, 18, 24 months.

Results: In the systematic review 15 eligable studies were identified covering a total of 2668 children and adolescents. Analysis of the impact of methylphenidate was performed in 1511 subjects. Six studies did not support the hypothesis of a correlation between a growth deficit and treatment. Nine studies ($n=1003$) found significant changes on height, weight and BMI z scores. Height deficit appeared more evident during the first 6–12 months with a subsequent normalization. 4 studies revealed a dose dependent effect.

In the prospective study at the 24 month observation, absolute values of height and weight continued to increase in all subjects. BMI Z-score decreased significantly at T12 ($p<0.001$) with no further at T24. Height Z-score showed a slight decrease only from T12 to T24 ($p=0.062$). Growth velocity SDS at T12 was not significantly different when compared to T24.

Height deficit compared to expected height was -1.26 ± 4.61 at 24 months.

Height deficit appeared significantly related to dosage pro/kg/day ($p=0.02$).

No significant difference was found regarding absolute values ??of height, weight, BMI and BMI Z-score at baseline between DN and PR. Both groups had a significant decrease in BMI Z-score at T12 ($p<0.001$).

Height deficit appeared related to dosage for DN at T12 ($p=0.02$) and for PR at baseline ($p=0.05$).

Discussion: These studies indicate that long-term treatment with methylphenidate might result in a slight growth deficit, in particular with respect to height. Further larger studies are needed to confirm that this slight growth deficit may be dependent on the maximum dose taken pro die rather than on the length of treatment.

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ANALYSIS

TOO MUCH MEDICINE

Attention-deficit/hyperactivity disorder: are we helping or harming?

Rae Thomas *senior research fellow*[1], Geoffrey K Mitchell *professor of general practice and palliative care*[2], Laura Batstra *assistant professor*[3]

[1]Centre for Research in Evidence-Based Practice, Bond University, 4229 Australia; [2]School of Medicine, University of Queensland, 4072 Australia; [3]Department of Special Needs Education and Youth Care, University of Groningen, Netherlands

This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies

Prevalence and prescribing rates for attention-deficit/hyperactivity disorder (ADHD) have risen steeply over the past decade, partly in response to concerns about underdiagnosis and undertreatment.[1 2] But although clinicians have become better at recognising, diagnosing, and treating children with ADHD, recent US data showed that 86% of children diagnosed with ADHD are described as having "mild or moderate" disorder,[3] and some diagnosed without fulfilling diagnostic criteria for ADHD.[4]

Mental health diagnoses are vulnerable to overdiagnosis because decisions are based predominantly on observed or self reported behaviours and interpretations of the severity of certain behaviours and whether they should be described as abnormal are subjective. There are no definitions in the UK, US, or Australian guidelines or in DSM-5 that quantify mild or moderate ADHD (box 1).[5-7] We argue that the overdiagnosis of ADHD resides within the clinical subjectivity of impairment.

What is ADHD?

To be diagnosed with ADHD, a child, adolescent, or adult should meet clear diagnostic criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) or *International Classification of Diseases* (ICD-10). In the DSM-5 definition symptoms fall within two main areas—inattention and hyperactivity/impulsivity—and can include difficulties sustaining attention, disorganisation, lack of follow through on tasks, being easily distracted, restless, and persistently interrupting.[8] This results in three subtypes (predominantly inattentive, predominantly hyperactive/impulsive, and combined). The ICD-10 calls the condition hyperkinetic disorder and requires hyperactivity, impulsivity, and inattention to be present. The more restrictive diagnostic criteria of ICD-10 result in smaller prevalence rates than ADHD diagnosed using DSM criteria.[4] However, most practitioners use DSM.

