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AJNR Am J Neuroradiol. 2014 Jun;35(6 Suppl):S55-63.

MR IMAGING-DETECTABLE METABOLIC ALTERATIONS IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER: FROM PRECLINICAL TO CLINICAL STUDIES.

Altabella L, Zoratto F, Adriani W, Canese R.

MR spectroscopy represents one of the most suitable in vivo tool to assess neurochemical dysfunction in several brain disorders, including attention deficit/hyperactivity disorder. This is the most common neuropsychiatric disorder in childhood and adolescence, which persists into adulthood (in approximately 30%-50% of cases). In past years, many studies have applied different MR spectroscopy techniques to investigate the pathogenesis and effect of conventional treatments. In this article, we review the most recent clinical and preclinical MR spectroscopy results on subjects with attention deficit/hyperactivity disorder and animal models, from childhood to adulthood. We found that the most investigated brain regions were the (pre)frontal lobes and striatum, both involved in the frontostriatal circuits and networks that are known to be impaired in this pathology. Neurometabolite alterations were detected in several regions: the NAA, choline, and glutamatergic compounds. The creatine pool was also altered when an absolute quantitative protocol was adopted. In particular, glutamate was increased in children with attention deficit/hyperactivity disorder, and this can apparently be reversed by methylphenidate treatment. The main difficulties in reviewing MR spectroscopy studies were in the nonhomogeneity of the analyzed subjects, the variety of the investigated brain regions, and also the use of different MR spectroscopy techniques. As for possible improvements in future studies, we recommend the use of standardized protocols and the analysis of other brain regions of particular interest for attention deficit hyperactivity disorder, like the hippocampus, limbic structures, thalamus, and cerebellum.

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American Journal of Perinatology. 2014;32:399-404.

CENTRAL AUDITORY PROCESSING DISORDER PROFILE IN PREMATURE AND TERM INFANTS.

Amin SB, Orlando M, Monczynski C, et al.

Objective The aim of this study is to compare central auditory processing disorder (CAPD) profile between children born prematurely and at term.

Methods A retrospective study involving children 7 to 13 years of age who were referred for CAPD evaluation over the past 3 years. Parental reports and medical records were used to collect information. Children with a score (greater-than or equal to) two standard deviations below the mean for at least one ear on at least two different CAPD tests were considered to have CAPD.

Results A total of 82 children were evaluated for CAPD of which 22 met exclusion criteria, resulting in 60 children with CAPD (15 premature and 45 term). Premature children had higher prevalence of cesarean section delivery and neonatal jaundice compared with term children. Premature children had a higher total number of failed CAPD tests compared with the term children. Among CAPD tests, there was an increased frequency of abnormal Phonemic Synthesis test (PST) and decreased frequency of abnormal Staggered Spondaic Word test (SSW) among premature children compared with term children.

Conclusion Premature children differ in CAPD profile compared with term children. Findings suggest possible etiological differences for CAPD such as jaundice or differential susceptibility of premature children for altered PST and SSW performance when compared with the term children.

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

Ann Acad Med Singapore. 2010;39:S63.

OCCUPATIONAL THERAPY AND FUNCTIONAL OUTCOMES IN CHILD PSYCHIATRY: A CASE REPORT OF A SCHOOL-AGED CHILD WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Seah CH, Tai EYL.

Background/Hypothesis: Children with attention deficit hyperactivity disorder (ADHD) may exhibit challenges with self-regulation, sensory integration and psychosocial development. These impair on their ability to function in self-care, school and play roles. Occupational therapists provide therapy to improve their role performances. This research presents a case report exploring the effects of occupational therapy provided for a 10-year-old boy diagnosed with ADHD. The treatment aims to address social, emotional and behavioural issues which interfered with his ability to assume age-appropriate roles and learning in a mainstream school.

Methods: At the beginning of therapy, 2 target functional outcomes were identified for the participant, in collaboration with his parents. The outcomes were operationalised and measured using the Goal Attainment Scale. Interventions, such as the Alert program, DIR/Floortime model, parenting strategies and clinical reasoning were applied by the occupational therapist in the clinic and followed up by his family at home. The participant was not on any concurrent interventions, such as medications, except reviews by the medical consultant.

Results: The participant responded well to occupational therapy in a one-to-one outpatient intervention. There were significant improvements in the targeted functional outcomes of self-regulation and self-esteem after a 9-month intervention. There was a 4-point improvement in self-regulation and a 3-point improvement in self-esteem on the Goal Attainment Scale. The participant also demonstrated decreased frequency of disruptive behaviours, with an increase in functional role performance.

Discussion & Conclusion: Findings supported the application of occupational therapy for children with social, emotional and behavioural issues. The Alert program, DIR/Floortime model, parenting strategies, clinical reasoning and professional experience were effective in improving role performances of school-aged children when used together.

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Ann Acad Med Singapore. 2010;39:S126.

THE RELATION BETWEEN WEIGHT AND CLINICAL SYMPTOMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVE DISORDER.

Loo CJ, Fung DSS, Caroline WL, et al.

Background/Hypothesis: In a review, Cortese et al concluded that attention deficit hyperactive disorder (ADHD) was linked to increased rates of obesity. However, we recently reported a bi-modal distribution in the body mass indices (BMI) of ADHD children, suggesting two distinct ADHD subtypes based on BMI. Here, we compare the metabolic and psychiatric profiles of ADHD children according to their BMI clusters.

Methods: Participants were 46 patients aged 9-16 recruited from a psychiatric clinic. All participants met diagnostic criteria for ADHD on the Diagnostic Interview Schedule for Children. BMI, resting heart rate, and blood pressure were recorded. As measures of externalising behaviour, the child behavior checklist (CBCL) and reactive-proactive aggression questionnaire (RPQ) were used.

Results: Participants' BMI peaked bi-modally at 15 to 18 and 20 to 23. A median split at BMI = 19 was used to form a lower (L-BMI) and higher BMI group (H-BMI). In a multivariate analysis of variance, H-BMI participants had significantly higher systolic and diastolic blood pressure than L-BMI participants and were more likely to react aggressively (higher RPQ reactive-aggression scores). There was a non-significant trend for H-BMI participants to show more delinquency (higher CBCL rule-breaking scores and comorbidity for oppositional defiant or conduct disorder). However, H- and L-BMI participants did not differ on ADHD-specific measures (CBCL inattention scores and classification for ADHD inattentive vs hyperactivity subtypes) nor on resting heart rates.

Discussion & Conclusion: Our findings suggest ADHD children with higher BMI may have a more severe clinical profile. They show increased resting blood pressure, react more aggressively, and may be more delinquent. It could be that ADHD and having higher BMI share a common pathway (e.g. dopaminergic or noradrenergic) or are indicators of a common problem (e.g. metabolic syndrome); if so, treatment choice could be individualised according to BMI cluster.

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Ann Acad Med Singapore. 2011;40:S208.

A CRITICAL REVIEW OF THE ROLE OF OCCUPATIONAL THERAPISTS WITH FAMILIES OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Loh H.

Background & Hypothesis: Attention deficit/hyperactivity disorder (ADHD) is a common neurobiological childhood disorder that affects many families (Helitzer et al, 2002; Holowenko, 1999). Occupational therapists are involved by helping parents manage daily living tasks with their children (Case-Smith, 2005; Lougher, 2001). Yet, the roles they play are not clearly defined. Increasing number of studies are looking at the role of occupational therapist in families of children with ADHD (Olson and Esdaile, 2004; Heizer et al., 2002). However, no studies presently had critically appraised and collated these relevant findings. Therefore, the aim of this paper is to identify and critically appraise literature regarding the role of occupational therapists with families of children with ADHD and provide recommendations for practice and research.

Methods: Search of 11 electronic databases was supplemented by manual search to yield 13 articles which conformed to specified inclusion and exclusion criteria, all of which were published post 2000. Critical appraisal tools were used to determine methodological quality.

Results: Evaluation of the findings from 13 studies suggests that there is a role for occupational therapists with such families. They include providing family focus interventions, supporting and educating the family. However, these findings were difficult to generalise due to the studies' methodological limitations such as small sample sizes.

Discussion & Conclusion: There is a role for occupational therapists with families of children with ADHD via family focus interventions, family support and educating the family. These roles help families cope better with their child's behaviour and daily engagement in occupations. Better quality studies on occupational therapists' involvement with such families are recommended for the profession practice.

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Ann Acad Med Singapore. 2014;43:S316.

RISK FACTORS FOR DEVELOPING DEPRESSION IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH CONDUCT DISORDER OR OPPOSITIONAL DEFIANT DISORDER.

Koukouna E, Fung DSS.

Background & Hypothesis: Attention deficit hyperactivity disorder (ADHD), conduct disorder (CD) and oppositional defiant disorder (ODD) have an estimated prevalence of more than 5% of the population. Previous studies suggest that combinations of ADHD with CD or ODD may be comorbid with emotional disorders and increase the risk of developing depression.This present study aims to investigate the relationship between depression with ADHD and comorbid CD and ODD. We would like to test the following hypotheses: 1) Children and adolescents with ADHD and CD/ODD have a higher prevalence of positive symptoms for depression than those with only ADHD, and 2) Age, IQ and gender are significant factors that affect depression scores.

Methods: A total of 282 participants between the ages of 6 to 16 with a diagnosis of ADHD and/or CD/ODD were recruited. Diagnosis was made on a structured clinical interview and IQ scores were obtained from the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). Anxious/Depressed and Withdrawn/Depressed Scales were drawn from the Child Behaviour Checklist.

Results: The comorbid group of ADHD with CD/ODD did not exhibit significantly more depressive symptoms than the ADHD-alone group. Age, IQ and gender were not found to be statistically significant moderators between comorbidity and depressive symptoms.

Discussion & Conclusion: The results suggest that comorbidity alone does not lead to depressive symptoms. It is likely that personality traits, genetic and environmental factors have an additive effect which may not manifest immediately but over time. There is a need for longitudinal studies on the emotional outcomes of ADHD, CD and ODD.

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Ann Acad Med Singapore. 2014;43:S340.

EFFECTIVENESS OF OMEGA-3 FATTY ACIDS SUPPLEMENTATION ON SLEEP IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Tan X, Lee XY, Lim CG, et al.

Background & Hypothesis: Previous studies suggest that omega-3 fatty acids supplementation could reduce sleep difficulties in children with attention deficit hyperactivity disorder (ADHD). This study aims to investigate the effectiveness of this supplementation on sleep difficulties in children and adolescents with ADHD.

Methods: A total of 107 participants, aged 6 to 16 years old, diagnosed with ADHD, were included in this analysis. These participants were recruited as part of a larger randomised controlled trial examining the effects of supplements and social skills on children with disruptive behaviour disorders. Dropouts and those with missing data were excluded from the analysis. Sleep difficulties were measured using the School Sleep Habits Survey, particularly the Sleepiness Scale and the Sleep-wake Behaviour Problems Scale, which was administered at baseline and at 6 months. Participants were placed into either the active or placebo group.

Results: The active group did not exhibit significantly reduced sleep difficulties than the placebo group. In fact, the placebo group showed a greater trend of reductions in daytime sleepiness and sleep-wake behaviour problems as compared to the active group. Results did not differ greatly when controlled for medication or age group.

Discussion & Conclusion: The results suggest that omega-3 fatty acids supplementation is not any more effective in treating sleep problems in ADHD children and adolescents compared to a placebo. This may suggest that the belief in the positive effects of the supplementation has a similar, if not stronger, effect on sleeprelated problems. However, this could be due to the small sample size. Larger scale studies would be required to obtain more significant trends.

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Arq Neuro-Psiquiatr. 2015;73:227-36.

INTERVENTION FOR EXECUTIVE FUNCTIONS IN ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Menezes A, Dias NM, Trevisan BT, et al .

This study aimed to investigate if an executive functions (EF) intervention could promote these skills in individuals with attention deficit and hyperactivity disorder (ADHD). Eighteen children and adolescents, 7-13 years old, divided into experimental (EG, N = 8) and control (CG, N = 10) groups, were assessed in the Block Design and Vocabulary subtests of the WISC III and seven tests of EF. Parents answered two scales, measuring EF and inattention and hyperactivity signs. EG children participated in a program to promote EF in twice-weekly group sessions of one hour each. After 8 months of intervention, groups were assessed again. ANCOVA, controlling for age, intelligence quotient and pretest performance, revealed gains in attention/inhibition and auditory working memory measures for the EG. No effect was found for scales or measures of more complex EF. Results are not conclusive, but they illustrate some promising data about EF interventions in children and adolescents with ADHD.

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Arq Neuro-Psiquiatr. 2015;73:223-26.

ERROR RELATED NEGATIVITY AND MULTI-SOURCE INTERFERENCE TASK IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER-COMBINED TYPE.

Huerta-Albarran R, Poblano A, Santana-Vargas D, et al.

Objective: To compare performance of children with attention deficit hyperactivity disorders-combined (ADHD-C) type with control children in multi-source interference task (MSIT) evaluated by means of error related negativity (ERN).

Method: We studied 12 children with ADHD-C type with a median age of 7 years, control children were age- and gender-matched. Children performed MSIT and simultaneous recording of ERN.

Results: We found no differences in MSIT parameters among groups. We found no differences in ERN variables between groups. We found a significant association of ERN amplitude with MSIT in children with ADHD-C type.

Some correlation went in positive direction (frequency of hits and MSIT amplitude), and others in negative direction (frequency of errors and RT in MSIT).
Conclusion: Children with ADHD-C type exhibited a significant association between ERN amplitude with MSIT. These results underline participation of a cingulofronto- parietal network and could help in the comprehension of pathophysiological mechanisms of ADHD.

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Arq Neuro-Psiquiatr. 2015;73:96-103.

CLINICAL AND NEUROPSYCHOLOGICAL ASSESSMENT OF ATTENTION AND ADHD COMORBIDITY IN A SAMPLE OF CHILDREN AND ADOLESCENTS WITH IDIOPATHIC EPILEPSY.

Da Costa CRCM, Oliveira GM, Gomes MM, et al.

Children with epilepsy present significant problems concerning attention and comorbidity with attention deficit hyperactivity disorder (ADHD). Objective: To determine the prevalence of attention complaints, ADHD diagnosis and attention profile in a sample of children and adolescents with idiopathic epilepsy. Method: 36 children and adolescents with idiopathic epilepsy and 37 genre and age matched healthy controls underwent several procedures to diagnose their neuropsychological profile and comorbidity with ADHD. Results: The prevalence of ADHD was higher in patients with epilepsy [x2= 4.1, p = 0.043, 6 (16.7%) vs 1 (2.7%)], with worse results in attention related WISC items and factors in patients with epilepsy comparing to the controls, but not between patients with and without ADHD. Clinical characteristics did not influence those results. Conclusion: This study found a greater prevalence of problems wih attention in pediatric patients with idiopathic epilepsy, but not a distinct profile between those with or without ADHD.

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Aust New Zealand J Psychiatry. 2015;49:255-65.

ATTENTION-BASED CLASSIFICATION PATTERN, A RESEARCH DOMAIN CRITERIA FRAMEWORK, IN YOUTHS WITH BIPOLAR DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Kleinman A, Caetano SC, Brentani H, et al.

Objective: The National Institute of Mental Health has initiated the Research Domain Criteria (RDoC) project. Instead of using disorder categories as the basis for grouping individuals, the RDoC suggests finding relevant dimensions that can cut across traditional disorders. Our aim was to use the RDoCs framework to study patterns of attention deficit based on results of Conners Continuous Performance Test (CPT II) in youths diagnosed with bipolar disorder (BD), attentiondeficit/hyperactivity disorder (ADHD), BD+ADHD and controls.
Method: Eighteen healthy controls, 23 patients with ADHD, 10 with BD and 33 BD+ADHD aged 1217 years old were assessed. Pattern recognition was used to partition subjects into clusters based simultaneously on their performance in all CPT II variables. A Fishers linear discriminant analysis was used to build a classifier.
Results: Using cluster analysis, the entire sample set was best clustered into two new groups, A and B, independently of the original diagnoses. ADHD and BD+ADHD were divided almost 50% in each subgroup, and there was an agglomeration of controls and BD in group B. Group A presented a greater impairment with higher means in all CPT II variables and lower Childrens Global Assessment Scale. We found a high cross-validated classification accuracy for groups A and B: 95.2%. Variability of response time was the strongest CPT II measure in the discriminative pattern between groups A and B.
Conclusion: Our classificatory exercise supports the concept behind new approaches, such as the RDoC framework, for child and adolescent psychiatry. Our approach was able to define clinical subgroups that could be used in future pathophysiological and treatment studies.

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Basic and Clinical Pharmacology and Toxicology. 2015;116:349-53.

EARLY DISCONTINUATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DRUG TREATMENT: A DANISH NATIONWIDE DRUG UTILIZATION STUDY.

Pottegard A, Bjerregaard BK, Kortegaard LS, et al.

Knowledge of patterns of treatment discontinuation in attention-deficit/hyperactivity disorder (ADHD) drug treatment is of importance, for both the clinical practice and the study of long-term treatment outcomes. The purpose of this study was to describe early discontinuation of ADHD drug treatment. Using the Danish National Prescription Registry, all first-time users of the ADHD drugs methylphenidate and atomoxetine were identified between 2000 and 2012. Early discontinuation was defined as failing to fill a second prescription for any ADHD drug within 6 months. Analyses were conducted stratified by calendar year, drug formulation, patient sex, age and region of residence. 59,116 first-time users of methylphenidate and atomoxetine with at least 6 months of eligible follow-up were identified. Overall, 12.6% (n = 7441) failed to fill a second prescription within 6 months. This proportion changed over time, dropping from 20.8% in 2000 to 12.5% in 2012. The proportion of early discontinuation was considerably lower among children than among adults. Proportions were comparable when stratifying by index drug. Proportions of early discontinuation were similar between regions of Denmark, except in the capital region, where it remained at around 20% among 18- to 49-year-olds throughout the study period (22.6% in 2012). In conclusion, we found that the proportion of early discontinuation among ADHD drug users in Denmark dropped markedly during the past decade for both sexes, all age groups and all regions, except for adults in the capital region. Overall, early discontinuation was somewhat lower than expected, considering rates of side effects or non-response to ADHD drug treatment.

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Behav Genet. 2015.

CHILDHOOD ODD AND ADHD BEHAVIOR: THE EFFECT OF CLASSROOM SHARING, GENDER, TEACHER GENDER AND THEIR INTERACTIONS.

De Zeeuw EL, Van Beijsterveldt CEM, Lubke GH, et al.

One criterion for a diagnostic and statistical manual of mental disorders (DSM-IV) diagnosis of attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) is that symptoms are present in at least two settings, and often teacher ratings are taken into account. The short Connersnull Teacher Rating ScalesnullRevised (CTRS-R) is a widely used standardized instrument measuring ODD and ADHD behavior in a school setting. In the current study CTRS-R data were available for 7, 9 and 12-year-old twins from the Netherlands Twin Register. Measurement invariance (MI) across student gender and teacher gender was established for three of the four scales (Oppositional Behavior, Hyperactivity and ADHD Index) of the CTRS-R. The fourth scale (ATT) showed an unacceptable model fit even without constraints on the data and revision of this scale is recommended. Gene-environment (GxE) interaction models revealed that heritability was larger for children sharing a classroom. There were some gender differences in the heritability of ODD and ADHD behavior and there was a moderating effect of teachernulls gender at some of the ages. Taken together, this indicates that there was evidence for GxE interaction for classroom sharing, gender of the student and gender of the teacher.

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Brain and Behavior. 2015.

INTEGRATION OF AN EEG BIOMARKER WITH A CLINICIAN'S ADHD EVALUATION.

Snyder SM, Rugino TA, Hornig M, et al.

