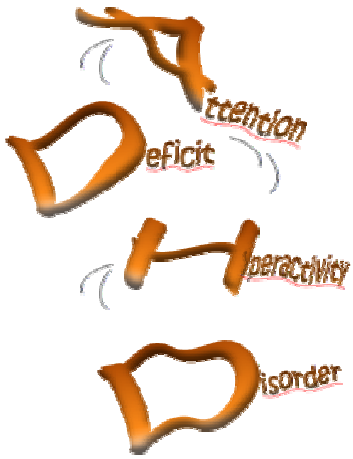
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD FEBBRAIO 2014

ADHD Atten Deficit Hyperact Disord. 2013;5:361-67.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ALEXITHYMIA: A PILOT STUDY.

Donfrancesco R, Di Trani M, Gregori P, et al.

Although the relationship between alexithymia and psychopathology has been studied extensively in adults, research is lacking on alexithymia in childhood psychopathology. The aim of this study was to investigate the relationship between alexithymia and attention-deficit/hyperactivity disorder (ADHD). The Italian version of the Alexithymia Questionnaire for Children was administered to a sample of 50 children with a DSM-IV diagnosis of ADHD, as assessed by means of the K-SADS PL, and to 100 healthy, age- and sex-matched children without ADHD. The total alexithymia score as well as the difficulty in identifying feelings (DIF) and externally oriented thinking factors were significantly associated with ADHD. The total alexithymia score, the DIF, and the difficulty in describing feelings factors were also significantly associated with symptoms of hyperactivity/impulsivity. No significant relationship between alexithymia and inattentiveness symptoms emerged. Results provide preliminary data on the relationship between alexithymia and ADHD. Findings point to an association between difficulty in identifying emotions and hyperactivity/impulsivity. Future studies conducted on larger patient samples, as well as longitudinal designs, are warranted to confirm our findings.

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ADHD Atten Deficit Hyperact Disord. 2013;5:353-60.

COMORBIDITY AND CONTINUITY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) FROM CHILDHOOD TO ADOLESCENCE IN TURKEY.

Cak HT, Dinc GS, Tuzun Z, et al.

The aim of this study was to examine clinical outcomes, psychiatric comorbidity and neuropsychological characteristics in Turkish adolescents with an attention deficit hyperactivity disorder (ADHD) diagnosis in childhood. A total of 45 children with ADHD diagnosis and 28 children with a psychiatric diagnosis other than ADHD in a 1-year cohort of 7-10-year-olds were reevaluated 6 years later using Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version and Wechsler Intelligence Scale for Children-Revised and Stroop Test TBAG version. This study shows that the clinical outcomes and the comorbidity patterns for ADHD from childhood to adolescence in Turkey are similar to reported rates in the Western countries. In the ADHD group, 75.6 % still has impairing ADHD symptoms and 46.6 % has comorbid psychiatric disorders. The main difference is anxiety disorders being the most common comorbid disorders (37.8 %) in Turkish ADHD youth. These findings stress the high comorbidity associated with ADHD and support the importance of assessment and treatment for ADHD and comorbidities during adolescence.

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

ADHD Atten Deficit Hyperact Disord. 2013;5:387-95.

A NON-INTERVENTIONAL STUDY OF EXTENDED-RELEASE METHYLPHENIDATE IN THE ROUTINE TREATMENT OF ADOLESCENTS WITH ADHD: EFFECTIVENESS, SAFETY AND ADHERENCE TO TREATMENT.

Sobanski E, Dopfner M, Ose C, et al.

This multi-centre, open-label, non-interventional study evaluates effectiveness, safety and adherence to treatment of a specific extended-release methylphenidate with a 50 % immediate and a 50 % extended-release component (Medikinet(registered trademark) retard) in the clinical routine treatment of 381 adolescents with ADHD and a mean age of 14.0 (plus or minus) 1.9 years. ADHD and associated psychiatric symptoms, medication status and dosage frequency, treatment adherence and adverse events were assessed at baseline and after a median treatment length with Medikinet(registered trademark) retard of 70 days. Primary outcome criterion was the change of ADHD symptom severity from baseline to endpoint according to the ADHD-KGE (German: ADHS-Klinische Gesamteinschatzung) change score. At baseline, 4.2 % of the patients were treatment naive, 92.7 % had previously received different methylphenidate formulations and 3.1 % had received atomoxetine or amphetamine. During the study, patients received a mean daily dose of 35.7 (plus or minus) 15.1 mg Medikinet(registered trademark) retard. At endpoint, in 78 % of patients, the total ADHD symptom severity was reduced, in 20.4 %, it remained unchanged and in 1.6 %, it was worsened. The mean ADHD-KGE total ADHD symptom score was reduced from 1.8 (plus or minus) 0.7 (moderate) at baseline to 0.8 (plus or minus) 0.5 (mild; $p < 0.001$) at endpoint; the mean ADHD-KGE total-associated symptom score was reduced from 1.9 (plus or minus) 0.7 (moderate) at baseline to 1.0 (plus or minus) 0.6 (mild; $p < 0.0001$) at endpoint. After the medication switch from previous methylphenidate formulation to Medikinet(registered trademark) retard, multiple dosing with (greater-than or equal to)3 daily medication intakes was reduced from 12.9 % at baseline to 3.1 % at endpoint ($p < 0.001$). Adherence to treatment was improved in 37 % of patients. Most frequent adverse events were loss of appetite and gastrointestinal problems. The findings suggest that pharmacologically treated adolescents with ADHD and insufficient symptom reduction and/or treatment adherence benefit from switching to Medikinet(registered trademark) retard and that it is well tolerated when given in clinical routine care.

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ADHD Atten Deficit Hyperact Disord. 2013;5:377-85.

ATOMOXETINE RESPONSE IN THE INATTENTIVE AND COMBINED SUBTYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A RETROSPECTIVE CHART REVIEW.

Ercan ES, Akyol Ardic U, Kabukcu Basay B, et al.

The DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 1994, American Psychiatric Association) describes attention deficit hyperactivity disorder (ADHD) as a heterogeneous disorder; providing diagnostic criteria for three subtypes: hyperactive/impulsive (ADHD/HI), inattentive (ADHD/I), and combined type (ADHD/C). Differences among the subtypes are well defined, but there may be also differences in terms of treatment responses. The aim of this study is to assess the responses of ADHD/I and ADHD/C to atomoxetine treatment. The medical records of the January-June 2012 term, first time referrals to outpatient clinic, were reviewed, and 37 ADHD diagnosed primary school age children (18 ADHD/I, 19 ADHD/C) that were treated with atomoxetine were determined. Thirty-five of them who completed 8 weeks of treatment duration were recruited for the study. The children with an ADHD medication use history in 2 months time prior to onset of treatment and/or the children receiving additional psychopharmacologic treatment to atomoxetine were excluded. Baseline and eighth week assessment, records were evaluated. Efficacy assessments included Turgay DSM-IV ADHD Screening and Rating Scale parent and teacher forms (T-DSM-IV) and Clinical Global Impression Scale-Severity and Improvement subscales. Safety assessments included laboratory and body weight assessments, ECG, heart rate, and blood pressure evaluations (baseline and eighth week) along a scale filled by the parents at the eighth week to review side effects. Atomoxetine was found to be effective in both ADHD/I and ADHD/C groups. Atomoxetine also decreased the opposition defiance subscale scores of T-DSM-IV (both parent and teacher forms), whereas it was not found to make statistically significant difference in the conduct disorder subscale scores. Mean difference in 8-week time in T-DSM-IV hyperactivity subscale and total scores of parent and teacher forms; inattention subscale scores of only parent forms and the CGI- severity

subscale scores; differed significantly among the ADHD/I and ADHD/C groups; that ADHD/C types responded better to medication. Results of this study revealed that atomoxetine is effective both in ADHD/I and ADHD/C subtypes. ADHD/C types may be responding better to atomoxetine treatment than the ADHD/I subtypes.

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Atten Defic Hyperact Disord. 2014 Mar;6(1):49-58.

THE USE OF ACTIGRAPHY IN THE MONITORING OF METHYLPHENIDATE VERSUS PLACEBO IN ADHD: A META-ANALYSIS.

De Crescenzo F, Armando M, Mazzone L, et al.

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. There is an increasing need to find objective measures and markers of the disorder in order to assess the efficacy of the therapy and to improve follow-up strategies. Actigraphy is an objective method for recording motor activity and sleep parameters using small, computerized, watch-like devices worn on the body, and it has been used in many clinical trials to assess methylphenidate efficacy and adverse effects in ADHD. Our article aim is to systematically review and perform a meta-analysis of the current evidence on the role of actigraphy in both the detection of changes in activity and in sleep patterns in randomized clinical trials that compared methylphenidate against placebo in the treatment of ADHD. A comprehensive literature search of PubMed/MEDLINE, Scopus, Embase, Cochrane Library, CINHAL and PsycINFO databases was carried out to find randomized clinical trials comparing methylphenidate versus placebo in children with ADHD, using actigraphic measures as an outcome. No start date limit was used and the search was updated until June 2013. The primary outcome measures were 'total sleep time' and daytime 'activity mean'. As secondary outcomes, we analyzed 'sleep onset latency', 'sleep efficiency' and 'wake after sleep onset'. Eight articles comprising 393 patients were included in the analysis. Children with ADHD using MPH compared to placebo have a significant difference of a large effect with a diminishing value in the activity mean. For the total sleep time, we found a significant and large effect in the decrease in sleep in MPH group. This study shows that MPH may effectively reduce mean activity in ADHD children, but it may negatively affect total sleep time.

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ADHD Atten Deficit Hyperact Disord. 2014;1-10.

INTERNALIZING AND EXTERNALIZING BEHAVIOR IN ADULT ADHD.

Jacob C, Gross-Lesch S, Jans T, et al.

Although there are many studies available investigating internalizing and externalizing behavior in childhood and adolescent manifestations of attention-deficit/hyperactivity disorder, there is limited information about their relevance in adults featuring persistence of the disease. We examined a large sample of 910 adults affected with attention-deficit/hyperactivity disorders (AADHD) for internalizing and externalizing behavior. Regarding correlates of internalizing behavior, AADHD probands showed significantly higher scores of the anxiety- and depression-related personality traits Neuroticism and Harm Avoidance, compared with reference values. The lifetime comorbidity of depressive disorders, anxiety disorders, and anxious or fearful Cluster C personality disorders (PDs) is elevated in AADHD patients compared with general population. Regarding correlates of externalizing behavior, patients affected with AADHD show significantly lower scores of Conscientiousness and significantly higher scores of Novelty Seeking than the published German reference values. Emotional, dramatic, or erratic Cluster B PDs were most frequent in AADHD. Internalizing and externalizing behavior notably affected psychosocial status to a similar extent. The frequency of both internalizing and externalizing behavior in AADHD might reflect an underlying emotional regulation disorder.

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Ann Pharm Fr. 2014.

METHYLPHENIDATE-RISPERIDONE COMBINATION IN CHILD PSYCHIATRY: A RETROSPECTIVE ANALYSIS OF 44 CASES.

Javelot H, Glay-Ribau C, Ligier F, et al.

Introduction: Psychotimulant-antipyschotic combinations are frequently used in child psychiatry, but have been rarely described in the literature.

Method and patients: We propose here a retrospective study of 44 children who received the combination methylphenidate (MPH)-risperidone (RIS). The sample is composed of children who received either MPH (n = 28) or RIS (n = 16) as primary treatment. A vast majority of the children had a comorbid attention deficit hyperactivity disorder (ADHD) diagnosis.

Results: For over 60% of patients, regardless of their initial monotherapy, bitherapy decreased the symptoms of ADHD and conduct disorder, sleep disorders and anxiety. Concerning the safety of the bitherapy, a compensation effect on weight gain and appetite was respectively observed in 70% and 50% of patients. Even though iatrogenic tachycardia can be encountered with both drugs, it has never been reported when they are associated and we have reported a total of 3 cases in our study. We have also observed a case of dyskinesia resolved with the discontinuation of the treatment.

Discussion/conclusion: MPH-RIS bitherapy appears to be particularly effective in ADHD with conduct disorder symptoms. Although tolerance may limit its use, the benefit/risk ratio seems favourable for a number of children.

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Ann Pharmacother. 2014;48:86-92.

USE OF SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS IN THE TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN PEDIATRICS.

Park P, Caballero J, Omidian H.

Objective: To review the current literature on the efficacy and safety of serotonin norepinephrine reuptake inhibitors in the treatment of attention-deficit hyperactivity disorder (ADHD) in the pediatric population.

Data Sources: A literature search from 1996 to August 2013 was conducted using MEDLINE, CINAHL, and EMBASE databases. Search terms included attention-deficit hyperactivity disorder, serotonin norepinephrine reuptake inhibitor, pediatric attention-deficit hyperactivity disorder, venlafaxine, duloxetine, desvenlafaxine, milnacipran, and nefazodone.

Study Selection and Data Extraction: Relevant articles on duloxetine and venlafaxine for the treatment of pediatric ADHD were reviewed; 5 studies on venlafaxine and 1 study on duloxetine were evaluated. Studies included open-label and randomized, double-blind trials. Case studies in pediatric populations and all studies in adult populations were excluded.

Data Synthesis: Patients 6 to 17 years old were evaluated in the venlafaxine and duloxetine studies. Trials on venlafaxine, ranging from 2 to 6 weeks, showed patient improvement as measured by the Conners Rating Scale and ADHD Rating Scale. Venlafaxine was initiated at 12.5 to 25 mg/d and titrated up to 1.4 to 3.8 mg/kg/d to a maximum of 150 mg/d. Duloxetine showed minimal efficacy in treating ADHD symptoms at doses of 60 mg/d at 6 weeks. The most common side effects for venlafaxine and duloxetine included drowsiness and decreased appetite, respectively.

Conclusions: Data for venlafaxine and duloxetine are limited. However, venlafaxine may be considered as an alternative agent when patients cannot tolerate or fail stimulants, tricyclic antidepressants, or bupropion. Duloxetine has been studied in children; however, with only 1 study available, it is difficult to recommend.

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Arch Psychiatry Psychother. 2013;15:45-49.

THE STUDY COMPARING PARENTING STYLES OF CHILDREN WITH ADHD AND NORMAL CHILDREN.

Moghaddam MF, Assareh M, Heidaripoor A, et al.

Aim: Attention deficit-hyperactivity disorder is one of the most often diagnosed psychiatric disorders in children and adolescents based on hyperactivity, attention deficit and impulsivity criteria. This disorder causes a lot of problems at home, school and social situations. Considering the family and parenting

factors in growth and development of ADHD children, the parenting interventions are consider as a primary intervention programs for this children. Parenting management training, based on social learning models, is an effective and practical way for treatment of children with incongruent behavior. In this study, we evaluate parenting styles of ADHD children and normal children.
Methods: This study was conducted in Zahedan in 2012. Subjects aged 7 to 12. They were divided into patient and normal groups. Parenting styles were evaluated with Baumrind's questionnaire. The data were analyzed with SPSS ver.18.
Results: The findings showed that the parents of ADHD children have lower permissive score than the normal group, but authoritarian score was lower in the normal group. The authoritative score has no significant difference between the two groups. In addition, age, gender, and parent's education affected the parenting styles.
Discussion: The present study indicates that parents with ADHD children have different parenting styles; and factors like gender and parents education are influential in parenting methods. This finding were also present in some past surveys. Many studies have shown that teaching-parenting styles to parents with ADHD children improves the inner family relationship.
Conclusion: The results indicated that parents of children with ADHD are less permissive but more authoritarian in their parenting.

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Basic Clin Neurosci. 2013;4:50-56.
CLOCK FACE DRAWING TEST PERFORMANCE IN CHILDREN WITH ADHD.
Ghanizadeh A, Safavi S, Berk M.
Introduction: The utility and discriminatory pattern of the clock face drawing test in ADHD is unclear. This study therefore compared Clock Face Drawing test performance in children with ADHD and controls.
Methods: 95 school children with ADHD and 191 other children were matched for gender ratio and age. ADHD symptoms severities were assessed using DSM-IV ADHD checklist and their intellectual functioning was assessed. The participants completed three clock-drawing tasks, and the following four functions were assessed: Contour score, Numbers score, Hands setting score, and Center score.
Results: All the subscales scores of the three clock drawing tests of the ADHD group were lower than that of the control group. In ADHD children, inattention and hyperactivity/ impulsivity scores were not related to free drawn clock test scores. When pre-drawn contour test was performed, inattentiveness score was statistically associated with Number score while none of the other variables of age, gender, intellectual functioning, and hand use preference were associated with that kind of score. In pre-drawn clock, no association of ADHD symptoms with any CDT subscales found significant. In addition, more errors are observed with free drawn clock and Pre-drawn contour than pre-drawn clock.
Discussion: Putting Numbers and Hands setting are more sensitive measures to screen ADHD than Contour and Center drawing. Test performance, except Hands setting, may have already reached a developmental plateau. It is probable that Hand setting deficit in children with ADHD may not decrease from age 8 to 14 years. Performance of children with ADHD is associated with complexity of CDT.

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Behav Sleep Med. 2014;12:53-68.
ASSOCIATIONS BETWEEN SLEEP PROBLEMS AND ATTENTIONAL AND BEHAVIORAL FUNCTIONING IN CHILDREN WITH ANXIETY DISORDERS AND ADHD.
Hansen BH, Skirbekk B, Oerbeck B, et al.
This study examined associations between sleep problems and attentional and behavioral functioning in 137 children aged 7 to 13 years with anxiety disorders (n=39), attention deficit hyperactivity disorder (ADHD; n=38), combined anxiety disorder and ADHD (n=25), and 35 controls. Diagnoses were made using the semistructured diagnostic interview Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version. Sleep problems were assessed using the Children's Sleep Habits Questionnaire, attention was measured by the Attention Network Test, and behavioral problems were

measured by teacher ratings on the Achenbach System of Empirically Based Assessment, Teacher Report Form. Sleep problems were associated with reduced efficiency of the alerting attention system for all children and with increased internalizing problems in children with anxiety disorders.

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Behav Sleep Med. 2014;12:84-87.

ADHD, ANXIETY AND SLEEP: A WINDOW TO UNDERSTANDING THE INTERPLAY BETWEEN SLEEP, EMOTIONAL REGULATION AND ATTENTION IN CHILDREN?

Gruber R.

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Behav Sleep Med. 2014;12:69-83.

SLEEP OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: ACTIGRAPHIC AND PARENTAL REPORTS.

Moreau V, Rouleau N, Morin CM.

The objectives of this study were to characterize the sleep of children with attention deficit hyperactivity disorder (ADHD), using actigraphy and parental questionnaires, and examine the potentially moderating role of psychostimulant medication and psychiatric comorbidity. Children with ADHD significantly differed from controls on parental and actigraphic measures of sleep, with parental reports indicating more severe sleep disturbances, and actigraphic recordings of longer sleep onset latency, lower sleep efficiency, and lower total sleep time. Both medicated and unmedicated ADHD subgroups differed from the control group on sleep measures, but did not differ from each other. Only the subgroup with comorbid psychiatric symptoms differed from the control group on actigraphic measures. The presence of psychiatric comorbidity, but not psychostimulant medication use, was associated with more severe sleep disturbances. The main implication of these findings is that clinicians should systematically attend to sleep disturbances in children with ADHD, particularly when other psychiatric symptoms are also present.

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Behav Genet. 2013;43:527.

ADHD, EXTERNALIZING BEHAVIOR AND SUBSTANCE USE; A CROSS-LAGGED MODEL USING MULTIPLE PHENOTYPES, TIMEPOINTS, AND MEASUREMENTS.

Kuja-Halkola R, Larsson H, D'Onofrio B, et al.

The association between ADHD and externalizing behavior is well established. ADHD has also been linked to substance use with a significant genetic overlap. However, the developmental direction of these effects is still unclear. Data came from the Swedish Twin Study of Child and Adolescent Development (TCHAD) where twins and their parents have answered questionnaires at ages 13-14, 15-16 and 18-19 (2,548 twins). The main analyses were based on parent- and self-reports using the Child Behavior Checklist. Sensitivity analyses also included a DSM-based ADHD scale and self-reports of criminality and substance use. Each phenotype was modeled as a latent construct, which we allowed multiple measures and multiple raters to contribute to. At each timepoint we fitted trivariate ACE models to estimate the overlap in genetics and environments between phenotypes, together with a longitudinal cross-lagged model, where each phenotype at a timepoint may affect all the phenotypes in the following time-point. All analyses were made using the software OpenMx. Heritability was moderate for all three phenotypes at each time-point (e.g. externalizing at age 13-14; h2=0.557, p-value<0.001). ADHD, externalizing behavior and substance use had substantial overlap within time-points, and most age-specific genetic correlations were significant (e.g. ADHD and externalizing behavior at age 15-16; rA=0.813, p-value<0.001). Analyses showed that there were phenotypic stability for all phenotypes (e.g., using standardized regression estimates [b], alcohol/drug use at age 13-14 predicted alcohol/drug use at age 15-16; b=0. 521, p-value<0.001). The analyses indicated that ADHD and externalizing behavior predicted the other phenotypes while substance use did not (e.g., ADHD at age 15-16 predicted externalizing at age 18-19; b = 0.116, p-value<0.001). Similar results were obtained in sensitivity analyses using models including different operationalizations of the

phenotypes; suggesting that genetically influenced ADHD and externalizing behaviors influence subsequent development of substance use, whereas the opposite does not seem to be the case.

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Behav Genet. 2013;43:520-21.

META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES ON ADHD: A DIMENSIONAL APPROACH.

Groen-Blokhuis M, Whitehouse A, Tiemeier H, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a highly heritable trait, especially at younger ages. No genetic variants have been identified to date that reach significance at a genome-wide level. So far, most genome-wide association studies (GWAS) on ADHD considered patient samples and have been conducted in case-control designs. However, ADHD can also be considered a dimensional trait, where clinical ADHD cases are at the extreme end of a continuum. Under this scenario, statistical power may be increased by analyzing the underlying dimension instead of the dichotomized phenotype. Within the EAGLE (EArly Genetics & Lifecourse Epidemiology) consortium, parent and/or teacher ratings of symptoms of ADHD are available for ~20,000 children. Cohorts are typically population based, and use behavioral screening instruments like the Child Behavior Checklist (CBCL), Strengths and Difficulties Questionnaire (SDQ) and Conners' Rating Scale to assess ADHD symptoms. Genome- wide genotype data have been imputed using the 1,000 Genomes reference panel for all ethnicities. Cohorts will run a linear regression of the total ADHD score on genotype dosage scores, corrected for sex and age at measurement. A meta-analysis based on p-values will be performed and replication will be sought for the top hits. Analyses were run on CBCL data from the Netherlands Twin Register. The most promising result for maternal ratings of Attention Problems (n=1,605) was rs13006098, a SNP located in the PDE11A gene which encodes a phosphodiesterase that regulates cAMP and cGMP signaling. The top hit in the teacher ratings (n=1,227) was rs1825366 which is located in the ZFHX4 gene, encoding a homeodomain- zinc finger protein. Overlap between the results of the mother and teacher ratings was limited; 90 SNPs were present in the top 1,000 of both analyses.

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Biol Psychiatry. 2014.

CONNECTOMIC DISTURBANCES IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A WHOLE-BRAIN TRACTOGRAPHY ANALYSIS.

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

Background: Few studies have sought to identify, in a regionally unbiased way, the precise cortical and subcortical regions that are affected by white matter abnormalities in attention-deficit/hyperactivity disorder (ADHD). This study aimed to derive a comprehensive, whole-brain characterization of connectomic disturbances in ADHD.