ADHD is diagnosed more often in boys than girls (about 3:1) and usually within the primary school years.[9] However, girls are more likely to meet criteria for the inattentive subtype of ADHD.[10] Although this subtype was dropped from DSM-III-R, it was reintroduced in DSM-IV, corresponding to a substantial increase in diagnoses among girls.[11]

ADHD is usually diagnosed by paediatricians and psychiatrists after a child in whom the diagnosis is suspected has been referred by their primary care physician.[5 12 13] In the US, however, primary care paediatricians predominantly provide diagnoses.[6] Diagnosis depends on an evaluation of the child's behaviour in at least two contexts (usually home and school or workplace) and different people (often parents and teachers) completing the evaluations. Symptoms must impair functioning in social, academic, or work settings.[8] Although there are some assessment scales that attempt to quantify impairment (such as the Children's Global Assessment Scale), the DSM-5 and national ADHD guidelines leave it to individual clinicians to decide impairment severity.[5-7] Guidelines suggest that medical, psychosocial, and developmental assessments are also carried out.[5-7]

Children who meet DSM's ADHD criteria always have problems in academic achievement[14] and social interaction. Often children also experience peer rejection and an increased risk of injury.[15 16] Longitudinal studies show that they are less likely to attend tertiary education, more likely to be unemployed or perform suboptimally at work,[17] more likely to engage in delinquent or criminal behaviour,[18] and more likely to use alcohol, tobacco, and illegal drugs than those without ADHD.[19] Observational studies suggest that untreated adults with ADHD are more likely to have car crashes and traffic violations than treated adults and adults without ADHD.[20]

Correspondence to: R Thomas rthomas@bond.edu.au

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Summary box

Clinical context—The prevalence of attention-deficit/hyperactivity disorder (ADHD) has increased substantially in the past decade, with most children diagnosed with ADHD described as having mild or moderate ADHD. Medication prescription rates have also increased twofold for children and fourfold for adolescents and adults

Diagnostic change—Definitions of ADHD have been broadened in successive editions of DSM

Rationale for change—Concern that ADHD is underdiagnosed in some children and adults

Leap of faith—Identifying and treating more people with ADHD will improve their quality of life

Impact on prevalence—The prevalence of parent reported diagnosis of ADHD in the US rose from 6.9% in 1997 to 9.5% in 2007. In the Netherlands it doubled over a similar period and other countries have also seen similar rises

Evidence of overdiagnosis—Severity of ADHD criteria is subjective. Prevalence varies markedly within and between countries and there is evidence that inappropriate developmental comparisons, sex, and heuristics contribute to inappropriate diagnoses

Harms from overdiagnosis—Medication costs of inappropriately diagnosed ADHD are estimated to be between $320m (£200m; €230m) and $500m in the US and some children have adverse drug reactions. While a diagnosis may help children and families it also carries stigma; children labelled as having ADHD are perceived as lazier and less clever by peers, and teachers and parents have low academic expectations of them potentially creating a self fulfilling prophecy

Limitations—Longitudinal data on the prognosis of ADHD and effects of treatments are limited

Conclusions—Reducing the threshold for diagnosing ADHD devalues the diagnosis in those with serious problems. A conservative stepped diagnostic approach could reduce the risk of overdiagnosis

Box 1: Mild, moderate, and severe ADHD

DSM-IV and DSM-5 provide no criteria to differentiate mild, moderate, and severe ADHD.

Mild ADHD

The UK, US, and Australian guidelines do not mention mild ADHD[5-7]

Moderate ADHD

- Guidelines from the UK National Institute for Health and Care Excellence (NICE) define moderate ADHD as having symptoms in either hyperactivity/impulsivity, inattention, or a combination of both and that the individual must have moderate impairment but do not defined "moderate"
- Moderate ADHD is not mentioned in the Australian draft guidelines and not defined in the US clinical practice guidelines

Severe ADHD

- Severe ADHD is defined in the NICE guidelines as having symptoms in the hyperactive/impulsive and inattention categories, corresponding with the ICD-10 criteria
- Neither the US nor the Australian guidelines define severe ADHD

There is no consistent way to assess severity of ADHD symptoms. These terms usually refer to impairment of an individual's level of functioning. There are some assessment scales that attempt to quantify impairment (eg Children's Global Assessment Scale) but many use frequency as a proxy for impairment or rely on lay (parent, teacher) interpretations of "normal" and "abnormal" behaviour