Background: This study is the first to evaluate an assessment aid for attention-deficit/hyperactivity disorder (ADHD) according to both Class-I evidence standards of American Academy of Neurology and De Novo requirements of US Food and Drug Administration. The assessment aid involves a method to integrate an electroencephalographic (EEG) biomarker, theta/beta ratio (TBR), with a clinician's ADHD evaluation. The integration method is intended as a step to help improve certainty with criterion E (i.e., whether symptoms are better explained by another condition).

Methods: To evaluate the assessment aid, investigators conducted a prospective, triple-blinded, 13-site, clinical cohort study. Comprehensive clinical evaluation data were obtained from 275 children and adolescents presenting with attentional and behavioral concerns. A qualified clinician at each site performed differential diagnosis. EEG was collected by separate teams. The reference standard was consensus diagnosis by an independent, multidisciplinary team (psychiatrist, psychologist, and neurodevelopmental pediatrician), which is well-suited to evaluate criterion E in a complex clinical population.
Results: Of 209 patients meeting ADHD criteria per a site clinician's judgment, 93 were separately found by the multidisciplinary team to be less likely to meet criterion E, implying possible overdiagnosis by clinicians in 34% of the total clinical sample (93/275). Of those 93, 91% were also identified by EEG, showing a relatively lower TBR (85/93). Further, the integration method was in 97% agreement with the multidisciplinary team in the resolution of a clinician's uncertain cases (35/36). TBR showed statistical power specific to supporting certainty of criterion E per the multidisciplinary team (Cohen's d, 1.53). Patients with relatively lower TBR were more likely to have other conditions that could affect criterion E certainty (10 significant results; P (less-than or equal to) 0.05). Integration of this information with a clinician's ADHD evaluation could help improve diagnostic accuracy from 61% to 88%.
Conclusions: The EEG-based assessment aid may help improve accuracy of ADHD diagnosis by supporting greater criterion E certainty.

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Brain Dev. 2015.

POOR TODDLER-AGE SLEEP SCHEDULES PREDICT SCHOOL-AGE BEHAVIORAL DISORDERS IN A LONGITUDINAL SURVEY.

Kobayashi K, Yorifuji T, Yamakawa M, et al .

Objective: Behavioral problems are often associated with poor sleep habits in children. We investigated whether undesirable toddler-age sleep schedules may be related to school-age behavioral problems.
Methods: We analyzed the data of a nationwide longitudinal survey with available results from 2001 to 2011. The participants were 41,890 children. The predictors were waking time and bedtime at 2. years of age, and the outcomes were assessed by determining the presence or absence of three attention problems and four aggressiveness problems at 8. years of age. In logistic regression models with adjustments for confounding factors, we estimated odds ratios (ORs) and confidence intervals (CIs) for the association between toddler sleep schedules and behavior during primary-school age years.
Results: The outcomes of attention problems and aggressiveness problems were observed in 1.7% and 1.2% of children, respectively, at 8. years of age. The OR of an irregular or late morning waking time at 2. years of age with the outcome of aggressiveness problems was 1.52 (95% CI, 1.04-2.22) in comparison to an early waking time. The OR of an irregular or late bedtime with attention problems was 1.62 (95% CI, 1.12-2.36), and the OR of an irregular or late bedtime with aggressiveness problems was 1.81 (95% CI, 1.19-2.77) in comparison to an early bedtime.
Conclusion: Poor toddler-age sleep schedules were found to predict behavioral problems during primary-school age years. Thus, good and regular sleep habits appear to be important for young children's healthy development.

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Cardiol Young. 2015;25:663-69.

THE PREVALENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FOLLOWING NEONATAL AORTIC ARCH REPAIR.

Sistino JJ, Atz AM, Simpson KN, et al.

Objective: We sought to determine the prevalence of attention-deficit/hyperactivity disorder in a population of children who underwent neonatal heart surgery involving repair of the aortic arch for Norwood Stage I, interrupted aortic arch, and combined repair of aortic coarctation with ventricular septal defect.
Methods: Children between the ages of 5 and 16 were surveyed using the ADHD-IV and the Child Heath Questionnaire-50. Classification as attention-deficit/hyperactivity disorder was defined for this study as either a parent-reported diagnosis of attention-deficit/hyperactivity disorder or ADHD-IV inattention score of (greater-than or equal to)93 percentile.

Results: Of the 134 surveys, 57 (43%) were returned completed. A total of 25 (44%) children either had a diagnosis of attention-deficit/hyperactivity disorder and/or ADHD-IV inattention score (greater-than or equal to)93 percentile. Eleven of the 13 (85%) children with interrupted aortic arch, 3 of the 7 (42.9%) children with combined coarctation/ventricular septal defect repair, and 9 of the 33 (27.3%) children with hypoplastic left-heart syndrome were classified as having attention-deficit/hyperactivity disorder. Only 7 of the 25 (28%) children received medical treatment for this condition. Quality of life indicators in the Child Heath Questionnaire-50 Questionnaire were highly correlated with the ADHD-IV scores.
Conclusion: The risks for the development of attention-deficit/hyperactivity disorder are multifactorial but are significantly increased in this post-surgical population. This study revealed a low treatment rate for attention-deficit/hyperactivity disorder, and a significant impact on the quality of life in these children.

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Child Neuropsychol. 2015.

SLEEP DISTURBANCE AND NEUROPSYCHOLOGICAL FUNCTION IN YOUNG CHILDREN WITH ADHD.

Schneider HE, Lam JC, Mahone EM.

Sleep disturbance, common among children with ADHD, can contribute to cognitive and behavioral dysfunction. It is therefore challenging to determine whether neurobehavioral dysfunction should be attributed to ADHD symptoms, sleep disturbance, or both. The present study examined parent-reported sleep problems (Childrennulls Sleep Habits Questionnaire) and their relationship to neuropsychological function in 64 children, aged 4null7 years, with and without ADHD. Compared to typically developing controls, children with ADHD were reported by parents to have significantly greater sleep disturbancenullincluding sleep onset delay, sleep anxiety, night awakenings, and daytime sleepinessnull(all p (less-than or equal to) .01), and significantly poorer performance on tasks of attention, executive control, processing speed, and working memory (all $p < .01$). Within the ADHD group, total parent-reported sleep disturbance was significantly associated with deficits in attention and executive control skills (all p (less-than or equal to) .01); however, significant group differences (relative to controls) on these measures remained ($p < .01$) even after controlling for total sleep disturbance. While sleep problems are common among young children with ADHD, these findings suggest that inattention and executive dysfunction appear to be attributable to symptoms of ADHD rather than to sleep disturbance. The relationships among sleep, ADHD symptoms, and neurobehavioral function in older children may show different patterns as a function of the chronicity of disordered sleep.

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Child Neuropsychol. 2015.

COMBINED COGNITIVE AND PARENT TRAINING INTERVENTIONS FOR ADOLESCENTS WITH ADHD AND THEIR MOTHERS: A RANDOMIZED CONTROLLED TRIAL.

Steeger CM, Gondoli DM, Gibson BS, et al.

This study examined the individual and combined effects of two nonpharmacological treatments for attention deficit/hyperactivity disorder (ADHD): Cogmed working memory training (CWMT) for adolescents and behavioral parent training (BPT) for mothers. Ninety-one adolescents (ages 11null15) and their mothers were randomized to one of four CWMT and BPT treatment and active control (placebo) group combinations of 5-week interventions. At pre- and posttest, mothers and teachers completed rating forms, and adolescents completed neuropsychological measures of working memory (WM). Individual intervention effects showed that treatment CWMT significantly improved WM spans, whereas there were no significant differences for treatment or control BPT on reports of parent-related outcomes. Combined treatment effects indicated an overall pattern of greatest improvements for the control CWMT/treatment BPT group, as compared to the other three groups, on adolescent WM deficit, behavioral regulation problems, and global executive deficit. Most significant effects for outcomes were main effects of improvements over time. A combination of CWMT and BPT did not result in increased treatment gains. However, potential effects of combined treatment may have been masked by greater perceived benefits arising from lack of struggle in the nonadaptive, CWMT active control condition. Future combined intervention research should focus on specific, theoretically driven WM deficits among individuals with ADHD, should include possible adaptations to the standard CWMT program, should examine effectiveness of

cognitive treatments combined with contextual interventions and should utilize appropriate control groups to fully understand the unique and combined effects of interventions.

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Child Neuropsychol. 2015.

EXECUTIVE AND ATTENTIONAL CONTRIBUTIONS TO THEORY OF MIND DEFICIT IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Mary A, Slama H, Mousty P, et al.

Attention deficit/hyperactivity disorder (ADHD) in children has been associated with attentional and executive problems, but also with socioemotional difficulties possibly associated with deficits in Theory of Mind (ToM). Socioemotional problems in ADHD are associated with more negative prognoses, notably interpersonal, educational problems, and an increased risk of developing other psychiatric disorders that emphasize the need to clarify the nature of their ToM deficits. In this study, we hypothesized that ToM dysfunction in children with ADHD is largely attributable to their attentional and/or executive deficits. Thirty-one children with ADHD (8null12 years, IQ > 85) and 31 typically developing (TD) children were assessed using executive functions (inhibition, planning, and flexibility) and attentional tasks, as well as two advanced ToM tasks (Reading the Mind in the Eyes and Faux Pas) involving different levels of executive control. Children with ADHD performed more poorly than TD children in attentional, executive function, and ToM tasks. Linear regression analyses conducted in the ADHD group indicated that inhibition scores predicted performance on the nullFaux Pasnull task the best, while attention scores were the best for predicting performance on the Reading the Mind in the Eyes task. When controlled for inhibition and attentional variables, ToM performance in children with ADHD was actually similar to TD children. Contrarily, controlling for ToM scores did not normalize performance for inhibition and attentional tasks in children with ADHD. This unidirectional relationship suggests that deficits in the EF and attentional domains are responsible for ToM deficits in ADHD, which therefore may contribute to their socioemotional difficulties.

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Cogn Behav Pract. 2015.

NOVEL APPROACHES TO COGNITIVE-BEHAVIORAL THERAPY FOR ADULT ADHD.

Canu WH, Wymbs BT.

While in the past two decades attention-deficit/hyperactivity disorder (ADHD) has been recognized as a disorder that persists into adulthood in most cases, the development of empirically supported therapies for affected individuals beyond childhood has lagged considerably. Cognitive-behavioral therapy and related approaches, however, lead the developing literature in this area, at least with regard to psychosocial interventions. The articles in the current special series expand upon this existing work by demonstrating how treatment can (a) be extended to adolescent and college student groups, (b) incorporate a romantic couples approach, (c) productively add mindfulness as an active therapy component, and (d) engage clients in identifying and adaptively weighing overly optimistic thoughts that may be all too common for those with ADHD. Each article provides a theoretical and research review along with descriptions of interventions and case examples, maximizing the utility for clinicians and researchers alike.

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Cultural Diversity and Ethnic Minority Psychology. 2015.

UNDERSTANDING PARENTAL LOCUS OF CONTROL IN LATINO PARENTS: EXAMINATION OF CULTURAL INFLUENCES AND HELP-SEEKING INTENTIONS FOR CHILDHOOD ADHD.

Lawton KE, Kapke TL, Gerdes AC.

Objective: To address the disparities that exist in utilization of mental health services for ADHD among Latino families and to further our understanding of factors that influence parents' decisions to seek treatment for ADHD, the goal of the current study was to examine parental locus of control (PLOC) in a community sample of Latino

parents. Specifically, the current study investigated cultural influences on PLOC, as well as the influence of PLOC on help-seeking.
Method: Seventy-four primarily Spanish-speaking, Latino parents of school-age children completed measures to assess their help-seeking intentions, PLOC, and cultural orientation.
Results: Results indicated that U.S. mainstream orientation was associated with increased feelings of parental control and decreased beliefs in fate/chance and several Latino cultural values were associated with increased beliefs in fate/chance, and decreased feelings of parental efficacy and parental control. In addition, 2 PLOC domains (e.g., parental efficacy and fate/chance) were associated with beliefs that the behaviors of a child with ADHD would go away on their own.
Conclusions: Results highlight the need for interventions aimed at modifying parenting behavior to take parents' cultural beliefs and values into account in order to accommodate and engage Latino families more effectively.

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Dyslexia. 2015.
BEHAVIOURAL DIFFICULTIES THAT CO-OCCUR WITH SPECIFIC WORD READING DIFFICULTIES: A UK POPULATION-BASED COHORT STUDY.
Russell G, Ryder D, Norwich B, et al.
This study aimed to examine the association between specific word reading difficulties (SWRD) identified at age 7years using a discrepancy approach and subsequent dimensional measures of behavioural difficulties reported by teachers and parents at age 11years. Behavioural problems were assessed using the Strengths and Difficulties Questionnaire. Secondary analysis of a UK representative population-based sample of children (n=12631) was conducted using linear regression models. There were 284 children (2.2%) identified with SWRD at age 7years. Children with SWRD had significantly higher scores on all measures of behavioural difficulties in unadjusted analysis. SWRD was associated with elevated behavioural difficulties at age 11years according to parent report, and with greater emotional problems, hyperactivity and conduct issues according to teachers, even after having controlled for baseline difficulties. These results were replicated for children with low reading attainment, but no cognitive ability discrepancy. Categories of special educational need into which children with SWRD were classed at school were varied. Given high rates of co-occurring behavioural difficulties, assessment that identifies each individual child's specific functional, rather than categorical, difficulties is likely to be the most effective way of providing classroom support.

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Environ Health Perspect. 2015;123:271-76.
ENVIRONMENTAL LEAD EXPOSURE AND ATTENTION DEFCIT/HYPERACTIVITY DISORDER SYMPTOM DOMAINS IN A COMMUNITY SAMPLE OF SOUTH KOREAN SCHOOL-AGE CHILDREN.
Hong S-B, Im M-H, Kim J-W, et al.
Background: Low-level environmental exposure to lead has been associated with both reduced intelligence and symptoms of attention deficit/hyperactivity disorder (ADHD). However, few studies have estimated the association of lead and intelligence independent of ADHD, and it is not clear from previous studies whether lead is associated with both inattention and impulsivity ADHD symptoms. oBjectives: We estimated mutually adjusted associations of environmental lead exposure with both intelligence and ADHD symptoms, and associations between lead and specific ADHD-related domains.
Methods: Blood lead concentrations were measured in a general population of 1,001 children 8null11 years of age. We used multivariable linear regression models to estimate associations of blood lead concentrations with IQ scores, teacher and parent ratings of ADHD symptoms, and measures of inattention and impulsivity. Models were adjusted for demographic variables and other environmental exposures (blood levels of mercury and manganese, urinary concentrations of cotinine, phthalate metabolites, and bisphenol A).
Results: Associations of blood lead with lower IQ and higher impulsivity were robust to adjustment for a variety of covariates. When adjusted for demographic characteristics, other environmental exposures, and ADHD symptoms or IQ, a 10-fold increase in blood lead concentration was associated with lower Full-Scale IQ (null7.23; 95% CI: null13.39, null1.07) and higher parent- and teacher-rated hyperactivity/impulsivity scores

(ADHD Rating Scale, 1.99; 95% CI: 0.17, 3.81 and 3.66; 95% CI: 1.18, 6.13, respectively) and commission errors (Continuous Performance Test, 12.27; 95% CI: null0.08, 24.62). Blood lead was not signifcantly associated with inattention in adjusted models.
Conclusions: Low-level lead exposure was adversely associated with intelligence in school-age children independent of ADHD, and environmental lead exposure was selectively associated with impulsivity among the clinical features of ADHD.

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Eur Child Adolesc Psychiatry. 2015.

SEX-SPECIFIC AND TIME-DEPENDENT EFFECTS OF PRENATAL STRESS ON THE EARLY BEHAVIORAL SYMPTOMS OF ADHD: A LONGITUDINAL STUDY IN CHINA.

Zhu P, Hao J-H, Tao R-X, et al.

There is increasing evidence that prenatal stressful life events (SLEs) may be a potential risk factor for attention-deficit hyperactivity disorder (ADHD), but the sex-specific and time-dependent effects of prenatal stress on ADHD are less clear. In this prospective longitudinal study, data on prenatal SLEs during different stages of gestation and indicators of buffers against stress, including maternal social support and avoidance coping, were obtained from 1765 pregnant women at 32 weeks of gestation. The behavioral symptoms of ADHD in children aged 48null54 months were evaluated by reports from the parents. There were 226 children (12.8 %) above the clinically significant cutoff for ADHD. After adjusting for potential confounders, boys whose mother experienced severe SLEs in the second trimester had a significantly increased risk (OR = 2.41, 95 % CI: 1.03null5.66) of developing ADHD symptoms compared with boys whose mothers did not experience severe SLEs at this time. However, no significantly increased risk of ADHD symptoms was observed in girls born to mothers experienced prenatal severe SLEs. Additionally, significant interaction effects of prenatal SLEs, social support and coping style on ADHD symptoms were found in males. Boys whose mothers experienced severe SLEs during the second trimester accompanied by a higher score for avoidance coping (OR = 3.31, 95 % CI: 1.13null9.70) or a lower score for social support (OR = 4.39, 95 % CI: 1.05null18.31) were likely to be at a higher risk for ADHD symptoms. The epidemiological evidence in this prospective follow-up study suggests that the effect of prenatal SLEs on ADHD symptoms in offspring may depend on the timing of prenatal stress and may vary according to the sex of the offspring.

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Eur J Radiol. 2015.

ALTERED TEMPORAL FEATURES OF INTRINSIC CONNECTIVITY NETWORKS IN BOYS WITH COMBINED TYPE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Wang X-H, Li L.

Purpose: Investigating the altered temporal features within and between intrinsic connectivity networks (ICNs) for boys with attention-deficit/hyperactivity disorder (ADHD); and analyzing the relationships between altered temporal features within ICNs and behavior scores.
Materials and methods: A cohort of boys with combined type of ADHD and a cohort of age-matched healthy boys were recruited from ADHD-200 Consortium. All resting-state fMRI datasets were preprocessed and normalized into standard brain space. Using general linear regression, 20 ICNs were taken as spatial templates to analyze the time-courses of ICNs for each subject. Amplitude of low frequency fluctuations (ALFFs) were computed as univariate temporal features within ICNs. Pearson correlation coefficients and node strengths were computed as bivariate temporal features between ICNs. Additional correlation analysis was performed between temporal features of ICNs and behavior scores.
Results: ADHD exhibited more activated network-wise ALFF than normal controls in attention and default mode-related network. Enhanced functional connectivities between ICNs were found in ADHD. The network-wise ALFF within ICNs might influence the functional connectivity between ICNs. The temporal pattern within posterior default mode network (pDMN) was positively correlated to inattentive scores. The subcortical network, fusiform-related DMN and attention-related networks were negatively correlated to Intelligence Quotient (IQ) scores.

Conclusion: The temporal low frequency oscillations of ICNs in boys with ADHD were more activated than normal controls during resting state; the temporal features within ICNs could provide additional information to investigate the altered network patterns of ADHD.

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Int J Psychiatry Clin Pract. 2015;19:18-23.

INTERNET ADDICTION IS RELATED TO ATTENTION DEFICIT BUT NOT HYPERACTIVITY IN A SAMPLE OF HIGH SCHOOL STUDENTS.

Yilmaz S, Herguner S, Bilgic A, et al.

Objective. To assess the effects of attention-deficit/hyperactivity disorder (ADHD) symptom dimensions on Internet addiction (IA) after controlling for Internet usage features among high school students.

Methods. This study consisted of 640 students (331 females and 309 males) ranging from 14 to 19 years of age. The Internet Addiction Scale, the Conners-Wells' Adolescent Self-Report Scale-Short Form, and a personal information form were completed by the participants. Statistical analyses were conducted for both sexes and the total sample.