Methods: Using diffusion tensor imaging, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in 71 children and adolescents with ADHD compared with 26 healthy control subjects. White matter differences were further delineated between patients with (n=40) and without (n=26) the predominantly hyperactive/impulsive subtype of ADHD.

Results: A significant network comprising 25 distinct fiber bundles linking 23 different brain regions spanning frontal, striatal, and cerebellar brain regions showed altered white matter structure in ADHD patients ($p<.05$, family-wise error-corrected). Moreover, fractional anisotropy in some of these fiber bundles correlated with attentional disturbances. Attention-deficit/hyperactivity disorder subtypes were differentiated by a right-lateralized network ($p < .05$, family-wise error-corrected) predominantly linking frontal, cingulate, and supplementary motor areas. Fractional anisotropy in this network was also correlated with continuous performance test scores.

Conclusions: Using an unbiased, whole-brain, data-driven approach, we demonstrated abnormal white matter connectivity in ADHD. The correlations observed with measures of attentional performance underscore the functional importance of these connectomic disturbances for the clinical phenotype of ADHD. A distributed pattern of white matter microstructural integrity separately involving frontal, striatal,

and cerebellar brain regions, rather than direct frontostriatal connectivity, appears to be disrupted in children and adolescents with ADHD.

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Biol Psychol. 2014;95:31-44.

COMPARING TOMOGRAPHIC EEG NEUROFEEDBACK AND EMG BIOFEEDBACK IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Maurizio S, Liechti MD, Heinrich H, et al.

Two types of biofeedback (BF), tomographic electroencephalogram (EEG) neurofeedback (NF) and electromyographic biofeedback (EMG-BF), both with phasic and tonic protocols, were compared for treatment effects and specificity in attention-deficit/hyperactivity disorder (ADHD). Thirteen children with ADHD trained their brain activity in the anterior cingulate cortex (ACC), and twelve trained activity of arm muscles involved in fine motor skills. In each training session, resting state 24-channel EEG and training performances were recorded. Both groups showed similar behavioral improvements and artifact reduction in selected conditions, with no significant advantages despite medium effect sizes on primary outcomes for NF. Only the EMG-BF group, however, showed clear improvement in training regulation performance, and specific motor coordination effects. The NF group tended to present individual normalization of trained frequency bands in the ACC during rest across training. The results provide evidence for some specific effects in our small sample, albeit only to a small extent.

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Biopolym Cell. 2013;29:79.

CORRELATIONS OF NEUROMETABOLITES IN DORSOLATERAL PREFRONTAL AREAS WITH ADHD SYMPTOMS.

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

Background: ADHD is the most prevalent neuropsychiatric disorder in childhood with the unknown pathomechanisms. Symptoms of this diagnosis are categorized into three clusters: hyperactivity, impulsivity and inattention. The alterations of prefrontal cortex structure, function and neurometabolite levels are the consistent findings in children and adults with ADHD. Despite number of studies evaluating the neurometabolite differences between ADHD and control subjects, there is the lack of evidence of neurometabolite associations with ADHD symptoms. We aimed to find out the correlations of neurometabolites with ADHD symptoms evaluated by clinicians and parents.

Methods: Twenty medication null naive ADHD children at the age of 11.4 (plus or minus) 1.27 years were examined by single-voxel 1H-MRS. The spectra were taken from dorsolateral prefrontal cortex (DLPFC, 8 ml) and white matter behind DLPFC (anterior semioval center, 7.5 ml), bilaterally. Neurometabolites were correlated with ADHD Rating Scale IV (ADHD-RS-IV) score evaluated by clnicians and Conners Parent Rating Scale (CPRS) and Daily Parent Rating of Evening and Morning Behavior (DPREMB) subscale scores evaluated by parents.

Results: NAA/Cr in the right DLPFC positively correlated with the CPRS subscale IVnull learning problems and negatively correlated in the left white matter with the DPREMB morning behavior subscale and ADHD-RS-IV score. Glx/Cr positively correlated in the right white matter with the ADHD-RS-IV and negatively correlated in the left white matter with the DPREMB morning behavior subscale score. Cho/Cr in the left white matter negatively correlated with the DPREMB morning behavior subscale and ADHDRS-IV score.

Conclusion: ADHD symptoms are significantly associated with neurometabolite levels in prefrontal areas. The dysbalancies between the left- and the right-hemisphere prefrontal circuits could play an important role in ADHD.

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BMJ Case Rep. 2014.

SMITH-MAGNEIS SYNDROME: BEHAVIOURAL PHENOTYPE MIMICS ADHD.

Gnanavel S.

A mentally retarded 7-year-old male child presented with inattention and hyperactivity which was initially diagnosed as attention deficit hyperactivity disorder (ADHD). However, a careful evaluation of symptomatology along with clues provided by specific features of facial dysmorphism in this case along with genetic testing clinched the diagnosis of Smith-Magneis syndrome the behavioural phenotype of which closely resembles ADHD.

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Child Health Care. 2014;43:54-71.

PARENTAL ACCEPTANCE OF TREATMENTS FOR INSOMNIA IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AUTISTIC SPECTRUM DISORDER, AND THEIR TYPICALLY DEVELOPING PEERS.

Goodday A, Corkum P, Smith IM.

A web-based vignette design was used to examine parental acceptability of treatments for insomnia in school-aged children. Parents (n=353) of children with typical development (TD), autistic spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) were randomly assigned to a vignette condition that described a boy (TD, ASD, ADHD) who was experiencing insomnia. Parents were more accepting of non-pharmacological than pharmacological interventions, and medication was rated as more acceptable in special needs children, whereas self- help was more acceptable for TD children. In conclusion, clinicians need to be aware of the key factors that may affect acceptance of treatment for children's sleep problems.

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Circulation. 2013;128.

ADHD STIMULANT MEDICATION USE IS ASSOCIATED WITH CARDIAC AUTONOMIC DYSFUNCTION AND ARTERIAL STIFFNESS IN CHILDREN AND ADOLESCENTS.

Kelly AS, Rudser KD, Dengel DR, et al.

Background: Stimulant medications are used as the primary treatment for attention deficit hyperactivity disorder (ADHD) among children and adolescents but little is known about their effects on cardiac autonomic regulation and arterial stiffness. We conducted a case-control study comparing cardiovascular health in youth with ADHD currently using stimulant medication to healthy controls.

Methods: Eighty-four children and adolescents (mean age 11.2 (plus or minus) 2.8 years; 65 boys) using methylphenidate or amphetamine preparations and 53 siblings without ADHD (mean age 11.1 (plus or minus) 3.8 years; 28 boys) were enrolled. Measured variables included blood pressure, heart rate, heart rate variability: standard deviation of the RR interval (SDRR) and low frequency to high frequency (LF:HF) ratio, carotid-radial pulse wave velocity, and carotid and radial artery augmentation index. Comparisons were evaluated using general estimating equations with an exchangeable working correlation structure for family clusters and adjusted for sex, race, and Tanner stage. Robust variance estimation was used for confidence intervals and P-values.

Results: Participants with ADHD vs. controls had higher systolic blood pressure (113 (plus or minus) 11 vs. 109 (plus or minus) 12 mmHg, p<0.01), diastolic blood pressure (61 (plus or minus) 8 vs. 56 (plus or minus) 8 mmHg, p<0.001), heart rate (84 (plus or minus) 12 vs. 73 (plus or minus) 11 beats/minute, p<0.001), LF:HF ratio (1.55 (plus or minus) 1.31 vs. 1.03 (plus or minus) 0.77, p<0.001), carotid artery augmentation index (2.71 (plus or minus) 14.9 vs. -2.29 (plus or minus) 16.6%, p<0.01), a trend toward higher pulse wave velocity (7.4 (plus or minus) 1.2 vs. 7.1 (plus or minus) 1.2 meters/second, p=0.09), and lower SDRR (0.07 (plus or minus) 0.03 vs. 0.10 (plus or minus) 0.04 seconds, p<0.001).

Conclusion: Children and adolescents being treated with stimulant medication for ADHD exhibit signs of cardiac autonomic dysfunction, characterized by increased sympathetic tone, and show evidence of arterial stiffening. The long-term significance of these findings, particularly whether the cardiovascular effects persist into adulthood, warrant further investigation.

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Clin Nucl Med. 2014;39:e129-e134.

SEARCHING FOR A NEUROBIOLOGICAL BASIS FOR SELF-MEDICATION THEORY IN ADHD COMORBID WITH SUBSTANCE USE DISORDERS: AN IN VIVO STUDY OF DOPAMINE TRANSPORTERS USING 99MTC-TRODAT-1 SPECT.

Silva N, Szobot CM, Shih MC, et al.

PURPOSE: Attention-deficit/hyperactivity disorder (ADHD) and substance use disorders (SUD) frequently co-occur. Although several studies have shown changes in striatal dopamine transporter (DAT) density in these disorders, little is known about the neurobiological basis of the comorbidity. The aim of this study was to evaluate striatal DAT density in treatment-naive ADHD adolescents with SUD (ADHD+SUD) and without SUD (ADHD), compared to SUD adolescents without ADHD (SUD) and healthy control subjects (HC).

PATIENTS AND METHODS: Sixty-two male age-matched subjects diagnosed with DSM-IV criteria were included: ADHD+SUD (n=18), SUD (n=14), HC (n=19), and ADHD (n=11). Urine tests confirmed participants' drug use. All subjects performed SPECT scans with Tc-TRODAT-1 to evaluate DAT density in the striatum.

RESULTS: The mean right striatum specific binding were 1.68 (ADHD), 1.38 (ADHD + SUD), 1.19 (HC), 1.17 (SUD), and in left striatum 1.65 (ADHD), 1.39 (ADHD+SUD), 1.19 (HC), and 1.17 (SUD). The ADHD group presented significantly higher striatal DAT density compared with ADHD + SUD, SUD, and HC groups. Adolescents with ADHD + SUD had significantly lower DAT density than those with ADHD, but significantly higher DAT density than those with SUD only and no significant difference from the healthy control group.

CONCLUSION: The ADHD + SUD group had lower striatal DAT density in comparison with ADHD without SUD. It is possible to speculate that the use of cannabis and cocaine is responsible for the lower striatalDAT density in this group which would help in understanding the neurobiological basis for the self-medication theory in ADHD adolescents.

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CNS Drugs. 2014;1-12.

TRANSDERMAL THERAPY FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH THE METHYLPHENIDATE PATCH (MTS).

Findling RL, Dinh S.

Transdermal technology is currently approved in the US for the administration of more than 20 medications. This current review describes the clinical research pertaining to the use of a methylphenidate patch in the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adolescents. PubMed searches were conducted using the search term 'methylphenidate transdermal system', and were limited to clinical trials. No limits were set for dates of publication. A total of 21 citations were identified. Studies evaluating the safety and efficacy of the methylphenidate transdermal system (MTS) in children and adolescents were included in this review. Additional studies were identified from bibliographies and the 'Related Citations' section of PubMed searches. The MTS delivers a range of methylphenidate doses using a drug-in-adhesive matrix patch. According to current labeling, the patch should be applied to the hip once daily for a maximum of 9 h. Serum methylphenidate levels increase over wear time, with mean time to maximum concentration (tmax) reached between 8 and 10 h for a 9-h wear time, and the elimination half-life for methylphenidate is 3-4 h after patch removal. In clinical trials, ADHD symptoms were measured using the ADHD Rating Scale, Version IV, and several parent-, teacher-, and patient-rated scales. Treatment effects show statistically significant differences from baseline symptom scores starting at the first evaluation, 2 h after the patch is applied, with significant benefit lasting up to 12 h with a 9-h wear time. Adverse events with the MTS are similar to those seen with other formulations of methylphenidate, with the exception of skin-related reactions at the site of application, which were generally mild to moderate in severity. The incidence of contact allergic dermatitis with MTS is <1 %. Statistically significant improvements in health-related quality of life and medication satisfaction were also observed with the MTS compared with placebo, and after switching from oral extended-release (ER) methylphenidate. Transdermal drug delivery is an effective and safe means of administering methylphenidate for patients with ADHD.

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Emot Behav Difficulties. 2014.

ADHD IN THE CONTEXT OF FINNISH BASIC EDUCATION.

Honkasilta J, Sandberg E, Narhi V, et al.

Students with Attention Deficit/Hyperactivity Disorder (ADHD) are a growing group served under special education services in many western societies. This article describes the history and current state of the services, as well as the assessment procedure. Our conclusion is that the status of students with ADHD in Finnish basic education (Grades 1 to 9) is still unclear. Based on the comparison of the prevalence and the population served in special education we can assume that this group is probably underserved in the Finnish school system. We also present findings from two recent studies among families with ADHD children in Finland. Family viewpoint can contribute to our knowledge and understanding about the diversity of the symptoms' manifestation as well as the extent and completeness of the possible outcomes of the disorder. In the context of schooling, studying these families' viewpoints can be of additional use in evaluating the present state of school practices in relation to institutional enactments established in educational acts. Future challenges about meeting the variety of pupils' needs according to inclusive pedagogy are discussed.

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Emot Behav Difficulties. 2014.

THE PRACTICES OF DEALING WITH CHILDREN WITH SPECIAL NEEDS IN SCHOOL: A NORWEGIAN PERSPECTIVE.

Haug P.

The article has two parts. Part one deals with some historical developments in the field of special education in Norway. There has been a change in formulated policy from a clearly segregated system, then integration and mainstreaming and now intentions about inclusion as an ideal. The second part is about children with behavioural difficulties and especially children diagnosed with ADHD (Attention Deficit and Hyperactivity Disorders) and how they are treated within the education system. Knowledge about these children's situation is not very well developed or widespread in the Norwegian education system. The numbers of children with an ADHD diagnosis vary a lot between schools. Both diagnosis and treatment connected to ADHD have been highly controversial in Norway, as in many other countries. The gap between ideals and realities is a striking element in special education in Norway and also for these children. The inclusion criteria have not been met. The reasons for this are discussed.

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Eur Arch Psychiatry Clin Neurosci. 2014;1-8.

FURTHER EVIDENCE FOR THE ASSOCIATION BETWEEN A POLYMORPHISM IN THE PROMOTER REGION OF SLC6A3/DAT1 AND ADHD: FINDINGS FROM A SAMPLE OF ADULTS.

de Azeredo LA, Rovaris DL, Mota NR, et al.

The dopamine transporter (SLC6A3/DAT1) plays a key role in the regulation of dopaminergic neurotransmission and is the major site of action for methylphenidate, a first-line medication for attention deficit hyperactivity disorder (ADHD). Most genetic association studies with ADHD have investigated a 40-bp variable number of tandem repeats (VNTR) polymorphism in the 3'-untranslated region (UTR) of the DAT1, but these investigations have reported heterogeneous findings. The few studies focused on the 5' region have reported promising results. Despite rs2652511 not being included, nor having any proxy SNP available in GWAS, the few candidate gene studies that analyzed it suggested an association with ADHD and schizophrenia. Here, we analyzed the -839 C/T (rs2652511) promoter variant and the 3'-UTR and intron 8 (Int8) VNTR polymorphisms in 522 adults with ADHD and 628 blood donor controls. The diagnostic procedures followed the DSM-IV criteria. A significant association was detected (P = 0.002) between the rs2652511 C-allele with ADHD. In addition, the 6-repeat allele of Int8 VNTR was associated with higher inattention scores (P=0.034). The haplotype analysis including DAT1 3'-UTR and Int8 VNTR polymorphisms did not reveal associations with ADHD susceptibility or severity dimensions. These findings

extend to adult samples previous findings from children samples on the role of the rs2652511 polymorphism in the promoter region of DAT1 as a risk factor for ADHD susceptibility.

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Eur Child Adolesc Psychiatry. 2014;1-5.

SEXUAL MATURATION AMONG YOUTH WITH ADHD AND THE IMPACT OF STIMULANT MEDICATION.

Greenfield B, Hechtman L, Stehli A, et al.

Objective: Evaluate the differences in achieving puberty between ADHD and non-ADHD participants and the effects of medication on that process among ADHD participants.

Procedure: A subset of participants with ADHD from the Multimodal Treatment study of ADHD (n=342) were compared with respect to Tanner staging to participants from a comparison group without ADHD (n=159) at the 36-month follow-up assessment. Further comparisons were made for Tanner stages and Auxology of the participants in the ADHD group who were always (n=61), never (n=56), newly (n=74) and inconsistently (n=116) treated with stimulants.

Results: No statistically significant differences in Tanner stages of sexual development were found between the ADHD and non-ADHD groups at the age of assessment (between 10 and 14 years of age) or among the ADHD medication subgroups, although a trend was observed for stimulant-associated delayed pubertal initiation using auxological analysis.

Conclusion: Children with or without ADHD did not differ in Tanner stages at the 3-year follow-up assessment, and exposure to stimulant medication does not appear to affect sexual development within this age range.

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Eur Neuropsychopharmacol. 2014;24:232-41.

SUBSTANCE USE DISORDERS IN ASSOCIATION WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, CO-MORBID MENTAL DISORDERS, AND MEDICATION IN A NATIONWIDE SAMPLE.

Steinhausen HC, Bisgaard C.

Background: The association of substance use disorders (SUD) with attention-deficit disorder (ADHD), co-morbid mental disorders, and medication has only been studied in isolation and in rather small samples.

Procedure: Data were based on four Danish national registers covering a total of 20,742 patients with ADHD, their dispensed medications, co-morbid mental disorders, and associated SUD between 1994 and 2010. The analyses considered the risk of various medications (methylphenidate only, antidepressants only, antipsychotic only, mixed medication) in comparison to a control group of non-medicated patients with ADHD, various co-morbid disorders, duration of medication, age at diagnosis, year of birth, and sex for developing SUD.

Results: The observation period of the cohort ranged between 2.25 and 66.21 years and the prevalence for SUD was 9.51%. The SUD rates were significantly higher prior to, compared to following the onset of medication in the methylphenidate and the mixed medication subgroup, whereas they were significantly higher following onset of medication in the antidepressants and the antipsychotics subgroups. However, the SUD rates were significantly higher in all drug conditions except for methylphenidate after onset of medication compared to the non-medicated subgroup. Risk factors obtained by regression analysis did not include methylphenidate but did include antidepressants, antipsychotics, and mixed medications, in combination with co-morbid mood, anxiety, personality, and conduct disorders, and older age at diagnosis. Longer duration of medication and female sex were protective factors.

Conclusions: This representative study based on a large nationwide psychiatric sample provides solid evidence into the patterns of SUD in patients with ADHD based on medication use and co-morbidities.

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Iran J Psychiatry. 2013;8:195-200.

EFFECTIVENESS OF REBOXETINE IN TREATMENT OF OUTPATIENT CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER WITH COMORBID ANXIETY DISORDERS.

Riahi F, Tashakori A, Izadi-Mazidi S, et al.

Objective: Some previous studies have reported that ADHD is often comorbid with anxiety disorders. The aim of the present study was to evaluate the effectiveness of reboxetine in treating outpatient children and adolescents with ADHD and comorbid anxiety disorders.

Method: In this open-label study, 25 outpatient children and adolescents, aged 6-16 years were selected by convenient sampling and underwent treatment with 4mg reboxetine for four weeks. Data were collected at baseline, two weeks and four weeks after the start of the medication using Conners' Parent Questionnaire, Hamilton's Rating Scale for Anxiety, Clinical Global Assessment Scale, Clinical Global Impression-Severity Scale and Side Effects Form. Data were analyzed using repeated measure, analyses of variance (ANOVA), Tukey post hoc test and paired t-test.

Results: There were significant reduction in the total score of ADHD ($F=31.441$; $P<0.001$) at the end of the treatment compared to baseline (Table1). The differences between T0 and T2 in the subscales of attention deficit, hyperactivity and confrontation ($F=20.691$; $P<0.001$, $F=28.810$; $P <0.001$, and $F=17.463$; $P<0.001$, respectively) were also significant. Findings also indicated significant differences between T0 and T1 ($P<0.01$) and T1 and T2 ($P<0.01$) in all of the subscales except for confrontation. A significant improvement was observed in the severity of ADHD and anxiety disorders during different courses of the treatment ($p<0.001$). No significant changes were observed in systolic and diastolic blood pressure and pulse and weight of the patients during the study. The most common complications were headache and anorexia.

Conclusions: The short-term treatment with reboxetine was effective in improving ADHD with comorbid anxiety disorders. Therefore, reboxetine could be used as a treatment option for ADHD in those children who experience comorbid anxiety disorders or in those who are non-responsive or intolerant to methylphenidate.

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Isr Med Assoc J. 2013 Nov;15:705-09.

DISORDERED SLEEP IN PEDIATRIC PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN OVERVIEW.

Ganelin-Cohen E, Ashkenasi A.

There is a well-established correlation between sleep disturbances and attention deficit hyperactivity disorder (ADHD). A large number of pediatric patients diagnosed with ADHD have sleep problems, while patients with sleep disturbances often display behavioral patterns that resemble some features of ADHD. Despite these observations, the relationship between sleep problems and ADHD is not yet fully understood. It is often difficult to pinpoint which of the disorders is the primary and which a byproduct of the other. A complicating factor is that stimulant medication such as methylphenidate, a drug of choice for ADHD, may adversely affect sleep quality in ADHD patients. However, there have also been reports that it may actually improve sleep quality. This review examines the latest trends in the contemporary literature on this clinical dilemma.

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JAMA Psychiatry. 2014 Jan;71:71-80.

PARSING DIMENSIONAL VS DIAGNOSTIC CATEGORY-RELATED PATTERNS OF REWARD CIRCUITRY FUNCTION IN BEHAVIORALLY AND EMOTIONALLY DYSREGULATED YOUTH IN THE LONGITUDINAL ASSESSMENT OF MANIC SYMPTOMS STUDY.

Bebko G, Bertocci MA, Fournier JC, et al.

IMPORTANCE: Pediatric disorders characterized by behavioral and emotional dysregulation pose diagnostic and treatment challenges because of high comorbidity, suggesting that they may be better conceptualized dimensionally rather than categorically. Identifying neuroimaging measures associated with behavioral and emotional dysregulation in youth may inform understanding of underlying dimensional vs disorder-specific pathophysiologic features.

OBJECTIVE: To identify, in a large cohort of behaviorally and emotionally dysregulated youth, neuroimaging measures that (1) are associated with behavioral and emotional dysregulation pathologic dimensions (behavioral and emotional dysregulation measured with the Parent General Behavior Inventory 10-Item Mania Scale [PGBI-10M], mania, depression, and anxiety) or (2) differentiate diagnostic categories (bipolar spectrum disorders, attention-deficit/hyperactivity disorder, anxiety, and disruptive behavior disorders).
DESIGN, SETTING, AND PARTICIPANTS: A multisite neuroimaging study was conducted from February 1, 2011, to April 15, 2012, at 3 academic medical centers: University Hospitals Case Medical Center, Cincinnati Children's Hospital Medical Center, and University of Pittsburgh Medical Center. Participants included a referred sample of behaviorally and emotionally dysregulated youth from the Longitudinal Assessment of Manic Symptoms (LAMS) study (n=85) and healthy youth (n=20).
MAIN OUTCOMES AND MEASURES: Region-of-interest analyses examined relationships among prefrontal-ventral striatal reward circuitry during a reward paradigm (win, loss, and control conditions), symptom dimensions, and diagnostic categories.
RESULTS: Regardless of diagnosis, higher PGBI-10M scores were associated with greater left middle prefrontal cortical activity (r=0.28) and anxiety with greater right dorsal anterior cingulate cortical (r=0.27) activity to win. The 20 highest (t=2.75) and 20 lowest (t=2.42) PGBI-10M-scoring youth showed significantly greater left middle prefrontal cortical activity to win compared with 20 healthy youth. Disruptive behavior disorders were associated with lower left ventrolateral prefrontal cortex activity to win (t=2.68) (all P<.05, corrected).
CONCLUSIONS AND RELEVANCE: Greater PGBI-10M-related left middle prefrontal cortical activity and anxiety-related right dorsal anterior cingulate cortical activity to win may reflect heightened reward sensitivity and greater attention to reward in behaviorally and emotionally dysregulated youth regardless of diagnosis. Reduced left ventrolateral prefrontal cortex activity to win may reflect reward insensitivity in youth with disruptive behavior disorders. Despite a distinct reward-related neurophysiologic feature in disruptive behavior disorders, findings generally support a dimensional approach to studying neural mechanisms in behaviorally and emotionally dysregulated youth.