Rising diagnosis and treatment

The reported prevalence of ADHD is rising in several countries.[21] In US population surveys the prevalence of parent reported diagnosis of ADHD rose from 6.9% in 1997 to 9.5% in 2007,[3] and there is wide variation in point prevalence rates within[22] and between countries,[21] raising questions about diagnostic practices contributing to part of the rise. It is likely that clinicians are better at detecting and diagnosing ADHD but it is also thought that some of the rise reflects overdiagnosis or misdiagnosis.[23 24]

In parallel, prescribing rates for commonly used drugs such as dexamfetamine, methylphenidate, and atomoxetine for children diagnosed with ADHD have increased. Australian data on prescribing rates for ADHD medication show an increase of 72.9% between 2000 and 2011.[25] In the UK prescription of these same medications increased twofold for children and adolescents between 2003 and 2008 and fourfold for adults.[26] Prescribing of methylphenidates and amfetamines in the US increased steadily between 1996 and 2008, with the greatest increase in adolescents aged 13-18 years.[27] In the Netherlands prevalence and prescribing rates for children who had ADHD diagnosed doubled between 2003 and 2007.[28]

How effective is treatment?

Systematic reviews reach differing conclusions about the benefits of treatment in the short term,[29 30] and few studies have examined long term benefits.[31] Parent training programmes are effective for preschool children and their families.[30] Among children aged 6 years and older drug treatment with or without parent training was effective, but parent training alone had no benefit.[29 31] The longest trial of ADHD treatment outcomes available is the Multimodal Treatment Study of Children with ADHD. Although not without methodological controversies, the study reported short term benefits for medication alone and combination treatments compared with behaviour treatment alone or community care. At three, six, and eight year follow-up, children were, on average, performing better than at baseline, although they were still underperforming compared with their peers and there were no differences in treatment groups.[32]

Drivers of overdiagnosis

Shifting definitions

An important contributor to the increasing prevalence of ADHD is changes to the diagnostic criteria in differing editions of the DSM (table⇓).[21 33] The figure⇓ shows individual and average pooled prevalence from 104 studies that used DSM criteria. These show a significant increase in ADHD prevalence between each version of DSM. Field trials of proposed changes to ADHD diagnostic criteria (from DSM III-R to DSM-IV) flagged an expected increase in prevalence of 15%.[33] However, the increase exceeded this prediction, and prevalence is expected to rise further with the adoption of DSM-5, launched earlier this year.

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DSM-5 widens the definition of ADHD by expanding behavioural descriptions to include more examples and increasing the maximum age of symptom onset from 7 to 12 years.[8] These changes are a cause for concern because they increase the risk of confusing ADHD with normal development processes, such as pubertal restlessness and distractibility.[35] And although the term impaired functioning remains a constant diagnostic criterion from DSM-IV to DSM-5, the wording has changed from "clinically significant" to "interfere with or reduce the quality of social, academic, or occupational functioning." DSM-5 has also included, for the first time, criteria for diagnosis of ADHD in adults.

Unmet criteria

The DSM criteria for ADHD state that behavioural symptoms must be present in different contexts, be severe, affect functioning, have occurred for more than six months, and have started in childhood or early adolescence.[8] However, behavioural measures often characterise severity and impairment by frequency rather than compromised functioning. Frequency is not the same as impairment, and disregarding this important criterion increases reported prevalence.[4 36] Many prevalence studies use parent or teacher report of symptoms and do not apply the severity or time criteria included in the full DSM diagnostic criteria.[37 38] Unsurprisingly such studies report higher prevalences than those in which clinicians have diagnosed ADHD.[39 40]

ADHD diagnosis may also be influenced by heuristics and gender stereotypes. In one study, specialists in child and adolescent mental health (including child psychologists, psychiatrists, and social workers) were asked to identify children with ADHD from a series of vignettes.[41] Although the study provided participants with information on the optimal and minimal behavioural symptoms for diagnosis, 20% of clinicians diagnosed ADHD when criteria were not fulfilled.