Results. According to the logistic regression analysis, attention deficit and playing online games were significant predictors of IA in both sexes. Other predictors of IA included behavioral problems for females, total weekly Internet usage time, and lifelong total Internet use for males. Hyperactivity and other Internet usage features did not predict IA.

Conclusion. These results suggest that attention deficit and playing online games are important determinants of IA in this age group.

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JAMA Psychiatry. 2014;71:1299-300.

ATTENTION NETWORK HYPOCONNECTIVITY IN ADULTS DIAGNOSED AS HAVING ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER IN CHILDHOOD: TO THE EDITOR.

McCarthy H, Skokauskas N, Frodl T.

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J Affective Disord. 2015;178:149-59.

COMPARATIVE EFFICACY AND ACCEPTABILITY OF ATOMOXETINE, LISDEXAMFETAMINE, BUPROPION AND METHYLPHENIDATE IN TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS: A META-ANALYSIS WITH FOCUS ON BUPROPION.

Stuhec M, Munda B, Svab V, et al.

Objectives There is a lack of comparative effectiveness research among attention deficit hyperactivity disorder (ADHD) drugs in terms of efficacy and acceptability, where bupropion is compared with atomoxetine, lisdexamfetamine and methylphenidate. The main aim of this work was to compare the efficacy and acceptability of these drugs in children and adolescents using a metaanalysis.

Methods A literature search was conducted to identify double-blind, placebo-controlled, noncrossover studies of ADHD. PubMed/Medline and Clinicaltrials.gov were searched. Comparative drug efficacy to placebo was calculated based on the standardized mean difference (SMD), while the comparative drug acceptability (all cause discontinuation) to placebo was estimated on the odds ratio (OR).

Results In total 28 trials were included in the meta-analysis. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD=-0.32, 95% CI; -0.69, 0.05), while modest efficacy was shown for atomoxetine (SMD=-0.68, 95% CI; -0.76, -0.59) and methylphenidate (SMD=-0.75, 95% CI; -0.98, -0.52) and high efficacy was observed for lisdexamfetamine (SMD=-1.28, 95% CI; -1.84, -0.71). Compared to placebo treatment discontinuation was statistically significantly lower for methylphenidate (OR=0.35, 95% CI; 0.24, 0.52), while it was not significantly different for atomoxetine (OR=0.91, 95% CI; 0.66, 1.24), lisdexamfetamine (OR=0.60, 95% CI, 0.22, 1.65), and bupropion (OR=1.64, 95% CI; 0.5, 5.43).

Limitations The heterogeneity was high, except in atomoxetine trials. The crossover studies were excluded. The effect sizes at specific time points were not computed. Studies with comorbid conditions, except those reporting on oppositional defiant disorder, were also excluded. All studies involving MPH were combined.
Conclusions The results suggest that lisdexamfetamine has the best benefit risk balance and has promising potential for treating children and adolescents with ADHD. More research is needed for a better clinical evaluation of bupropion.

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J Affective Disord. 2015;176:171-75.

COMORBIDITY OF ADHD AND SUICIDE ATTEMPTS AMONG ADOLESCENTS AND YOUNG ADULTS WITH BIPOLAR DISORDER: A NATIONWIDE LONGITUDINAL STUDY.

Lan W-H, Bai Y-M, Hsu J-W, et al.

Background Suicide is among the leading causes of death among people with bipolar disorder and has gained substantial attention in the psychiatric and public health fields. However, the role of attention deficit hyperactivity disorder (ADHD) in suicide among adolescents and young adults with bipolar disorder remains unknown.
Methods Using Taiwan's National Health Insurance Research Database, we identified 500 adolescents and young adults from 2002 to 2008 aged between 15 and 24 years with bipolar disorder and ADHD. The sample was matched according to age and sex with 1500 (1:3) patients with bipolar disorder only and observed until the end of 2011. The patients who attempted suicide during the follow-up period were identified.
Results Adolescents and young adults with bipolar disorder and ADHD had a greater incidence of attempted suicide than did those with bipolar disorder only (3.0% vs. 1.1%, p=0.005). After adjustment for demographic factors and psychiatric comorbidities, a Cox regression analysis determined that ADHD was an independent risk factor for attempted suicide (hazard ratio: 2.38, 95% confidence interval: 1.13-5.00) later in life among adolescents and young adults with bipolar disorder.
Discussion Adolescents and young adults with bipolar disorder and ADHD had an increased likelihood of attempted suicide compared with adolescents and young adults with bipolar disorder only. Further study is required to investigate the possible pathophysiology among ADHD, bipolar disorder, and attempted suicide, and to assess whether prompt intervention for ADHD may reduce the risk of attempted suicide.

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J Autism Dev Disord. 2015;45:742-51.

EVIDENCE FOR SPECIFICITY OF MOTOR IMPAIRMENTS IN CATCHING AND BALANCE IN CHILDREN WITH AUTISM.

Ament K, Mejia A, Buhlman R, et al.

To evaluate evidence for motor impairment specificity in autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD). Children completed performance-based assessment of motor functioning (Movement Assessment Battery for Children: MABC-2). Logistic regression models were used to predict group membership. In the models comparing typically developing and developmental disability (DD), all three MABC subscale scores were significantly negatively associated with having a DD. In the models comparing ADHD and ASD, catching and static balance items were associated with ASD group membership, with a 1 point decrease in performance increasing odds of ASD by 36 and 39 %, respectively. Impairments in motor skills requiring the coupling of visual and temporal feedback to guide and adjust movement appear specifically deficient in ASD.

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Journal of Babol University of Medical Sciences. 2015;17:28-36.

COMPARISON OF THE NUTRITIONAL STATUS OF BOYS WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mousavi P, Darabi M, Malek A, et al.

BACKGROUND AND OBJECTIVE: Attention deficit hyperactivity disorder (ADHD) is one of the most common mental disorders in children. Nutritional deficiency may play a role in the etiology of this disorder. The purpose of this study was to determine and compare the nutritional status (dietary intake and anthropometric indices) of boys with and without ADHD.

METHODS: This case-control study was conducted on 36 boys with ADHD (case group) and 37 normal children (control group), aged 6-12 years. The case subjects were assesssed by an expert psychiatrist via clinical evaluations and psychiatric questionnaires. Height, weight, and body mass index (BMI) of the subjects were measured. Dietary intake was recorded, using a three-day food record (three non-consecutive days including one holiday and two weekdays) and analyzed using Nutritionist IV software.
FINDINGS: The mean weight, height, and BMI values were higher in children with ADHD, compared to the control group (p<0.05); the mean(plus or minus)SD of BMI was 17.28(plus or minus)2.44 in the case group and 15.14(plus or minus)2.34 in the control group (p<0.001). There was no significant difference in terms of energy, macronutrient, or micronutrient intake between the two groups. However, folate and selenium intake in the two groups was lower than the recommended dietary allowance.
CONCLUSION: The results showed no signifcant difference between the energy intake of children with ADHD and healthy boys. However, boys with ADHD were taller and heavier than healthy subjects, and their BMI was higher.

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J Child Adolesc Psychopharmacol. 2015;25:182.
FEAR OF STIMULANT THERAPY FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Johnson MR.

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J Child Adolesc Psychopharmacol. 2015;25:180.
CARDIOVASCULAR SAFETY OF STIMULANTS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Kiely B, Adesman A.

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J Child Adolesc Psychopharmacol. 2015;25:176-79.
PHARMACOTHERAPEUTIC CHALLENGES IN TREATMENT OF A CHILD WITH "THE TRIAD" OF OBSESSIVE COMPULSIVE DISORDER, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND TOURETTE'S DISORDER.
Rice T, Coffey B.

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J Clin Psychopharmacol. 2015;35:209-11.
ACUTE FOCAL DYSTONIC REACTION AFTER ACUTE METHYLPHENIDATE TREATMENT IN AN ADOLESCENT PATIENT.
Tekin U, Soyata AZ, Oflaz S.

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J Psychiatr Res. 2015;62:92-100.
CHILDHOOD PREDICTORS OF ADOLESCENT AND YOUNG ADULT OUTCOME IN ADHD.
Cheung CHM, Rijdijk F, McLoughlin G, et al.
Background: Attention-deficit/hyperactivity disorder (ADHD) often persists into adulthood, but it remains unclear which childhood factors predict future outcome.
Aim: To identify childhood predictors of ADHD outcome using both dimensional and categorical approaches.
Methods: 116 adolescents and young adults with childhood ADHD were followed up on average 6.6 years later. ADHD outcome variables were interview-based parent-reported ADHD symptoms and impairment. Childhood predictors included parent- and teacher-rated ADHD symptoms and co-occurring behaviours; actigraph

measures of activity level; socio-economic status (SES); and cognitive measures previously associated with ADHD.
Results: Of the sample, 79% continued to meet clinical criteria of ADHD in adolescence and young adulthood. Higher parent-rated ADHD symptoms and movement intensity in childhood, but not teacher-rated symptoms, predicted ADHD symptoms at follow up. Co-occurring symptoms of oppositional behaviours, anxiety, social and emotional problems were also significant predictors, but these effects disappeared after controlling for ADHD symptoms. IQ and SES were significant predictors of both ADHD symptoms and impairment at follow up, but no other cognitive measures significantly predicted outcome.
Conclusions: SES and IQ emerge as potential moderators for the prognosis of ADHD. Childhood severity of ADHD symptoms, as measured by parent ratings and actigraph movement intensity, also predicts later ADHD outcome. These factors should be considered when identifying ADHD children at most risk of poor long-term outcomes and for the development of interventions to improve prognosis.

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J Sport Health Sci. 2015;4:97-104.

THE EFFECT OF ACUTE EXERCISE ON COGNITIVE PERFORMANCE IN CHILDREN WITH AND WITHOUT ADHD.

Piepmeier AT, Shih C-H, Whedon M, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common childhood disorder that affects approximately 11% of children in the United States. Research supports that a single session of exercise benefits cognitive performance by children, and a limited number of studies have demonstrated that these effects can also be realized by children with ADHD. The purpose of this study was to examine the effect of acute exercise on cognitive performance by children with and without ADHD.
Methods: Children with and without ADHD were asked to perform cognitive tasks on 2 days following treatment conditions that were assigned in a random, counterbalanced order. The treatment conditions consisted of a 30-min control condition on 1 day and a moderate intensity exercise condition on the other day.
Results: Exercise significantly benefited performance on all three conditions of the Stroop Task, but did not significantly affect performance on the Tower of London or the Trail Making Test.
Conclusion: children with and without ADHD realize benefits in speed of processing and inhibitory control in response to a session of acute exercise, but do not experience benefits in planning or set shifting.

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J Am Acad Child Adolesc Psychiatry. 2015;54:275-82.

GROUP THERAPY FOR ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED CONTROLLED TRIAL.

Vidal R, Castells J, Richarte V, et al.

Objective To determine the efficacy of group cognitive-behavioral therapy (CBT) on adolescents with attention-deficit/hyperactivity disorder (ADHD) who were in pharmacological treatment but still had persistent symptoms.
Method We conducted a multicenter, randomized, rater-blinded, controlled trial between April 2012 and May 2014 in a cohort of 119 adolescents (15-21 years of age). Participants were randomly assigned to 12 manualized group CBT sessions (n = 45) or a waiting list control group (n = 44). Primary outcomes were assessed by a blinded evaluator (ADHD Rating Scale [ADHD-RS], Clinical Global Impression Scale for Severity [CGI-S], Global Assessment of Functioning [GAF]) before and after treatment, as well as by self-report and parent informant ratings.
Results Of the initial 119 participants enrolled, 89 completed treatment. A mixed-effects model analysis revealed that participants who were assigned to the group CBT sessions experienced significantly reduced ADHD symptoms compared to the control group (ADHD-RS Adolescent: -7.46, 95% CI = -9.56 to -5.36, p <.001, d = 7.5; ADHD-RS Parents: -9.11, 95% CI = -11.48 to -6.75, p <.001, d = 8.38; CGI-S Self-Report: -0.68, 95% CI = -0.98 to -0.39, p <.001, d = 3.75; CGI-S Clinician: -0.79, 95% CI = -0.95 to -0.62, p <.001; d = 7.71). Functional impairment decreased significantly in the CBT group according to parents (Weiss Functional Impairment Scale -4.02, 95% CI = -7.76 to -0.29, p <.05, d = 2.29) and according to the blinded evaluator (GAF: -7.58, 95% CI = -9.1 to -6.05, p <.001, d = 7.51).

Conclusion Group CBT associated with pharmacological treatment is an efficacious intervention for reducing ADHD symptoms and functional impairment in adolescents.
Clinical trial registration information - CBT Group for Adolescents With ADHD: a Randomized Controlled Trial; http://clinicaltrials.gov/; NCT02172183.

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J Am Acad Child Adolesc Psychiatry. 2015;54:164-74.

COGNITIVE TRAINING FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: META-ANALYSIS OF CLINICAL AND NEUROPSYCHOLOGICAL OUTCOMES FROM RANDOMIZED CONTROLLED TRIALS.

Cortese S, Ferrin M, Brandeis D, et al.

Objective The authors performed meta-analyses of randomized controlled trials to examine the effects of cognitive training on attention-deficit/hyperactivity disorder (ADHD) symptoms, neuropsychological deficits, and academic skills in children/adolescents with ADHD.
Method The authors searched Pubmed, Ovid, Web of Science, ERIC, and CINAHAL databases through May 18, 2014. Data were aggregated using random-effects models. Studies were evaluated with the Cochrane risk of bias tool.
Results Sixteen of 695 nonduplicate records were analyzed (759 children with ADHD). When all types of training were considered together, there were significant effects on total ADHD (standardized mean difference [SMD] = 0.37, 95% CI = 0.09-0.66) and inattentive symptoms (SMD = 0.47, 95% CI = 0.14-0.80) for reports by raters most proximal to the treatment setting (i.e., typically unblinded). These figures decreased substantially when the outcomes were provided by probably blinded raters (ADHD total: SMD = 0.20, 95% CI = 0.01-0.40; inattention: SMD = 0.32, 95% CI = -0.01 to 0.66). Effects on hyperactivity/impulsivity symptoms were not significant. There were significant effects on laboratory tests of working memory (verbal: SMD = 0.52, 95% CI = 0.24-0.80; visual: SMD = 0.47, 95% CI = 0.23-0.70) and parent ratings of executive function (SMD = 0.35, 95% CI = 0.08-0.61). Effects on academic performance were not statistically significant. There were no effects of working memory training, specifically on ADHD symptoms. Interventions targeting multiple neuropsychological deficits had large effects on ADHD symptoms rated by most proximal assessors (SMD = 0.79, 95% CI = 0.46-1.12).
Conclusion Despite improving working memory performance, cognitive training had limited effects on ADHD symptoms according to assessments based on blinded measures. Approaches targeting multiple neuropsychological processes may optimize the transfer of effects from cognitive deficits to clinical symptoms.

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J Am Acad Child Adolesc Psychiatry. 2015;54:322-27.

SHARED GENETIC INFLUENCES BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) TRAITS IN CHILDREN AND CLINICAL ADHD.

Stergiakouli E, Martin J, Hamshere ML, et al.

Objective Twin studies and genome-wide complex trait analysis (GCTA) are not in agreement regarding heritability estimates for behavioral traits in children from the general population. This has sparked a debate on the possible difference in genetic architecture between behavioral traits and psychiatric disorders. In this study, we test whether polygenic risk scores associated with variation in attention-deficit/hyperactivity disorder (ADHD) trait levels in children from the general population predict ADHD diagnostic status and severity in an independent clinical sample.
Method Single nucleotide polymorphisms (SNPs) with p <.5 from a genome-wide association study of ADHD traits in 4,546 children (mean age, 7 years 7 months) from the Avon Longitudinal Study of Parents and Children (ALSPAC; general population sample) were selected to calculate polygenic risk scores in 508 children with an ADHD diagnosis (independent clinical sample) and 5,081 control participants. Polygenic scores were tested for association with case-control status and severity of disorder in the clinical sample.
Results Increased polygenic score for ADHD traits predicted ADHD case-control status (odds ratio = 1.17 [95% CI = 1.08-1.28], p =.0003), higher ADHD symptom severity ((beta) = 0.29 [95% CI = 0.04-0.54], p = 0.02), and symptom domain severity in the clinical sample.

Conclusion This study highlights the relevance of additive genetic variance in ADHD, and provides evidence that shared genetic factors contribute to both behavioral traits in the general population and psychiatric disorders at least in the case of ADHD.

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J Am Acad Child Adolesc Psychiatry. 2015;54:263-74.

EFFECTIVENESS OF A TELEHEALTH SERVICE DELIVERY MODEL FOR TREATING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A COMMUNITY-BASED RANDOMIZED CONTROLLED TRIAL.

Myers K, Vander SA, Zhou C, et al.

Objective To test the effectiveness of a telehealth service delivery model for the treatment of children with attention-deficit/hyperactivity disorder (ADHD) that provided pharmacological treatment and caregiver behavior training.

Method The Children's ADHD Telemental Health Treatment Study (CATTS) was a randomized controlled trial with 223 children referred by 88 primary care providers (PCPs) in 7 communities. Children randomized to the experimental telehealth service model received 6 sessions over 22 weeks of combined pharmacotherapy, delivered by child psychiatrists through videoconferencing, and caregiver behavior training, provided in person by community therapists who were supervised remotely. Children randomized to the control service delivery model received treatment with their PCPs augmented with a telepsychiatry consultation. Outcomes were diagnostic criteria for ADHD and oppositional defiant disorder (ODD) and role performance on the Vanderbilt ADHD Rating Scale (VADRS) completed by caregivers (VADRS-Caregivers) and teachers (VADRS-Teachers) and impairment on the Columbia Impairment Scale-Parent Version (CIS-P). Measures were completed at 5 assessments over 25 weeks.

Results Children in both service models improved. Children assigned to the telehealth service model improved significantly more than children in the augmented primary care arm for VADRS-Caregiver criteria for inattention ((chi)2[4] = 19.47, p <.001), hyperactivity ((chi)2[4] = 11.91, p =.02), combined ADHD ((chi)2[4] = 14.90, p =.005), ODD ((chi)2[4] = 10.05, p =.04), and VADRS-Caregiver role performance ((chi)2 [4] = 12.40, p =.01) and CIS-P impairment ((chi)2[4] = 20.52, p <.001). For the VADRS-Teacher diagnostic criteria, children in the telehealth service model had significantly more improvement in hyperactivity ((chi)2[4] = 11.28, p =.02) and combined ADHD ((chi)2[4] = 9.72, p =.045).

Conclusion The CATTS trial demonstrated the effectiveness of a telehealth service model to treat ADHD in communities with limited access to specialty mental health services.

Clinical trial registration information - Children's Attention Deficit Disorder With Hyperactivity (ADHD) Telemental Health Treatment Study; http://clinicaltrials.gov; NCT00830700.

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J Am Acad Child Adolesc Psychiatry. 2015;54:62-70.

TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND IRRITABILITY: RESULTS FROM THE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ADHD (MTA).

De La Cruz LF, Simonoff E, McGough JJ, et al.

Objective: Clinically impairing irritability affects 25% to 45% of children with attention-deficit/hyperactivity disorder (ADHD); yet, we know little about what interventions are effective in treating children with ADHD and co-occurring irritability. We used data from the Multimodal Treatment Study of Children With ADHD (MTA) to address 3 aims: to establish whether irritability in children with ADHD can be distinguished from other symptoms of oppositional defiant disorder (ODD); to examine whether ADHD treatment is effective in treating irritability; and to examine how irritability influences ADHD treatment outcomes.

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Neurocase. 2015.

THE EFFECT OF METHYLPHENIDATE ON SUSTAINED ATTENTION AMONG ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Lufi D, Bassin-Savion S, Rubel L.