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J Autism Dev Disord. 2014;1-10.

QUANTITATIVE LINKAGE FOR AUTISM SPECTRUM DISORDERS SYMPTOMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SIGNIFICANT LOCUS ON CHROMOSOME 7Q11.

Nijmeijer JS, Arias-Vasquez A, Rommelse NNJ, et al.

We studied 261 ADHD probands and 354 of their siblings to assess quantitative trait loci associated with autism spectrum disorder symptoms (as measured by the Children's Social Behavior Questionnaire (CSBQ)) using a genome-wide linkage approach, followed by locus-wide association analysis. A genome-wide significant locus for the CSBQ subscale addressing social interaction was found on chromosome 7q11, with suggestive signals supporting this locus on three other CSBQ subscales. We identified two other suggestive loci for the CSBQ total scale and individual subscales on chromosomes 4q35 and 7p12. Fine-mapping the significantly linked locus resulted in interesting candidate genes, although their association was not significant after permutation testing.

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J Clin Endocrinol Metab. 2014;99:E1-E8.

THE IMPACT OF GESTATIONAL THYROID HORMONE CONCENTRATIONS ON ADHD SYMPTOMS OF THE CHILD.

Pakkila F, Mannisto T, Pouta A, et al.

Context: Maternal hypothyroidism during pregnancy is associated with adverse neuropsychological development in the offspring.
Objective: The objective of the study was to evaluate the effect of maternal thyroid dysfunction during pregnancy on a child's attention-deficit/hyperactivity disorder (ADHD) symptoms.

Design, Settings, and Participants: The prospective, population-based Northern Finland Birth Cohort 1986 (9362 pregnancies; 9479 infants) included analysis of maternal TSH, free T4, and thyroid-peroxidase antibodies (TPO-Abs) from early pregnancy samples (5791 women). Teachers evaluated the children's ADHD symptoms at 8 years using the Rutter B2 scale (5131 mother-child pairs), in which a high score indicated probable psychiatric disorders and three questions focused directly on ADHD.
Main outcome measures: The odds ratios (ORs) and 95% confidence intervals (95% CIs) of child having ADHD symptoms and/or a high Rutter B2 score after exposure to increases in maternal TSH levels (after logarithmic transformation), low free T4 levels, and TPO-Ab positivity was tested with logistic regression, adjusting for maternal/family covariates. Data were stratified by the child's gender due to interaction.
Results: Among girls the odds of inattention (OR 1.18,95%CI 1.02-1.37), high Rutter B2 total score (OR 1.23, 95% CI 1.03-1.48), and combined ADHD symptoms (OR 1.39, 95% CI 1.07-1.80) significantly increased with every natural log increase in maternal TSH concentrations. Such findings were not evident in boys. No associations were seen between ADHD symptoms and low maternal free T4 levels or TPO-Ab positivity.
Conclusions: Increases in maternal TSH in early pregnancy showed weak but significant association with girls' ADHD symptoms.

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J Mol Neurosci. 2013;51:S33.

ABNORMAL PERCEPTUAL FUNCTIONS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Doron R, Polat U.

Background: Visual crowding, collinear facilitation, and contour integration are visual integration functions (VIF) that are critical for perceptual and cognitive processing. Our recent results support a common early neural basis for the development of VIF in young healthy children. The results show that there is a developmental cascade in which the existence of high levels of crowding in young children limits the developmental onset of collinear facilitation until about the age of 6 years when the crowding decreases to nearly an adult's level. Similarly, the onset of the contour integration skill developed after the maturation of collinear facilitation, between 6 and 9 years. Since development of some of the cognitive functions overlaps with this age period, we hypothesized that the development of VIF in ADHD subjects might be affected. The aim of this study was to explore whether VIF in ADHD subjects during the age of 6-18 years is normal.
Results: We found a high degree of crowding, higher thresholds for contour integration, and reduced collinear facilitation in the ADHD group compared with the agematched control group. We also found that their thresholds do not improve with age and remain immature, matching the threshold levels of younger children.
Conclusions: Contrary to the visual processing in young normal children, which improves with age, the neural mechanisms underlying global perception are immature in ADHD individuals. These results may suggest that abnormal development contributes to the perceptual processing in ADHD, which in turn may limit the development of some higher cognitive processing.

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J Mol Neurosci. 2013;51:S41.

HEAD MOTION IN CHILDREN WITH ADHD: HOW IT AFFECTS CONNECTIVITY RESULTS IN NEUROIMAGING STUDIES.

Kieling RR, Kieling C, Da Costa JC, et al .

Background: Recent reports have suggested that spurious but systematic correlations in resting state functional connectivity MRI (fcMRI) may arise from subject motion to the sensitivity of resting state data, typical preprocessing methods such as motion correction, regression of confounding signals and bandpass filtering are not sufficient to eliminate signal corruption caused by head movement. Here we analyzed the impact of head motion on seed-based functional connectivity. Data from the ADHD200 Consortium, comprising children and adolescents with ADHD and healthy controls, were used to estimate subject motion based upon head realignment using a rigid body six-parameter affine transform, summing the displacement at each TR. Mean displacements were calculated for translation and rotation. FcMRI was

calculated between two seeds within the DMN, the medial prefrontal cortex (mPFC) to the posterior cingulate cortex (PCC). A linear stepwise regression with rsfcMRI as the dependent variable and age and translation as independent variables was calculated.
Results: A total of 421 children (119 drug-naive and 302 controls) were included in this study. No statistical difference in age and IQ were observed groups (p>0.1). Children with ADHD exhibited excessive motion compared to controls within both modalities (p<0.05). Increased functional connectivity between the mPFC and PCC was observed within controls compared to patients (p00.036). Regression analyses showed that difference in rs-fcMRI between groups was lost (p00.091) when age and movement were incorporated in the analysis.
Conclusions: Head motion is one of the greatest factors that degrade fMRI data quality. Typically data with large displacements are discarded; however, discarding such data may induce selection bias. These results suggest that optimal handling of fcMRI data will need to take into account the consequence of motion artifacts to avoid the report of artifactual patterns of correlation.

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J Mol Neurosci. 2013;51:S117-S118.

NEUROPSYCHOLOGICAL SUBTYPES AMONG ADULTS WITH AND WITHOUT ADHD.

Spanier AB, Kolodny T, Geva AB, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a prevalent developmental disorder, defined by behavioral symptoms of inattention, and/or hyperactivity and impulsivity which affects approximately 10 % of children and 4 % of the adult population. ADHD has lately been conceptualized as a heterogeneous syndrome with multiple underlying cognitive mechanisms. In a recent study, Fair and colleagues (2012) applied a community detection algorithm to identify neuropsychological subtypes among children with ADHD and typically developing children. In the present study, we follow the four functions of attention model (Tsal et al., 2005) as a framework for ADHD, and by using graph theory and community detection, we explored whether datadriven attentional subtypes could improve discrimination of adults with/without ADHD.
Methods: 151 adult ADHD participants and 123 controls performed four visual attention tasks assessing performance of the sustained, selective, orienting and executive functions. Four summarizing measures from these four tasks were used as an input to the Newman's community structure in networks algorithm.
Results: Five subgroups were identified by Newman's algorithm. Each subgroup consisted of a similar number of ADHD and controls. In each of those subgroups an SVM classification algorithm was utilized which classified a novel participant as either ADHD or control, with an average of 66 % accuracy, 76 % sensitivity and 58 % specificity. Interestingly, different levels of correct classification were obtained in each of the clusters, ranging from 52 % to 82 %.
Conclusions: Multiple attentional profiles exist among adults with and without ADHD. This research demonstrated (a) how a graph theory approach can enrich the theoretical framework of ADHD by revealing the nature of the relations between the four functions of attention (b) how discrimination of ADHD and control participants can benefit from an identifying profile category.

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J Neural Transm. 2014;1-12.

ALTERED PERIPHERAL BDNF MRNA EXPRESSION AND BDNF PROTEIN CONCENTRATIONS IN BLOOD OF CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER.

Taurines R, Segura M, Schecklmann M, et al.

Findings from molecular genetic studies and analyses of postmortem and peripheral tissue led to the hypothesis that neurotrophins-as crucial moderators of neuroplasticity-impact on the pathophysiology of autism spectrum disorder (ASD). The study projects aimed to complement former results on the role of brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family with fundamental impact on brain development and function. The purpose of this work was to investigate peripheral BDNF mRNA expression and BDNF protein concentrations in ASD as potential surrogates for the effects observed in the

central nervous system. In a BDNF protein quantification study, serum concentrations were analyzed using Enzyme-Linked Immunosorbent Assays in 24 male patients with ASD, all with an IQ > 70 (age 13.9 (plus or minus) 3.0 years) and 20 age- and gender-matched healthy control subjects (age 14.4 (plus or minus) 2.1 years; p=0.522). In a further independent project, a BDNF mRNA expression analysis, mRNA levels from total blood were assessed by quantitative real-time polymerase chain reaction in a sample of 16 male ASD patients (age 10.8 (plus or minus) 2.2), 15 age- and gender-matched healthy controls (age 12.1 (plus or minus) 2.2) and 15 patients with attention deficit hyperactivity disorder as a clinical control group (age 11.8 (plus or minus) 2.2; p=0.207). In the protein quantification project, significantly decreased BDNF serum concentrations were found in ASD cases compared to healthy control children (t = -2.123, df = 42, p < 0.05). Analysis of covariance (ANCOVA) revealed this result in accordance with significant reductions in BDNF mRNA expression in ASD, observed in the mRNA expression study (F=3.65; df = 2.43; p<0.05); neither age nor IQ confounded the result, as indicated by ANCOVA (F=3.961; df = 2.41; p<0.05, (eta)2 = 0.162). Our study projects supported the notion that neurotrophins are involved in the pathophysiology of ASD. Further studies may eventually contribute to the identification of distinct peripheral mRNA expression and protein concentration patterns possibly supporting diagnostic and therapeutic processes.

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J Am Acad Child Adolesc Psychiatry. 2014;53:209-20.

GENETIC ASSOCIATIONS BETWEEN THE SYMPTOMS OF ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER AND EMOTIONAL LABILITY IN CHILD AND ADOLESCENT TWINS.

Merwood A, Chen W, Rijsdijk F, et al.

Objective Emotional lability is recognized as an associated feature of attention-deficit/hyperactivity disorder (ADHD). However, the degree of phenotypic and etiologic overlap between emotional lability and the ADHD dimensions of hyperactivity-impulsivity and inattention remains unclear. The present study examines these associations in a large, community twin sample.

Method Structural equation models were fit to data from 1,920 child and adolescent twin pairs (age range, 5-18 years). Symptoms of hyperactivity- impulsivity (HI) and inattention (IA) were assessed using a modified version of the DuPaul rating scale, completed by parents. Symptoms of emotional lability (EL) were assessed using the parent-rated Conners 10-item scale.

Results There were moderate to strong phenotypic correlations between HI, IA, and EL. Multivariate twin modeling revealed that a common pathway model best accounted for the covariance among these dimensions, represented by a highly heritable latent factor. Ad hoc analyses confirmed that all additive genetic influences on HI, IA, and EL were shared, and identified a significantly stronger association of EL with the latent ADHD factor in older than in younger individuals.

Conclusions Emotional lability was phenotypically and genetically associated with hyperactivity-impulsivity and inattention in children and adolescents. The finding that a single, heritable, latent factor accounted for covariation among these phenotypes indicates that their co-occurrence is primarily the result of overlapping genetic effects. These data support the hypothesis that emotional lability is etiologically relevant to the core ADHD phenotype, and that it should be targeted in assessment and treatment in clinical practice.

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Med Hypotheses. 2014;82:341-45.

MEAN PLATELET VOLUME IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Yorbik O, Mutlu C, Tanju IA, et al.

The mean platelet volume (MPV), the accurate measure of platelet size, is considered a marker and determinant of platelet function. MPV can be a potentially useful prognostic biomarker in patients with cardiovascular disease. After reviewing literature, we hypothesized that attention deficit hyperactivity disorder (ADHD) in childhood may be a risk factor for coronary heart disease (CHD) in adulthood. The aim of this study was investigation of MPV and platelet count (PLT) in children with ADHD and healthy subjects. The MPV and the PLT were measured in 70 children with ADHD (aged 6-16. years), and compared with 41 healthy controls. The MPV was found to be significantly increased in ADHD group compared to control

group (p=.006). There was no significant difference in the PLT between groups (p>.05). To our knowledge, this was the first study of investigating the levels of MPV and PLT in children with ADHD. Although significance and cause of increased MPV level in ADHD remain unclear in present study, further studies are warranted to investigate relationships among MPV, ADHD in childhood and CHD in adulthood.

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Nature. 2014 Feb;506:146-48.
MEDICATION: THE SMART-PILL OVERSELL.
Sharpe K.

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Neuropediatrics. 2014.
PHARMACOTHERAPY OF ATTENTION DEFICIT IN NEUROFIBROMATOSIS TYPE 1: EFFECTS ON COGNITION.
Lidzba K, Granstroem S, Leark RA, et al.
Aim Attention deficit with or without hyperactivity (AD[H]D) is a common comorbidity of neurofibromatosis type 1 (NF 1). We tested the hypothesis that permanent medication with methylphenidate can improve cognitive functioning in children with NF 1 and comorbid AD(H)D.
Patients and Method We retrospectively analyzed data of a clinical sample of patients with NF 1 with or without AD(H)D, who underwent standardized neuropsychological diagnostics twice (age range: T1, 6-14 years; T2, 7-16 years; mean interval, 49.09 months). A total of 16 children without AD(H)D (nine females) were compared with 14 unmedicated children with AD(H)D (eight females) and to 13 medicated children with AD(H)D (two females). Effects of medication and attention on cognitive outcome (IQ) were tested by repeated measures analysis of covariance (rmANCOVA).
Results Medicated children with NF 1 improved significantly in full-scale IQ from T1 to T2 (IQ[T1] =80.38, IQ[T2] =98.38, confidence interval [diff]: -25.59 to -10.40, p<0.0001), this effect was not evident for the other groups. With attention measures as covariates, the effect remained marginally significant.
Conclusion Children and adolescents with NF 1 and comorbid AD(H)D may profit from MPH medication regarding general cognition. This effect could be specific for the group of patients with NF 1, and cannot be explained solely by improvements in attention. Controlled, prospective studies are warranted to corroborate our findings.

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Neuropsychiatr Dis Treat. 2014;10:147-51.
TIPEPIDINE IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A 4-WEEK, OPEN-LABEL, PRELIMINARY STUDY.
Sasaki T, Hashimoto K, Tachibana M, et al.
Background: Tipepidine (3-[di-2-thienylmethylene]-1-methylpiperidine) has been used solely as a nonnarcotic antitussive in Japan since 1959. The safety of tipepidine in children and adults has already been established. It is reported that tipepidine inhibits G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. The inhibition of GIRK channels by tipepidine is expected to modulate the level of monoamines in the brain. We put forward the hypothesis that tipepidine can improve attention deficit/hyperactivity disorder (ADHD) symptoms by modulating monoaminergic neurotransmission through the inhibition of GIRK channels. The purpose of this open-label trial was to confirm whether treatment with tipepidine can improve symptoms in pediatric patients with ADHD.
Subjects and methods: This was a 4-week, open-label, proof-of-efficacy pilot study for pediatric subjects with ADHD. Ten pediatric ADHD subjects (70% male; mean age, 9.9 years; combined [inattentive and hyperactive/impulsive] subtype, n=7; inattentive subtype, n=3; hyperimpulsive subtype, n=0) received tipepidine hibenzate taken orally at 30 mg/day for 4 weeks. All subjects were assessed using the ADHD Rating Scale IV (ADHD-RS), Japanese version, and the Das-Naglieri Cognitive Assessment System (DN-CAS), Japanese version.

Results: A comparison of baseline scores and 4-week end-point scores showed that all the ADHD-RS scores (total scores, hyperimpulsive subscores, and inattentive subscores) improved significantly (P,0.001). Furthermore, a comparison of baseline DN-CAS total scores and 4-week end-point scores showed a mild trend of improvement (P=0.093). Tipepidine was well tolerated, with no patients discontinuing medication because of side effects.
Conclusion: Our pilot study suggests that tipepidine therapy may prove to be an effective alternative treatment for pediatric patients with ADHD. Nonetheless, more detailed randomized, double-blind trials are needed to confirm tipepidine's efficacy.

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Neuropsychiatr Dis Treat. 2014;10:85-88.

BALANCE DEFICITS AND ADHD SYMPTOMS IN MEDICATION-NAIVE SCHOOL-AGED BOYS.

Konicarova J, Bob P, Raboch J.

Background and objectives: Functional disturbances developed early in life include balance deficits which are linked to dysfunctions of higher levels of cognitive and motor integration. According to our knowledge, there are only a few studies suggesting that balance deficits are related to behavioral disturbances in attention-deficit/hyperactivity disorder (ADHD).
Methods: We tested the extent to which balance deficits were related to ADHD symptoms in 35 medication-naive boys of school age (8-11 years) and compared the results with a control group of 30 boys of the same age.
Results: ADHD symptoms in medication-naive boys had specific relationships to disturbances of postural and gait balance.
Conclusion: To our knowledge, this study provides the first evidence in the medical literature for a direct relationship between ADHD symptoms and balance deficits, that cannot be attributed to medication and the presence of any neurological disease.

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

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

BenAmor L.

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in school aged children. Functional abnormalities have been reported in brain imaging studies in ADHD populations. Psychostimulants are considered as the first line treatment for ADHD. However, little is known of the effect of stimulants on brain metabolites in ADHD patients.
Objectives: To compare the brain metabolite concentrations in children with ADHD and on stimulants with those of drug naive children with ADHD, versus typically developed children, in a homogenous genetic sample of French Canadians.
Methods: Children with ADHD on stimulants (n=57) and drug naive children with ADHD (n=45) were recruited, as well as typically developed children (n=38). The presence or absence of ADHD diagnosis (Diagnostic and Statistical Manual of Mental Disorders IV criteria) was based on clinical evaluation and The Diagnostic Interview Schedule for Children IV. All children (n=140) underwent a proton magnetic resonance spectroscopy session to measure the ratio of N-acetyl-aspartate, choline, glutamate, and glutamate-glutamine to creatine, respectively, in the left and right prefrontal and striatal regions of the brain, as well as in the left cerebellum.
Results: When compared with drug naive children with ADHD, children with ADHD on stimulants and children typically developed were found to have higher choline ratios in the left prefrontal region (P=0.04) and lower N-acetyl-aspartate ratios in the left striatum region (P=0.01), as well as lower glutamate-glutamine ratios in the left cerebellum (P=0.05). In these three regions, there was no difference between children with ADHD on stimulants and typically developed children.

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

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Neuropsychiatr Dis Treat. 2014;10:231-42.

Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity DISORDER: DATA FROM QUANTITATIVE ELECTROENCEPHALOGRAPHY, EVENT-RELATED POTENTIALS, AND A GO/NO-GO TEST.

Ogrim G, Kropotov J, Brunner JF, et al.

Background: We searched for predictors of the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder (ADHD), emphasizing variables from quantitative electroencephalography, event-related potentials (ERPs), and behavioral data from a visual go/no-go test.

Methods: Nineteen-channel electroencephalography (EEG) was recorded during the resting state in eyes-open and eyes-closed conditions and during performance of the cued go/no-go task in 98 medication-naive ADHD patients aged 7-17 years and in 90 controls with the same age and sex distribution as the patients. For patients, the recording was followed by a systematic trial on stimulant medication lasting at least 4 weeks. Based on data from rating scales and interviews, two psychologists who were blind to the electrophysiological results independently rated the patients as responders (REs) (N=74) or non-responders (non-REs) (N=24). Using a logistic regression model, comparisons were made between REs and non-REs on the EEG spectra, ERPs (cue P3, contingent negative variation, and P3 no-go of the ERP waves and independent components [ICs] extracted from these waves), reaction time, reaction time variability, number of commission and omission errors, intelligence quotient, age, sex, ADHD subtype, and comorbidities.

Results: The two groups differed significantly on eight of the variables, with effect sizes (Cohen's d) ranging from 0.49 to 0.76. In the multivariate logistic regression analysis, only three of these variables were significantly associated with clinical outcome. The amplitude of the IC cue P3, which has a parietal-occipital distribution, was normal in REs but significantly smaller in non-REs, whereas the centrally distributed IC P3 no-go early was smaller in REs than in non-REs and controls. In addition, the REs had more power in the EEG theta band. A quartile-based index was calculated using these three variables. The group with the lowest scores comprised only 36% REs; response rates in the three other groups were 83%, 86%, and 89%.

Conclusion: The clinical outcome of stimulant medication was best predicted by electrophysiological parameters. The brain dysfunctions of the REs appear to be primarily associated with prefrontal lobe hypoactivation. The non-REs were deviant from the controls in parietal-occipital functions.

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Neuropsychology. 2013 Nov;27:713-24.

NEUROPSYCHOLOGICAL DEFICITS ASSOCIATED WITH HEAVY PRENATAL ALCOHOL EXPOSURE ARE NOT EXACERBATED BY ADHD.

Glass L, Ware AL, Crocker N, et al.

Objective: Neuropsychological functioning of individuals with attention-deficit/hyperactivity disorder (ADHD) or heavy prenatal alcohol exposure has been well documented independently. This study examined the interaction between both factors on cognitive performance in children.

Method: As part of a multisite study, 344 children (8–16 y, M=12.28, SD=2.52) completed a comprehensive neuropsychological battery. Four subject groups were tested: children with histories of heavy prenatal alcohol exposure (AE) and ADHD (AE+, n=90), alcohol-exposed without ADHD, (AE-, n=38), nonexposed with ADHD (ADHD, n=80), and nonexposed without ADHD (CON, n=136).

Results: Separate 2(AE) × 2(ADHD) MANCOVAs revealed significant main and interactive effects of ADHD and AE on overall WISC-IV, D-KEFS, and CANTAB performance. Individual ANOVAs revealed significant interactions on 2 WISC-IV indices [Verbal Comprehension (VCI), Perceptual Reasoning (PRI)], and four D-KEFS and CANTAB subtests [Design Fluency, Verbal Fluency, Trail Making, Spatial Working

Memory]. Follow-up analyses demonstrated no difference between AE+ and AE- groups on these measures. The combined AE+/- group demonstrated more severe impairment than the ADHD group on VCI and PRI, but there were no other differences between clinical groups.
Conclusions: These results support a combined AE+/- group for neuropsychological research and indicate that, in some cases, the neuropsychological effects seen in ADHD are altered by prenatal alcohol exposure. The effects of alcohol exposure on verbal comprehension and perceptual reasoning were greater than those related to having ADHD without alcohol exposure, although both conditions independently resulted in cognitive impairment compared to controls. Clinically, these findings demonstrate task-dependent patterns of impairment across clinical disorders.