Commercial influence

Among the work group advisers of DSM-5 for ADHD and disruptive behaviour disorders, 78% disclosed links to drug companies as a potential financial conflict of interest.[42] Despite disclosure, transparency does not mitigate bias and whether this affected decisions regarding changes to ADHD criteria is unknown.

The influence of direct to consumer advertising by pharmaceutical companies on driving patient demand for, and doctors prescribing rates of, drug treatments is well known.[43-45] Advertising on the internet through "mental health information websites"[46] is also an effective tool to promote discussion about mental healthcare. Mitchell and Read reported that pharmaceutical funding was ubiquitous in business, non-government organisation, educational, professional, and consumer websites providing information on ADHD.[46] Pharmaceutical companies have also used celebrities to "raise awareness" of ADHD[47] and sponsor websites that promote self diagnosis (and potentially misdiagnosis) using six questions and seeking help.[48]

Patient advocacy groups are not immune from potential bias either. Financial support and medication information is provided by drug companies to both the US advocacy group Children and Adults with Attention Deficit/Hyperactivity Disorder[49] and the National Attention Deficit Disorder Information and Support Service[50] in the UK.

Potential harms of overdiagnosis

Medication costs

About 87% of children diagnosed with ADHD in the US in 2010 subsequently received medication.[12] Decreasing symptom thresholds for impairment may mean unnecessary and possibly harmful medical treatment for some individuals. Data from the Centers for Disease Control and Prevention show that most children with ADHD are classified as having mild (46.7%) or moderate (39.5%) problems. Less than 14% have severe ADHD.[3] On the basis of a relative age effect where children with birthdays in the latter part of the school year were more likely to have ADHD diagnosed than children born earlier in the year, Elder estimated that between $320 (£200m; €230m) and $500 million is spent annually on medication for individuals inappropriately diagnosed with ADHD.[51]

Prescription rates for children in paediatric primary care exceeded expected community based care prescription rates and children in primary care were more likely than those in specialist mental health clinics to be prescribed medication.[52] When per capita use of ADHD medication is compared with a nation's gross domestic product, Australia, the US, and Canada have greater than expected use, and subsequent cost, of ADHD drugs.[53]

Adverse events

The main medications for ADHD are methylphenidates and amfetamines,[27 28] which can cause adverse reactions such as weight loss, hepatotoxicity, and suicide ideation,[54] and in the short term may suppress pubertal growth.[55] Longitudinal studies from childhood to adulthood have not been completed and so long term effects on growth are not known.[56] Correll et al reported significant gains in weight, body mass index, and waist circumference in children and young people taking risperidone (used off-label for ADHD) over 12 weeks.[57]

Psychological harms

A diagnostic label is value laden and has the potential to cause harm and, paradoxically, increase mental health problems. Compared with children with asthma, children with ADHD have been described as lazier, less clever, and less caring, and they are also more likely to be stigmatised and socially excluded.[58] Teacher and parent expectations of academic achievements are also low, and these are associated with actual lower achievement scores.[59]

Towards conservative diagnosis and treatment

Severe cases of ADHD are obvious, but in mild and moderate cases—which constitute the bulk of all ADHD diagnoses[3]—subjective opinions of clinicians differ. For these cases, we propose a conservative treatment approach similar to that recommended by UK guidelines.[5] These advocate a watchful waiting period of 10 weeks, referral to a parent training programme (without the need for a diagnosis), and then referral to secondary care if symptoms do not improve. In addition to stepped care, we propose stepped diagnosis, an approach including five steps of care before definite diagnosis (box 2). The goal is to reduce unnecessary diagnoses without risking undertreatment of those who really need psychiatric help.