Twenty-seven adolescents diagnosed as having attention-deficit hyperactivity disorder (ADHD) were tested twice with a computerized MATH-CPT (mathematics continuous performance test). In one administration, the participants took medication (methylphenidate, MPH) 1.5 hr before being tested. In another administration, the MATH-CPT was administered without the medication. Treatment with MPH improved the nulloverall attention levelnull and in measures of nullreaction timenull and nullimpulsivity.null MPH did not improve the performance in the four measures of sustained attention. Knowing that treatment with MPH does not improve sustained attention can be helpful in reaching a decision of whether or not a child should be treated with MPH.

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NeuroImage Clin. 2015;7:653-60.

ADHD SEVERITY IS ASSOCIATED WITH WHITE MATTER MICROSTRUCTURE IN THE SUBGENUAL CINGULUM.

Cooper M, Thapar A, Jones DK.

Aims This analysis examined hypothesised associations between microstructural attributes in specific white matter (WM) tracts selected a priori and measures of clinical variability in adolescents with a diagnosis of attention deficit hyperactivity disorder (ADHD). Firstly, associations were explored between WM microstructure and ADHD severity in the subgenual cingulum. Secondly, to ensure that tract-specific approaches afforded enhanced rather than differential sensitivity, associations were measured between WM microstructure and autistic traits in the right corticospinal tract based on results of a previously-published voxelwise analysis.

Methods 40 right-handed males aged 14-18 years (19 with DSM-IV combined type ADHD and 21 healthy controls) underwent a 60 direction diffusion MRI scan. Clinical ADHD and autism variation were assessed by validated questionnaires. Deterministic tractography based on spherical deconvolution methods was used to map the subgenual cingulum and corticospinal tract.

Results Fractional anisotropy was positively correlated and radial diffusivity was negatively correlated with a) ADHD severity in the left subgenual cingulum and b) autistic traits in the inferior segment of the right corticospinal tract. No case-control differences were found.

Conclusions Results shed light on possible anatomical correlates of ADHD severity and autistic symptoms in pathways which may be involved in the ADHD phenotype. They provide further evidence that tract-specific approaches may a) reveal associations between microstructural metrics and indices of phenotypic variability which would not be detected using voxelwise approaches, and b) provide improved rather than differential sensitivity compared to voxelwise approaches.

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NeuroMol Med. 2015.

CIRCULATING MICRORNA LET-7D IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wu LH, Peng M, Yu M, et al.

Up to date, there has been no molecular signature available in the clinical practice for attention-deficit/hyperactivity disorder (ADHD). To investigate circulating miRNA let-7d significance in ADHD, we investigated serum miRNA let-7d in 35 newly diagnosed ADHD subjects who were randomly selected from 406 patients out of 7450 children, paired with gender- and age-matched control through casenullcontrol study. We observed that circulating miRNA let-7d was significantly higher in ADHD subjects than in control ($p < 0.05$). Higher circulation level of miRNA let-7d was significantly associated with ADHD (odds ratio 16.7; 95 % confidence, $p < 0.05$). Meanwhile, serum galectin-3 level was down-regulated in ADHD subjects and the subjects with low galectin-3 expression accounted for 66 % in ADHD. The difference of the serum galectin-3 levels between ADHD and non-ADHD groups reached significance ($p < 0.05$). In 1-year follow-up, a significantly higher rate of clinical improvement was noted in subjects with low level of circulating miRNA let-7d ($p < 0.05$)

than those with high level of circulating miRNA let-7d. Our data demonstrated that miRNA let-7d was elevated in the serum of ADHD subjects, which might be a novel, useful molecule signature for ADHD.

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Neuropsychiatria i Neuropsychologia. 2014;9:120-26.

NEUROANATOMICAL AND FUNCTIONAL CORRELATES OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN THE LIGHT OF TWO DEVELOPMENTAL MODELS: DEVIANT BRAIN MATURATION VS. DEVELOPMENTAL LAG.

Giertuga KA, Cybulska-Klosowicz A.

Attention deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders among children. Worldwide prevalence of ADHD is estimated as about 5% of school-age children. ADHD is characterized by developmentally inappropriate levels of inattention, hyperactivity and impulsivity. Investigations on the etiology of ADHD highlight its heterogeneity and complexity. Many studies have examined its neuronal correlates. The most commonly used methods investigating the neurobiological basis of ADHD are EEG and fMRI/ sMRI. Results obtained with these methods have indicated altered brain activity and structure in ADHD subjects as compared to healthy children. Recent research indicates that ADHD is related to some developmental trends, since its symptoms change greatly over time. Nevertheless, there are divergent opinions whether ADHD is related to deviation in brain maturation or to maturation lag. The deviant brain maturation model assumes that the process of maturation is altered and leads to permanent impairment in ADHD subjects' brain anatomy and functionality. On the other hand, there are studies suggesting that ADHD is related to a lag in brain maturation. They assume that this pathological behavior is related to postponed maturation processes and that these will equalize to the level of healthy subjects when children become adults. This paper reviews the most recent reports concerning ADHD neuroimaging and interprets them in the context of the two above mentioned theories of ADHD.

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Nord J Psychiatry. 2015;69:216-23.

VALIDATION OF THE WORLD HEALTH ORGANIZATION ADULT ADHD SELF-REPORT SCALE FOR ADOLESCENTS.

Sonnby K, Skordas K, Olofsdotter S, et al.

Background: The World Health Organization Adult ADHD Self Report Scale (ASRS) is a widely used diagnostic tool for assessment of attention-deficit hyperactivity disorder (ADHD) symptoms in clinical psychiatry in Sweden. The ASRS consists of 18 questions, the first six of which can be used as a short screening version (ASRS-S). There is a version for adolescent - sASRS-Adolescent (ASRS-A) - and the corresponding screening version (ASRS-A-S), which has not been validated to date.

Aim: The aim was to validate the ASRS-A and the ASRS-A-S for use in adolescent clinical populations.

Methods: Adolescent psychiatric outpatients (n = 134, mean age 15 years, 40% boys) reported on the ASRS-A, and were interviewed with the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS), a semi-structured interview, together with a parent.

Results: Internal consistency was 0.79 for the ASRS-A-S and 0.92 for the ASRS-A (Cronbach's alpha). Internal consistency values were 0.79 and 0.87 for the inattention subscale, and 0.68 and 0.89 for the hyperactivity subscale, respectively. Concurrent validity values, measured with Spearman's correlation coefficient, between the total K-SADS ADHD symptom severity score and the sum of ASRS-A-S and ASRS-A total scores were 0.51 and 0.60, respectively. Psychometric properties of the ASRS-A-S and the ASRS-A were: sensitivity 74% and 79%; negative predictive value 81% and 84%; specificity 59% and 60%; and positive predictive value 49% and 51%, respectively. Both versions showed better properties for girls than for boys.

Conclusion: Both the ASRS-A-S and the ASRS-A showed promising psychometric properties for use in adolescent clinical populations.

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Pediatrics. 2015;135:e672-e677.

MEDICAL AUGMENTATION OF LABOR AND THE RISK OF ADHD IN OFFSPRING: A POPULATION-BASED STUDY.

Henriksen L, Wu CS, Secher NJ, et al.

BACKGROUND AND OBJECTIVE: Oxytocin for labor augmentation is widely used in obstetric care in Western countries. Two recent, smaller studies found opposing results regarding the association between prenatal exposure to oxytocin for labor augmentation and attentiondeficit/ hyperactivity disorder (ADHD). In Denmark, oxytocin is the medication used for nearly all medical augmentations of labor, and we examined the association between medical augmentation of labor and ADHD in a large cohort study based on national register data.

METHODS: All singletons born after spontaneous onset of labor in Denmark between 2000 and 2008 (N = 546 146) were included in the study. Data from the Danish Medical Birth Registry on medical augmentation of labor (yes/no) were used to identify exposed children. ADHD was defined based on the diagnostic codes of International Classification of Diseases, 10th Revision, for hyperkinetic disorder and information on dispensed ADHD medication. A multivariate proportional hazards regression model was used to test the association.

RESULTS: Among 546 146 deliveries, 26% included medical augmentation of labor, and 0.9% of the children were identified as having ADHD (n = 4617). We found no association between augmentation of labor and ADHD in the offspring (hazard ratio: 1.05 [95% confidence interval: 0.98-1.13]).

CONCLUSIONS: Our study does not support an association between medical augmentation of labor and ADHD in the child.

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Psychiatr Genet. 2015;25:59-70.

COPY NUMBER VARIANTS IN ATTENTION-DEFICIT HYPERACTIVE DISORDER: IDENTIFICATION OF THE 15Q13 DELETION AND ITS FUNCTIONAL ROLE.

Valbonesi S, Magri C, Traversa M, et al.

Objectives Evidence has supported a role for rare copy number variants in the etiology of attention-deficit hyperactivity disorder (ADHD), in particular, the region 15q13, which is also a hot spot for several neuropsychiatric disorders. This region spans several genes, but their role and the biological implications remain unclear.

Methods We carried out, for the first time, an analysis of the 15q13 region in an Italian cohort of 117 ADHD patients and 77 controls using the MLPA method, confirmed by a genome single-nucleotide polymorphism array. In addition, we probed for downstream effects of the 15q13 deletions on gene expression by carrying out a transcriptomic analysis in blood.

Results We found 15q13 deletions in two ADHD patients and identified 129 genes as significantly dysregulated in the blood of the two ADHD patients carrying 15q13 deletions compared with ADHD patients without 15q13 deletions. As expected, genes in the deleted region (KLF13, MTMR10) were downregulated in the two patients with deletions. Moreover, a pathway analysis identified apoptosis, oxidation reduction, and immune response as the mechanisms that were altered most significantly in the ADHD patients with 15q13 deletions. Interestingly, we showed that deletions in KLF13 and CHRNA7 influenced the expression of genes belonging to the same immune/inflammatory and oxidative stress signaling pathways.

Conclusion Our findings are consistent with the presence of 15q13 deletions in Italian ADHD patients. More interestingly, we show that pathways related to immune/inflammatory response and oxidative stress signaling are affected by the deletion of KFL13 and CHRNA7. Because the phenotypic effects of 15q13 are pleiotropic, our findings suggest that there are shared biologic pathways among multiple neuropsychiatric conditions.

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Psychiatry Clin Neurosci. 2015;69:161-70.

INCREASED PREFRONTAL HEMODYNAMIC CHANGE AFTER ATOMOXETINE ADMINISTRATION IN PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AS MEASURED BY NEAR-INFRARED SPECTROSCOPY.

Ota T, Iida J, Nakanishi Y, et al.

Aim Atomoxetine, approved in Japan for the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD) in April 2009, is a nonstimulant that is thought to act presynaptically via the inhibition of norepinephrine reuptake.

Near-infrared spectroscopy is a non-invasive optical tool that can be used to study oxygenation and hemodynamic changes in the cerebral cortex. The present study examined the effects of a clinical dose of atomoxetine on changes in prefrontal hemodynamic activity in children with ADHD, as measured by near-infrared spectroscopy using the Stroop Color-Word Task.
Methods Ten children with ADHD participated in the present study. We used 24-channel near-infrared spectroscopy to measure the relative concentrations of oxyhemoglobin in the frontal lobes of participants in the drug-naive condition and those who had received atomoxetine for 8 weeks. Measurements were conducted every 0.1 s during the Stroop Color-Word Task. We used the ADHD Rating Scale-IV-Japanese version (Home Version) to evaluate ADHD symptoms.
Results We found a significant decrease in ADHD Rating Scale-IV-Japanese version scores, from 30.7 to 22.6 (P = 0.003). During the Stroop Color-Word Task, we found significantly higher levels of oxyhemoglobin changes in the prefrontal cortex of participants in the atomoxetine condition compared with those in the drug-naive condition.
Conclusions This increase in oxyhemoglobin changes might indicate an intensified prefrontal hemodynamic response induced by atomoxetine. Near-infrared spectroscopy is a sensitive tool for measuring the pharmacological effects of atomoxetine in children with ADHD.

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Psychiatry Res Neuroimaging. 2015.
ABNORMALITIES OF STRUCTURAL COVARIANCE NETWORKS IN DRUG-NAIVE BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Li X, Cao Q, Pu F, et al.
The aim of this study is to investigate whether the anatomical organization of large-scale brain systems would change in ADHD patients compared to healthy controls. We utilized a structural covariance network (SCN) mapping approach to investigate large-scale networks in 30 drug-naive ADHD boys and 30 gender- and age-matched controls. The regions showing significant between-group differences in gray matter (GM) volume were defined as seed regions of interest. Then, the SCNs derived from these seeds were statistically compared between ADHD and controls. Significant regional GM volume decreases (P<0.05, corrected) were observed in the right insula and the right orbito-frontal cortex (OFC) in ADHD relative to controls. Both SCNs derived from these two seeds showed more localized topology in ADHD group. Furthermore, significantly decreased structural connectivity were found between insula and right hippocampus, bilateral olfactory cortex, and between OFC and bilateral caudate nucleus (P<0.05, corrected) in ADHD group. Significantly increased association was observed between insula and left middle temporal gyrus (P<0.05, corrected) in ADHD group. Taken together, our results reveal abnormal regional brain anatomy as well as aberrant structural covariance networks in ADHD, supporting previous findings of dysfunction in distributed network organization in patients with ADHD.

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Psychiatry Res Neuroimaging. 2015.
RELATIONSHIP BETWEEN WHITE MATTER MICROSTRUCTURE ABNORMALITIES AND ADHD SYMPTOMATOLOGY IN ADOLESCENTS.
Witt ST, Stevens MC.
The present study sought to evaluate whether white matter microstructure abnormalities observed in a cohort of adolescents with attention-deficit/hyperactivity disorder (ADHD) have specific relationships with either or both Hyperactivity/Impulsivity and Inattentive ADHD symptom domains that would support a dimensional view of ADHD as adopted in the DSM-V. Diffusion tensor imaging (DTI) data were acquired on 22 adolescents diagnosed with ADHD. Multiple regression analyses were performed to determine whether scalar DTI measures in 13 tracts-of-interest demonstrated meaningful associations with Hyperactivity/Impulsivity or Inattentive symptom severity. Fractional anisotropy and radial diffusivity measures of white matter integrity exhibited significant linear relationships with Hyperactivity/Impulsivity and Inattentive symptom severity. However, only radial diffusivity in the right superior longitudinal fasciculus was specifically linked to Inattentive symptom severity and not Hyperactivity/Impulsivity symptom severity. Our results provide preliminary evidence that symptom

domains in ADHD are linked to neuroanatomical substrates and confirm the value in examining ADHD from a dimensional perspective.

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Psychiatry Res. 2015;226:425-33.

ASSOCIATION OF NOREPINEPHRINE TRANSPORTER (NET, SLC6A2) GENOTYPE WITH ADHD-RELATED PHENOTYPES: FINDINGS OF A LONGITUDINAL STUDY FROM BIRTH TO ADOLESCENCE.

Hohmann S, Hohm E, Treutlein J, et al.

Variation in the gene encoding for the norepinephrine transporter (NET, SLC6A2) has repeatedly been linked with ADHD, although there is some inconsistency regarding the association with specific genes. The variants for which most consistent association has been found are the NET variants rs3785157 and rs28386840. Here, we tested for their association with ADHD diagnosis and ADHD-related phenotypes during development in a longitudinal German community sample. Children were followed from age 4 to age 15, using diagnostic interviews to assess ADHD. Between the ages of 8 and 15 years, the Child Behavior Checklist (CBCL) was administered to the primary caregivers. The continuous performance task (CPT) was performed at age 15. Controlling for possible confounders, we found that homozygous carriers of the major A allele of the functional promoter variant rs28386840 displayed a higher rate of ADHD lifetime diagnosis. Moreover, homozygous carriers of the minor T allele of rs3785157 were more likely to develop ADHD and showed higher scores on the CBCL externalizing behavior scales. Additionally, we found that individuals heterozygous for rs3785157 made fewer omission errors in the CPT than homozygotes. This is the first longitudinal study to report associations between specific NET variants and ADHD-related phenotypes during the course of development.

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Psychiatry Res. 2015;226:515-16.

FASTING BLOOD GLUCOSE AND HBA1C IN CHILDREN WITH ADHD.

Lindblad F, Eickhoff M, Forslund AH, et al.

Reports of hypocortisolism and overweight in pediatric ADHD motivate an investigation of blood glucose regulation in this group. Fasting blood glucose and HbA1c were investigated in 10 children (10-15 years) with ADHD and 22 comparisons. Fasting blood glucose was similar in both groups. HbA1c values were higher in the ADHD-group. BMI-SDS was also higher in the ADHD-group but did not predict HbA1c. The results suggest an association between ADHD and an altered blood glucose homeostasis.

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Psychiatry Res. 2015;226:507-12.

MATERNAL PSYCHIATRIC HISTORY IS ASSOCIATED WITH THE SYMPTOM SEVERITY OF ADHD IN OFFSPRING.

Lopez SF, Aguado-Gracia J, Mundo-Cid P, et al.

Controversy exists about the role of parent psychopathology in persistence and severity of attention deficit hyperactivity disorder (ADHD) symptoms in their children. Here we aimed to analyse the potential association between the severity of ADHD symptoms in children and the presence of psychiatric and ADHD symptoms in their biological parents. Seventy-three triads of children and their parents who were in active treatment for their diagnosed ADHD were evaluated in our Child and Adolescent Mental Health Centers. The mental health of the parents was also assessed. The general psychopathology of the parents was evaluated using the Symptom Checklist-90-R (SCL-90-R), and symptoms of hyperactivity were examined using the Adult ADHD Self-Report Scale (ASRS v.1.1). The severity of symptoms in children was assessed using the ADHD Rating Scale-IV (ADHD-RS-IV). Variables that could have affected the clinical development of ADHD such as sex, evolution time, age, academic level and the presence of comorbidities were controlled. The severity of the symptoms in children with ADHD was significantly related to the psychiatric history of their mother, the younger age of the child and

the presence of a comorbid conduct disorder in the child. We discussed the importance of screening for parental psychopathology in clinical practice.

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Psychol Assess. 2015.

DISC PREDICTIVE SCALES (DPS): FACTOR STRUCTURE AND UNIFORM DIFFERENTIAL ITEM FUNCTIONING ACROSS GENDER AND THREE RACIAL/ETHNIC GROUPS FOR ADHD, CONDUCT DISORDER, AND OPPOSITIONAL DEFIANT DISORDER SYMPTOMS.

Wiesner M, Windle M, Kanouse DE, et al.

The factor structure and potential uniform differential item functioning (DIF) among gender and three racial/ethnic groups of adolescents (African American, Latino, White) were evaluated for attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) symptom scores of the DISC Predictive Scales (DPS; Leung et al., 2005; Lucas et al., 2001). Primary caregivers reported on DSM-IV ADHD, CD, and ODD symptoms for a probability sample of 4,491 children from three geographical regions who took part in the Healthy Passages study (mean age = 12.60 years, SD = 0.66). Confirmatory factor analysis indicated that the expected 3-factor structure was tenable for the data. Multiple indicators multiple causes (MIMIC) modeling revealed uniform DIF for three ADHD and 9 ODD item scores, but not for any of the CD item scores. Uniform DIF was observed predominantly as a function of child race/ethnicity, but minimally as a function of child gender. On the positive side, uniform DIF had little impact on latent mean differences of ADHD, CD, and ODD symptomatology among gender and racial/ethnic groups. Implications of the findings for researchers and practitioners are discussed.

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Psychol Assess. 2015.

INTEGRATION OF SYMPTOM RATINGS FROM MULTIPLE INFORMANTS IN ADHD DIAGNOSIS: A PSYCHOMETRIC MODEL WITH CLINICAL UTILITY.

Martel MM, Schimmack U, Nikolas M, et al.