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Pediatrics. 2014 Jan;133:96-104.
TWO-YEAR IMPACT OF THE ALTERNATIVE QUALITY CONTRACT ON PEDIATRIC HEALTH CARE QUALITY AND SPENDING.
Chien AT, Song Z, Chernew ME, et al .
OBJECTIVE: To examine the 2-year effect of Blue Cross Blue Shield of Massachusetts' global budget arrangement, the Alternative Quality Contract (AQC), on pediatric quality and spending for children with special health care needs (CSHCN) and non-CSHCN.
METHODS: Using a difference-in-differences approach, we compared quality and spending trends for 126,975 unique 0- to 21-year-olds receiving care from AQC groups with 415,331 propensity-matched patients receiving care from non-AQC groups; 23% of enrollees were CSHCN. We compared quality and spending pre (2006-2008) and post (2009-2010) AQC implementation, adjusting analyses for age, gender, health risk score, and secular trends. Pediatric outcome measures included 4 preventive and 2 acute care measures tied to pay-for-performance (P4P), 3 asthma and 2 attention-deficit/hyperactivity disorder quality measures not tied to P4P, and average total annual medical spending.
RESULTS: During the first 2 years of the AQC, pediatric care quality tied to P4P increased by +1.8% for CSHCN (P<.001) and +1.2% for non-CSHCN (P<.001) for AQC versus non-AQC groups; quality measures not tied to P4P showed no significant changes. Average total annual medical spending was ~5 times greater for CSHCN than non-CSHCN; there was no significant impact of the AQC on spending trends for children.
CONCLUSIONS: During the first 2 years of the contract, the AQC had a small but significant positive effect on pediatric preventive care quality tied to P4P; this effect was greater for CSHCN than non-CSHCN. However, it did not significantly influence (positively or negatively) CSHCN measures not tied to P4P or affect per capita spending for either group.

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Pediatrics. 2014 Jan;133:e14-e22.
ENVIRONMENTAL RISK FACTORS BY GENDER ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Silva D, Colvin L, Hagemann E, et al.
BACKGROUND: Early environmental risk factors associated with attention-deficit/hyperactivity disorder (ADHD) have been increasingly suggested. Our study investigates the maternal, pregnancy, and newborn risk factors by gender for children prescribed stimulant medication for treatment of ADHD in Western Australia.
METHODS: This is a population-based, record linkage case-control study. The records of all non-Aboriginal children and adolescents born in Western Australia and aged <25 years who were diagnosed with ADHD and prescribed stimulant medication (cases=12,991) were linked to the Midwives Notification System (MNS) to obtain maternal, pregnancy, and birth information. The control population of 30,071 children was randomly selected from the MNS.
RESULTS: Mothers of children with ADHD were significantly more likely to be younger, be single, have smoked in pregnancy, have labor induced, and experience threatened preterm labor, preeclampsia, urinary tract infection in pregnancy, or early term delivery irrespective of the gender of the child, compared with the

control group. In the fully adjusted model, a novel finding was of a possible protective effect of oxytocin augmentation in girls. Low birth weight, postterm pregnancy, small for gestational age infant, fetal distress, and low Apgar scores were not identified as risk factors.
CONCLUSIONS: Smoking in pregnancy, maternal urinary tract infection, being induced, and experiencing threatened preterm labor increase the risk of ADHD, with little gender difference, although oxytocin augmentation of labor appears protective for girls. Early term deliveries marginally increased the risk of ADHD. Studies designed to disentangle possible mechanisms, confounders, or moderators of these risk factors are warranted.

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PLoS ONE. 2013;8.
RCT OF WORKING MEMORY TRAINING IN ADHD: LONG-TERM NEAR-TRANSFER EFFECTS.
Hovik KT, Saunes BK, Aarlien AK, et al.
Objective: The aim of the study is to evaluate the long-term near-transfer effects of computerized working memory (WM) training on standard WM tasks in children with Attention-Deficit/Hyperactivity Disorder (ADHD).
Method: Sixty-seven children aged 10-12 years in Vestfold/Telemark counties (Norway) diagnosed with F90.0 Hyperkinetic disorder (ICD-10) were randomly assigned to training or control group. The training group participated in a 25-day training program at school, while the control group received treatment-as-usual. Participants were tested one week before intervention, immediately after and eight months later. Based on a component analysis, six measures of WM were grouped into composites representing Visual, Auditory and Manipulation WM.
Results: The training group had significant long-term differential gains compared to the control group on all outcome measures. Performance gains for the training group were significantly higher in the visual domain than in the auditory domain. The differential gain in Manipulation WM persisted after controlling for an increase in simple storage capacity.
Conclusion: Systematic training resulted in a long-term positive gain in performance on similar tasks, indicating the viability of training interventions for children with ADHD. The results provide evidence for both domain-general and domain-specific models. Far-transfer effects were not investigated in this article.
Trial Registration: Controlled-Trials.com ISRCTN19133620

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PLoS ONE. 2013;8.
ABERRANT DEVELOPMENT OF FUNCTIONAL CONNECTIVITY AMONG RESTING STATE-RELATED FUNCTIONAL NETWORKS IN MEDICATION-NAIVE ADHD CHILDREN.
Choi J, Jeong B, Lee SW, et al.
Objective: The aim of this study was to investigate the compromised developmental trajectory of the functional connectivity among resting-state-related functional networks (RSFNs) in medication-naive children with attention-deficit/hyperactivity disorder (ADHD).
Subjects and Methods: Using both independent component analysis and dual regression, subject-specific time courses of 12 RSFNs were extracted from both 20 medication-naive children with ADHD, and 20 age and gender-matched control children showing typical development (TDC). Both partial correlation coefficients among the 12 RSFNs and a resting-state resource allocation index (rsRAI) of the salience network (SN) were entered into multiple linear regression analysis to investigate the compromised, age-related change in medication-naive ADHD children. Finally, correlation analyses were performed between the compromised RSFN connections showing significant group-by-age interaction and rsRAI of SN or clinical variables.
Results: Medication-naive ADHD subjects failed to show age-related increment of functional connectivity in both rsRAI of SN and two RSFN connections, SN-Sensory/motor and posterior default mode/precuneus network (pDMN/prec) - anterior DMN. Lower SN-Sensory/motor connectivity was related with higher scores

on the ADHD Rating Scale, and with poor scores on the continuous performance test. The pDMN/prec-aDMN connectivity was positively related with rsRAI of SN.
Conclusions: Our results suggest that medication-naive ADHD subjects may have delayed maturation of the two functional connections, SN-Sensory/Motor and aDMN-pDMN/prec. Interventions that enhance the functional connectivity of these two connections may merit attention as potential therapeutic or preventive options in both ADHD and TDC.

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PLoS ONE. 2013;8.
DRD4 RARE VARIANTS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): FURTHER EVIDENCE FROM A BIRTH COHORT STUDY.
Tovo-Rodrigues L, Rohde LA, Menezes AMB, et al.
The dopamine receptor D4 (DRD4) is one of the most studied candidate genes for Attention-Deficit/Hyperactivity Disorder (ADHD). An excess of rare variants and non-synonymous mutations in the VNTR region of 7R allele in ADHD subjects was observed in previous studies with clinical samples. We hypothesize that genetic heterogeneity in the VNTR is an important factor in the pathophysiology of ADHD. The subjects included in the present study are members of the 1993 Pelotas Birth Cohort Study (N=5,249). We conducted an association study with the 4,101 subjects who had DNA samples collected. The hyperactivity-inattention scores were assessed through the parent version of the Strengths and Difficulties Questionnaire at 11 and 15 years of age. The contribution of allele's length and rare variants to high hyperactivity/inattention scores predisposition was evaluated by multivariate logistic regression. No effect of allele length was observed on high scores of hyperactivity-inattention. By contrast, when resequencing/haplotyping was conducted in a subsample, all 7R rare variants as well as non-synonymous 7R rare variants were associated with high hyperactivity/inattention scores (OR=2.561; P=0.024 and OR=3.216; P=0.008 respectively). A trend for association was observed with 4R rare variants. New coding mutations covered 10 novel motifs and many of them are previously unreported deletions leading to different stop codons. Our findings suggest a contribution of DRD4 7R rare variants to high hyperactivity-inattention scores in a population-based sample from a large birth cohort. These findings provide further evidence for an effect of DRD4 7R rare variants and allelic heterogeneity in ADHD genetic susceptibility.

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PLoS ONE. 2013;8.
WHAT TIME PERIODS OF THE DAY ARE CONCERNING FOR PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER?
Usami M, Okada T, Sasayama D, et al.
Background/Aim: The questionnaire-children with difficulties (QCD) is a parent-assessed questionnaire designed to evaluate a child's difficulties in functioning during specific time periods of the day. In this study, the QCD was applied to determine the time periods of the day that are concerning for the parents of children with attention deficit hyperactivity disorder (ADHD). The results were compared with those for a community sample.
Methods: Elementary and junior high school students with ADHD (243 boys, 55 girls) and a community sample of children (518 boys, 618 girls) were enrolled in this study. Their behaviors were assessed by the QCD, the ADHD-rating scale (ADHD-RS), and the Oppositional Defiant Behavior Inventory (ODBI). The effects of gender (boy/girl) and diagnosis (ADHD/community sample) on the total QCD score were analyzed across each school grade (elementary/junior high school). Correlation coefficients between QCD and ADHD-RS/ODBI scores were analyzed.
Results: The QCD score for the ADHD group was significantly lower than that for the community sample ($P<0.001$). There were significantly strong correlations between "evening" and ADHD-RS and ODBI scores for all children with ADHD ($r>0.41$, $P<0.001$) and between "night" and inattention and oppositional symptoms for the girls with ADHD ($r>0.40$, $P<0.001$).

Conclusions: Parents reported that children with ADHD faced greater difficulties in completing basic daily activities compared with the community controls, particularly in the evening. Furthermore, these difficulties were related to the severity of ADHD symptoms. The parents' perceptions depended on the gender, ADHD and oppositional symptoms, and the time period of the day. This study determined that children with ADHD face greater difficulties in daily functioning compared with community sample children, that these difficulties are time-dependent, and that these difficulties were particularly experienced in the evening.

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Prostaglandins Leukotrienes Essent Fatty Acids. 2014.

WHICH POLYUNSATURATED FATTY ACIDS ARE ACTIVE IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER RECEIVING PUFA SUPPLEMENTATION? A FATTY ACID VALIDATED META-REGRESSION ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

Puri BK, Martins JG.

Concerns about growth retardation and unknown effects on long-term brain development with stimulants have prompted interest in polyunsaturated fatty acid supplementation (PUFA) as an alternative treatment. However, randomized controlled trials (RCTs) and meta-analyses of PUFA supplementation in ADHD have shown marginal benefit, and uncertainty exists as to which, if any, PUFA might be effective in alleviating symptoms of ADHD. We conducted an updated meta-analysis of RCTs in ADHD together with multivariable meta-regression analyses using data on PUFA content obtained from independent fatty acid methyl ester analyses of each study PUFA regimen. The PubMed, Embase and PsycINFO databases were searched with no start date and up to 28th July 2013. Study inclusion criteria were: randomized design, placebo controlled, PUFA preparation as active intervention, reporting change scores on ADHD rating-scale measures. Rating-scale measures of inattention and hyperactive-impulsive symptoms were extracted, study authors were contacted to obtain missing data, studies not reporting negative findings had these data imputed, and study quality was assessed using the Jadad system plus other indicators. Random-effects models were used for pooled effects and for meta-regression analyses. Standardized mean differences (SMD) in inattention, hyperactive-impulsive and combined symptoms were assessed as rated by parents, teachers or all raters. The influence of study characteristics and PUFA regimen content was explored in multivariable meta-regression analyses. The overall pooled estimate from 18 studies showed that combined ADHD symptoms rated by all raters decreased with PUFA supplementation; SMD -0.192 (95% CI: -0.297, -0.086; P<0.001). However, when analyzed by rater, only parent-rated symptoms decreased significantly. Multivariable meta-regression showed that longer study duration, (gamma)-linolenic acid (GLA), and the interaction between GLA and eicosapentaenoic acid (EPA) were associated with significant decreases in inattention; however, PUFA regimen content was unrelated to changes in hyperactive-impulsive symptoms. Certain fatty acids present in placebo preparations may potentially have been psychoactive. This meta-analysis provides modest evidence of PUFA effectiveness in ADHD, especially GLA and EPA for inattention symptoms; however, evidence of reporting bias, publication bias, variable methodological quality, and use of potentially psychoactive placebos limit the generalizability of these findings.

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Psychiatr Invest. 2014;11:65-75.

NEUROPSYCHOLOGICAL AND BEHAVIORAL PROFILES IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER CHILDREN OF PARENTS WITH A HISTORY OF MOOD DISORDERS: A PILOT STUDY.

Park S, Hong KEM, Yang YH, et al.

Objective We aimed to investigate the neurocognitive and behavioral endophenotypes of premorbid mood disorder. We compared intelligence, neuropsychological functioning, and behavioral problems among three groups: 1) a high-risk group [attention-deficit hyperactivity disorder (ADHD) children of parents with a history of a mood disorder], 2) a low-risk group (ADHD children of parents without a history of a mood disorder), and 3) normal comparison subjects.

Methods We used the Korean Educational Development Institute Wechsler Intelligence Scale for Children-Revised (KEDI-WISC-R), the Stroop Color Word Interference Test (Stroop), the Wisconsin Card Sorting Test (WCST), and the Rey-Osterrieth Complex Figure Test (RCFT) as neurocognitive measures, and we used the Child Behavior Checklist (CBCL) as a behavioral measure. Performance on these neuropsychological tests and score on the CBCL of 18 high-risk children were compared to those of 20 low-risk children and 24 healthy children. We also assessed the children's current mood state and familial functioning to control for the confounding effects of these variables.
Results Compared to low-risk and healthy children, high-risk children were impaired on the Picture Completion and Stroop Word subtest and showed higher scores on the CBCL subscales representing internalizing symptoms. These significant group differences persisted even after adjustment for the children's current mood state and familial functioning.
Conclusion Neuropsychological deficits in the offspring of parents with a mood disorder may be associated with the current mood state rather than with innate characteristics, while their internalizing symptoms may partially stem from innate characteristics that are endophenotypes of a premorbid mood disorder.

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Psychiatry Res. 2014;215:260-61.
ASSOCIATION BETWEEN THE POLYMORPHISMS OF THE SELECTED GENES ENCODING DOPAMINERGIC SYSTEM WITH ADHD AND AUTISM.
Nikolac Perkovic M, Nedic Erjavec G, Stefulj J, et al.

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Psychiatry Res Neuroimaging. 2014;221:169-71.
GYRIFICATION DIFFERENCES IN CHILDREN AND ADOLESCENTS WITH VELOCARDIOFACIAL SYNDROME AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PILOT STUDY.
Mous SE, Karatekin C, Kao CY, et al.
We used magnetic resonance imaging to investigate brain gyrification patterns between 19 children with attention-deficit/hyperactivity disorder (ADHD), 9 children with velocardiofacial syndrome (VCFS), and 23 control children. We found that VCFS is associated with widespread decreases in gyrification. In ADHD, we found minor differences from control children. No evidence was found for common gyrification patterns between VCFS and ADHD children.

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Res Autism Spectr Disord. 2014;8:472-79.
SELF MONITORING TO PROMOTE ON-TASK BEHAVIOR BY TWO HIGH FUNCTIONING BOYS WITH AUTISM SPECTRUM DISORDERS AND SYMPTOMS OF ADHD.
Stasolla F, Perilli V, Damiani R.
We assessed a self-monitoring procedure to promote on-task behavior in classroom by two high functioning boys with autism spectrum and attention deficit hyperactivity disorders. A second aim of the study was to reduce stereotyped behaviors for both boys. Finally, a third goal was to verify the effects of the intervention on the participant's mood. The study was conducted according to a non concurrent multiple baseline design across participants. Results show an increase of on-task behavior and indices of happiness during the intervention phase. Moreover, the stereotyped behaviors decreased during intervention phase for both boys. Participants maintained their performance during the maintenance phase, which occurred a month after the end of the intervention. The effectiveness of the rehabilitation program was confirmed by 72 university students involved in a social validation assessment as raters. Psychological and practical implications of the findings are discussed.

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Res Dev Disabil. 2014.

PSYCHOLOGICAL DISTRESS IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Missiuna C, Cairney J, Pollock N, et al.

This study explored whether or not a population-based sample of children with developmental coordination disorder (DCD), with and without comorbid attention deficit/hyperactivity disorder (ADHD), experienced higher levels of psychological distress than their peers. A two-stage procedure was used to identify 244 children: 68 with DCD only, 54 with ADHD only, 31 with comorbid DCD and ADHD, and 91 randomly selected typically developing (TD) children. Symptoms of depression and anxiety were measured by child and parent report. Child sex and caregiver ethnicity differed across groups, with a higher ratio of boys to girls in the ADHD only group and a slightly higher proportion of non-Caucasian caregivers in the TD group. After controlling for age, sex, and caregiver ethnicity, there was significant variation across groups in both anxiety (by parent report, $F(3,235)=8.9$, $p<0.001$; by child report, $F(3,236)=5.6$, $p=0.001$) and depression (parent report, $F(3,236)=23.7$, $p<0.001$; child report, $F(3,238)=9.9$, $p<0.001$). In general, children in all three disorder groups had significantly higher levels of symptoms than TD children, but most pairwise differences among those three groups were not significant. The one exception was the higher level of depressive symptoms noted by parent report in the ADHD/DCD group. In conclusion, children identified on the basis of motor coordination problems through a population-based screen showed significantly more symptoms of depression and anxiety than typically developing children. Children who have both DCD and ADHD are particularly at heightened risk of psychological distress.

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Sleep Med. 2013;14:e125.

OBSTRUCTIVE SLEEP APNEA AND P300 ABNORMALITIES IN CHILDREN WITH ATTENTION DEFICIT.

Henriques Filho P, Pratesi R, Gandolfi L, et al.

Introduction: Obstructive sleep apnea (OSA), that causes abnormal breathing or chronic intermittent hypoxia during sleep, can cause attention and working memory deficits which can be related to cognitive impairment throughout the developing nervous system.

Aims: To verify the ability to sustain attention in children and adolescents diagnosed with OSA compared to a control group.

Materials and methods: 80 participants of a local school (49 boys and 31 girls) aged 6 to 17 years (mean 10.85 , (plus or minus)2.25), with attention complaints by the school, accepted to participate in this study and underwent overnight polysomnography and P300 evoked potential test. This test was divided into three repeated series with 10 min interval between series and lasting 15 min each series. None of the participants had been using medication or had previous diagnoses of developing mental disorder.

Results: Among the 80 participants, 26 (32.5%) received the diagnosis of OSA and 61 (76.3) had varied abnormalities at P300 tests, from these 26 met both OSA and ADD deficit attention disorder criteria, 19 participants had no altered results and composed the control group. Considering the entire sample, OSA was significantly correlated with lower amplitudes ($r=.79$; $r=.77$ and $r=.81$, $p=.000$) and longer latencies ($r=.60$; $r=.57$; $r=76$, $p=.000$) in all three tests, respectively. Two-Way ANOVA and repeated measures analyses showed no effect of age and gender on the P300 waves, though boys had a greater variability in all values. The apnea and hypoapnea index (IAH) had mainly effect on amplitudes of all tests and at latency of test 3 ($F>2.23$, $p<.010$) and OSA diagnosis had effect over all P300 variables ($F>34.39$, $p<.000$). Also, the group with OSA also presented decay in amplitude along the three tests, as showed by the repeated measures analyses, over all the three P300 amplitude measures ($F=297.57$, $p=.000$), but not to latency, differently from the group without OSA that kept the values at the same levels during the three tests.

Conclusion: This study has found evidence of the relationship between OSA and P300 evoked potentials, amplitudes and latencies. These findings are in accordance with the literature showing that sleep disturbances might disrupt sustaining attention abilities leading to school complaints of learning capacity. Also, this may help to clarify the diagnosis of attention deficit disorder, when sleep disorder is present.

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Sleep Med. 2013;14:e272.

RESTLESS LEGS SYNDROME IN ATTENTION DEFICIT-HIPERACTIVITY DISORDER: WHAT ABOUT THE ROLE OF TREATMENT? A MULTICENTER STUDY.

Soria-Bretones C, Escriba-Alepuz J, Giner-Bayarri P, et al.

Introduction: In our clinical practice we find a high co-morbidity of Attention Deficit-Hyperactivity Disorder (ADHD) and Restless Legs Syndrome (RLS). Our aim is to describe the prevalence of RLS in children diagnosed of ADHD, as well as find out if ADHD treatment plays a role in RLS symptoms and prevalence.

Materials and methods: Observational descriptive cross- sectional study in children diagnosed of ADHD referred from Neuropediatrics and Child Psychiatry to Clinical Neurophysiology departments in two hospitals (in Cuenca and Valencia, Spain): n=36, ages 5-17. These were divided in non-treated (n=16) and treated (n=20) subgroups. Measures: questionnaire based on Owen's test for RLS and Periodic Leg Movements (PLM), answered by parents by phone or live interviews. International RLS Study Group criteria for RLS (2002) were followed.

Results: Global RLS prevalence in our ADHD patients: 36.1%. Among them, criteria of definite RLS are fulfilled in 30.8%, probable RLS in 46.1% and possible RLS in 23.1%. RLS prevalence in non-treated group: 50.0%. Definite RLS in 12.5%, probable in 62.5% and possible in 25.0% of them. RLS prevalence in treated group: 25.0%. Definite RLS in 60.0%, probable in 20.0% and possible in 20.0%.

Conclusion: The prevalence of RLS symptoms in children with ADHD is higher than in normal population, according to the reviewed literature. In treated ADHD, overall RLS prevalence is only 50% of that in non-treated group, while nullDefinite RLSnull prevalence is 4.8 times higher.

These findings suggest: The symptoms of ADHD and RLS may be overlapping and lead to misdiagnosis of both disorders. In the same way, a lower prevalence of RLS in treated ADHD could be explained by an improvement in ADHD or in RLS symptoms. Further studies are needed to better understand these findings, as well as the specific role of the different drugs commonly used in ADHD.

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SLEEP ARCHITECTURE DISTURBANCES IN CHILDREN WITH BIPOLAR DISORDER VERSUS ATTENTION DEFICIT AND HYPERACTIVITY DISORDER: A PILOT STUDY.

Estrada Prat X, Alvarez Guerrico I, Principe A, et al.

Introduction: Sleep disturbances on Bipolar Disorder have been widely described and, bidirectionally, some reports point on sleep role on Bipolar Disorder physiopathology. Pediatric Bipolar Disorder (PBD) and Attention Deficit and Hyperactivity Disorder (ADHD) comorbidity is common. Useful biological markers should be found in order to achieve the correct management of both diseases. The aim of this study is to describe sleep architecture on PBD patients and compare to ADHD children.

Materials and methods: **Participants**: 4 PBD children (3 males; 4 European Hispanic) and 4 ADHD children (4 males; 3 European Hispanic) aged from 7 to 18 years were recruited from the Child and Adolescent Mental Health Services.

Instruments: International Neuropsychiatric Interview for Kids and Adolescents (MINI-Kid) was used for diagnostic purposes. WISC-IV below 70 was an exclusion criterion. Socio-demographic data were recorded. BEARS Algorithm and Sleep Disturbance Scale for Children (SDSC) were applied for sleep disturbances screening. Child Depression Inventory (CDI), Child Mania Rating Scale (CMRS) and Young Mania Rating Scale parent's version (p-YMRS) were measured the same day of Nocturnal Polysomnography (NPSG) was performed. Hypnogram characteristics were manually scored. Parameters analyzed were Sleep Efficiency, Sleep Time in N1, N2, N3 and REM stages, NoREM and REM Sleep Latencies, duration and number of REM cycles and REM density values.