Some evidence suggests that evidence based parent management training programmes may be effective for preschool children "at risk" of ADHD[60] and effective and cost effective for some

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Box 2: Stepped diagnostic approach to ADHD

Step 1: Gather baseline data from more than one source—eg school and home. If problems are urgent, recurring, or persistent and specific go directly to step 6. For other cases follow steps 2-5 first

Step 2: Look for other explanations of behavioural problems —for example, concentration problems and agitation may be a result of sleep deprivation, over challenging in school, workload, or tensions at home or at school

Step 3: Watchful waiting—assess, monitor, and follow-up with no pretence of a definitive diagnosis or active treatment

Step 4: If problems remain, offer a minimal intervention like bibliotherapy (such as information brochures) or self help training for parents of hyperactive children. Avoid the term ADHD, and speak in terms of concentration problems, restlessness, or behavioural difficulties

Step 5: If minimal intervention is not sufficient provide brief (five or six sessions) counselling using simple techniques to teach new attitudes and coping skills for dealing with hyperactivity and concentration problems

Step 6: If concentration and behaviour problems and impairment persist, more intensive therapy, usually in secondary care, is needed. Refer the patient to a developmental paediatrician or psychiatrist for definite diagnosis and treatment

families of older children.[60] However, it is unclear whether interventions like parental training are prescribed in mild to moderate cases of ADHD and if outcomes for these children were similar or better than medication alone. Data from the Multimodal Treatment of ADHD study show that even if medication is still indicated, lower doses are needed if parental training is tried first.[32]

Unanswered questions

Despite extensive research into factors contributing to ADHD aetiology, we are no closer to understanding the cause or causes of this disorder. Social factors such as political environment, education funding, and disability services may contribute to seeking a diagnosis of ADHD and are under-researched.[61] Much research funding is funnelled into biomarkers and neurobiological causes of ADHD that have limited clinical value at present. Less emphasis is placed on methodologically sound trials comparing different treatment options that may provide helpful information, particularly about mechanisms of change, and for whom different interventions work best.

The broadening of the diagnostic criteria in DSM-5 is likely to increase what is already a significant concern about overdiagnosis. It risks resulting in a diagnosis of ADHD being regarded with scepticism to the harm of those with severe problems who unquestionably need sensitive, skilled specialist help and support.

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Table

Table 1| **Changing DSM criteria over time**

	DSM-III	DSM-III-R	DSM-IV-TR	DSM-5
Age of onset (years)	<7	<7	<7	<12
Duration (months)	>6	>6	>6	>6
Impairment wording changed	No	No	"clinically significant impairment"	"interfere with or reduce the quality"
No of symptoms	5 for inattention	14 (1 category)	9 for inattention	9 for inattention
	6 for impulsivity		9 for hyperactivity/impulsivity	9 for hyperactivity/impulsivity
	5 for hyperactivity			Examples broadened
Required No for diagnosis	3/5; 3/6; 2/5	8/14	6/9; 6/9	6/9; 6/9
				5/9; 5/9 for those aged ≥17 years and older
Different contexts needed	No	"Usual in more than one, but not necessary"	≥2 settings	≥2 settings

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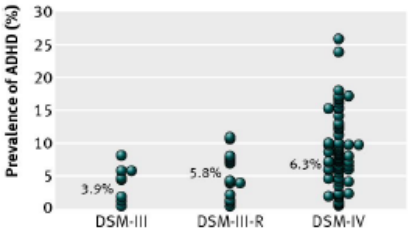
Figure



Prevalence of ADHD in studies using different DSM criteria[34]

Re: Attention-deficit/hyperactivity disorder: are we helping or harming?

Samuele Cortese, Child Neuropsychiatrist
Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ

9 November 2013

Thomas et al.[1] are concerned that the recent change in the maximum age of symptoms onset in the ADHD diagnostic criteria (from 7 years in the DSM-IV [2] to 12 years in the DSM-5 [3]) may increase "the risk of confusing ADHD with normal developmental processes, such as pubertal restlessness and distractibility". Whilst it is legitimate to be concerned about medicalising normal processes, I am not aware of any empirical evidence supporting such concern.

Indeed, a prospective study by Polanczyk et al. [4] conducted in a cohort of 2,232 British children showed that extending the age-of-onset criterion from 7 to 12 years resulted in an increase of ADHD prevalence of only 0.1%. If raising the maximum age of onset led to diagnose non-pathological behaviors as ADHD, one would expect a significant increase in the prevalence of this disorder. Additional results of this study are consistent with other research reports showing that individuals with retrospectively reported ADHD symptoms onset before or after 7 years do not significantly differ in terms of ADHD severity, comorbid disorders [5, 6], and outcome [7].