The Diagnostic and Statistical Manual of Mental Disorder-Fifth Edition explicitly requires that attention-deficit/hyperactivity disorder (ADHD) symptoms should be apparent across settings, taking into account reports from multiple informants. Yet, it provides no guidelines how information from different raters should be combined in ADHD diagnosis. We examined the validity of different approaches using structural equation modeling (SEM) for multiple-informant data. Participants were 725 children, 6 to 17 years old, and their primary caregivers and teachers, recruited from the community and completing a thorough research-based diagnostic assessment, including a clinician-administered diagnostic interview, parent and teacher standardized rating scales, and cognitive testing. A best-estimate ADHD diagnosis was generated by a diagnostic team. An SEM model demonstrated convergent validity among raters. We found relatively weak symptom-specific agreement among raters, suggesting that a general average scoring algorithm is preferable to symptom-specific scoring algorithms such as the "or" and "and" algorithms. Finally, to illustrate the validity of this approach, we show that averaging makes it possible to reduce the number of items from 18 items to 8 items without a significant decrease in validity. In conclusion, information from multiple raters increases the validity of ADHD diagnosis, and averaging appears to be the optimal way to integrate information from multiple raters.

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Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2015;6:13-18.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Badpa S, Hosseinian T, Zarin F.

Attention deficit hyperactivity disorder (ADHD) is a syndrome in early childhood recognized as an important social-medical problem that appears with symptoms such as hyperactivity, impulsivity, inattention, perception, cognition and behavioral disturbances. The symptoms effect on patient personal and social functioning. Studies

show greater impairment among boys than in girls, that with negligence in treating, the disease will continue into adulthood.

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Rev Neurol. 2015;60:S75-S80.

NEUROFUNCTIONAL DIFFERENCES IN THE P300 FREQUENCY FOR MULTI-SENSORY STIMULATION IN KIDS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Soria-Claros AM, Serrano I, Serra A, et al.

Introduction. Attention deficit/hyperactivity disorder (ADHD) is characterized by inattention, motor hyperactivity, impulsivity, or a combination of all. The P300 is a non-invasive neurophysiological that has shown its effectiveness to detect differences between subjects with ADHD but results are not yet conclusive.

Aim. To assess brain information processing by the P300 component, auditory, visual and tactile modality in children with ADHD. Subjects and methods. The P300 components auditory, visual and tactile 17 children with ADHD (11 combined and 7 inattentive) and 15 control children aged between 7 and 10 years were recorded.

Results. In response reaction times found a more pronounced trend in the auditory and visual time but not statistically significant in any of the three responses. In the error rate increased in children with ADHD compared to the control group. Children with ADHD have a significant increase in latency of visual P300 wave while there is no significant decrease in tactile and auditory P 300. We found increased cortical areas in the P300 component in children with ADHD during visual and auditory test, but not touch.

Conclusions. Our results support the hypothesis of the existence of increased brain areas during auditory and visual sensory processing in ADHD group, except for tactile stimulation happens otherwise.

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Rev Neurol. 2015;60:S69-S74.

EMOTIONAL SELF-REGULATION IN INFANTILE ATTENTION DEFICIT HYPERACTIVITY DISORDER AND P300 EVOKED POTENTIALS.

Roca P, Mulas F, Ortiz-Sanchez P, et al.

Introduction. The difficulties that patients with attention deficit hyperactivity disorder (ADHD) have when it comes to emotional regulation have aroused a great deal of interest in recent years and there is a line of research working on the identification of the neurophysiological correlates.

Aims. To analyse measures of emotional functioning and their correlation with the P300 component in a sample of children with ADHD with and without treatment.

Patients and methods. The sample was made up of 71 children with ADHD, almost half of whom were taking some form of medication. The auditory potential P300 was analysed. The parents filled in a scale to assess executive behaviour at home, the Behaviour Rating Inventory of Executive Function (BRIEF), which the emotional self-regulation index and the emotional expression scale were taken from.

Results. Significant correlations were found between the amplitude of the P300 and the emotional self-regulation index from the version of the BRIEF for preschoolers, and a relation was observed between P300 latency and the severity of the symptoms.

Conclusions. The results highlight the usefulness of evoked potentials for the study of executive correlates and associated conditions in the day-to-day functioning of children with ADHD.

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Rev Neurol. 2015;60:S115-S120.

COGNITIVE-BEHAVIOURAL GUIDANCE INTERVENTIONS IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Valls-Llagostera C, Vidal R, Abad A, et al.

Introduction. Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that may become manifest at any time in life. In 50-70% of children diagnosed with the disorder it presents in adolescence. Young

people with ADHD have high rates of comorbidity with other psychiatric disorders and a high degree of functional compromise.
Aims. To review the literature on cognitive-behavioural interventions that have been applied to the treatment of ADHD in adolescence.
Development. The studies that have been conducted on psychological treatment to date were reviewed, and the interventions were classified into: psychosocial treatments, mindfulness therapy and cognitive-behavioural treatment (individual and in groups). The only study on cognitive-behavioural therapy for adolescents with ADHD is also reviewed, as well as a new intervention protocol for application to groups designed at the Hospital Universitari Vall dnullHebron.
Conclusions. Although there has been a recent increase in the number of publications dealing with the psychological treatment of ADHD in adolescents, there is a need for a greater development of intervention protocols and studies on their efficacy/effectiveness.

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Rev Neurol. 2015;60:S8-S13.

CHANGE IN THE THERAPEUTIC STRATEGY WHEN FACED WITH AN INADEQUATE RESPONSE TO THE PHARMACOLOGICAL TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gandia-Beneto R, Mulas F, Roca P, et al.

Introduction. Attention deficit hyperactivity disorder (ADHD) is a disorder of a biological origin affecting the neurodevelopment of the brain. It is estimated that 3-7% of school-age children present ADHD. The most commonly used pharmacological treatments are amphetamines and methylphenidate (MPH). Although response rates to MPH are high, full remission rates reach only 56%. The 25% of patients who do not respond to MPH would show a response to other stimulants and vice-versa.
Aims. To clinically evaluate patients by detecting inadequate responses and the efficacy of a change to lisdexamfetamine dimesylate (LDX). Patients and methods. The study was prospective and observation-based. Inadequate responses were considered to be those that presented non-coverage or no effect. The Attention-Deficit/Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV) and Clinical Global Impression-Severity (CGI-S) assessment scales were used for the clinical assessment, together with the Weiss Functional Impairment Rating Scale (WFIRS) and the Child Health and Illness Profile (CHIP-AE). Data regarding adverse side effects were also collected.
Results. Forty-one patients met criteria for inadequate response to treatment: 13.6 (plus or minus) 3.4 years, 54.6 (plus or minus) 13.2 kg, 158.5 (plus or minus) 17.2 cm and body mass index of 20.9 (plus or minus) 3.5 kg/m2. Reasons for change (non-exclusive): non-coverage (76%), lack of intensity of effect (68%) and presence of adverse side effects with the previous medication (16%). The mean score both at baseline and at nine months, on the ADHD-RS, was 24.54 (plus or minus) 6.3 versus 12.01 (plus or minus) 3.2 ($p < 0.01$), respectively, and for the CGI-S values were 5.09 (plus or minus) 0.5 versus 2.91 (plus or minus) 0.8 ($p < 0.01$), respectively. The safety profile coincided with that of other stimulant-based treatments for ADHD.
Conclusions. When the response to MPH presents non-coverage or lack of effect, changing to LDX has proved to be effective, with an improvement in 86.7% of cases, which is similar to that of other studies. It is therefore a good therapeutic option in these patients.

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Riv Psichiatr. 2015;50:34-37.

SCQ AS A TOOL FOR SCREENING ASD COMORBIDITIES WITH ADHD.

De GA, De GC, Balducci R, et al.

The aim of the study is to evaluate the effectiveness of the Social Communication Questionnaire (SCQ) to early recognize autistic spectrum disorder (ASD) patients with a comorbidity of attention deficit hyperactivity disorder (ADHD). The SCQ is a 40 items questionnaire developed as a screening tool for ASD in children, with yes/no questions (presence of symptoms with a score of 1/ absence of symptoms with a score of 0) and a risk cutoff. We have analyzed 75 questionnaires completed by both parents of the 75 children referred to the Child Neuropsychiatry Unit of the "Aldo Moro" University of Bari for a psychopathological assessment. These patients

received a diagnosis of ASD with a comorbidity of ADHD (24) or without a comorbidity with ADHD (51). Results indicate a higher score of SCQ in patients with overlap diagnosis rather than patients with pure ASD. In particular, the items with a higher frequency are deficit in sociability, empathy and impulse control. Furthermore, patients with intellectual disabilities have a higher score. Findings highlight the use of the SCQ in the assessment of ASD population to early detect potential comorbidity with ADHD.

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Seizure. 2015;25:80-83.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND INTERICTAL EPILEPTIFORM DISCHARGES: IT IS SAFE TO USE METHYLPHENIDATE'.

Socanski D, Aurlien D, Herigstad A, et al.

Purpose This study investigated whether interictal epileptiform discharges (IED) on a baseline routine EEG in children with ADHD was associated with the occurrence of epileptic seizures (Sz) or influenced the use of methylphenidate (MPH) during 2 years follow-up.

Methods A retrospective chart-review of 517 ADHD children with EEG revealed IED in 39 cases. These patients (IED group) were matched on age and gender with 39 patients without IED (non-IED group). We measured at baseline, 1 year and 2 years Sz occurrence, the use of MPH and antiepileptic drug (AED).

Results At baseline, 12 patients in the IED group had active epilepsy and three of them had Sz during the last year. 36 (92.3%) patients were treated with MPH. Initial positive response to MPH was achieved in 83.3% compared with 89.2% in the non-IED group. At 1 and 2 years follow-up, three patients who also had Sz at baseline and difficult to treat epilepsy, had Sz, without changes in seizure frequency. We found no statistically significant differences between the groups with respect to MPH use at 1 year and at 2 years. Ten patients from IED group, who did not have confirmed epilepsy diagnosis, temporarily used AEDs during the first year of follow-up.

Conclusion Despite the occurrence of IED, the use of MPH was safe during 2 years follow-up. IED predict the Sz occurrence in children with previous epilepsy, but does not necessarily suggest an increased seizure risk. A caution is warranted in order not to overestimate the significance of temporarily occurrence of IED.

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Sleep Med. 2011;12:S49.

CIRCADIAN TENDENCIES AND BEHAVIOURAL FACTORS AS PREDICTORS OF BED TIME RESISTANCE AND SLEEP ONSET INSOMNIA AMONG CHILDREN WITH ADHD.

Bergmame L, Banu C, Michaelsen S, et al.

Introduction and Objectives: Studies indicate a higher prevalence of sleep problems among children with ADHD compared to controls; however, the specific association between sleep and ADHD remains unclear. Biological and behavioural factors are proposed as potential mechanisms for nullgoingto- sleepnull issues among children with ADHD. The objective of this study was, therefore, to investigate the relative contributions of behavioural problems (externalization) and circadian tendencies to bedtime resistance and Sleep Onset Insomnia among children with ADHD and controls.

Materials and Methods: Participants with ADHD (N = 26) were asked to discontinue stimulant medication, and all participants (N = 75; aged 7 to 11) were asked to avoid caffeinated products 48 hours before evaluation. Parents completed the Child Sleep Habits Questionnaire, and documented their child's bedtime routine over four nights using sleep logs. On the fifth night, sleep was recorded using ambulatory assessment of sleep architecture afforded by portable polysomnograph (PSG) equipment (Vitaport-3 System). Circadian tendency was evaluated with the Child Morning-Evening Preference Scale and externalizing problems were assessed using the Child Behaviour Check List.

Results: Regression analyses revealed that externalizing problems contributed significantly to bedtime resistance (Beta = 0.35, $p=0.01$), whereas evening circadian tendency contributed to both parental reports of sleep onset delay (Beta = -0.49, $p<0.001$), and PSG-measured sleep-onset latency (Beta = -0.46, $p<0.001$) in both groups.

Conclusion: The results demonstrated that children's behavioural problems and circadian tendencies contributed to different bedtime issues, suggesting that bedtime problems vary in etiology. Moreover, they emphasize the need for accurate diagnoses of sleep problems. A better understanding of these factors is needed to further the development of more effective intervention strategies for such children.

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Sleep Med. 2011;12:S18-S19.

SELF-REPORTED SLEEP PROPLEMS AND NEUROPSYCHOLOGICAL PERFORMANCE IN ADHD.

Fisher B, Garges D, Fulda S.

Introduction and Objectives: To explore the impact of self-reported sleep problems (disturbed sleep and hypersomnia/sleepiness) on neuropsychological performance in subjects with ADHD without a diagnosed sleep disorder.

Materials and Methods: Retrospective chart review of 607 adults and adolescents (15-73 years, 229 females, 378 males) with diagnosed ADHD (Inattentive Type) and without diagnosed sleep disorder or brain injury/ insult. Neuropsychological tests used the Trail Making Tests, the Stroop test and the SDMT-W. Self-reported problems initiating ormaintaining sleep (sleep disturbance) and hypersomnia or sleepiness were extracted from the Personal History Checklist for Adults. Univariate ANOVAs were used to assess the effect of sleep problems while controlling for age, sex, depression, anxiety, and pre-morbid intelligence level (NART-R).

Results: Self-reported sleep problems had no influence on performance in the Trails Making-B, Stroop test or SDMT-W. Subjects with self-reported problems initiating or maintaining sleep performed worse on the Trail Making-A ($F(1,601)=8.77$, $p=0.003$).

Conclusion: Self-reported sleep problems in ADHD had an impact only on a speeded sequencing measure. There was no impact seen on a measure of whole brain functioning that is also dependent upon speed. Similarly, there was no influence seen on a task of divided attention measuring distractibility or a task of cognitive flexibility that assesses executive function when controlling for age, gender, depression, anxiety and pre-morbid intelligence. While we have found that more ADHD subjects report sleep problems, these problems were found to influence performance on only one of the test measures assessed, which is a task highly dependent upon speed.

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Sleep Med. 2011;12:S50.

EXAMINING SLEEP ARCHITECTURE IN CHILDREN WITH ADHD, AND THEIR TYPICALLY DEVELOPING PEERS.

Benoit A, Richards J, Corkum P.

Introduction and Objectives: Over the last 30 years, various polysomnography (PSG) sleep studies have found inconsistent results when comparing the EEG sleep architecture profiles of children diagnosed with ADHD and their typically developing (TD) peers (e.g., Sadeh, 2007). Nevertheless, methodological issues (e.g., participant medication status, co-morbidities) could have accounted for the published studies' non-significant group differences. Therefore, the present study used PSG technology to analyze sleep quality and sleep architecture variables of a medication-naive, rigorously diagnosed sample of children aged 6 - 12 years with ADHD, comparative to their TD peers.

Materials and Methods: The (n=15) children who comprised the ADHD sample had (1) a new diagnosis of ADHD based on a comprehensive clinical diagnostic assessment, (2) were medication-naive, and (3) had not been diagnosed with another primary mental health disorder known to impact sleep (e.g., depression, anxiety disorder). The (n=15) children who comprised the TD sample were not diagnosed with any mental health disorderconfirmed through parent-completed rating scales. All PSG testing was performed at the Chronobiology Laboratory in the Department of Psychiatry at the QEII HSC in Halifax.

Results: Multivariate analysis (MANOVA) revealed significant differences in both sleep quality and sleep architecture between ADHD and TD groups. Specifically, children in the ADHD group had a significantly longer latency to REM sleep, significantly fewer REM cycles, as well as significantly less Stage 1 sleep than TD peers. Also, children in the ADHD sample had significantly larger sleep onset values, but also had significantly shorter sleep duration values than their TD peers.

Conclusion: These results provide evidence to suggest children with ADHD may have underlying etiological issues regulating sleep architecture patterns compared to TD peers.

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Lancet. 2015.

MORTALITY IN CHILDREN, ADOLESCENTS, AND ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NATIONWIDE COHORT STUDY.

Dalsgaard S, Otergaard SD, Leckman JF, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common mental disorder associated with factors that are likely to increase mortality, such as oppositional defiant disorder or conduct disorder, criminality, accidents, and substance misuse. However, whether ADHD itself is associated with increased mortality remains unknown. We aimed to assess ADHD-related mortality in a large cohort of Danish individuals.

Methods: By use of the Danish national registers, we followed up 1(middle dot)92 million individuals, including 32 061 with ADHD, from their first birthday through to 2013. We estimated mortality rate ratios (MRRs), adjusted for calendar year, age, sex, family history of psychiatric disorders, maternal and paternal age, and parental educational and employment status, by Poisson regression, to compare individuals with and without ADHD.

Findings: During follow-up (24(middle dot)9 million person-years), 5580 cohort members died. The mortality rate per 10 000 person-years was 5(middle dot)85 among individuals with ADHD compared with 2(middle dot)21 in those without (corresponding to a fully adjusted MRR of 2(middle dot)07, 95% CI 1(middle dot)70-2(middle dot)50; p<0(middle dot)0001). Accidents were the most common cause of death. Compared with individuals without ADHD, the fully adjusted MRR for individuals diagnosed with ADHD at ages younger than 6 years was 1(middle dot)86 (95% CI 0(middle dot)93-3(middle dot)27), and it was 1(middle dot)58 (1(middle dot)21-2(middle dot)03) for those aged 6-17 years, and 4(middle dot)25 (3(middle dot)05-5(middle dot)78) for those aged 18 years or older. After exclusion of individuals with oppositional defiant disorder, conduct disorder, and substance use disorder, ADHD remained associated with increased mortality (fully adjusted MRR 1(middle dot)50, 1(middle dot)11-1(middle dot)98), and was higher in girls and women (2(middle dot)85, 1(middle dot)56-4(middle dot)71) than in boys and men (1(middle dot)27, 0(middle dot)89-1(middle dot)76).

Interpretation: ADHD was associated with significantly increased mortality rates. People diagnosed with ADHD in adulthood had a higher MRR than did those diagnosed in childhood and adolescence. Comorbid oppositional defiant disorder, conduct disorder, and substance use disorder increased the MRR even further. However, when adjusted for these comorbidities, ADHD remained associated with excess mortality, with higher MRRs in girls and women with ADHD than in boys and men with ADHD. The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents.

Funding: This study was supported by a grant from the Lundbeck Foundation.

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Z Kinder- Jugendpsychiatr Psychother. 2015;43:133-44.

CLINICAL DIAGNOSTICS OF ADHD IN PRESCHOOL-AGED CHILDREN.

Merkt J, Petermann F.

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in childhood and adolescence and has many negative consequences for both the child and the family. Early identification of children with ADHD would be helpful for the prevention of long-term consequences. This review appraises questionnaires and clinical interviews that can be used for the diagnosis of ADHD in preschool-aged children (3-5 years). We compare and discuss both German and international methods. The role of questionnaires and clinical interviews in the diagnostic process of ADHD is discussed.

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Zh Nevrologii Psihiatrii im S S Korsakova. 2014;2014:112-15.

EMOTIONAL DISORDERS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Chutko LS, Yu SS, Bondarchuk YL.

The article presents an overview of scientific publications devoted to the study of epidemiology, etiology, clinical manifestations and basic approaches to the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children. An analysis of the results shows a high frequency of comorbidity between ADHD and emotional disorders (anxiety) that determines the severity of the main clinical symptoms and leads to severe social maladaptation. Inclusion of anxiolytics and nootropics in treatment of ADHD is required.

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Zh Nevrologii Psihiatrii im S S Korsakova. 2014;2014:19-24.

THE RESULTS OF THE PHARMACOLOGICAL TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: EVALUATION WITH NEUROPSYCHOLOGICAL METHODS.

Zavadenko NN, Suvorinova NY.

To investigate the dynamics of behavioral indicators, attention and memory in children with attention deficit hyperactivity disorder (ADHD) treated with noofen (capsules 250 mg).