Results: All PBD and ADHD participants had at least one current comorbid Axis I disorder. Sleep architecture showed a wide diversity. Significant differences in NPSG values according to PBD or ADHD conditions were not found. Only REM density showed a higher mean value on PBD than on ADHD children. 100% of PBD and 75% of ADHD participants were taking psychotropic medication. Correlations between sleep architecture and current medical treatments could not be established. No correlation between scales for the assessment of mood and sleep variables was found.

Conclusion: Sleep architecture in PBD and ADHD patients presents heterogeneous patterns. REM density seems to play an important role as biological marker in differential diagnosis of PBD and ADHD. New trials should be applied in order to establish correlations between NPSG variables and PBD or ADHD conditions, psychotropic drugs effects and mood disturbances.

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MEASURING ATTENTION DEFICIT WITH DASS TEST IN CHILDREN WITH OBSTRUCTIVE SLEEP APNEA.

Vaher H, Vaikjarv R, Veldi M, et al.

Introduction: **Objective**: To investigate the relationship between attention deficit and obstructive sleep apnea (OSA). We hypothesized that the severity of obstructive sleep apnea (OSA) correlates positively with negative DASS (Divided Attention Steering Simulation) test scores, which is a measure of attention ability.

Materials and methods: DASS tests were administered to 16 children with OSA symptoms and 16 children symptom free. Both groups were similar in age, gender, and body mass index (BMI). Polysomnography testing was given to both groups. OSA measures were: apnea hypopnea index (AHI), mean oxygen desaturation (SpO2), lowest mean SpO2. Attention deficit measures were DASS test scores: mean response time, off-road events per hours, failed responses.

Results: 18 boys and 14 girls participated in the study. The mean age of the study group and control group was 10.3 years, the mean BMI was 20.1 for the study group and 19.9 for controls. For the OSA symptom group: AHI was 2.2 (95% CI 1.9-2.5), mean lowest SpO2 and lowest SpO2 were 97.4% and 90.6 % (95% CI 89.5-91.7); for the DASS testing the average response time was 2.2 s, off road events per hour 75.6, failed responses 13.2. For the control group: AHI was 0.8 (95% CI 0.6- 1.0); mean lowest SpO2 and lowest SpO2 were 98.0% and 96.4% (95% CI 96.0-96.9); for the DASS testing the average response time was 1.4 s, off-road events per hour 10.1; failed responses 1.9. AHI value increase per 1 unit produced the increase of average response time of 0.44 units ($p<.0001$). The increase in AHI value was significantly related also to the number of off-road events ($p<.0014$) and to failed responses ($p<.0001$). Decrease in lowest mean SpO2 leads to increase in average reaction time ($p<.0002$; $p<.0001$). There was also an increase in off road events when AHI was higher ($p=.0014$), also decrease in lowest mean SpO2 resulted in higher number of off-road events ($p < .0074$). Higher AHI with lower mean SpO2 and mean lower SpO2 led to more failed responses during the DASS test ($p<.0001$; $p<.0005$; $p<.0001$).

Conclusion: The severity of sleep disordered breathing is related to worse outcomes of DASS testing in case of OSA. DASS test can be used as a diagnostic instrument to measure OSA-related attention deficit problems in children.

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Sleep Med. 2013;14:e245-e246.

SLEEP AND ADHD.

Ciopat O, Diaz Roman M, Urdanibia Centelles O, et al.

Introduction: Published studies have examined the differences between Attention Deficit and Hyperactivity Disorders (ADHD) subtypes and sleep problems, nevertheless revealing inconsistent results. Retrospective description of subjective and objective sleep parameters in children with ADHD subtypes.

Materials and methods: We studied a sample of 25 patients (24 boys and 1 girl), aged 6-17 years old, sent for further PSG study for sleep disorders, that were clinically diagnosed ADHD according to the DSM-IV criteria (5 hyperactive-impulsive subtype (ADHD-HI), 10 inattentive subtype (ADHD-I), and 10 combined subtype (ADHD-C), twelve taking specific medication. The subjective sleep variables were given by parents in a scheduled clinical interview following a sleep questionnaire. The objective variables were obtained by a one night polysomnography (PSG) study performed in our sleep laboratory.

Results: More than 50% of the patients suffered of more than one sleep symptom, the most frequent being: Motor activity during sleep was referred by 60%, somniloquy (56%), bruxism (56%) and awakenings from sleep (56%). Snoring (56%) was reported by parents, observed sleep apnea was in 8% of patients.

Other symptoms observed were daytime Sleepiness (24%) and Rest legs Syndrom (RLS) (20%). According to subtypes, the most relevant findings were that the motor activity during sleep was more common in ADHD-H-I (100%), and ADHD-C (60%). Parasomnias were present in the ADHD-H-I (80%). The snoring was more frequent in the ADHD-H-I (60%) and ADHD-I (70%). RLS was more prominent in ADHD-H-I (40%) and daytime sleepiness in ADHD-I (40%). PSG recordings had similar efficiency and the same sleep structure characteristics in all subtypes, except in the ADHD-I, it was found the maximum awakening time from sleep (WASO), more arousals and periodic limb movement, but only in 30% of them the index was higher than 5/hour. Regarding respiratory disorders, we found a pathological respiratory disturbance index (RDS) in 12% of ADHD patients, 8% out of these belonged to ADHD-C.
Conclusion: There are many different subjective complaints about sleep in ADHD patients, but the objective PSG dates showed alterations only in ADHD-I and ADHD-C. The ADHD-I that showed the highest sleep fragmentation and motor activity also had the highest percentage of daytime sleepiness. The percentage of SA cases found in ADHD was scared.

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Sleep Med. 2013;14:e55.

SLEEP, SYMPTOM-RATINGS AND SERUM FERRITIN LEVELS IN CHILDREN WITH ADHD.

Abou-Khadra M, Amin O, Shaker O, et al.

Introduction: The present study was conducted to describe sleep problems in a sample of Egyptian children with ADHD and to examine the effect of low serum ferritin levels on their sleep and symptom-ratings.
Materials and methods: The parents of 41 ADHD children, aged 6- 12 years, filled out the Children's Sleep Habits Questionnaire (CSHQ) and Conners' Parent Rating Scale-Revised: long version (CPRS-R:L) in Arabic. Serum ferritin levels of the children were determined with the enzyme-linked immunosorbent assay method. The parents of 62 normal control children filled out the CSHQ.
Results: The ADHD group had significantly higher scores on bedtime resistance, sleep anxiety, parasomnias, sleep-disordered breathing, daytime sleepiness and global sleep disturbance (CSHQ total score) than in the control group. Children with serum ferritin levels <30 ng/mL had more disturbed sleep than children with serum ferritin levels (greater-than or equal to)30 ng/mL. There were significant negative correlations between sleep duration subscale, total score of CSHQ, and serum ferritin levels ($p<0.05$). There were no significant differences in ADHD symptoms in regard to ferritin levels ($p>0.05$).
Conclusion: Sleep problems are common among this sample of children with ADHD. This study suggests an association between low serum ferritin levels and sleep disturbances among Egyptian children with ADHD.

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Sleep Med. 2013;14:e55.

SLEEP PATTERNS AND PROBLEMS AMONG EGYPTIAN CHILDREN WITH ADHD: THE IMPACT OF SYMPTOMS SEVERITY AND SUBTYPES.

Amin O, Abou-Khadra M.

Introduction: Sleep problems are common among children with attention deficit hyperactivity disorder (ADHD). The present study was conducted to describe sleep patterns and problems in a sample of Egyptian children with ADHD and to examine the impact of symptoms severity and subtypes on their sleep.
Materials and methods: The parents of 100 ADHD children, aged 6- 12 years, filled out the Children's Sleep Habits Questionnaire (CSHQ) and Conners' Parent Rating Scale-Revised: long version (CPRS-R:L) in Arabic. The parents of 100 normal control children filled out the CSHQ.
Results: The ADHD group had significantly higher scores on bedtime resistance, sleep duration, sleep anxiety, parasomnias, daytime sleepiness and global sleep disturbance (CSHQ total score) than in the control group. There were significant positive correlations between oppositional, hyperactivity, cognitive problems/inattention, and ADHD index subscales raw score and CSHQ scale scores. Children with Combined subtype had significantly higher scores than controls in bedtime resistance ($p<0.001$), sleep

anxiety (p<0.001), parasomnias (p=0.001), daytime sleepiness (p=0.014), and total score (p<0.001). There were no significant difference between ADHD subtypes in regard to CSHQ scale scores (p>0.05).
Conclusion: Sleep problems are common among this sample of children with ADHD. This study suggests that sleep disturbances are related to symptoms severity and ADHD subtype.

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Sleep Med. 2013;14:e73-e74.

SLEEPINESS AND DRIVING PERFORMANCE IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Bioulac S, Capelli A, Claret A, et al.

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a triad of symptoms involving hyperactivity, impulsivity and inattention. Several studies in children with ADHD showed a high prevalence of excessive daytime sleepiness. To our knowledge, no study has objectively assessed sleepiness in adults with ADHD. Moreover, it has been shown that adults with ADHD were at risk for driving accidents. The objectives of this study are to quantify objective sleepiness and its impact on driving performance in adult with ADHD.
Materials and methods: 36 subjects with ADHD (age (mean (plus or minus) SE) =36.3 (plus or minus) 1.6) and 18 control subjects (age (mean (plus or minus) SE) =31.2 (plus or minus) 1.2) were included. Nocturnal polysomnography was performed to identify potential sleep disorder. The next day patients were submitted to a Maintenance Wakefulness Test (MWT) at 10H, 12H, 14H, 16H to examine their level of daytime sleepiness. After a training of 15 min, a driving test of 1 h was carried out at 17H on a simulator (Oktal) to evaluate driving performance.
Results: ADHD subjects were divided into 2 groups according to their level of sleepiness at the MWT: the nullsleepynull group consisted of twenty subjects (mean sleep latency (SL) =23.9 (plus or minus) 1.3 min) and the nullalertnull group included sixteen subjects (LE=37.3 (plus or minus) 1 min)(p=0.001). We observed that more than half of the ADHD subjects exhibit a sleep disorder: 31% among the alert ADHD subjects and 65% among sleepy ADHD subjects. But 35% of the sleepy ADHD subjects did not presented a sleep disorder. About driving performance, there were significant differences between driving performance (observed by the number of lines crossing) between the control group and the alert ADHD group (p=0.05) and the control group and the sleepy ADHD group (p=0.02).
Conclusion: This study supports the hypothesis that there is a sub group of ADHD patients that present pathological sleepiness. In our sample, half of the patients suffer of excessive daytime sleepiness. But it is appropriate to question the origin of the sleepiness found in the other patients and to wonder if they represent a particular phenotype. ADHD impacts on driving performances, but it is not possible today to clearly explain them: attention deficit and/or sleepiness? But it is important to focus on this question to provide therapeutic strategy modulated by the clinic.

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Sleep Med. 2013;14:e93.

SALIVARY DETERMINATION OF DIM LIGHT MELATONIN ONSET AS A TOOL IN ATTENTION DEFICIT HYPERACTIVITY DISORDER DIAGNOSIS.

Pitarch Castellano I, Puertas Cuesta F, Perez Pitarch A.

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) has an estimated worldwide prevalence of 5.29%. Prevalence is estimated to be 6.48% (4.62-8.35) in children population and 2,74% (2.04-3.45) in adolescents. Biochemical, neuroimaging or electrophysiological tests are not available as confirmatory tools for ADHD clinical diagnosis. The aim of the present study is to determine ifADHAchildren show alterations of melatonin circadian rhythm by means of Dim Light Melatonin Onset (DLMO) salivary determination and to evaluate the suitability of this test as a tool in ADHD diagnosis.
Materials and methods: A sample (N=146) of 6-11 year old patients (98 ADHD children and 48 healthy controls) was selected and 730 determinations of salivary melatonin were carried out (5 per subject). Suitable samples were centrifuged 10 min to remove particulate material and frozen at -70 (degrees) C

until analysis. Quantitative determination of melatonin was performed by a direct non-extraction ELISA assay using DSX analyser. DLMO levels for each patient were determined and were then classified as normal o altered (advanced, delayed and irregular). Detection of melatonin circadian secretion alterations was compared between groups by means of statistical analysis.
Results: The following parameter were calculated: Odds (ADHD/ no DLMO level disorder) =1.36; Odds (ADHD/ DLMO level disorder) = 34.00; OR=25.0 (p=0.0018); CI 95% (OR) = [3.3; 189.0]. DLMO determination as a test for ADHD detection had a SENSIBILITY of 34.69%, a SPECIFICITY of 97.92%, a positive predictive value (PPV) of 53,57% and a negative predictive value (NPV) of 95.58%.
Conclusion: Salivary determination of DLMO cannot be considered as a screening tool due to the low sensibility in disorder detection but can be a useful confirmatory test in ADHD diagnosis. The high specificity of the proposed test makes it suitable for false positive diagnosis prevention.

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Sleep Med. 2013;14:e65-e66.

SLEEP DISTURBANCES IN CHILDREN WITH ATTENTION DEFICIT.

Ashou Helal S.

Introduction: The aim of the work was to study sleep disturbances associated with attention deficit hyperactivity, in a trial to clarify more the pathogenesis of this disturbances to allow better management and good quality of life.
Materials and methods: Twenty-four children with ADHD diagnosed according to the DSMIV, and Conner's rating scale for ADHD to assess severity and diagnosis, were included in this study. They were all psychotropic drugs naive, with absence of comorbid psychiatric conditions, as confirmed by appropriate rating scales. They were subjected to IQ testing, sleep habit questionnaire, digital electroencephalography and polysomnogram study. They were compared to 20 healthy children.
Results: There was a significant decrease in the sleep efficiency, number of the stage shifts, number of REM periods, REM stage percentage and total sleep time. There was significant increase in the number of awakening. 41.7% of the patients had abnormal digital EEG, 75% had bed time resistance and increased movement during sleep. 58.6% of the patients had short sleep onset latency.
Conclusion: From the results of the present study ADHD is certainly associated with sleep disturbances, this might be a clue for a better management and hence a better quality of life.

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ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SLEEP DISORDERED BREATHING IN PEDIATRIC POPULATIONS: A META-ANALYSIS.

Sedky K, Bennett DS, Carvalho KS.

A relationship between attention deficit hyperactivity disorder (ADHD) and sleep disordered breathing (SDB) in children and adolescents has been suggested by some authors. Yet, this topic remains highly controversial in the literature. A meta-analysis was conducted in order to examine the extent of relationship between SDB and ADHD symptoms in pediatric populations and whether there are differences in ADHD symptoms pre- versus post-adenotonsillectomy in pediatric populations. PubMed/Medline, PsychInfo and Cochrane databases were searched using the key words "attention deficit hyperactivity disorder" or "ADHD" and "obstructive sleep apnea" or "OSA" or "sleep disordered breathing" (SDB) or "SDB". English language publications through September 2012 were surveyed. Meta-analysis was conducted to assess the relationship between SDB and ADHD symptoms in the first part of the study, and the extent of change in ADHD symptoms before and after adenotonsillectomy in the second part. Eighteen studies satisfied the inclusion criteria for the first part of the study. This represented 1113 children in the clinical group (874 diagnosed with SDB who were examined for ADHD symptoms; 239 diagnosed with ADHD who were examined for SDB) and 1405 in the control-group. Findings indicate that there is a medium relationship between ADHD symptoms and SDB (Hedges' g = 0.57, 95% confidence interval: 0.36-0.78; p = 0.000001). A high apnea hypopnea index (AHI) cutoff was associated with lower effect sizes, while child age, gender

and body mass index did not moderate the relationship between SDB and ADHD. Study quality was associated with larger effect sizes. In the second part of the study, twelve studies were identified assessing pre- versus post-surgery ADHD symptoms. Hedges' g was 0.43 (95% confidence interval = 0.30-0.55; $p < 0.001$; $N = 529$) suggesting a medium effect, as adenotonsillectomy was associated with decreased ADHD symptoms at 2-13 months post-surgery. The findings of this meta-analysis suggest that ADHD symptoms are related to SDB and improve after adenotonsillectomy. Therefore, patients with ADHD symptomatology should receive SDB screening. Treatment of comorbid SDB should be considered before medicating the ADHD symptoms if present.

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ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ASSOCIATED PERINATAL RISK FACTORS IN PRETERM CHILDREN.

Cak HT, Gokler B.

Aim: The aim of this study is to examine Attention Deficit Hyperactivity Disorder (ADHD) and its association with perinatal risk factors in preterm children at the age of 5.

Material and Method: The cohort was derived from children born between 30-36 weeks of gestation and hospitalized in the Neonatal Intensive Care Unit. Children who have survived beyond age 5, without a history of congenital anomaly, neurological or chronic disease and mental motor retardation. 106 children who met the inclusion criteria were evaluated when they were five years old. The Perinatal Risk Factors Form was completed for each child. All children and their parents were interviewed using the schedule for affective disorders and schizophrenia for school aged children- present and lifetime version for psychiatric diagnosis. Approval from the ethics committee (HEK 08/3-4) and written assent from all parents were obtained.

Results: 20.8% of the children were diagnosed as ADHD. Diagnosis of ADHD was more common in children who had smaller gestational age and lower birth weight, who developed respiratory distress syndrome, received surfactant therapy and mechanical ventilation treatment and had longer hospitalization period. ADHD was less prevalent among children from high socioeconomic status families. Among the perinatal factors assessed, gestational age was found to be the main predictor for ADHD.

Conclusions: In the long term follow up of premature children, with regard to perinatal risk factors, psychopathologies and especially ADHD should be taken into account for early recognition and intervention.

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ORIGINAL ARTICLE

Attention-deficit/hyperactivity disorder and alexithymia: a pilot study

Renato Donfrancesco · Michela Di Trani · Paola Gregori · Giovanna Auguanno · Maria Grazia Melegari · Sabrina Zaninotto · Joan Luby

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Abstract Although the relationship between alexithymia and psychopathology has been studied extensively in adults, research is lacking on alexithymia in childhood psychopathology. The aim of this study was to investigate the relationship between alexithymia and attention-deficit/hyperactivity disorder (ADHD). The Italian version of the Alexithymia Questionnaire for Children was administered to a sample of 50 children with a DSM-IV diagnosis of ADHD, as assessed by means of the K-SADS PL, and to 100 healthy, age- and sex-matched children without ADHD. The total alexithymia score as well as the difficulty in identifying feelings (DIF) and externally oriented thinking factors were significantly associated with ADHD. The total alexithymia score, the DIF, and the difficulty in describing feelings factors were also significantly associated with symptoms of hyperactivity/impulsivity. No significant relationship between alexithymia and inattentiveness symptoms emerged. Results provide preliminary data on the relationship between alexithymia and ADHD. Findings point to an association between difficulty in identifying emotions and hyperactivity/impulsivity. Future studies conducted on larger patient samples, as well as longitudinal designs, are warranted to confirm our findings.

Keywords Attention-deficit/hyperactivity disorder · Alexithymia · Children

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Introduction

Coined by Sifneos (1973) from the Greek (a = lack, lexis = word, thymos = emotion), the term alexithymia refers to a cluster of clinically observable aspects including a constellation of cognitive and behavioral characteristics related to the expression and experience of affects. Specifically, Nemiah et al. (1976) formulated alexithymia as a construct with the following salient features: difficulty identifying feelings, differentiating among the range of common affects, and distinguishing between feelings and the bodily sensations of emotional arousal; difficulty finding words to describe feelings to other people; constricted imaginal processes; and a thought content characterized by a preoccupation with the minute details of external events, named externally oriented cognitive style. Moreover, people with high alexithymia level also have difficulties in recognizing and empathizing with the emotional states of others (Taylor and Bagby 2013). Several studies found that alexithymic subjects showed impaired ability in identifying facial expressions of emotion, comparing with non-alexithymic subjects (Parker et al. 1993; Mann et al. 1994; Jessimer and Markham 1997; Lane et al. 2000; Sonnby-Borgstro 2009).

The construct initially was of interest primarily to psychoanalysts investigating and treating patients with classic

psychosomatic diseases. As alexithymia theory advanced, however, the construct moved beyond the field of psychosomatics and became incorporated into the broader field of research on emotional processing and affect pathology (Taylor and Bagby 2013). Nowadays, alexithymia is conceptualized as a deficit in the cognitive-experiential component of the emotional response systems and in the interpersonal regulation of emotions (Taylor et al. 1997; Taylor and Bagby 2013).

Although the importance of acquiring the ability to think, express, and modulate one's emotions is acknowledged in the field of developmental psychopathology, little is as yet known about alexithymia in childhood. Some studies on this topic have reported a relationship between alexithymia and somatic problems in children and adolescents (Fukunishi et al. 2001; Rieffe et al. 2004, 2006, 2010). Moreover, alexithymia scores were found to be higher in groups of adolescents with anorexia nervosa (Zonnevylle-Bender et al. 2004) and chronic fatigue syndrome (van de Putte et al. 2007), than in normal adolescents with no psychiatric disorder. Furthermore, studies have also investigated the relationship between alexithymia and internalizing (Karukivi et al. 2010a; Rieffe et al. 2010) and externalizing (Honkalampi et al. 2009) symptoms in samples of children and adolescents from the general population. As regards the relationship between alexithymia and disruptive behaviors, Zimmermann (2006) reported that alexithymia was the strongest discriminatory factor for juvenile delinquency, while Manninen et al. (2011) found that reform school adolescents were significantly more alexithymic than control adolescents, and that alexithymia levels correlated with numerous psychiatric problems, some of which are related to thought problems and self-reported aggression.

Despite a variety of evidence suggesting that persons with attention-deficit/hyperactivity disorder (ADHD) may have deficits in emotion-related domains and that symptoms of the disorder indicate the presence of both receptive and expressive difficulties (Rapport et al. 2002), no study has examined the relationship between alexithymia and ADHD in children. In a sample of 73 adult ADHD, Edel et al. (2010) found that 22 % of the subjects were alexithymic (20 Item Toronto Alexithymia Scale-20 score >61), though this work was flawed by the lack of a control group.

Several studies, however, evaluated the ability in identifying facial expressions of emotion in ADHD samples. Specifically, research showed that ADHD children performed worse than typically developing children on facial emotion recognition tasks (Shapiro et al. 1993; Corbett and Glidden 2000; Cadesky et al. 2000; Sinzig et al. 2008) and made more mistakes when matching facial emotions with the appropriate context (Shapiro et al. 1993; Singh 1998; Yuill and Lyon 2007; Da Fonseca et al. 2009). In adulthood, some studies found that ADHD subjects took longer time and demonstrated less accuracy than controls in emotional face recognition tasks (Rapport et al. 2002; Markovska-Simoska 2010).

Moreover, Barkey's theory (1997) predicts that the regulation of emotional responses should be adversely affected in ADHD persons. According to Barkley, the locus of disruption in the interpersonal interaction of ADHD subjects is the self-regulation of emotion as it is experienced and expressed. This prediction was supported by Rapport et al. (2002), who found greater intensity of experienced emotion in adults with ADHD than control group. The level of experienced emotion was inversely related to affect recognition ability. Moreover, the presence of a deficit in identifying own feelings in ADHD children was supported by Casey (1996) that showed a reduced ability to recognize their own emotions in ADHD group, compared with control group.