Such evidence supported the DSM-5 change in the age of onset criterion, aimed at reducing false negative diagnoses in adults. It has been shown that only 50% of adults referred for ADHD assessment retrospectively recall an onset of symptoms before age 7; on the other hand, 95% report ADHD an onset be¬fore age 12 [8]. However, the study by Polanczyk et al. [4] showed that adults who retrospectively report onset of ADHD between 7 and 12 years very likely had symptoms before 7 years. Therefore, keeping the maximum age of onset at 7 years would contribute to underdiagnose ADHD in a substantial number of adults.

The practitioner should also keep in mind that, to avoid labelling transitory processes as "ADHD", DSM-5 criteria include a note specifying that "…symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level…". Thus, DSM-5 criteria are unlikely to increase the risk of misdiagnosing pubertal restlessness and distractibility as ADHD.

In sum, the concern that the DSM-5 age of onset criterion contributes to confuse ADHD with normal developmental processes, leading to an inappropriate increase in the diagnosis of this disorder, is currently not supported by empirical evidence. However, as Thomas et al. [1] thoughtfully remind us, transitory restlessness and distractibility during puberty should be considered in the differential diagnosis of ADHD.

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Re: Attention-deficit/hyperactivity disorder: are we helping or harming?

Iain McClure, **Child & Adolescent Psychiatris**
NHS Lothian, The Esk Centre, Ladywell Way, Musselburgh, EH21 6AB

21 November 2013

In their helpful overview, Thomas et al explain that ADHD is probably being overdiagnosed because ascertainment of degree of impairment (as mild, moderate, or severe) is subjective and therefore unreliable1.
However, the ADHD concept itself is inherently subjective. ADHD is diagnosed according to the recorded presence (or abscence) of attention deficit, hyperactivity and impulsivity. These are all behavioural signs observed by informants (parents, teachers) or the clinician and then rated (as being present or absent) subjectively. They are rarely spontaneously complained about by the child or adolescent patient and are not therefore symptoms.
In other child or adolescent psychiatric conditions, the pitfall of observer subjectivity is tempered by the possibility of patient self report. In depression, anxiety, eating disorders or psychosis, the patient both experiences and complains of symptoms. They are aware of their differences of thinking or feeling (which, in turn may affect their behaviour). Additionally, in some neurodevelopmental psychiatric conditions, the thinking differences which cause behavioural difference are directly assessable, such as the reduced empathy found in autism or the cognitive impairments of intellectual disability. In many cases, such thinking differences are also self-reported.
In its current construct, ADHD cannot consistently deliver this extra layer of clinical information. Decades of ADHD research have not even attempted to deliver valid and reliable measurement of the patient's subjective experience2. Despite this, DSM-5 has continued the expansion of the ADHD paradigm1 3.
Why have child psychiatrists allowed purely behavioural constructs, such as ADHD, to become labelled as 'psychiatric'?
It is time for psychiatry to get back to thinking about thinking.

1 Thomas R, Mitchell GK, Batstra L. Attention-deficit/hyperactivity disorder: are we helping or harming? BMJ 2013;347:f6172–2.
2 McClure I. Prescribing methylphenidate for moderate ADHD. BMJ 2013;347:f6216–6.
3 Association AP. DSM-5 Development. www.dsm5.org. http://www.dsm5.org/Pages/Default.aspx (accessed 6 Jan2013).

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Re: Attention-deficit/hyperactivity disorder: are we helping or harming?

Maurizio Bonati, Head, Department of Public Health, **Laura Reale**
IRCCS - "Mario Negri" Pharmacological Research Institute, Via G. La Masa 19, 20156 Milan, Italy

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Thomas's analysis focused extensively on different issues concerning the overdiagnosis and overtreatment of ADHD, and concluded that "the overdiagnosis of ADHD resides within the clinical subjectivity of impairment" [1].