Material and method. In an open study, 50 patients were randomized to 2 equal groups: patients of group 1 were treated with noofen (15null20 mg/kg (500null700 mg) per day perorally in 2null3 doses); the control group received low doses of multivitamins. Duration of treatment was one month.

Results. The results of neuropsychological testing revealed the improvement of cognitive functions, including the indicators of self-control, sustained, directed and divided attention, acoustic-verbal memory, to the end of treatment.

Conclusion. The initial positive changes may be the basis for obtaining better clinical results during long-term treatment.

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REVIEW ARTICLE
METABOLIC BRAIN MAPPING

MR Imaging–Detectable Metabolic Alterations in Attention Deficit/Hyperactivity Disorder: From Preclinical to Clinical Studies

L. Altabella, F. Zoratto, W. Adriani, and R. Canese

ABSTRACT

MR spectroscopy represents one of the most suitable in vivo tool to assess neurochemical dysfunction in several brain disorders, including attention deficit/hyperactivity disorder. This is the most common neuropsychiatric disorder in childhood and adolescence, which persists into adulthood (in approximately 30%–50% of cases). In past years, many studies have applied different MR spectroscopy techniques to investigate the pathogenesis and effect of conventional treatments. In this article, we review the most recent clinical and preclinical MR spectroscopy results on subjects with attention deficit/hyperactivity disorder and animal models, from childhood to adulthood. We found that the most investigated brain regions were the (pre)frontal lobes and striatum, both involved in the frontostriatal circuits and networks that are known to be impaired in this pathology. Neurometabolite alterations were detected in several regions: the NAA, choline, and glutamatergic compounds. The creatine pool was also altered when an absolute quantitative protocol was adopted. In particular, glutamate was increased in children with attention deficit/hyperactivity disorder, and this can apparently be reversed by methylphenidate treatment. The main difficulties in reviewing MR spectroscopy studies were in the nonhomogeneity of the analyzed subjects, the variety of the investigated brain regions, and also the use of different MR spectroscopy techniques. As for possible improvements in future studies, we recommend the use of standardized protocols and the analysis of other brain regions of particular interest for attention deficit hyperactivity disorder, like the hippocampus, limbic structures, thalamus, and cerebellum.

ABBREVIATIONS: ACC = anterior cingulate cortex; ADHD = attention deficit/hyperactivity disorder; Cho = total choline (phosphorylcholine + glycerolphosphorylcholine); GABA = γ-aminobutyric acid; PFC = prefrontal cortex; PRESS = point-resolved spectroscopy sequence; tCr = total creatine (creatine + phosphorylcreatine)

Attention deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disease in children and adolescents. Marked differences in the ADHD prevalence are thought to exist among countries. In fact, the estimated prevalence is 4%–7% in the United States and 1%–3% in Europe.[1] ADHD, which is 2–4 times more frequent in males than in females, is characterized by traits of inattention, impulsivity, and motor hyperactivity. These can significantly impact many aspects of behavior in children and adolescents and can affect their performance, both at school and at home.[2]

The symptoms of ADHD have a negative impact on the individual throughout childhood, adolescence, and well into adult life, especially if not managed optimally. In approximately 80% of children with ADHD, symptoms persist into adolescence and may persist into adulthood in approximately 30%–50% of cases. ADHD adolescents and adults retain from infancy the traits of inattention and impulsivity. Moreover, they start to show a propensity for sensation-seeking and risk-taking and are more likely to develop substance abuse and pathologic dependence from risky activities, including gambling. ADHD is classically considered an executive dysfunction characterized by poor decision-making.[2] However, it can also be viewed as a motivational dysfunction, arising from altered processing of reward values by the frontostriatal circuits, characterized by attempts to escape or avoid any situation that requires procrastination, such as waiting for the mere elapsing of time, slow gathering of information, active withholding of impulses, and prolonged focusing of attention.[1,3] From this perspective, ADHD may be a consequence of a psychological inability to give a correct account of and to represent mentally a reward that is not immediately present or accessible. Subjects with ADHD show, as well, diminished concerns for the potential risk of any unforeseen interference and/or negative unexpected outcome. These deficits in cognitive control and/or

Received April 16, 2013; accepted after revision June 14.

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This work was funded by ERA-net "NeuroGenMRI" (to W.A.).

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http://dx.doi.org/10.3174/ajnr.A3843

motivation, usually seen in children with ADHD, highlight the importance of the disruption of the dopaminergic and serotonergic systems in this syndrome.[4] The variability of ADHD subpopulations reported in the medical literature may be partly due to differences in the relative dysfunction between the dopamine and serotonin systems.[1,5]

The diagnosis is based on behavioral observation and semistructured interviews; it does not imply a biologic marker or other objective evidence. Thus, the symptoms of ADHD are difficult to define unequivocally because it is difficult to determine where normal levels of inattention, hyperactivity, and impulsivity end and clinically significant levels (requiring medical intervention) begin. Additionally, the same symptoms can be difficult to differentiate from those indicative of other disorders.

Appropriate management has a significant impact on the symptoms of ADHD. Management options include educational strategies, behavioral treatments, and medical pharmacotherapy. Psychostimulant medications are the treatment of first choice. When nonpharmacologic psychotherapy–based approaches (recommended in those who display mild symptoms) do not succeed in relieving ADHD symptoms and psychostimulant drugs are prescribed, a clear benefit derives from the treatment. Methylphenidate and atomoxetine are the most frequently prescribed drugs for the treatment of ADHD.[6,7] While such pharmacologic therapy has been shown to improve behavior for the short-term, persistent benefits or adverse effects are largely unknown because of the lack of long-term follow-up studies.

Several brain areas have been identified as abnormal in ADHD. MR imaging offers reliable and noninvasive methods to study in vivo brain morphology and neurochemical compounds.

MR Spectroscopy

Based on MR imaging, there have been findings of volumetric and functional brain abnormalities in subjects with ADHD reported in the literature.[8] The volumetric abnormalities involve the frontostriatal network, also with a widespread reduction in the volume of the total cerebrum and cerebellum, in particular for children. More recent reviews considered the dysfunction of the cingulofrontal-parietal cognitive-attention network[9] as well as a deficit in timing functions[10] in subjects with ADHD. In this framework, MR spectroscopy can also play an important role in the understanding of the pathogenetic mechanisms that are the basis of this disorder.

Studies of psychiatric diseases are perhaps the most challenging applications of MR spectroscopy because they require stable and reproducible measurements of minute alterations in metabolite concentration. Moreover, MR spectroscopy is a safe, noninvasive in vivo technique for investigating biochemical and metabolic brain features, without the use of radioactive tracers. ^{1}H-MR spectroscopy can detect and, in particular conditions, quantify several metabolites from a specific brain region. The most relevant MR imaging–detectable neurometabolites are alanine, aspartate, creatine, γ-aminobutyric acid (GABA), glucose, glutamate, glutamine, glycerol-phosphoryl-choline, guanidoacetate, phosphoryl-choline, myo-Inositol, lactate, *N*-acetylaspartate, *N*-acetylaspartylglutamate, phosphor-creatine, scyllo-Inositol, and taurine. At conventional clinical magnetic fields, metabolites that have resonances overlapping or very close are also given as their sum: total choline (Cho; phosphorylcholine + glycerol-phosphorylcholine), Glx (glutamate + glutamine), total creatine (tCr; creatine + phosphorylcreatine).

Different spectroscopic localizing techniques have been developed in the past—from the single-voxel ^{1}H-MR spectroscopy techniques[11] to the 2D or 3D MR spectroscopy imaging (MR spectroscopy), also called chemical shift imaging.[12] The former, stimulated echo acquisition mode and point-resolved spectroscopy sequence (PRESS), are the most used MR spectroscopy techniques because they reveal neurometabolites from an a priori chosen localized region. Furthermore, the quantification of metabolite contents is expressed not only as a ratio, usually with respect to tCr, but also as an absolute concentration if a quantitative protocol is applied.[13,14] On the other hand, chemical shift imaging allows investigating a wider region (a section or a slab) compared with single-voxel techniques as well as comparing different regions of interest within the selected section during postprocessing, but quantification is more critical and usually ratios to tCr are provided. An intrinsic problem of chemical shift imaging is to ensure that selected voxels consist mainly of gray matter because of the partial volume effect. For this reason, corrections for differences in gray and white matter are usually introduced. Peak overlapping prevents revealing some brain metabolites (ie, GABA) that could be of particular interest for specific pathologies. To overcome this problem, GABA spectral editing is a spectroscopic technique that reveals only these metabolites. Spectral editing can be used with spectroscopic techniques such as MEGA-PRESS or 2D J-resolved MR spectroscopy and correlated spectroscopy-based methods.[15]

^{31}P-MR spectroscopy is also applied in the study of brain metabolism: ^{31}P-MR spectroscopy is less sensitive than ^{1}H MR spectroscopy, but it provides information about high-energy phosphate metabolism as well as membrane phospholipid synthesis and degradation.

The differences in actually applied methodology and the rare use of a quantitative protocol make it more difficult to review spectroscopy ADHD studies, both in clinical and preclinical settings. Moreover, there are a limited number of ^{31}P-MR spectroscopy studies.

The aim of this present work was to review the most recent findings in preclinical and clinical studies, conducted on ADHD by using MR spectroscopy.

Why Spectroscopy for ADHD Studies?

The brain undergoes several metabolic changes during the transition from childhood to adolescence.[16,17] MR spectroscopy provides a snapshot of these neurochemical alterations and can also be useful in tracking the progress of a neurologic and/or psychiatric disease in longitudinal studies. Several metabolism alterations have indeed been detected in psychiatric disorders such as schizophrenia,[18] depression, bipolar disorder,[19] and autism spectrum disorder.[20] Recent MR spectroscopy studies on ADHD, both at preclinical and clinical levels, have revealed metabolite alterations that can perhaps account for the dopaminergic and/or glutamatergic dysregulation, known to be at the basis of this pathology.[21]

The prefrontal cortex (PFC) and the striatum are the most studied regions in subjects with ADHD because these regions belong to the prefrontal striatal thalamo-frontal circuits, well known to be involved in cognition, emotion, and attention processes.[9]

Rodent Models of ADHD

In behavioral neuroscience, animal models enable the investigation of brain-behavior relations under controlled conditions (eg, standardized housing and testing), with the aim of gaining insight into the neurobiology and pathophysiology of normal and abnormal human behavior and its underlying neuronal and neuroendocrinologic processes.[22] By exploiting genetic and environmental manipulations, pharmacologic treatments, and so forth, the use of animal models is essential for obtaining information that cannot be gained in other ways. Indeed, in vitro approaches cannot model the interactions in complex systems, such as the brain-behavior relations in live mammals. Thanks to animal models of behavioral dysfunctions, research can lead to both disease prevention and improvements in diagnosis and treatment.

In the development of an animal model of behavioral dysfunction, the concept of validity is of primary importance.[22] Regarding ADHD, the phenotypic resemblance to human disease (ie, face validity) has been the primary aim for developing animal models of ADHD since the first proposed one, the 6-hydroxydopamine-lesioned rat.[23] However, the notion that patients with ADHD can be classified into a predominantly inattentive type, predominantly hyperactive-impulsive type, and combined type, together with preclinical results indicating that inattention, impulsivity, and hyperactivity may not share a common neurobiological substrate,[5] suggests that an animal model of ADHD does not need to exhibit all the behavioral symptoms of ADHD to possess an adequate face validity.

An animal model that possesses face validity for ADHD may meet other criteria that render it suitable for the study of ADHD. The increase in extracellular dopamine induced by drugs used to treat ADHD (eg, methylphenidate and atomoxetine) normally produces an increase in motor activity but ameliorates symptoms in patients with ADHD. An animal model of ADHD that shows a similar reduction in symptom expression following drug administration achieves predictive validity.

On the basis of their ability to meet ≥1 of these criteria, >10 animal models of ADHD have been developed since the 6-hydroxydopamine-lesioned rat.[23] The 4 most extensively studied animal models of ADHD are the neonatal 6-hydroxydopamine-lesioned rat, the coloboma mutant mouse, the dopamine transporter–knockout/down mouse, and the spontaneously hypertensive rat. The behavioral and neurochemical features of each of these models, with a focus on the features that they share, have been recently reviewed by Fan et al.[24]

The Lenti-dopamine transporter is an innovative and promising animal model, developed through brain inoculation of self-inactivating, regulatable lentiviruses, targeting the dopamine transporter gene and protein expression.[25,26] Specifically, these animals could serve as a model for symptoms observed in cases of comorbidity between ADHD and pathologic gambling. The Lenti-dopamine transporter model was indeed analyzed in vivo by ^{1}H-MR spectroscopy.[26] Changes among groups were detected mainly in bioenergetic metabolites (tCr), indicating a functional upregulation of the dorsal striatum due to enhancement of the dopamine transporter and, conversely, a downregulation of the ventral striatum (ie, the nucleus accumbens) due to silencing of dopamine transporter. As a result, the rat group, termed "dopamine transporter+silencers," receiving combined dopamine transporter overexpression and silencing within the nucleus accumbens, displayed opposite rearrangement of function within the dorsal-versus-ventral striatum. These 2 regions do respectively subserve an increased habit-based behavior and decreased feedback regulation by evaluation of actual reward.[27] This profile leads to an impulsive and risk-prone phenotype, whereby the "risk" is represented by a low-feeding payoff. An altered accumbal dopamine transporter function, resulting in a modified dopaminergic tone, may subserve a sensation-seeker phenotype and the vulnerability to impulse-control disorders.[25,26]

Compared with dopamine transporter–knockout and dopamine transporter–knockdown rodents, the principal advantages of Lenti-dopamine transporter rats are localization and inducibility. Further studies on these rats will explore directly the effects of dopamine transporter–targeting drugs currently used in clinics, such as methylphenidate.

From the opposite perspective, an interesting model of reduced impulsivity and decreased risk proneness, which is one characteristic of ADHD, was obtained by exposure of rats to methylphenidate during adolescence.[28,29] With the aim of characterizing the metabolic forebrain changes induced in adult rats as a consequence of adolescent methylphenidate, a quantitative ^{1}H-MR spectroscopy analysis was performed in vivo. Most interesting, long-term changes implicated tCr and taurine, metabolites respectively involved in bioenergetics and synaptic efficiency. These were both upregulated in the dorsal striatum and conversely downregulated in the nucleus accumbens of methylphenidate-exposed rats. Unaltered tCr and an increased phosphorlcreatine/tCr ratio were detected in the PFC,[28] suggesting enhanced bioenergetics in this area, enabling a better top-down control over subcortical regions. In other words, the capability of the PFC to tune down instinctive drives and tune up elaboration of strategies (ie, self-control) may explain the profile of reduced impulsivity found in the pretreated animals. These findings highlight the role of these MR spectroscopy–detectable metabolites as a marker of functional status within forebrain areas, all of which are well known to subserve the regulation of impulsivity in rats as well as humans.

Clinical MR Spectroscopy Findings: Patients with ADHD

There are not many clinical MR spectroscopy studies on ADHD in the literature. All the results and methodology we presently reviewed are summarized in the Table.

A recent meta-analysis reviewed all MR spectroscopy studies of ADHD up to 2007.[30] The authors found, on MEDLINE (PubMed), 16 articles about MR spectroscopy in the prefrontal cortex, striatum, and frontal lobe in ADHD published up to the end of September 2007. Several of these studies revealed metabolic alteration for Cho, NAA, and Glx related to tCr signal in patients with ADHD. The meta-analysis was performed consid-

Summary of the most recent MRS studies on ADHD[a]

Study	Subjects: No. of ADHD (age, yr)	Subjects: No. of Controls (age, yr)	Method	Region	Findings
Children					
Perlov et al, 2009[30]	–	–	Meta-analysis	Left STR	↑ Cho
				Right frontal lobe	↑ Cho
Hammemess et al, 2012[31]	12	12	PRESS at 4T, TR/TE = 2000/30 ms	ACC	↑ Glu/mIns; Gln/mIns; Glx/mIns (trend)
Arcos-Burgos et al, 2012[32]	14 (8–54)	20 (8–54)	2D and 3D CSI at 1.5T, TR/TE = 1500/30 ms	Right PCC	↑ Glx/tCr
				STR, splenium; medial and lateral Thal; vermis (cerebellum)	Interaction of mIns/tCr, NAA/tCr, Glx/tCr with age and ADHD status
Tafazoli et al, 2013[34]	13 (12.3)	13 (12.2)	CSI at 1.5T, TR/TE = 1500/30 ms	Right DLPFC	↓ NAA; tCr; Cho; mIns
				Left DLPFC	–
Soliva et al, 2010[35]	17 (10.4)	17 (10.8)	PRESS at 1.5T, TR/TE = 2000/30 ms	Right frontal cortex	↓ tCr
				Left cerebellum	↓ NAA; mIns; tCr
Carrey et al, 2007[38]	13 (6–11)	10 (6–11)	PRESS at 1.5T, TR/TE = 2000/30 ms	Left striatum	↑ Glu; Gln; Glx; tCr
				Right PFC; left occipital lobe	–
Yang et al, 2010[39]	37 (13.9)	22 (14.8)	PRESS at 1.5T, TR/TE = 1600/35 ms	Right PFC	↓ tCr
				Left PFC	–
Stanley et al, 2008[42]	31 (8.1)	36 (8.1)	Multivoxel ^{31}P-MRS at 1.5T	Bilateral basal ganglia	↓ Membrane phospholipid precursor, ↑ membrane phospholipid precursor
				Inferior parietal region	
Edden et al, 2012[41]	13 (10.2)	19 (10.6)	MEGA-PRESS at 3T, TR/TE = 1800/68 ms	Primary motor cortex	↓ GABA
Adults					
Perlov et al, 2009[30]	–	–	Meta-analysis	Bilateral ACC	↑ Cho
Perlov et al, 2007[45]	28 (32.4)	28 (30.5)	CSI at 1.5T, TR/TE = 1500/30 ms	Right ACC	↓ Glx/tCr
Colla et al, 2008[44]	15 (36.1)	10 (33.2)	2D CSI at 1.5T, TR/TE = 1500/135 ms	Bilateral ACC	↑ Cho/tCr
Dramsdahl et al, 2011[46]	29 (32.9)	38 (29.8)	PRESS at 3T, TR/TE = 1500/35 ms	Left midfrontal region	↓ Glx/tCr
Kronenberg et al, 2006[47]	7 MPH (32.6)	7 no MPH (32.6)	2D CSI at 1.5T, TR/TE = 1500/135 ms	Left midfrontal region	↑ NAA; ↓ Cho after MPH
Perlov et al, 2010[48]	30 (32.1)	30 (29.9)	CSI at 1.5T, TR/TE = 1500/30 ms	Left cerebellum	↑ Glx/tCr
				Right cerebellum; vermis	–

Note:—STR indicates striatum; PCC, posterior cingulate cortex; MPH, methylphenidate; Thal, thalamus; Gln, glutamine; Glu, glutamate; CSI, chemical shift imaging; DLPFC, dorsolateral PFC; ↓, decreased level; ↑, increased level.

[a] For each study, we provide the number of subjects involved, age mean or range in years, the MRS technique, and the findings in each region.

ering metabolites and brain regions separately and led to the finding of an increase in the choline compounds within the left striatum and right frontal lobe for children diagnosed with ADHD.

One recent pilot study[31] has considered the effect of methylphenidate treatment on metabolite levels with respect to myo-Inositol in the anterior cingulate cortex (ACC). Ten subjects with ADHD underwent MR spectroscopy before and after a 6- to 8-week methylphenidate oral treatment at doses of 1.5 mg/kg/day. A control group of 12 healthy subjects was also analyzed. The main findings were a trend toward increased glutamate/mIns, glutamine/mIns, and Glx/mIns levels in subjects with ADHD compared with healthy controls. Moreover, these glutamatergic abnormalities were counteracted by the drug treatment.