In the present study, we examined the relationship between ADHD and alexithymia, defined as difficulty in identifying and communicating one's emotions, as well as an externally oriented cognitive style. Specifically, we tested the hypothesis that children with ADHD show higher levels of alexithymia than children without ADHD, and that alexithymia levels are significantly associated with ADHD severity, on the basis of the ADHD Rating Scale (including the Hyperactivity/impulsiveness and Inattention Scales).

Methods

Participants

We enrolled a total of 150 children between 8 and 14 years of age, and divided as follows:

- 50 children had a diagnosis of ADHD (41 boys and 9 girls; mean age = 10.56, sd = 1.85)
- 100 children, who were matched for age and gender with the ADHD group but did not have ADHD (85 boys and 15 girls; mean age = 10.56, sd = 1.84).

The children with ADHD were outpatients, enrolled consecutively between June and December 2010, from the "La Scarpetta" ADHD Reference Developmental Neurological and Psychiatric Disorders Clinic (ASL RM/A). All the children with ADHD were stimulant naïve since none had previously been diagnosed with this disorder. The diagnosis of ADHD was based on the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL; Kaufman et al. 1997), administered by the same experienced

child psychiatrist (RD), and on the DSM-IV TR (APA 2000) criteria for ADHD. All the ADHD children also fell within the pathological score range in the CBCL Attention Subscale (Achenbach 1991). The children were all Caucasian and had no neurological deficits or mental retardation.

The level of parental education (in years of study) in the ADHD group was: father—mean = 11.72 years, sd = 3.19; mother—mean = 11.70 years, sd = 3.47. The scores yielded by the ADHD Rating Scale (Marzocchi and Cornoldi 2000) administered to the children's parents were as follows: hyperactivity scale—mean = 18.47, sd = 5.32; inattention scale—mean = 19.15, sd = 5.92.

Moreover, as regards comorbidities, 30.6 % of the children in the ADHD group had no comorbid disorders, 36.1 % had a comorbid internalizing disorder (mood disorders or anxiety disorders), 27.8 % had a comorbid externalizing disorder (oppositional defiant disorder), and the remaining 5.5 % had a learning disorder.

As regards diagnostic subtypes, 25 subjects had the combined subtype, 15 subjects had the inattentive subtype, and the remaining 10 subjects had the hyperactive/impulsive subtype.

The control group, who were also all Caucasian, were randomly recruited from five primary schools in the area from which the ADHD children came. We contacted the principals of each of these schools for permission to ask parents for their written consent to administer the questionnaires to their children for research purposes. We were not refused permission by any of the principals or parents, and no child refused to fill in the questionnaires.

In order to ensure that none of the children enrolled in the control group had ADHD, those with an ADHD symptom *T* score of over 65 on the Attention subscale of the CBCL were excluded. Moreover, none of the control children displayed any internalizing or externalizing symptoms. The mean scores and standard deviations of *T* scores of the CBCL Internalizing, Externalizing, and Attention subscales for the two groups are shown in Table 1.

The level of parental education (in years of study) in the control group was as follows: father—mean = 12.85, sd = 3.29; mother—mean = 12.80, sd = 3.48.

Measures

A diagnostic assessment was conducted on all the subjects in the ADHD group using the following instruments:

- Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL; Kaufman et al. 1997). The K-SADS PL is a semi-structured interview designed for the assessment of current, and the past presence of, developmental psychopathology, according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV; APA 1994).
- Child Behavior Checklist 4-18 (CBCL 4-18; Achenbach 1991). The CBCL 4-18 is a parent-report questionnaire used to assess psychological and behavioral problems. It is a multi-axial empirically based assessment system that has good psychometric properties (range of test–retest value—.47–.79, range of internal consistency—.71–.95).
- ADHD Rating Scale, parents version, adapted for the Italian population (Marzocchi and Cornoldi 2000). This is a simple scale, similar in organization and scope to those largely used in other countries (e.g., DuPaul et al. 1998). It presents the 18 ADHD symptoms (described by DSM-IV-TR), whose frequency and intensity must be rated on 4-point scales from 0 to 3. Two subscales assess hyperactivity/impulsiveness behavior and inattention. The scale has been validated and standardized for the Italian population, and has shown good reliability ($r = .95$) and test–retest reliability ($r = .80$). The cutoff for considering a child for a possible diagnosis of ADHD is represented by a mean item rating above 1.5.
- Neurological examination to exclude neurological deficits.

All the subjects in both groups completed:

- Alexithymia Questionnaire for Children (AQC; Rieffe et al. 2006; Di Trani et al. 2009). The questionnaire, originally created by Rieffe et al. (2006), is a simplified version of the 20-Item Toronto Alexithymia Scale (TAS-20; Bagby et al. 1994), the self-report scale most widely used for the assessment of alexithymia in

Table 1 Means and standard deviations of CBCL Internalizing, Externalizing and Attention Scales in the two groups

	Internalizing Scale		Externalizing Scale		Attention Scale	
	m	sd	*m*	sd	*m*	sd
ADHD group	66.33	3.80	69.74	4.21	79.80	1.91
Non-ADHD group	55.02	6.11	57.30	4.99	56.21	2.30

adulthood. It is based on the 20 items in the adult scale, faithfully maintaining its structure and contents, but was developmentally adapted for children. Examples of items are: "I am often confused about the way I am feeling inside," "I find it difficult to say how I feel inside," "When I am upset, I don't know if I am sad, scared or angry." In Italy, it was translated and validated by Di Trani et al. (2009, 2010) on a population of 1,265 children aged from 8 to 14 years. Additional analysis was performed to confirm the three-factor structure [difficulty in identifying feelings(DIF), difficulty in describing feelings (DDF), externally oriented thinking (EOT)], which had in turn previously been confirmed in the TAS-20 for adults and in the version proposed by Rieffe et al. (2006). Furthermore, a multi-group analysis demonstrated the stability of the factor structure as regards the division of the sample into 4 groups (males and females aged 8–10 and 11–14 years). The questionnaire yields single-factor scores and a total score, the latter being proportional to the degree of alexithymia, i.e., the higher the score, the higher the degree of alexithymia. For the whole sample, the mean scores were: Total score $m = 37.65$, sd = 5.70; DIF factor mean (m) = 12.48, sd = 3.16; DDF factor $m = 9.36$, sd = 2.16; EOT factor $m = 15.80$, sd = 2.65. As concerns reliability, the questionnaire displayed an adequate internal consistency (total score Cronbach's $\alpha = .66$) and a very good test–retest stability (total score intra-class correlation = .91). Correlations between the total score of the scale and the factor scores were all significant ($p < .05$).

Procedure

The Alexithymia Questionnaire for Children in ADHD group was administered at the end of the diagnostic assessment, immediately before therapy started, in a calm and quiet environment, under the supervision of a psychologist.

Regarding the control group, questionnaires were administered using the same procedures as those used for the ADHD children.

Data analysis

To verify the homogeneity of the samples, gender, age, and level of parental education in the ADHD and non-ADHD groups were compared.

ANOVA was performed to compare the alexithymia scores (total and factor scores) of the ADHD and non-ADHD groups.

Pearson's correlations were calculated in the ADHD group between the total and factor scores of the AQC and the Hyperactivity/impulsiveness and Inattention Scale scores of the ADHD Rating Scale. Correlations between alexithymia level and age were also calculated.

Results

There were no differences between the ADHD and control groups in gender distribution (ADHD group: 41 males, 9 females; non-ADHD group: 85 males, 15 females; $df = 1$; $\chi^2 = .22$; $p = .64$) or age (ADHD group: mean age = 10.56, sd = 1.85; non-ADHD group: mean age = 10.56, sd = 1.84; $df = 149$; $F = .01$; $p = 1.00$). There were no significant differences between the groups in either the fathers' level of education (ADHD group: mean = 11.72 years of schooling, sd = 3.19; non-ADHD group: mean = 12.85 years of schooling, sd = 3.29; $df = 138$; $F = 2.90$; $p = .09$) or the mothers' level of education (ADHD group: mean = 11.72 years of schooling, sd = 3.47; non-ADHD group: mean = 12.80 years of schooling, sd = 3.48; $df = 142$; $F = 3.38$; $p = .07$).

However, significant differences emerged between the two groups in the total and factor scores of the AQC. Indeed, the total alexithymia level (Cohen's d effect size: $r = .31$; $df = 149$; $F = 15.18$; $p = .000$), Difficulty in Identifying Feelings-DIF score (Cohen's d effect size: $r = .28$; $df = 149$; $F = 11.84$; $p = .001$), and Externally Oriented Thinking-EOT score (Cohen's d effect size: $r = .25$; $df = 149$; $F = 8.04$; $p = .01$) were higher in the ADHD group, than in the control group. No significant difference was found on the DDF factor between the two groups. The mean scores and standard deviations of the AQC for the two groups are shown in Table 2.

Significant correlations emerged in the ADHD group between the total AQC score and the Hyperactivity/impulsiveness Scale score of the ADHD Rating Scale ($r = .46$; $p = .001$), whereas there was no correlation between alexithymia and the Inattention Scale.

As regards the alexithymia factors, significant correlations emerged between the Hyperactivity/impulsiveness Scale and DIF ($r = .42$; $p = .01$) and DDF ($r = .37$; $p = .02$). No significant correlations were found between the Hyperactivity/impulsiveness Scale and EOT factor and between the Inattention Scale and the alexithymia factors.

Finally, no significant correlation was found between alexithymia and age.

Discussion

Literature suggests that persons with ADHD may have deficits in emotional processing and that these disabilities could affect social interactions. The ability to interpret

Table 2 Means and standard deviations of the Alexithymia Questionnaire for children scores in the two groups

	Total score		DIF		DDF		EOT	
	m	sd	*m*	sd	*m*	sd	*m*	sd
ADHD group	39.18	6.00	13.46	3.26	9.46	2.24	16.02	2.73
Non-ADHD group	35.71	4.66	11.69	2.82	9.30	1.97	14.72	2.61
	$F = 15.18$; $p < .001$		$F = 11.84$; $p < .001$		$F = 6.23$; $p =$ n.s.		$F = 8.04$; $p < .05$	

DIF difficulty in identifying feelings, *DDF* difficulty in describing feelings, *EOT* externally oriented thinking

appropriately one's own and others' emotions is crucial for adapted interpersonal relationships.

This study, the first designed to investigate the relationship between alexithymia and ADHD in childhood, showed that children with ADHD have higher alexithymia levels than controls without ADHD. Results are consistent with those obtained by Edel et al. in adults (2010) and, indirectly, with the literature that showed a relationship between alexithymia and externalizing problems in children and adolescents (Zimmermann 2006; Honkalampi et al. 2009; Manninen et al. 2011). Moreover, difficulty in identifying and describing emotions appears to be related to the presence of dysregulated behaviors in adults and adolescents: high scores on alexithymia were found in subjects with various behavioral problems, such as eating disorders (Beales and Dolton 2000; Karukivi et al. 2010b) and sexual behavior disorders (Madioni and Mammana 2001), that may be ascribed to an impulse dyscontrol. These findings are consistent with Krystal's view (1979) indicating that unawareness of feelings may contribute to engage in uncontrollable behavior; they are also compatible with Taylor's theory on affect regulation (1997), suggesting that alexithymia could occur as a result of a failure in one or more of the elements of psychic elaboration, such that the activity of the biological component of affect would be poor regulated by cognitive processes and lead to somatic symptoms or be discharged through actions. Moreover, our results are consistent with Rapport et al. (2002), which found greater intensity of experienced emotion in adults with ADHD than control group. Alexithymic subjects, indeed, may experience a lack of emotion or a high and dysregulated emotional arousal (Taylor et al. 1997).

Furthermore, regarding AQC factors, ADHD children showed higher scores on difficulty in identifying feelings and externally oriented thinking factors, compared to controls. The difficulty in contacting emotions can be consider the core of the alexithymic construct, and high levels in this feature underline a specific disability of ADHD children in identifying and differentiating among different affects. High levels of externally oriented thinking could be associated with low attention to emotions and "internal" events in ADHD children, and consequently with a way of thinking that is oriented toward "external" events and objects.

Hyperactivity, impulsiveness, and inattention are certainly crucial factors contributing to difficulties in social interaction (e.g., Barkey 1997). Findings of the current study suggest that deficits in understanding one's own emotions may be another critical factor underlying social difficulties in children with ADHD, since people with high alexithymia levels show difficulties in recognizing and empathizing with the emotional states of others (Taylor and Bagby 2013).

Specifically, the results of our study confirm the initial hypothesis that significant correlations would be found between the total alexithymia score and the Hyperactivity/impulsiveness Scale of the ADHD Rating Scale. By contrast, no significant correlations emerged between the total alexithymia score and the Inattention Scale. In fact, the first result is consistent with theories about alexithymia, where they state that unelaborated and dysregulated emotion may be expressed in action, while no theoretical link between alexithymia and inattention was proposed in the literature.

One limitation of this study is the small sample size. The possibility to detect more dimensionally stronger associations would be enhanced by a larger sample, which would allow the detection of differences in the ADHD clinical subtypes, i.e., combined, primarily hyperactive, and primarily inattentive. Since a significant correlation was found only between alexithymia and hyperactivity and not with inattention, it is highly probable that stronger differences in alexithymia may be found between primarily hyperactive ADHD subjects and controls, while differences in primarily inattentive subjects might appear trivial. The cross-sectional design of this study is another limitation that prevents any inferences being made regarding the direction of the association found. The high levels of comorbidity present in this sample are another limitation as comorbid disorders are known to influence the outcomes of statistical evaluations. Thus, future studies conducted on larger patient samples in which comorbidity can be assessed, as well as longitudinal designs, are warranted to confirm our findings. In addition, a critical feature is the method to measure alexithymia. AQC is the only Italian instrument for assessing alexithymia in children but, recently, self-

rating questionnaires for alexithymia have been seriously criticized. Regarding adult populations, and more for children, a potential problem of these scales is that valid judgment about own's ability to contact and report emotions may require the relative absence the trait that is measured (i.e., alexithymia).

Confirmation of these results would suggest that more attention needs to be paid to emotion awareness in ADHD children, an area that is often ignored in this patient population. In this regard, a validated questionnaire on alexithymia would serve as a useful clinical and research tool in this population. Specific interventions, such as emotional alphabetization therapy, could consequently be adopted to attempt to remediate this problem. When treating children with hyperactive behavior, it is important to recognize their alexithymic features, particularly the inability to identify feelings.

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REVIEW ARTICLE

The use of actigraphy in the monitoring of methylphenidate versus placebo in ADHD: a meta-analysis

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Abstract Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. There is an increasing need to find objective measures and markers of the disorder in order to assess the efficacy of the therapy and to improve follow-up strategies. Actigraphy is an objective method for recording motor activity and sleep parameters using small, computerized, watch-like devices worn on the body, and it has been used in many clinical trials to assess methylphenidate efficacy and adverse effects in ADHD. Our article aim is to systematically review and perform a meta-analysis of the current evidence on the role of actigraphy in both the detection of changes in activity and in sleep patterns in randomized clinical trials that compared methylphenidate against placebo in the treatment of ADHD. A comprehensive literature search of PubMed/MEDLINE, Scopus, Embase, Cochrane Library, CINHAL and PsycINFO databases was carried out to find randomized clinical trials comparing methylphenidate versus placebo in children with ADHD, using actigraphic measures as an outcome. No start date limit was used and the search was updated until June 2013. The primary outcome measures were 'total sleep time' and daytime 'activity mean'. As secondary outcomes, we analyzed 'sleep onset latency', 'sleep efficiency' and 'wake after sleep onset'. Eight articles comprising 393 patients were included in the analysis. Children with ADHD using MPH compared to placebo have a significant difference of a large effect with a diminishing value in the activity mean. For the total sleep time, we found a significant and large effect in the decrease in sleep in MPH group. This study shows that MPH may effectively reduce mean activity in ADHD children, but it may negatively affect total sleep time.

Keywords Methylphenidate · Actigraphy · Attention-deficit disorder with hyperactivity · Children · Meta-analysis

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder and among the most extensively studied mental disorders of childhood. It is characterized by inattention, including increased distractibility and difficulty in sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor over activity and motor restlessness and can affect learning, behavior, self-esteem, social skills and family function (Kliegman et al. 2011). ADHD has a lifetime prevalence of 8.1 % (Kessler et al. 2005). The median age of onset is between seven and nine (Kessler et al. 2007) and

95 % of people affected are diagnosed before 12 years old (Kessler et al. 2005). It is highly associated with disability in adulthood, and it causes a substantial economic burden on society, with the 30 % of adult patients receiving a disability pension (Mordre et al. 2012).

The features of ADHD are not yet completely characterized as the diagnosis is made subjectively with diagnostic criteria which vary in different countries (e.g., DSM IV TR criteria are different from ICD 10). There is an increasing need to find objective measures and markers of the disease that overcome the differences in definitions which still exist. It is important to find objective measures for many reasons, including clinical and research purposes, in order to assess the efficacy of the therapy and to thereby improve follow-up strategies.

The treatments most widely used for this condition, alongside the psychosocial and/or the behaviorally orientated treatment—whose efficacy has not been effectively proven though (Sonuga-Barke et al. 2013)—are psychostimulant medications, including methylphenidate (MPH), amphetamine and/or various amphetamine and dextro-amphetamine preparations (Kliegman et al. 2011). MPH is considered as the medication of first choice for children with ADHD in order to reduce inappropriate levels of inattention, impulsivity and hyperactivity (Taylor et al. 2004). It belongs to the class of amphetamines which act by blocking both the dopamine and norepinephrine transporters and enhancing dopamine release from presynaptic terminals in the central nervous system. Dopamine is dysregulated in ADHD (Rosa-Neto et al. 2005; Ludolph et al. 2008), and MRI voxel-based morphometry studies have shown that basal ganglia regions such as the right globus pallidus, the right putamen and the caudate nucleus are structurally affected in children with ADHD. Variations in limbic regions such as the anterior cingulate cortex and amygdala are more pronounced in the untreated population, and treatment seems to have positive effects on brain structure resulting in the recovery of structural deficits (Frodl and Skokauskas 2012). The results from functional studies have been pooled together in a recent meta-analysis (Cortese et al. 2012), which showed in ADHD, relative to comparison subjects, a hypoactivation in the frontoparietal network and in the ventral attentional network, and a hyperactivation in the default, ventral attention, and somatomotor networks.

MPH efficacy has been widely evaluated and demonstrated by various meta-analyses of clinical trials, which used qualitative measures of hyperactivity such as clinical or parent and teacher ratings as the primary outcomes (Hanwella et al. 2011; Van Wyk et al. 2012; Castells et al. 2011; Faraone 2012; Van der Oord et al. 2008; Faraone et al. 2002; Schachter et al. 2001).

Actigraphy is an objective method for recording motor activity and sleep parameters using small, computerized, watch-like devices (actigraphs) worn on the body (usually on the wrist of the nondominant arm). The raw activity scores (e.g., in minute-long epochs) are translated to sleep-wake scores based on computerized scoring algorithms. The main motor activity parameter assessed by actigraphy is the 'activity mean,' which is the mean of raw activity scores recorded by the actigraph and translated to digital counts across a predetermined period of time. This method allows reliable data collection of general or highly specific motor activities for extended time periods without disturbance of everyday activities, and hence reflecting the child's spontaneous behavior (Sadeh 2011). Sleep parameters are derived from nighttime activity scores. The sleep time period considered for the analysis is manually set, and it is normally derived from sleep diaries. Sleep bouts are differentiated from wake bouts by considering the activity as lower than a certain threshold, which is variable and depends on the type of device. Based on that threshold then, computer algorithms generate various measures of sleep parameters: 'total sleep time' (which is the sleep time excluding all periods of wakefulness); 'wake after sleep onset' (which is the periods of wakefulness after the sleep onset); 'sleep onset latency' (which is the time in minutes from getting into bed to actigraphically defined sleep onset, which happens after the first 10 min interval of activity below the threshold set for determining wake); and 'sleep efficiency' (which is the ratio of total sleep time, to nocturnal time in bed). Poor reliability may be due to additional time spent inactive, which may be interpreted as 'sleep' by the actigraph, or to frequent nocturnal arousals, which may cause sleep to be underestimated. The parameter 'total sleep time' is considered as the most reliable (Martin and Hakim 2011).

Over the last two decades, actigraphy has become a major assessment tool, especially in sleep research and sleep medicine with a higher rate of publications when compared to polysomnography (PSG). It is a reliable (Martin and Hakim 2011), valid (Morgenthaler et al. 2007), cost-effective (Sadeh 2011), noninvasive assessment method. In addition to ADHD, it is also used to evaluate motor activity for other medical conditions in addition to ADHD, namely circadian rhythm disorders (Martin and Hakim 2011), autistic spectrum disorder (Hare et al. 2006) and mood disorders (St-Amand et al. 2012; Indic et al. 2012; Ritter et al. 2012), although on this parameter less evidence is available (Quested et al. in preparation).

Actigraphic outcomes reported in the studies have never been reviewed nor are they considered as outcomes in a Cochrane Collaboration protocol published for a systematic review considering MPH efficacy (Storebø et al. 2012). Nonetheless many clinical trials in children use actigraphic

devices. The only meta-analysis currently available is from Cortese et al. (2009), which differentiates subjective (reported by parents or child) and objective parameters (PSG and actigraphy) in observational studies on sleep in ADHD. It showed that children with ADHD have significantly more sleep disturbances than controls.

Our hypothesis is that actigraphy may be a valid measure of the benefits and harms of MPH, by establishing efficacy by the reliable measurement of the mean activity level in ADHD patients and in monitoring its impact on the sleep patterns of patients.

Our study therefore aims to systematically review and quantitatively synthesize the current evidence on the role of actigraphy in the detection of changes in activity and sleep patterns in randomized clinical trials (RCTs) that compared methylphenidate against placebo in the treatment of ADHD. We will not make a distinction among ADHD subtypes, since some studies have not succeeded in finding differences in the activity pattern between them (Dane et al. 2000).

Methods

A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, Embase, Cochrane Library, CINHAL and PsycINFO databases was carried out to find relevant peer-reviewed articles on randomized clinical trials comparing methylphenidate versus placebo in children with ADHD and having actigraphic measures as an outcome. A search algorithm based on a combination of the terms: (a) 'ADHD OR attention deficit OR hyperactivity disorder' AND (b) 'actigrap* OR actimet* OR actograp* OR actomet* OR accelerometer OR motor activity' was used. No start date limit was used, and the search was updated until June 2013. To expand our search, references of the retrieved articles and reviews were screened for additional studies.

All studies or subsets of studies using MPH in an ADHD population and with actigraphic measures as outcomes were eligible for inclusion.

The exclusion criteria were (a) articles not within the field of interest of this review (i.e., studies with no therapy, or with no ADHD population or with no actigraphic outcome); (b) review articles, editorials or letters, comments and conference proceedings; (c) case reports, case series, observational studies and other studies which were not RCTs; (d) studies with a comparison population who used other therapies and not placebo; (e) studies with patients aged more than 18 years; and (f) MPH trials in ADHD patients with a serious concomitant medical illness.

Three researchers (MC, CF and FDC) independently reviewed the titles and the abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. These three researchers then independently reviewed the full-text version of the articles to confirm their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data were extracted independently and entered into RevMan 5.1 software by two review authors (MC, FDC) who also assessed the risk of bias in the included studies using the tool described in the Cochrane Collaboration Handbook as a reference guide (Higgins and Green 2011). We paid particular attention to the adequacy of random sequence generation, allocation concealment and double blinding, and we included only studies with a low or unclear risk of bias in these parameters. For each included study, information was collected concerning the basic study (author names, journal, year of publication, country of origin and type of study), patient characteristics (number of patients with MPH vs. placebo, mean age, gender and diagnosis), methodological aspects of actigraphy (device used, where it was worn, the storage rate of the information done mechanically by the device and in which part of the day the actigraph was used) (Table 1) and intervention. Any final disagreements were resolved by consensus. The primary outcome measures were the analyses of 'total sleep' time and of 'activity mean'. As secondary outcomes, we analyzed 'sleep onset latency', 'sleep efficiency' and 'wake after sleep onset', which are considered less reliable parameters (Martin and Hakim 2011).