We argue that the core issue lies in the fact that there are two different steps in which clinicians are required to quantify the impairment level. The first concerns the evaluation of symptom severity as part of the diagnostic path; the second concerns a global functioning severity assessment before deciding for a pharmacological intervention. Overtreatment could therefore depend not only on the diagnosis, but also on the assessment of the ADHD impairment severity when the disorder has already been diagnosed.

According to the new Diagnostic and Statistical Manual of Mental Disorders (DSM), clinicians should distinguish the severity of symptoms and functional impairment between mild, moderate, and severe [2]. As pointed out by McClure in a recent editorial, the evidence-based recommendations from NICE were that the pharmacological treatment be considered in cases of "severe" ADHD [3]. Thus the following is questionable: is the rising trend of stimulant prescriptions related to an increase in "severe" ADHD prevalence, even though NICE reports a stable 1% [4], or is it rather related to an inadequate assessment?

In clinical practice, the clinicians' subjectivity is often intrinsic to the psychiatric area and plays a role not only in mental health diagnosis [5], but also in the wide variation in prescription rates by country, region, and even within the same city [6]. In the ADHD context, as Thomas and coll. pointed out, practice guidelines only suggest that a medical, psychosocial, and developmental evaluation should be carried out to define ADHD severity, leaving it up to individual clinicians to rate this impairment. Unfortunately, the categorical or dimensional types of classifications (such as mild, moderate, and severe) are more academic attitudes than useful approaches in/for the practice.

As in the Wolverhampton experience,[7] different initiatives were set up in local settings to oversee the implementation of the guidelines, but only a more systematic, shared, and widespread (national) approach can prevent (or reduce the risk of) the harms of overdiagnosis and disease mongering.

In June 2011, following a previous, national drug oriented registry set up in 2007 [8-9], an official regional registry was activated in the Lombardy Region in an attempt to limit the problems outlined above, guaranteeing appropriate ADHD management to each child and adolescent from the moment the disorder is first suspected or reported. In practice, a strict diagnostic assessment of the disorder prior to treatment, as well as its systematic monitoring during treatment, must be guaranteed by each of 18 local reference centres accredited by the regional health authorities.

An "Assessment Group" was established within the register's Working Group, consisting of a clinician from each centre and a group of researchers at the Coordinating Centre (IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"). The aim of this group was to define a complete, evidence-based, shared assessment pathway for all children and adolescents aged 5–17 years who accessed any of the 18 reference centres for a suspected ADHD diagnosis. This pathway, consisting of 6 mandatory steps, including the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) for a complete psychopathology overview and the Clinical Global Impressions scale for Severity (CGI-S) and Children's Global Assessment Scale (C-GAS) to quantify symptoms and global functioning severity, respectively, was agreed, approved, and shared (sometimes laboriously) by all centres. Moreover, because of the great concern about both safety and overuse of drugs and overdiagnosis in ADHD, the Coordinating Centre organises training sessions and discussion meetings for the reference centres' clinicians. Further educational events are also provided for community pediatricians, families, and other health professionals to diffuse more comprehensive knowledge on ADHD that is based on recent, evidence-based practice and European guidelines.

In such a context, the prevalence rate of ADHD was stable at around 0.5‰ in the 6-17 year old population, and, from 2011 to 2012, the rate of drug users among children and adolescents with ADHD decreased from 24 to 16%. This trend is different from other Italian regions, and from other European countries and the US, where ADHD overdiagnosis and overtreatment had already started with the previous editions of the DSM. Thus, the message to be learnt from the Lombardy Region's registry is that "limiting overdiagnosis and disease mongering is possible!" if adequate resources are available, appropriate training initiatives are taken, and patients' interests in care guide the decisions (even those concerning the manual classifications).

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IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI
DIPARTIMENTO DI SALUTE PUBBLICA
Laboratorio per la Salute Materno Infantile
Via Giuseppe La Masa, 19 - 20156 Milano MI - Italia - www.marionegri.it
tel +39 02 39014.511 - fax +39 02 3550924 - mother_child@marionegri.i