Arcos-Burgos et al[32] investigated, by using multivoxel 2D and 3D chemical shift imaging, a variety of brain regions: the striatum, cingulate gyrus, splenium of the corpus callosum, medial and lateral thalamus, and cerebellar vermis. They chose these regions on the basis of a previous study[33] whereby morphologic abnormalities were reported in subjects with ADHD. The study involved 34 subjects with ADHD (21 females, 8 males) and 20 controls with a wide age range from 8 to 54 years. A significantly higher Glx/tCr in the right posterior cingulate cortex of subjects with ADHD was detected. More differences in metabolite ratios were found when considering interactions between metabolite, age, and ADHD status: mIns/Cr and Glx/tCr in the left posterior cingulate; NAA/tCr in the splenium, right posterior cingulate, and left posterior cingulate; and, finally, mIns/tCr and NAA/tCr in the right striatum. These findings suggest that, in ADHD, a different metabolic pattern is followed, with respect to controls, during ontogeny and progression of age.

In 2013, Tafazoli et al[34] investigated the bilateral middle frontal gyrus (or dorsolateral prefrontal cortex) in subjects with ADHD (8 boys, 5 girls; mean age, 12.3 years) compared with healthy subjects (8 boys, 5 girls; mean age, 12.2 years) by short-TE chemical shift imaging by using a quantitative protocol. In addition to short TE and water as internal references, the authors used a self-made software to correct for CSF. They found a significant reduction in NAA, tCr, Cho, and mIns in the right middle frontal gyrus of the ADHD group. This lateralization may reflect a right-sided asymmetry in ADHD. The authors underlined some limitations of this study: the estimated percentage of white (roughly 40%) and gray (roughly 50%) matter within the voxel that can affect quantification and the small and heterogeneous sample. Furthermore, 3 subjects with ADHD were stimulant-treated at the time of the study, though they were medication-free on the day of the MR imaging. This is not a real limitation because a previous study published in 2010[35] found no significant correlations between dose or time length of medication and neurometabolite levels in the frontal gyrus. This research group, by adopting a quantitative protocol, investigated the right frontal cortex and the left cerebellar hemisphere of subjects with ADHD (15 boys, 2 girls; mean age, 10.41 years; mean methylphenidate dose, 30.29 mg/kg; medication time, 18.21 months) and healthy controls (15 boys, 2 girls; mean age, 10.76 years). They found a significant reduction of mIns, NAA, and tCr in the left cerebellum and a reduction of tCr in the right prefrontal cortex. The reduction in tCr in both regions had a weaker significance level, and the authors themselves suggested caution in the interpretation of these findings.

Quantitative Protocol

Beyond the study of Soliva et al[35] described above, only a few studies adopted a quantitative protocol to investigate ADHD neurometabolic alterations. The protocol included short TE, water signal as an internal reference, and an LCModel (Stephen Provencher, Oakville, Ontario, Canada) fitting program. The LCModel method analyzes in vivo spectra as a linear combination of model in vitro spectra from individual metabolite solutions,[36,37] and it is the most widely used software for metabolic spectral quantification. Differences in tissue composition within the voxel can affect the quantification; therefore, it is important to carefully estimate the percentage of gray matter, white matter, and CSF content in the localized region, especially in human studies.

In 2007, Carrey et al[38] investigated 13 male subjects with ADHD and 10 healthy male subjects between 6 and 11 years of age by applying short-TE ^{1}H-MR spectroscopy in the right PFC, left striatum, and left occipital lobe. They found an increase in glutamate, Glx, and tCr in subjects with ADHD only in the left striatum. Furthermore, the authors investigated subjects with ADHD after 8 weeks of methylphenidate administration. The pharmacologic treatment significantly reduced only the tCr concentration in subjects with ADHD, but there was a trend toward reduction in striatal glutamate and Glx. These findings are in line with the study of Hammerness et al,[31] in which Glx/mIns was partially reduced in ACC as an effect of methylphenidate treatment.

A more recent study that includes a quantitative protocol was carried out by Yang et al[39] on 37 adolescents with ADHD (13 boys, 2 girls; mean age, 13.88 years) and 22 control subjects (14 boys, 8 girls; mean age, 14.85 years). The bilateral prefrontal areas of adolescent brains were studied by using short-TE ^{1}H-MR spectroscopy. The authors found a reduction in the tCr level in the right PFC. No sex or age effects were found, probably because the age range of the sample was not enough wide. Here, the authors compared the absolute metabolic levels and their ratio with tCr. With the latter quantification method, NAA/tCr in the right PFC showed a significant increase within the ADHD group, but this finding clearly depends on the reduction of tCr rather than on increased NAA.

Another study involved the use of methods for absolute metabolite quantification in male adults.[40] Here, the left dorsolateral PFC and left striatum of 5 unmedicated subject with ADHD (mean age, 27.2 years) and control subjects (mean age, 27.0 years) were analyzed. Most interesting, the authors found a lower concentration of NAA for the ADHD group within the left dorsolateral PFC. No metabolic differences were detected for the striatum.

The alteration in tCr concentration found in this pathology, as reported by Yang and collegues,[39] highlights the notion that the use of tCr as a stable reference for the metabolite relative quantification is not correct.

More recently, the GABA-editing technique allowed investigation of the dysregulation of this important neurotransmitter in ADHD. Edden et al[41] studied the primary motor cortex of 13 children (11 boys, 2 girls; mean age, 10.2 years) diagnosed with ADHD compared with 19 control subjects (12 boys, 7 girls; mean

age, 10.6 years). Using MEGA-PRESS for GABA editing, they reported a significant reduction in the levels of this neurotransmitter for the subjects with ADHD.

^{31}P-MR Spectroscopy

^{31}P-MR spectroscopy is not yet widely used because it necessitates dedicated equipment (coils), a long acquisition time, and additional costs. On the other hand, ^{31}P-MR spectroscopy provides important information about the metabolism of phosphate compounds and the cellular energy metabolism.

Only two studies[42,43] have reported ^{31}P-MR spectroscopy data in patients with ADHD. In the most recent article,[42] Stanley et al compared 31 children with ADHD with 36 control subjects by using multivoxel ^{31}P-MR spectroscopy to find alterations in membrane phospholipid precursors. These included phosphomonoesters, phosphoethanolamine, and phosphocholine, which are precursors of membrane phospholipids, and the phosphodiesters, glycerophosphoethanolamine and glycerophosphocholine, which are breakdown products of membrane phospholipids. The results showed a significant reduction of the membrane phospholipid precursor in the bilateral basal ganglia and, conversely, an increase in the right inferior parietal lobe.

Adults

There are still few MR spectroscopy studies on adults with ADHD. In the meta-analysis of 2009,[30] only 3 studies were considered.[40,44,45] The work of Hesslinger et al[40] has already been discussed in the quantification section, and it is the only study that involved the left dorsolateral PFC and left striatum. The other 2 studies involved the bilateral ACC. Perlov et al[45] found Glx/tCr to be decreased in the right ACC of 28 subjects with ADHD (17 men, 11 women; mean age, 32.4 years) compared with 28 controls (15 men, 13 women; mean age, 30.5 years). This last finding is in line with the study of Colla et al,[44] in which 15 patients with ADHD (8 men, 7 women) were compared with 10 healthy controls (4 men, 6 women). Most interesting, these authors found an increase in choline compounds with respect to tCr not only in the right ACC but also in the left one. No alterations in glutamatergic metabolites were found, mainly because these authors used a long TE (135 ms).

Also, a more recent study[46] considered the bilateral midfrontal region, including the ACC, in ADHD pathology. This study compared the metabolite level ratio with tCr in 29 adults with ADHD (15 men, 14 women; mean age, 32.9 years) with respect to 38 healthy controls (15 men, 23 women; mean age, 29.8 years). The main finding was a reduction in Glx/tCr within the left midfrontal region. In the same region, Kronenberg et al[47] found, in 7 adults with ADHD, an increase in NAA and a reduction in Cho after a chronic (5–6 weeks) methylphenidate treatment but no change at all in glutamate compounds.

In 2010, Perlov et al[48] investigated the whole cerebellum, covering the vermis and the 2 hemispheres, of 30 patients with ADHD (18 men, 12 women; mean age, 32.1 years) and 30 healthy subjects (15 men and 15 women; mean age, 29.9 years) by using multivoxel MR spectroscopy. The Glx level with respect to tCr was significantly higher in the left cerebellar hemisphere in the ADHD group.

DISCUSSION

All the investigated regions in the above-mentioned MR spectroscopy studies have an important role in ADHD pathology.

While the dorsal striatum is classically thought to subserve innate or habit-based behavior, the ventral striatum (nucleus accumbens) is involved in reinforcement processes, subserving incentive motivation.[49] Specifically, the latter accounts for the affective evaluation of distinctive features in the outcome of one's own actions and for feedback modulation of future choice.[50] Sensation- and risk-seeking may result from either an over- or underactive nucleus accumbens, which may lead to a specific proneness toward an impulsive phenotype and/or gambling behaviors.[51]

The PFC may have a functional role in controlling (or causing) motor and cognitive impulsivity, being involved in the resolution of conflicting decisions through planning, feedback regulation, and inhibition of behavior.[52] Recent advances in ADHD research propose that the PFC is important for sustaining and shifting attention in an appropriate manner; screening sources of distractions; and inhibiting inappropriate emotions, impulses, and habits.[53] In more detail, the medial PFC is involved in the following: 1) monitoring of actions and their outcomes, for guiding decisions; and 2) goal-related planning, problem solving, and prediction of forthcoming events.[54] The orbital PFC is implicated in stimulus-reward associations, their change with time (ie, reversal learning), and in subjective attribution of reward value for choices involving a delayed reinforcement.[52] Indeed, by acting together, these 2 subdivisions direct behavior more efficiently than would be observed if subcortical drives, elicited within the dorsal and ventral striata, were left alone with no cortical control.[55]

The ACC and dorsolateral PFC are the main components of the cingulofrontal parietal cognitive-attention network.[9] With 7 studies in pediatric and 5 in adult subjects with ADHD, they are the most analyzed regions. The importance of the ACC in adults[44,46,48] is also indicated by a recent meta-analysis[56] on structural MR imaging findings in children and adults with ADHD. Indeed, that work reveals a decreased gray matter volume in the left ACC, but only in adults. Three studies in pediatric and 1 in adult patients with ADHD involved the striatum and basal ganglia, another node of the attention and cognition network. Recently, the cerebellum became a region of interest, so far with one pediatric study and another in adult subjects with ADHD.

Several metabolic alterations have been found in the reviewed studies: Glx, NAA, Cho, and tCr.

Glutamatergic metabolites (glutamate, glutamine) were found to be altered in ADHD: They increase within the ACC, right posterior cingulate cortex, and left striatum in pediatric ADHD, whereas they decrease within the right ACC, left midfrontal regions, and left cerebellar hemisphere in adult ADHD.[31,32,38,45,46,48] Glutamate is the principal excitatory neurotransmitter in the brain, and it plays a central role in neurotransmission, especially within the ACC where high glutamate levels have been associated with impulsivity.[57] MR spectroscopy findings in ADHD are in agreement with the hypothesis of Carlsson[58] of a deep glutamate/dopamine interaction, especially within the prefrontal circuits. A hypofunctionality within the do-

paminergic system can lead to higher glutamate concentrations in pediatric subjects with ADHD, which can be partially reverted by methylphenidate administration,[31,38] which increases the dopamine levels. In adults, glutamatergic decrease[45,46] within the midfrontal region, including the ACC, may contribute to the cognitive deficit.

Following the hypothesis of Todd and Botteron,[59] according to which ADHD could be considered an energy-deficit syndrome, altered energy metabolism of monoamines can cause the excess in glutamate, which is then not correctly absorbed into astrocytes. In this framework, the alterations found for the tCr (as detected by ^{1}H-MR spectroscopy) and for phosphorlcreatine (by ^{31}P-MR spectroscopy), which are metabolites related to bioenergetics of the human brain, can also be explained. Alterations in the Cr pool, as found in absolute quantitative studies, are also important because this notion implies that this metabolite is not a stable reference. As such, more caution should, therefore, be taken in relative quantitative studies in the choice of the reference. As a recommendation for future works, the use of absolute quantitative protocols is desirable.

GABA reduction[41] suggests that more neurotransmitter systems than previously thought are involved in ADHD. In particular, GABA concentration correlates with impulsive behavior.[60]

The decrease of NAA in the dorsolateral PFC and cerebellum of pediatric subjects[34,35] and in the dorsolateral PFC of adults[40] does not necessarily mean a neuronal cell loss, but it can also be interpreted as a neuronal dysfunction.[61] This metabolic reduction is reversed in adults by methylphenidate administration.[47] Here, despite the small size of the sample, a stimulant treatment significantly decreased the ACC Cho level, while it increased NAA in adult methylphenidate-responsive patients with ADHD. The increase in NAA can be due to mitochondrial respiratory chain enzyme activities induced by chronic methylphenidate exposure, especially in the PFC and striatum.[62]

Choline-containing compounds are the main components of cell membranes and products of membrane degradation. Changes in Cho are associated with acute demyelinating disease[63] or cellular turnover.[64] Choline is the precursor of acetyl-choline and influences the neural communication, mediated by transmitters like norepinephrine and dopamine. Alterations in choline compounds are observed in only a few of the above-mentioned works and cannot yet be correctly interpreted in the ADHD context.

CONCLUSIONS

All the reviewed studies give a deeper insight into the ADHD mechanisms. Neurochemical alterations found in several brain regions are in agreement with the most recent hypotheses regarding the pathogenetic processes at the basis of this pathology.

Methodologic improvements of MR spectroscopy procedures are desirable to evaluate the absolute concentrations rather than ratios. There is the need not only for standardized protocols to compare data acquired in different centers but also for smaller voxel sizes, to have high tissue purity and more spatial resolution. On the other hand, this approach would lead to a longer scanning time, which is problematic for subjects with ADHD. Starting from functional results and neurobiologic knowledge, other regions should be investigated with both ^{1}H and possibly ^{31}P-MR spectroscopy. These regions include the amygdala and the other limbic structures, which are known to play a key role in symptoms like impulsivity. Also, the hippocampus would need to be investigated as well as the thalamus and cerebellum (the latter being involved in a few studies up to now).

Finally, to improve the MR spectroscopy analyses, a balanced choice of subjects in the clinical samples, as far as age, sex, and psychiatric diagnosis are concerned, would be desirable.

Disclosures: Walter Adriani—*RELATED*: *Grant*: Italian Ministry of Health,* *Comments*: ERA-net "NeuroGenMRI," *UNRELATED*: *Patents (planned, pending or issued)*: Istituto Superiore di Sanità (50%),* Geropharm Ltd (50%),* *Comments*: O. Granstrem, W. Adriani, G. Laviola, M.C. Porfirio, P. Curatolo–provisional patent "Biomarkers for Validation of ADHD (Attention Deficit and Hyperactivity Disorder) Diagnosis and Monitoring of Therapy Efficacy" US Patent and Trademark Office EFS ID 13464574; Application No. 61681638 (10-AUG-2012). *Money paid to the institution.

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Original article 59

Copy number variants in attention-deficit hyperactive disorder: identification of the 15q13 deletion and its functional role

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Objectives Evidence has supported a role for rare copy number variants in the etiology of attention-deficit hyperactivity disorder (ADHD), in particular, the region 15q13, which is also a hot spot for several neuropsychiatric disorders. This region spans several genes, but their role and the biological implications remain unclear.

Methods We carried out, for the first time, an analysis of the 15q13 region in an Italian cohort of 117 ADHD patients and 77 controls using the MLPA method, confirmed by a genome single-nucleotide polymorphism array. In addition, we probed for downstream effects of the 15q13 deletions on gene expression by carrying out a transcriptomic analysis in blood.

Results We found 15q13 deletions in two ADHD patients and identified 129 genes as significantly dysregulated in the blood of the two ADHD patients carrying 15q13 deletions compared with ADHD patients without 15q13 deletions. As expected, genes in the deleted region (*KLF13*, *MTMR10*) were downregulated in the two patients with deletions. Moreover, a pathway analysis identified apoptosis, oxidation reduction, and immune response as the mechanisms that were altered most significantly in the ADHD patients with 15q13 deletions. Interestingly, we showed that deletions in *KLF13* and *CHRNA7* influenced the expression of genes belonging to the same immune/inflammatory and oxidative stress signaling pathways.

Conclusion Our findings are consistent with the presence of 15q13 deletions in Italian ADHD patients. More interestingly, we show that pathways related to immune/inflammatory response and oxidative stress signaling are affected by the deletion of *KFL13* and *CHRNA7*. Because the phenotypic effects of 15q13 are pleiotropic, our findings suggest that there are shared biologic pathways among multiple neuropsychiatric conditions. *Psychiatr Genet* 25:59–70

Psychiatric Genetics 2015, 25:59–70

Keywords: attention-deficit hyperactivity disorder, blood transcriptomics, copy number variant

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Received 25 October 2013 Revised 2 July 2014 Accepted 10 September 2014

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric condition. Meta-analysis shows that 5.3% of youth have this disorder and that the prevalence does not differ markedly worldwide (Polanczyk *et al.*, 2007). Particularly in Italy, a national registry under the control of the Italian National Health Service has estimated the prevalence of this disability to be within the range of 0.43–3.6% (Al-Yagon *et al.*, 2013). In a sample of Italian students, the prevalence was estimated of 3%, in line with other reports in European countries (Bianchini *et al.*, 2013).

It is characterized by behavioral and cognitive alterations leading to inattention, impulsivity, and hyperactivity.

The etiology is complex, with contributions from both genetic and environmental factors. The heritability has been estimated to be 76% (Faraone and Mick, 2010). Studies of common variants of candidate genes have not identified any genes definitively conferring a risk for ADHD (Gizer *et al.*, 2009). In addition, genome-wide association studies have been too underpowered to detect genome-wide significant associations with common single-nucleotide polymorphisms (SNPs) (Neale *et al.*, 2010), fitting with the polygenic and multifactorial model for ADHD, where many common variants of small effects contribute toward the pathological phenotype. Although no genome-wide significant SNPs for ADHD have been discovered, meta-analysis has confirmed the existence of a statistically significant polygenic background (Lee *et al.*, 2013; Yang *et al.*, 2013).

0955-8829

DOI: 10.1097/YPG.0000000000000056

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Moreover, cross-disorder genome-wide association studies show that ADHD shares common risk variants with other psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.*, 2013).

In addition to the common variants, rare deletions or duplications in the genome known as copy number variants (CNVs) also contribute toward the high heritability of the disorder. Thus, it seems likely that the high heritability of ADHD is because of both common and rare variations. Several studies have found an increased burden of large, rare CNVs in ADHD, some of which overlap with findings in autism (Elia *et al.*, 2010; Williams *et al.*, 2010, 2012; Lionel *et al.*, 2011). A CNV region of particular interest is 15q13, a hot spot for several neuropsychiatric disorders such as schizophrenia (Stefansson *et al.*, 2008; Stone *et al.*, 2008; Van Bon *et al.*, 2009; Stephens *et al.*, 2012), epilepsy (Dibbens *et al.*, 2009; Helbig *et al.*, 2009), autism (Pagnamenta *et al.*, 2009), developmental delay (DD), intellectual disability (ID), and dysmorphic features (Sharp *et al.*, 2008; Ben-Shachar *et al.*, 2009; Miller *et al.*, 2009), as well as ADHD (Lionel *et al.*, 2011; Williams *et al.*, 2012). The frequency of 15q11q13 CNVs was estimated by Williams *et al.* (2010) to be 1.91% in European cohorts.