Crossover design in clinical trials offers a number of advantages over parallel group trials: each participant acts as his or her own control eliminating between-participant variation, fewer participants are required to obtain the same power and every participant receives the same intervention, which allows the determination of the best intervention for an individual (Higgins and Green 2011). The most important problem is that of carryover in which the intervention given in a period persists and interferes with a subsequent period. In view of the pharmacokinetic properties of MPH (Shram et al. 2012), in particular its short half-life (2.4 h in children), we considered crossover trials suitable for a data analysis, even in those crossover trials in which a washout period was not considered. There is no statistical evidence of changes in actigraphic outcomes in clinical trials of MPH if comparing, within-therapeutic boundaries, different doses (Corkum et al. 2008), formulation (Pelham et al. 2001) or number of times per day administered (Stein et al. 1996), so we did not exclude studies on these bases, but we recorded information on the intervention in the table of included studies. When more than one group using MPH was available for data extraction, we extracted data on the group with the highest doses. When more than one group was considered in the analysis with the same dose of MPH, we combined groups to create

Table 1 Methodological aspects of actigraphic devices in studies included

Included studies	Type of device	Where worn	When recorded	Storage rate used
Uebel et al. (2010)	Actitrac device individual monitoring system	Dominant ankle	8 h from 9 a.m. to 5 p.m.	0, 5 min epoch
Corkum et al. (2008)	Basic mini-motionlogger actigraph, AMI Inc.	Nondominant wrist	24 h	NR
Gruber et al. (2007)	Miniature actigraph AW-64 series	Nondominant wrist	Night time	1 min epoch
Konrad et al. (2005)	Tiny actigraph, Cambridge Neurotechnology Version 2.56	Preferred wrist	First 90 min of each school day and 80 min of neuropsychological assessment	0, 25 min epoch
Schwartz et al. (2004)	Miniature actigraph AW-64 series	Nondominant wrist	Night time	1 min epoch
Swanson et al. (2002)	Basic mini-motionlogger actigraph, AMI Inc.	Nondominant wrist	24 h	1 min epoch
Stein et al. (1996)	NR	Wrist	18 h from 4 p.m. to 8 a.m.	NR
Tirosh et al. (1993)	Actigraph, Ambulatory Monitoring Inc.	Nondominant wrist	Night time	1 min epoch

a single pair-wise comparison as in Higgins and Green (2011).

Data for each study were expressed as standardized mean differences (SMD), since differences between the actigraphic devices and on-storage rate used suggested we should consider them as different measurement scales, using the random effects model which is more conservative than the fixed effects model (Higgins and Green 2011). Qualitative data have been presented descriptively. We used the I^2 index to assess the heterogeneity of effect sizes (Higgins et al. 2003). Its value lies between 0 and 100 and estimates the percentage of variation among effect sizes that can be attributed to heterogeneity. A significant I^2 suggests that the effect sizes analyzed are not estimating the same population effect (Higgins and Green 2011). Following Higgins et al. (2003), we agreed I^2 thresholds of 25, 50 and 75 % to differentiate low, moderate and high heterogeneity. We analyzed crossover trials using the generic inverse variance method in RevMan 5.1 software as described in Higgins and Green (2011). When SMD or standard errors (SE) were not directly reported, we calculated or imputed them following the Higgins technique. In interpreting SMD values, we considered SMD 'small' if <0.4, 'moderate' from 0.4 to 0.7 and 'large' >0.7.

Results

Selected studies

The literature search generated 1,110 articles. Reviewing titles and abstracts, articles were excluded applying the criteria mentioned above: 1,093 studies were excluded because they were not within the field of interest of this review and seventeen articles were retrieved in full text. Of these, two articles were excluded because of duplicate data (Gruber et al. 2006; Ironside et al. 2010); one article was excluded because it was not a RCT (Miller and Kraft 1994); two articles were excluded because they included adult patients aged more than 18 years (Kooij et al. 2001; Boonstra et al. 2007); one RCT was excluded because the comparison was atomoxetine and not placebo (Sangal et al. 2006); one study was not in humans but in rats (Fowler et al. 2010); one was a case report (Lahti et al. 2009); one was a review (Huang et al. 2011); and one was a RCT with MPH on a population of ADHD with fragile X syndrome (Hagerman et al. 1988). One additional study was found screening the references of the included and excluded articles (Tirosh et al. 1993).

Finally, eight articles comprising 393 patients were included in a qualitative and quantitative analysis (Corkum et al. 2008; Pelham et al. 2001; Stein et al. 1996; Tirosh et al. 1993; Uebel et al. 2010; Gruber et al. 2007; Konrad et al. 2005; Schwartz et al. 2004; Swanson et al. 2002) (see Fig. 2). The characteristics of the included studies are presented in Table 2.

Primary outcomes

Effect sizes with 95 % confidence intervals for each parameter from each individual study are shown in Fig. 1. Regarding the primary outcomes, the meta-analysis indicated that children with ADHD using MPH compared to placebo have a significant difference of a large effect with a diminishing value in the activity mean (SMD = −0.77;

Table 2 Table of included studies

Included studies	Methods	Participants	Interventions	Outcomes
Uebel et al. (2010)	Randomized double blind placebo-controlled crossover trial	82 children with ADHD and MPH-IR responders originally, finally 49 children with a mean age of 10 years, 43 males	Two and a half weeks with 6 days of each of Placebo, twice-daily MPH-IR or once-daily extended-release MPH with a mean dose of 22 ± 6 mg	Day-long actigraphy, German ADHD Rating Scale FBB-HKS
Corkum et al. (2008)	Randomized* double blind placebo-controlled crossover trial	28 children of ages 6–12 originally. Finally 21 children (15 males)	1-week baseline, plus 3 weeks randomized to placebo or 5–10 mg MPH or 10–15 mg MPH (depending whether under or above 25 kg), thrice a day	24-h actigraphy, sleep diary, Sleep Disturbances Scale For Children (SDSC), Conners' Parents and Teachers Rating Scale-Revised Short Form(CRS-R: S)
Gruber et al. (2007)	Randomized double blind placebo-controlled crossover trial	37 Children with ADHD (6–12 years) 31 males	1 week of placebo, 1 week of 0.5 mg/kg MPH twice a day	Sleep actigraphy, sleep diary, Cbcl, Conners' Continuous Performance Test (CPT), Clinical Global Impression Scale (CGI)
Konrad et al. (2005)	Randomized* double blind placebo-controlled crossover trial	44 Children with ADHD (8–12 years) 37 males	6-day period. Randomized administration of placebo, 0.25 mg/kg or 0.5 mg/kg MPH (but high never after placebo) twice a day	24-h actigraphy, Teacher Questionnaire, sustained attention task, stop-signal paradigma
Schwartz et al. (2004)	Randomized double blind placebo-controlled crossover trial	44 Children with ADHD (6–12 years) 37 males	1 week of Placebo, 1 week of 0.5 mg/kg MPH twice a day	Sleep actigraphy, Conners' Parents and Teachers Rating Scale-Revised (CRS-R), CGI, Restricted Academic Situation Scale (RASS), Conners' Continous Performance Task (CPT)
Swanson et al. (2002)	Randomized double blind placebo-controlled crossover trial	32 Children with ADHD (7–12), 28 males.	8-h period, every 30-min Placebo, or doses amounting to 18, 36 or 54 mg MPH	24-h Actigraphy, Swanson Kotkin Agler M-Flynn and Pelham rating scale (SKAMP)
Stein et al. (1996)	Randomized triple blind placebo-controlled crossover trial	25 Children with ADHD (6-12 years) 25 males	1-week baseline and 4 weeks with 1 week of each of Placebo, titration, two or three doses from 5 to 20 mg MPH based on weight	Conners' Parents Rating Scale (CPRS), ADD-H Comprehensive Teacher Rating Scale, Child Conflict Index (CCI), Sleep actigraphy, sleep diary, Child Depression Inventory (CDI), Stimulant Side Effects Rating Scale (SSERS), Test of Variables of Attention (TOVA)
Tirosh et al. (1993)	Randomized double blind placebo-controlled crossover trial	Eleven children with ADHD originally, finally ten children (6–12 years), eight males	8 days of Placebo, 8 days of 10 to 15 mg MPH, separated by a 3-day washout interval	Sleep actigraphy, Conners' Teacher Rating Scale

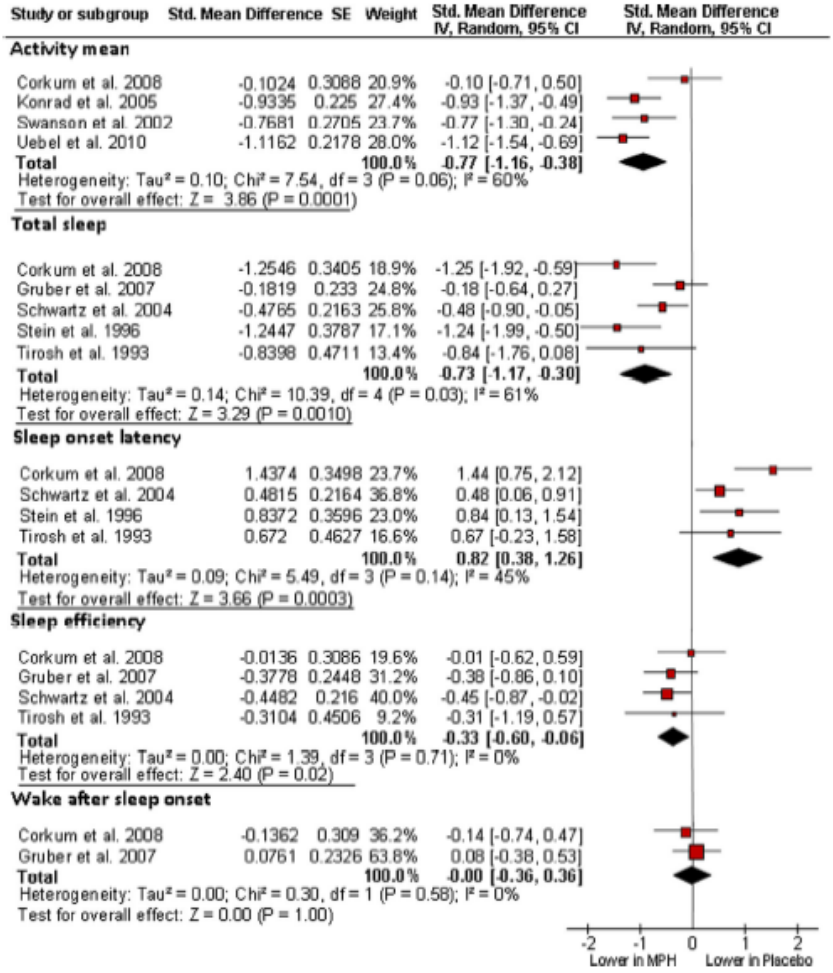


Fig. 1 Analyses of actigraphic outcomes in RCTs using MPH in ADHD children

CI = −1.16, −0.38; $z = 3.86$; $P = 0.0001$; $I^2 = 60$ %). For the total sleep time, the meta-analysis shows a significant and large effect in the decrease in sleep in MPH group with a moderate heterogeneity among the studies (SMD = −0.73; CI = −1.17, −0.3; $z = 3.29$; $P = 0.001$; $I^2 = 61$ %).

Secondary outcomes

The four secondary outcomes considered are all sleep parameters. Actigraphy data show:

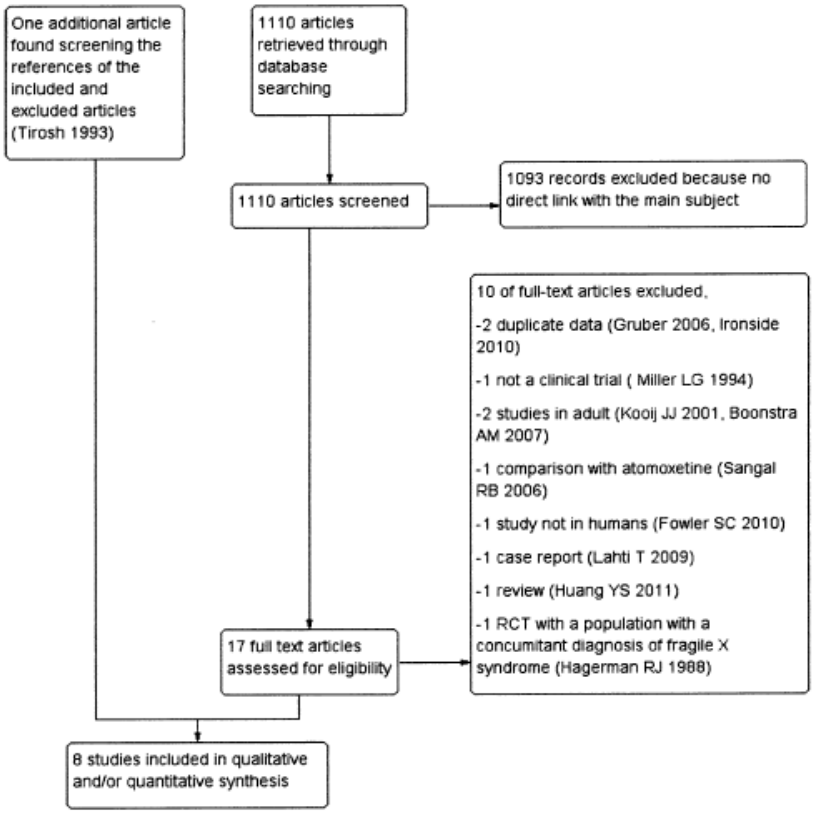
(a) that ADHD children taking MPH take significantly longer after getting into bed to falling asleep than placebo (Sleep onset latency: SMD = 0.82; CI = 0.38, 1.26; $z = 3.66$; $P = 0.0003$; $I^2 = 45$ %).

(b) Sleep efficiency, which is the ratio of total sleep time to nocturnal time in bed, is slightly, but significantly diminished in the MPH group compared to placebo (SMD = −0.33; CI = −0.6, −0.06; $z = 2.4$; $P = 0.02$; $I^2 = 0$ %). For the 'wake after sleep onset' outcome, we found only two studies which were comparable, and following the analysis no significant differences resulted (SMD = 0; CI = −0.36, 0.36; $z = 0$; $P = 1.00$; $I^2 = 0$ %).

Discussion

This study shows that MPH can negatively affect total sleep and reduce mean activity in ADHD children. To our knowledge, this is the first meta-analysis assessing actigraphic outcomes to evaluate MPH effects in children with ADHD. Its clinical efficacy is well documented in numerous studies, and it is not the aim of this article to

Fig. 2 Flow chart



demonstrate it but rather to consider the use of actigraphy as a tool in the studies, either assessing negative or positive outcomes.

We found a large effect of MPH with a significant difference to placebo in 'mean activity' (SMD $= -0.77$; $P = 0.0001$). The heterogeneity is moderate ($I^2 = 60$ %), due to different settings. In fact, we have to consider that Corkum et al. (2008) utilizes both daytime and nighttime activity, while Uebel et al. (2010), Konrad et al. (2005) and Swanson et al. (2002) consider only daytime activity during structured and unstructured sessions. A subgroup analysis of these three shows a higher homogeneity and a higher effect and level of significance (SMD $= -0.96$; CI $= -1.23$, -0.7; $z = 7.11$; $P < 0.00001$; $I^2 = 0$ %). Stein et al. (1996) also evaluated both daytime and nighttime activity pooled together; however, results were not statistical significant and have not been published. We must therefore interpret the results cautiously, although Stein et al. (1996) have a limited power, and we think it would not have affected the overall results excessively. We preferred to be conservative and to maintain Corkum et al. (2008) in the final analyses, but results would have been very homogeneous without this study. It is interesting that the only two studies, which failed in finding a significant difference in mean activity, were Corkum et al. (2008) and Stein et al. (1996) that used a mean activity from both daytime and nighttime. Swanson et al. (2002) and Konrad et al. (2005) focus their analysis on structured sessions. MPH may thus allow a significant loss of activity in structured sessions, while overall, considering the 24 h, the basal children's motor activity may be preserved. We think that the reduction in the activity mean—but not the 24-h children's motor activity—is desired in ADHD and that it can be interpreted as a proof of MPH efficacy.

Regarding the activity mean measurement, actigraphic studies have up to now failed to find a difference among different ADHD subtypes (Dane et al. 2000), but different studies found a significant difference between ADHD and healthy children (Kam et al. 2011). One possible hypothesis is that hyperactivity underlies all ADHD subtypes, although sometimes not being clinically evident.

Total sleep time seems to be significantly diminished by MPH compared to placebo. Although observing a moderate heterogeneity in the studies ($I^2 = 61$ %), there is a

significant and large effect (SMD = −0.73; $P = 0.001$) that, in view of an already recognized higher sleep disturbances rate among children affected by ADHD (Cortese et al. 2009), may be aggravating the problem. Indeed, sleep problems should be considered as undesired consequences of an otherwise effective treatment of ADHD hyperactivity symptoms. We think that this result is not strong though, since two studies of five (Tirosh et al. 1993, Gruber et al. 2007) fail to demonstrate a significant difference and one (Schwartz et al. 2004) finds a moderate effect. Basically a large effect is only based on Corkum et al. (2008) and Stein et al. (1996).Sleep onset latency (time in minutes from getting into bed to actigraphically detected sleep onset) is the secondary outcome with the largest effect and the highest significance (SMD = 0.82; $P = 0.0003$), but it is not a particularly reliable parameter. We know that actigraphy underestimates sleep onset latency, since actigraphy records as 'sleep onset' the first 10-min interval in which there is activity below a certain threshold (expressed in epochs and varying through the studies), and this implies that some immobile and awake individuals may be considered as sleeping (Cortese et al. 2009). Therefore, although we have a certain amount of evidence, we have to be cautious in saying that ADHD children taking MPH take longer to fall asleep. MPH has a small but significant effect in diminishing sleep efficiency (SMD = −0.33; $P = 0.02$), while we do not have enough evidence for the 'wake after sleep onset'.

A degree of caution should be expressed in the interpretation of our results because our rigorous criteria-based selection led to a somewhat limited number of studies to be included in the meta-analysis. Moreover, some trials had a smaller sample size with a larger standard error and less significance, and we had to impute some standard deviations because they were not published. We did not find significant evidence of allocation concealment, blinding or publication biases in the studies, but there were some dropouts, including sometimes for only actigraphic technical reasons. We also found a moderate heterogeneity in relation to the primary outcomes.

Although noting the concerns expressed above, we think that there is sufficient evidence to observe that actigraphy is able to determine that MPH affects sleep and improves the activity pattern in ADHD children. This may be related to the modifications that MPH can have on the circadian clock—as recently demonstrated in mice (Antle et al. 2012). In humans, a recent RCT showed the beneficial effect of melatonin for sleep problems in ADHD (Mohammadi et al. 2012); however, this effect will need to be replicated in future RCTs as other meta-analyses have not consistently supported the use of melatonin as a hypnotic.

The analysis of actigraphic signal have become very sophisticated and accurate (Martìn-Martìnez et al. 2012), and we think that actigraphy in ADHD may be used as a noninvasive, objective tool—complementary to the clinical criteria—to support the diagnosis and the follow-up.

In this study, we have assessed whether actigraphy shows consistency in the evaluation of side-effects and efficacy of MPH in ADHD children in both the experimental and clinical environments, and these findings open up new perspectives on the treatment of sleep problems in ADHD, which increase with treatment on MPH. Moreover, with DSM-V, the main concept of ADHD will remain unchanged, but some modifications in the criteria will likely lead to an increase in prevalence of the condition (Dalsgaard 2013); this could in turn lead to an increase in the use of MPH and the related sleep problems which need to be resolved.

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Self monitoring to promote on-task behavior by two high functioning boys with autism spectrum disorders and symptoms of ADHD

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ABSTRACT

We assessed a self-monitoring procedure to promote on-task behavior in classroom by two high functioning boys with autism spectrum and attention deficit hyperactivity disorders. A second aim of the study was to reduce stereotyped behaviors for both boys. Finally, a third goal was to verify the effects of the intervention on the participant's mood. The study was conducted according to a non concurrent multiple baseline design across participants. Results show an increase of on-task behavior and indices of happiness during the intervention phase. Moreover, the stereotyped behaviors decreased during intervention phase for both boys. Participants maintained their performance during the maintenance phase, which occurred a month after the end of the intervention. The effectiveness of the rehabilitation program was confirmed by 72 university students involved in a social validation assessment as raters. Psychological and practical implications of the findings are discussed.

1. Introduction

Children with autism spectrum disorders (ASD) are commonly characterized by social and communication impairment, stereotyped and tantrum behaviors, self-injuries and aggression (Lequia, Machalicek, & Rispoli, 2012; Matson, Rieske, & Williams, 2013; O'Reilly et al., 2010; Palmen & Didden, 2012). Moreover, they may generally show co-existing variables such as repetitive/ritualistic behaviors, intellectual disabilities and symptoms of attention deficit hyperactivity disorders (ADHD) (Mayes, Calhoun, Mayes, & Molitoris, 2012; White et al., 2011). Due to the neuro-developmental disorder, the aforementioned challenge behaviors interfere with academic activities, constructive engagement and adaptive skills, with negative consequences on controlling, regulating and directing the on-task behavior, even among high functioning ASD children (Jahromi, Bryce, & Swanson, 2013; Southall & Gast, 2011; Wilkinson, 2008). In fact, they are unable to modulate their emotional experiences or to achieve their goals, with poor interpersonal interactions and failures in school settings (Calkins, & Mackler, 2011; Singh et al., 2011). Many students are reported with learning difficulties, lack of organization skills, impulsivity, inabilities to discriminate relevant from irrelevant information, inattention and incapacities to process visual and auditory information (Mruzek, Cohen, & Smith, 2007). Since people with ASD frequently rely on support of

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caregivers, independent functioning is considered a crucial issue for children with high functioning ASD (Palmen, Didden, & Lang, 2012; Stasolla, Damiani, & Caffò, 2014). Furthermore, several studies analyzing the effectiveness of behavioral interventions on adaptive skills for children with ASD point out that early intensive behavioral intervention is the most successful approach (Cappadocia & Weiss, 2011; Makrygianni & Reed, 2010; Peters-Scheffer, Didden, Korzilius, & Sturney, 2011).

ASD children, with and without intellectual disabilities, have been the subject of most studies, and behavioral interventions such as task analysis, instruction cues, modeling, prompt, fading and differential reinforcements of other or alternative behaviors prove to be particularly effective (Koegel, Vernon, & Koegel, 2009; Paterson & Arco, 2007). Among high functioning children with ASD evidence for self-management and video (self)-modeling has also been found (Bellini & Akullian, 2007; Lee, Simpson, & Shogren, 2007). Specifically, Machalicek et al. (2008) and Palmen et al. (2012) reviewed studies about behavioral intervention on adaptive and social skills in school settings emphasizing that those strategies are strongly supported by empirical data, with practical and clinical implications. Beside the aforementioned behavioral techniques, self-monitoring has been adopted (Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009; Soares, Vannest, & Harrison, 2009; Williams & Happé, 2009).

Self-monitoring consists of an ongoing process allowing students to acquire and collect information about their task performance related to established standards. It prepares students to observe, record and track their own (on-task and off-task) behaviors. Students are requested to self-identify and self-monitor a specific target behavior. The procedure represents an alternative to teacher-managed activities or contingencies and has been successfully implemented for children with learning disabilities, ADHD and ASD in school, educational and rehabilitative settings (Afshari, 2012; Deutsch, Dube, & Mc Ilvane, 2008). The literature on self-monitoring is substantial (Cavalari & Romanczyk, 2012; Ganz, Heath, Davis, & Vannest, 2013; Parker & Kamps, 2011; Wilson, 2013). Most of the studies are focused on the reduction of challenge behaviors and the enhance of academic or vocational production (Plavnick, Ferreri, & Maupin, 2010; Purper-Ouakil, Wohl, Michel, Mouren, & Gorwood, 2004; Szymanski & Zolotor, 2001), using one or two components of intervention package (Soares et al., 2009). Surprisingly, the literature on the effects of self-monitoring on quality of life (e.g. indices of happiness) and on social validation assessment is lacking (Felce & Perry, 1995), as well as the evidence of self monitoring on its maintenance over the time (Matson, 2012, 2009).

The present study is an attempt to replicate and extend the applicability and the effectiveness of a self-monitoring procedure on two high functioning boys with ASD and symptoms of ADHD-C sub-type (combined) in school setting, and pursue three main objectives: (a) assess its validity over time (with a maintenance phase carried out after one month from the end of the study), (b) check out the effects of the intervention on the increase of on-task-behavior and on indices of happiness on one hand, and on the decrease of stereotyped behaviors on the other, and (c) conduct a social validation assessment involving 72 university students as raters.

2. Method

2.1. Participants and setting

The participants, Jack and Michael, were two high functioning ASD boys, they were 7.5 and 8.5 years old and showed a score of 44 and 48 to the *Childood Autism Rating Scale* (CARS), respectively (Schopler, Reichler, De Vellis, & Daly, 1980) at the beginning of the study. Although no formal IQ score was available, both were estimated as borderline between normal and mild intellectual disabilities from clinical observations. For this reason, they attended regular class with a special training. Furthermore, they presented symptoms of ADHD C-subtype (combined) with off-task and tantrum behaviors during classroom. Jack presented body rocking and voice noises, while Michael exhibited hand flapping and washing (stereotyped-behaviors). The study was carried out in school setting, during academic activities.

They had awareness of sphincter control and were able to communicate their needs, although their language was not easily understandable. Both participants were able to ambulate independently and autonomous on personal needs (i.e. hygiene), although they continuously needed reminders to be on task. Jack and Michael presented relationship problems with peers and caregivers, they had no resilience to frustration, showing aggressive behaviors against people around them. They were recruited for the study by their neurologist. Their families and teachers considered the intervention program high desirable and signed up a formal consent for the participation to the study for both boys, which was performed in accordance with the Helsinki Declaration and its later amendments and approved by the Review Board of the Institution.

2.2. Target behaviors

For both participants target behaviors consisted of: on-task behavior, stereotyped behaviors, indices of happiness. The on-task-behavior was recorded if Jack and Michael: (a) remained sitting on their desk, (b) kept silent, (c) listened to the teacher's explanation, (d) focused on their task, gazing on their sheet, reading carefully the task and achieving it. The stereotyped behaviors were recorded when Jack produced (a) voice noises, (b) body rocking and when Michael presented (a) hand washing, and (b) hand flapping. Finally, the indices of happiness were recorded when both boys were (a) smiling, (b) laughing, (c) exhibiting excited body movements with or without vocalizations, and (d) singing.

2.3. Coding systems

The on task-behavior was recorded according to a *total interval coding system*. Essentially, Jack and Michael should be on-task for the whole 10 s interval (see below the *sessions and data collection*). Conversely, the stereotyped behaviors and the indices of happiness were recorded according to a *partial interval coding system*. In the case of stereotypies, the coding system provided a 10 s interval: at the end of the 10 s interval, the participants were recorded as *positive to stereotypies* even if presented stereotyped behaviors for one second of the interval. In the case of indices of happiness, the coding system provided a 15 s interval: the first 10 s served to observe and the next 5 s to record the presence or absence of one or more index of happiness occurred in the previous observation interval (Lancioni et al., 2007a).

2.4. Materials

During baseline sessions (see Section 2.6) Jack and Michael did not required to self monitor their behavior. A first research assistant recorded their on-task behavior and a second research assistant recorded the stereotyped behaviors, using the above-mentioned intervals marked by acoustic cues recorded in a headset walkman. Finally, the support teacher recorded the indices of happiness. Each of them signed up the presence or the absence of the target behaviors in a two-columns grid.

During the intervention phase, Jack and Michael were required to self-monitor their behavior (on-task and stereotyped) and were provided with the same material available for the research assistant during baseline. The procedure was the same except for the duration of the intervals that become irregular, maintaining an average of 10 s. Materials did not interfere with the classroom activities and/or the school setting. To carry out the reliability of every target behavior, research assistants and teacher recorded the behavior too, according to the average scan of acoustic cues available for the participants. The percentages of reliability were computed by dividing the number of agreement by the total number of intervals, and multiplying by 100 (Lancioni et al., 2007b). The mean percentages of reliability exceeded 95% for both participants.

2.5. Sessions and data collection

Two to four sessions per day, five days per week, were carried out, according to school and participants availability. Each session lasted one hour, according to the academic activities, and was divided in 360 of 10 s-intervals of observation (on-task and stereotyped behavior) and in 240 of 15 s intervals (indices of happiness) respectively. During the maintenance phase, the 240 intervals for the indices of happiness were preserved, while a fading out of the observation intervals was carried out (from 360 of 10 s-intervals to 180 of 20 s-intervals) in line to promote a longer control on their behaviors. The study lasted approximately 4 months (including one month interval between the end of intervention and the maintenance phase, see Section 2.6). Overall, 324 sessions have been carried out along baseline, intervention and maintenance phases for both participants. Data collection concerned the aforementioned target behaviors (see above) and social validation rating involving 72 university students (see below).

2.6. Experimental conditions

The study was carried out according to a non concurrent multiple baseline design across participants, followed by a maintenance phase after one month from the end of intervention phase (Barlow, Nock, & Hersen, 2009). Since the baseline phase for Michael lasted more, their intervention and maintenance phases did not begin simultaneously.

2.6.1. Baseline

During baseline phase, both participants were asked to perform their daily academic activities proposed by the teacher without any material. Baseline lasted two days (6 sessions) for Jack and one week (12 sessions) for Michael. As mentioned above, research assistants and support teacher recorded the target behaviors. Each session lasted 60 min with 10 s observation intervals for on task and stereotyped behaviors, and 15 s observation intervals for indices of happiness, respectively.

2.6.2. Intervention

Jack and Michael were provided with the same materials available for the research assistants and the teacher during baseline (i.e. walkman, headset, acoustic cues, two column grid for each target behavior). They were required to self record (monitor) their own behaviors. They received a token for each correct response and lost it for any incorrect response. According to a token economy procedure, they received a primary reinforcement at the end of every day session, depending on the number of collected tokens (Kazdin, 2001; Kennedy, 2005). For each participant 90 sessions of intervention phase were carried out. The intervention phase lasted two months.

2.6.3. Maintenance

After one month from the end of intervention, a maintenance phase occurred for each participant. Experimental conditions were the same of intervention phase, except for the observation interval latency of on task and stereotyped behaviors. A *fading out* strategy was introduced, (Lancioni, Sigafoos, O'Reilly, & Singh, 2012) in which the observation

Table 1
Questionnaire items.

Do you think that the child enjoy (is comfortable with) this condition?
Do you think that this condition is suitable for the child?
Do you think that this condition has beneficial/rehabilitative effect for the child?
Do you think that this condition is useful for self-determination and independence of the child?
Do you think that this condition is practical/useful in school settings?
Do you think that this condition is practical/useful in home setting?
Do you support (agree with) this condition?

intervals were extended from 15 to 20 s. Within one hour session 180 observation intervals were available. No modifications were carried out to the indices of happiness intervals. For each participant 60 sessions of maintenance were performed. This phase lasted one month.

2.6.4. Social validation

Seventy-two under-graduated university students of educational sciences (mean age 23.5, with range 19–55) and standard deviation of 6.37 were involved in a social validation assessment. The students represented a convenience sample among students who were interested in the field of developmental disabilities (Pedhazur & Schmelkin, 1991). They were randomly and equally divided in three groups: the first group had to rate the baseline and intervention performance of both participants, the second group had to rate the baseline and maintenance performance of Jack and Michael, and the third group the intervention and maintenance performance of both boys. Twelve students of the first group watched an A–B sequence of 6 min video-clips (that is a standard 3 min of baseline session and a standard 3 min of intervention session), and twelve of them watched, conversely, a B–A sequence. To balance conditions, the same methodological strategy was applied for the second and the third group. Raters were asked to score the two videos on a seven items questionnaire (see below Table 1). For each item the raters (students) provided scores 1–5, which indicated the least and most positive ratings respectively.

3. Results

The mean percentages of on-task behavior on one hand and stereotyped behaviors and indices of happiness on the other are summarized over blocks of sessions and plotted in Figs. 1 and 2, respectively.

Jack completed his baseline phase with a mean percentage of on-task behavior of 11.5 (range 10–15). During the intervention phase, his mean percentage increased to 86.51 (range 65–99). During the maintenance, the participant hold up his mean percentage to 86.17 (range 80–95). Concerning the stereotyped behavior, Jack presented a mean percentage of 93.67 (range 90–100) during baseline. He decreased his mean percentage to 28.47 (range 15–67) during the intervention. Finally, he hold up his performance during the maintenance to a mean percentage of 18.93 (range 10–35). Regarding the indices of happiness, Jack ended his baseline with a mean percentage of 34.83 (range 32–38). During the intervention, his

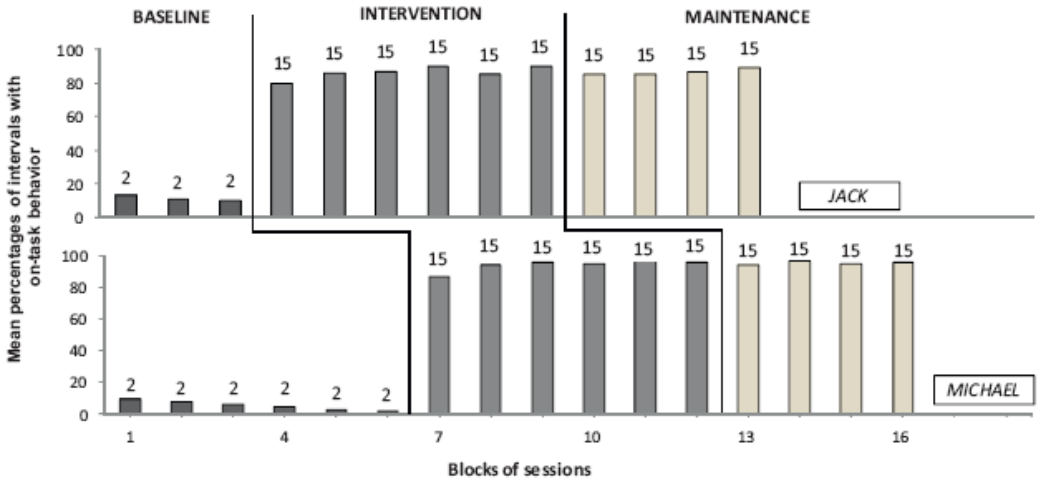

Fig. 1. The two graphs summarize the data for Jack and Michael. The black bars indicate the mean percentage of intervals with on-task behavior over block of baseline sessions. The gray and white bars refer to the mean percentage of intervals with on-task behavior over block of intervention sessions and maintenance sessions, respectively. The number of sessions included in each block/bar is indicated by the numeral above it.

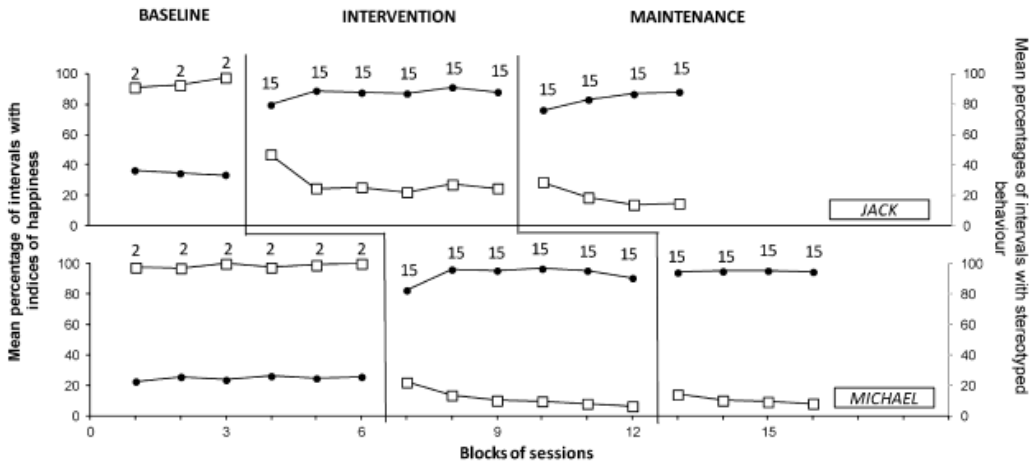

Fig. 2. The two graphs summarize the data for Jack and Michael. The black circles indicate the mean percentage of intervals of indices of happiness over blocks of baseline, intervention and maintenance sessions. The empty squares represent mean percentages of intervals with stereotyped behaviors over blocks of baseline, intervention and maintenance sessions. The number of sessions included in each block/bar is indicated by the numeral above it.

mean percentage of indices of happiness increased to 87.01 (range 66–97). The participant completed his maintenance with a mean percentage of indices of happiness of 83.45 (range 70–96).

Michael's mean percentage of on-task behavior, during baseline, was about 5.5 (range 2–10). During intervention, his performance increased to a mean percentage of 94.56 (range 70–100) and he hold up this high performance during the maintenance, showing a mean percentage 95.82 (range 85–100). His stereotyped behavior showed a mean percentage of 98.5 (range 95–100) during baseline. During the intervention his stereotypy decreased to a mean percentage of 11.43 (range 4–44) and he hold up that mean percentage during maintenance phase, reaching 10.2 (range 4–20). Finally, the mean percentage of his indices of happiness was 24.58 (range 20–27) during the baseline. He increased this mean percentage to 92.78 (range 75–100) during the intervention and hold up his mean percentage to 94.75 (range 90–99) during the maintenance. All differences between baseline, intervention and maintenance were statistically significant ($p < .01$) to Kolmogorov–Smirnov test (Siegel & Castellan, 1988), while no difference was recorded as statistically significant between intervention and maintenance phases.

Means and standard deviation for each item of the questionnaire of social validation are reported in Table 2. For all seven item considered, none of the rater scored over 3 for the baseline phase. All the raters scored at least 4 for each item concerning the intervention and the maintenance phases. Thus, paired *t*-test are included between 15.63 and 39.24 ($p < .0001$) for the all the questionnaire (Hastie, Tibshirani, & Friedman, 2009) between baseline and intervention on one hand and between baseline and maintenance on the other. No statistically significant differences were recorded for the third group watching intervention and maintenance conditions.

4. Discussion

The data of this study point out that self-monitoring is successful to ensure high functioning children with ASD and symptoms of ADHD (combined subtype) to acquire awareness of their own behavior autonomously. The self-monitoring procedure adopted had positive outcomes on the quality of life of both participants by increasing their on-task behavior and their indices of happiness and by reducing their stereotyped behaviors, with beneficial effects in the school setting. These

Table 2
Means and standard deviations (St. Dev.) for baseline (A), intervention (B), and maintenance (C) phases.

Items	Means A	Means B	Means C	St Dev. A	St Dev. B	St. Dev. C
Enjoyment	2.03	4.25	4.22	.66	.77	.75
Suitability	2.15	4.14	4.08	.72	.73	.61
Rehabilitation	2.27	4.33	4.27	.54	.88	.79
Independence	2.16	4.41	4.46	.82	.61	.68
School setting	2.12	4.55	4.62	.63	.52	.65
Home setting	2.32	4.29	4.18	.49	.91	.78
Support	2.09	4.37	4.21	.59	.84	.89

findings are largely supported by previous studies (Briesch & Daniels, 2013; Rafferty, 2012) and suggest the following considerations.

First, the intervention may represent a relevant objective by improving self-determination and awareness of their own behaviors by both participants. On the one hand was promoted the on-task behavior during academic activities, requiring the participants to self-adjust independently the behavior within the school context. On the other hand, the participants were helped to be more active and to have constructive engagement on their social and adaptive skills. Designing an intervention program enhancing the active role of students with ASD and symptoms of ADHD can be considered of high relevance to (a) counter their general withdrawal and disconnection from the context (off-task behavior), (b) minimize the applicability of strategies that do not consider personal centrality and initiatives, and (c) have positive consequences on their social image and desirability (Lancioni et al., 2010; Lancioni, Singh, M.B. O'Reilly, et al., 2009; Stasolla, Caffò, Picucci, & Bosco, 2013).

Second, applying the self-monitoring procedure on two different behaviors simultaneously (on task and stereotyped behaviors) can be viewed significant since it allows the students to acquire awareness of their *overall* behavior and, consequently, to regulate all their behaviors in the environment. Learning to self-monitor two different behaviors within the same rehabilitative intervention may promote adaptive skills on two different levels: (a) improving correct responses, and (b) increasing the opportunity to receive positive reinforcements (Lancioni et al., 2007a; Lancioni, Singh, M.F. O'Reilly, et al., 2009).

Third, the self-monitoring produces positive effects on stereotyped behaviors. Thus, increasing on-task behavior, constructive engagement and positive reinforcements led, at the same time, to reduce self-stimulation and stereotypies (Matson, 2012; Stasolla & Caffò, 2013). Furthermore, it can be argued that the intervention might produce two other beneficial consequences: (a) the reduction of the teacher's burden, and (b) the integration of the participants in classroom (Hendrie, Bebbington, Bower, & Leonard, 2011; Lancioni et al., 2007b).

Fourth, data indicate positive effects on mood (indices of happiness) of both participants and hypothetically on their quality of life. Indeed, the implementation of self-monitoring and the exposure to the token economy strategy have a relevant positive impact on their overall amount of pleasure and motivation (Dillon & Carr, 2007; Lancioni, O'Reilly, et al., 2006; Lancioni, Singh, et al., 2006; Stasolla et al., 2014).

Fifth, both participants hold up their overall performance (on each target behavior) during the maintenance phase. Jack and Michael preserved their social and adaptive skills, demonstrating that they were able to use self-monitoring positively in school setting during academic activities. These findings support the active role of the students in the procedure's execution, with positive long-terms effects (Hinshaw, 2005; Zentall, 2005).

Sixth, the data provided from social validation are very important as they may constitute: (a) a formal endorsement of the procedure's presumably benefits, and (b) personal supports of such strategy for helping children with ASD and ADHD' symptoms. Although students of educational sciences are not necessary experts of ASD and ADHD, their agreement can provide a relevant point of view on the clinical validity of the intervention program (Lancioni, O'Reilly, et al., 2006; Lancioni, Singh, et al., 2006; Perilli, Lancioni, Hoogeveen, et al., 2013; Perilli, Lancioni, Laporta, et al., 2013).

Concluding, future research would deal with the following topics: (a) the extension of the procedure to other participants with ASD and ADHD, (b) the generalization of the procedure to other settings (e.g. home setting and rehabilitative centers), (c) the applicability of the procedure to other target behaviors, and (d) the enlargement of the observation intervals to 30 s during the maintenance phase.

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How Attention-Deficit Disorder Went Global

World-wide sales of ADHD medication are likely to hit $14 billion in two years.

BY STEPHEN P. HINSHAW
AND RICHARD M. SCHEFFLER

In March 2013 the U.S. federal Centers for Disease Control and Prevention released data showing that 11% of school-age children in the U.S.—an astonishing 6.4 million kids—had received a medical diagnosis of attention-deficit hyperactivity disorder, a 41% increase in the past decade. Over two-thirds of kids with an ADHD diagnosis receive prescriptions for stimulants like Adderall or Ritalin. The data sparked a much-needed debate about whether American children were being overdiagnosed and overmedicated for ADHD.

That debate should now go global. Consider what's been going on in Israel. In 2010 alone the use of two medications, Ritalin and Concerta, skyrocketed by 76%. The following year, a study by Israel's Maccabi Healthcare Services found that as many as one in five Israeli children were prescribed stimulants without a proper ADHD diagnosis.

Israel and the U.S. are not alone. Growing awareness of ADHD combined with increasing pressure on children to achieve academically—in countries like China, India, South Korea and Saudi Arabia—has led to surging numbers of diagnoses and prescriptions world-wide. Between 2000 and 2010, global ADHD-medication sales soared 26% a year to more than $8 billion. The total is projected to reach as high as $14 billion in the next two years, and global sales outside the U.S. are rising at least twice as fast as in the U.S.

The marketing strategies and awareness efforts of multinational pharmaceutical companies have contributed to this trend. In Saudi Arabia, for instance, the Belgian company Janssen, which makes Concerta, is listed as the sole sponsor of a website for the Saudi ADHD Society, which increases awareness and treatment in that country.

As clinical and health-policy researchers who have watched this story unfold, we're concerned. ADHD is a seriously impairing neurodevelopmental condition, and in some cases medication is a godsend. Yet even in those cases we must bear in mind that the stimulants that treat ADHD can have serious side effects, including psychosis in rare cases, and may become addictive.

Yes, substantial evidence shows that ADHD medication—when truly warranted—not only boosts attention but also improves academic performance and a child's quality of life. But even as global sales surge, evidence accumulates that stimulants are no silver bullet.

Hundreds of controlled clinical trials around the world, as well as the National Institute of Mental Health's landmark Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study, have found that while ADHD medications have clear benefits in the short-term (measured in months or a few years) the long-term effects are not as clear. Prolonged use may in some cases promote brain growth but in other cases may alter brain chemistry, eliminating some of the medications' initial effectiveness. Relying solely on meds may mean that children lose the chance to benefit from behavioral therapies that teach academic, social and vocational skills,

The pressure to treat ADHD is growing particularly fast in countries like China and South Korea that are making a strong push to improve academic performance. Many elementary and secondary schools in China force children to sit for hours at length, attending lectures and cramming for tests. It is only natural that children in these circumstances need help to remain focused. More and more, that help is coming in a pill.

There are signs of resistance to this trend, particularly in Europe. In the U.K., for example, health officials advise that physicians resort to medication only *after* trying behavioral therapy. And in 2011, shocked by the surge in prescriptions, Israel's Ministry of Health made it illegal for doctors to prescribe stimulants for children or adults without a proper diagnosis of ADHD.

We hope other nations will treat ADHD medication with justified caution. Doctors should diagnose ADHD as professional medical associations recommend—obtaining thorough medical histories to rule out alternative reasons for attention problems, which may include child maltreatment, depression or learning disorders. They should also gather behavioral checklists from schools in order to pinpoint whether the child's behavior is truly an "outlier."

International ADHD research and advocacy groups should monitor benefits and potential drawbacks of stimulant use in multiple countries around the world. And even with a valid diagnosis, medication shouldn't necessarily be the first or only line of defense. As we globalize communications and marketing, let's do our best to also globalize diagnostic accuracy and common sense.

Mr. Hinshaw is a professor of psychology and psychiatry and Mr. Scheffler is a professor of health economics and public policy at the University of California, Berkeley. They are the authors of "The ADHD Explosion: Myths, Medication, Money and Today's Push for Performance," just published by Oxford University Press.

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