In this region, several significant deletions or duplications were found in which the beginning and end points vary across individuals. The region implicated by 15q13 CNVs spans several genes, including *CHRNA7* (cholinergic receptor, nicotinic, alpha 7), *KLF13* (Kruppel-like factor 13), *TRPM1* (transient receptor potential cation channel, subfamily M, member 1), *MTMR10* (myotubularin-related protein 10), and *OTUD7A* (OTU domain containing 7A) (Sharp *et al.*, 2008; Ben-Shachar *et al.*, 2009; Miller *et al.*, 2009; Van Bon *et al.*, 2009). Among these, only *CHRNA7* has been associated nominally with ADHD in common variant studies (Stergiakouli *et al.*, 2012; Williams *et al.*, 2012). This gene has been identified as the major candidate gene responsible for the predominant manifestations of 15q13.3 microdeletion syndrome (Hoppman-Chaney *et al.*, 2013; Le Pichon *et al.*, 2013).

To date, the mechanisms by which genes within the deleted region exert their effect are unclear. A recent paper, using immortalized lymphoblastoid cell lines, reported genome-wide differential expression of genes implicated in neurodevelopment and muscular function from a patient with 15q13.3 homozygous microdeletion syndrome (Le Pichon *et al.*, 2013). The 15q13.3 microdeletion syndrome is characterized by a wide range of phenotypic features, including ID, seizures, autism, and psychiatric conditions. This deletion is inherited in ~75% of cases and has been found in mildly affected and normal parents, consistent with variable expressivity and incomplete penetrance.

We followed up on these previous findings by carrying out, for the first time, an analysis of the 15q13 region in an Italian cohort of 117 ADHD patients and 77 healthy individuals. We also sought to investigate the molecular mechanisms associated with 15q13 region deletions by carrying out a microarray gene expression study in the blood of two drug-naive ADHD patients carrying 15q13 deletions and nine drug-naive ADHD patients without 15q13 deletions.

Methods

Participants

ADHD patients were enrolled by a network of Clinical Centres: Adolescent Neuropsychiatry Unit of Fatebenefratelli and Oftalmico, Milan; Department of Childhood and Adolescent Neuropsychiatry, Spedali Civili Brescia; Childhood and Adolescent Neuropsychiatry (UONPIA), Spedali Riuniti, Bergamo; Azienda Ospedaliera, Cremona, Rho, and Mantova. Patients were diagnosed with ADHD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria (American Psychiatric Association, 2000) and the guidelines of the Italian Institute of Health (2005). Moreover, revised Touwen neurological tests were performed. Exclusion criteria included childhood schizophrenia, autism, intelligence quotient (IQ) up to 70 [Wechsler Intelligence Scale for Children (WISC)], epilepsy, encephalitis, Tourette syndrome, and conduct disorder. They had moderate to severe ADHD.

The age at data collection was 11.37 ± 2.70 years and the proportion of males was 89.4%. Stratification according to diagnostic subtypes evidenced 70.8% for the ADHD combined type, 27.8% for the predominantly inattentive type, and 1.4% for the predominantly hyperactive–impulsive type.

The control group included unrelated volunteers not affected by ID, chronic and medical diseases, inflammatory diseases, and allergies, undergoing blood tests for a presurgical screening. They were also selected to exclude ADHD or conduct disorder. The age at data collection was 10.25 ± 2.15 years and the proportion of males was 77.9%.

All the participants enrolled in this study were Caucasoid and living in Northern Italy.

The study protocol was approved by the Local Ethics Committee and as the participants were all under-age youth, their parents were requested to provide written informed consent for the study as indicated on the approval note by the Local Ethics Committee. The parents of 11 ADHD patients provided written informed consent to be recalled for a blood Paxgene sample for whole expression studies. This study has therefore been carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments.

Genetic analysis

The DNA of all participants was extracted from blood samples or saliva using commercial standard kits. The MLPA assay was performed using the MLPA Kit P343-C1 produced by MRC-Holland (Amsterdam, the Netherlands) according to the manufacturer's protocol. The kit includes 49 probes: 26 probes contain complementary sequences of exons for genes in the 15q11-q13 region and 11 probes for genes in the 16p11.2 region.

MLPA statistical analysis

Analyses of results were carried out on the basis of the peak areas of each probe obtained using GeneMapper software v4.0 (Applied Biosystems, Foster City, California, USA). Coffalyser software (MRC-Holland, Amsterdam, the Netherlands) v9.4 was used to analyze the MLPA data for CNVs. Bin sizes were adjusted accordingly for the peak sizes observed. Data were normalized by dividing the peak area of each probe by the average peak area of the seven control probes in the probe mix obtained from the sample set. The normalized data were then divided by the median peak area of all samples to obtain an indication of copy number variation for each probe. A value of 0.7 or below and 1.3 and above were set as thresholds for loss and gain, respectively.

We tested the MLPA assay by analysis of three positive controls, obtained from the Tor Vergata General Hospital (Rome) and IRCCS Fatebenefratelli (Brescia), with known deletions and duplications in regions targeted by the probes. For all controls, the correct CNV was detected by MLPA analysis (data not shown).

SNP array analysis and generation of CNVs calls

Both samples from ADHD patients with the 15q13 deletions were genotyped by Affymetrix Human Mapping GeneChip 6.0 arrays with a total of two millions of probes, half of which were polymorphic. DNA was processed according to the instructions provided in the Affymetrix Genome-Wide Human SNP Nsp/Sty 6.0 Assay Manual. Initial analysis of the array to calculate the intensity data was carried out using Affymetrix GeneChip Command Console Software (AGCC, Santa Clara, California, USA). The AGCC probe cell intensity data were then analyzed using Genotype Console 3.01 (GTC3.01) to obtain genotype data. The copy number state calls were generated from the BRLMM-P-Plus algorithm implemented in GTC 3.0.1. This algorithm compared the intensity signal of each marker in each sample against a reference pool formed from a group of 270 samples derived from the HapMap database. After this comparison, the software generates a median intensity value for each marker. This value was then used by the Affymetrix segmentation algorithm to identify CNVs. To reduce the presence of false-positive CNVs, the segmentation algorithm parameters were set to consider as a CNV only those regions larger than 100 kb, comprised of at least 25 contiguous markers without a diploid state and with an average probe density lower than 10 kb.

RNA isolation and microarray gene expression analyses

Blood samples from the two drug-naive ADHD patients with the 15q13 deletions and drug-naive nine ADHD patients without 15q13 deletions were obtained by venipuncture in the morning using PaxGene Tubes (Qiagen, Hilden, Germany). The two ADHD patients with the 15q13 deletions and nine ADHD patients without 15q13 deletions were age and sex matched (mean age of participants with 15q13 deletions 11.50 ± 4.95; mean age of participants without 15q13 deletions 12.22 ± 3.27; $t = 0.26$, $P = 0.80$; 100% males).

RNA isolation was performed using the PaxGene Blood RNA Kit (Qiagen) according to the manufacturer's protocols and the quality and integrity of RNA were assessed using Nanodrop 2000 (ThermoScientific, Waltham, Massachusetts, USA).

Gene expression microarray assays were performed using Human Gene 1.1 ST array strips (Affymetrix Inc., Santa Clara, California, USA) on the Affymetrix Gene Atlas platform following the manufacturer's instructions (*http://www.affymetrix.com/support/technical/manuals.affx*).

Data analysis and pathway analysis

Gene expression microarray data were imported from the Gene Atlas instrument into Partek Genomics Suite 6.0 (Partek, St Louis, Missouri, USA) as CEL files using default parameters. Quality controls were performed using Affymetrix expression console software, whereas the analysis of variance to obtain a list of genes modulated differentially in the two groups was carried out using the Partek Genomic Suite. Pathway analysis was carried out using Pathway Studio Software 5.0 (Ariadne, Lausanne, Switzerland) with the standard Gene Set enrichment analysis, originally developed by the Broad Institute (*http://www.broad.mit.edu/gsea/*) (Mootha *et al.*, 2003). This algorithm uses a correlation-weighted Kolmogorov–Smirnov statistic on all gene expression changes and computes pathway enrichment scores by considering gene set membership information, gene list ranking, and gene–gene dependencies that reflect real biology.

Finally, we carried out a target prediction analysis (Ariadne) to determine the pathways influenced by the genes belonging to the 15q13 deletion (*KLF13*, *MTMR10*, *CHRNA7*).

Results

Out of 117 ADHD patients and 77 healthy individuals, we excluded one patient and six participants from the control group because of low-quality DNA. Among the patients, we identified two with a significant reduction in the peak areas for the probes of the *TRPM1*, *KLF13*, and

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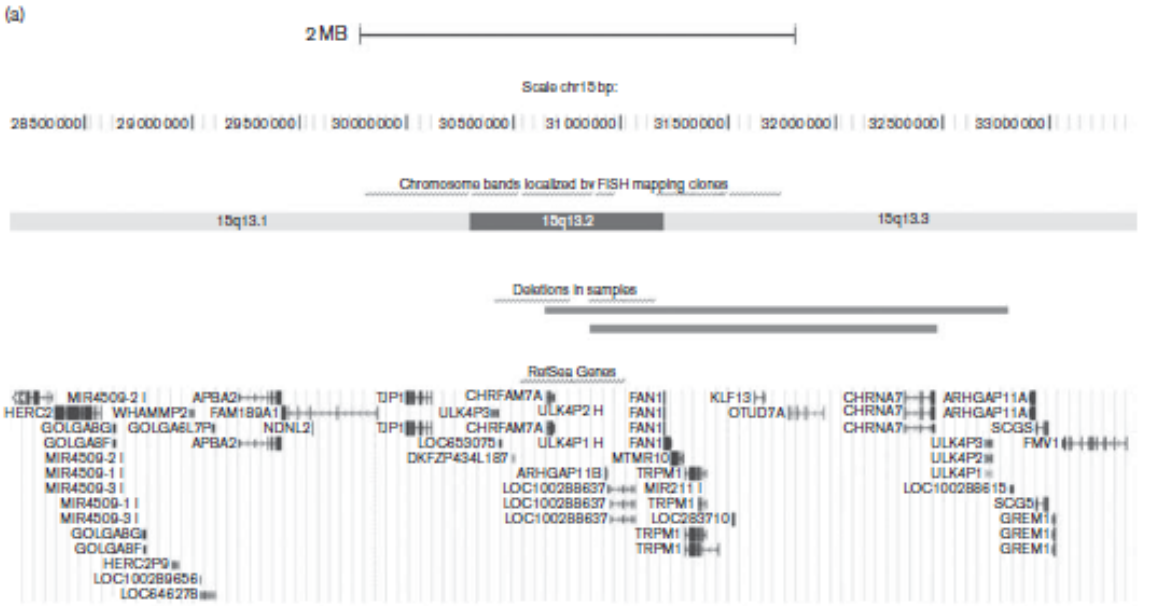
Fig. 1



(b)

Patient number	Imbalance	Size (Mbp)	Chromosome band	Chromosomal region
1	Heterozygous deletion	2.39	15q13.2-q13.3	Chr15:30,450,356-32,843,110
2	Heterozygous deletion	1.79	15q13.2-q13.3	Chr15:30,743,132-32,539,525

(a) Schematic representation of the deletions found at the 15q13.2-q13.3 region in two ADHD patients. (b) Size and chromosomal positions of the two deletions (assembly: GRCh37/hg19). ADHD, attention-deficit hyperactivity disorder.

CHRNA7 genes in the 15q13 region. From the statistical MLPA data analysis, we obtained probe signal values of 0.48, 0.43, and 0.45 for *KLF13*, *CHRNA7*, and *TRPM1* for patient 1 and values of 0.5, 0.44, and 0.46 for patient 2, defining two heterozygous deletions in 15q13.3 (Fig. 1a). The clinical features of these patients are reported in Table 1.

No genomic rearrangements in the 15q11-q13 region were found in the control samples. The 1.7% rate of 15q13 CNVs in cases did not differ significantly from the 0% rate in controls (Fisher's exact test, $P=0.53$). Moreover, no genomic rearrangements in the 16p11.2 region were found in the patient and the control samples by MLPA analysis.

The two CNVs observed in ADHD patients were confirmed and fine mapped using Affymetrix Human Genome-Wide SNP Arrays, defining a deletion of 2.39 Mbp in patient 1 and 1.79 Mbp in patient 2 (Fig. 1b). These two CNVs have an overlapping region, which spans the genes *ARHGAP11B* (Rho GTPase activating protein 11B), *FAN1* (FANCD2/FANCI-associated nuclease 1), *MTMR10*, *TRPM1*, *KLF13*, *OTUD7A*, and *CHRNA7* (Fig. 1a). No other CNVs greater than 100 kbp were found in nonpolymorphic regions for both patients. For patient 1, the breakpoints fell into two regions with low probe coverage. In particular, the most centromeric breakpoint fell in a region of 123 kbp, which was covered by only four probes. Because of the low coverage, however, we cannot formally exclude that the CNV breakpoint maps 123 kbp downstream and that the CNV is closer in size. As for the telomere breakpoint, the coverage is higher and the actual breakpoint falls in a range of 14 kbp.

As for patient 2, we can reasonably exclude that the CNV is smaller than what we reported as the internal boundaries of the deletion are well covered. We can reasonably exclude that the CNV is smaller than what we

Table 1 Clinical features of the two ADHD patients carrying 15q13 deletions

Features	Patient 1	Patient 2
ADHD rating scale	Predominantly inattentive type	Combined type
Demographic features		
Age, sex	8, Male	15, Male
Height (cm)	156	164
Weight (kg)	49	66.5
Cognitive and neuropsychological assessment		
Memory performance (TEMA, Digit Span of WISC)	No	Yes
Total intelligent quotient (WISC)	92	81
Verbal intelligent quotient	98	85
Performance intelligent quotient	87	81
Campanelle test (accuracy, sustained attention, row data/z)	127/−5.5	111/−3.2
Campanelle test (rapidity, selective attention, row data/z)	41/−3.38	47/−1
Continuous performance test (omission errors, mean/z)	2/2.4	–
Psychopathological features		
Conners for parents	79	87
Conners for teachers	49	90
Anxiety, depressive symptoms (CDI, K-SADS-PL)	No	Yes
Learning problems	No	No
Aggressiveness	No	Yes
Comorbidity features		
Autism	No	No

Note: Campanelle test (Biancardi and Stoppa, 1997), continuous performance test (paper format) values are presented in row data/z-scores (cut off = −2). IQs are obtained from the WISC.
ADHD, attention-deficit hyperactivity disorder; CDI, Children's Depression Inventory; IQ, intelligent quotient; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version; TEMA, Test of Memory and Learning; WISC, Wechsler Intelligence Scale for Children.

reported as the internal boundaries of the deletion are well covered. However, we cannot exclude that the CNV extends upstream of the more centromeric deleted probe for 74 kbp.

To assess the impact on the biological processes regulated by genes within the deleted region, we carried out gene expression microarray analyses in the blood obtained from the two ADHD patients carrying 15q13 deletions and nine ADHD patients without 15q13 deletions.

The analysis of variance analyses identified 129 significantly dysregulated transcripts [$P < 0.05$ and fold change (FC) < -1.5 or > 1.5] (Table 2). We then visualized the most significantly changed transcripts using a more stringent P value ($P < 0.01$ and FC < -1.5 or > 1.5) in the heatmap generated by hierarchical clustering analysis (Fig. 2).

As expected, some genes located in the 15q13 deleted region were downregulated in the two ADHD patients carrying 15q13 deletions: *KLF13*, P value: 3.26×10^{-5}, FC: −1.9; *MTMR10*, P value: 0.0032, FC: −1.9. *CHRNA7* did not show significant P values ($P = 0.9$, FC: −1.01), possibly because of its very low expression levels in the blood.

We then used the 129 transcripts that were modulated significantly in ADHD patients carrying the 15q13 deletion to carry out a pathways analysis and found several pathways to be significantly dysregulated in the ADHD deletion carriers ($P < 0.005$ after multiple test correction): apoptosis ($P = 2.44 \times 10^{-76}$), oxidative stress ($P = 1.75 \times 10^{-39}$), as well as immune response ($P = 2.93 \times 10^{-35}$) signaling (Table 3).

Interestingly, when we carried out a target prediction analysis for the genes belonging to the 15q13 deletion region (*KLF13*, *MTMR10*, *CHRNA7*) and that were significantly downregulated in ADHD patients carrying the 15q13 deletion (*KLF13*, *MTMR10*), we observed (Fig. 3) that many of these gene targets belonged to the same immune/inflammatory and oxidative stress signaling pathways. In Fig. 3, we show the main gene networks activated by the *KLF13* and *CHRNA7* genes. Interestingly, the same pathways that we found to be significantly modulated in the data set of the 129 dysregulated transcripts are also the main network activated by genes affected by the presence of 15q13 deletions.

Discussion

Our results showed the presence of 15q13 deletions in two ADHD patients, whereas no genomic rearrangements of this region were found in the control samples. The low frequency of 15q13 CNVs observed in our patients (1.72%) is similar to that observed for 15q11q13 CNVs by Williams *et al.* (2010) (1.91%), who carried out a genome-wide analysis of 410 children with ADHD, all of white UK origin.

To our knowledge, this is the first report of this recurrent CNV in Italy for ADHD patients. These findings are in line with other ADHD studies (Lionel *et al.*, 2011; Williams *et al.*, 2012), and also with studies that identified 15q13 CNVs in other psychiatric disorders, such as schizophrenia (Stefansson *et al.*, 2008; Stone *et al.*, 2008; Van Bon *et al.*, 2009; Stephens *et al.*, 2012), autism (Pagnamenta *et al.*, 2009), and epilepsy (Dibbens *et al.*, 2009; Helbig *et al.*, 2009). The overlap in CNV loci among disorders suggests pleiotropy of genes predisposing to these diseases (Moskvina *et al.*, 2009).

Moreover, both ADHD patients with 15q13 deletions had total IQs that are in the lower quartiles of normal (92 and 81). This confirms that the 15q13 deletion is associated with lower overall IQ in ADHD patients, as also reported in the study by Williams *et al.* (2010).

We also found a significant difference in gene expression profiles between ADHD patients carrying deletions in 15q13 and ADHD patients without deletions in that region. As expected, two genes from the 15q13 deleted region (*KLF13*, *MTMR10*) were significantly downregulated in the two patients carrying 15q13 deletions.

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Table 2 One hundred and twenty-nine genes significantly dysregulated in the blood of the two ADHD patients with deletions in 15q13 compared with nine ADHD patients without 15q13 deletions ($P < 0.05$ and fold change < -1.5 or > 1.5)

	Gene symbol	Gene assignment	P value (deletion)	Fold change
1	SIDT1	SID1 transmembrane family member 1	1.56E−05	−1.6
2	KLF13	Kruppel-like factor 13	3.26E−05	−1.9
3	CD38	CD38 molecule	3.72E−05	−1.7
4	STARD9	StAR-related lipid transfer (START) domain containing 9	6.87E−05	−1.6
5	CTU1	Cytosolic thiouridylase subunit 1 homolog (*Schizosaccharomyces pombe*)	7.19E−05	−1.5
6	CD81	CD81 molecule	7.34E−05	−1.6
7	IL27RA	Interleukin 27 receptor, alpha	8.16E−05	−1.7
8	HIST1H2BM	Histone cluster 1, H2bm	0.00017071	−1.9
9	FAM78A	Family with sequence similarity 78, member A	0.00022135	−1.5
10	ZAP70	Zeta-chain (TCR) associated protein kinase 70 kDa	0.00026375	−1.7
11	HIST1H3I	Histone cluster 1, H3i	0.00042204	−1.9
12	LLGL2	Lethal giant larvae homolog 2 (Drosophila)	0.00069374	−1.6
13	DUSP18	Dual specificity phosphatase 18	0.00085247	−1.5
14	YPEL1	Yippee-like 1 (Drosophila)	0.00088296	−1.5
15	SLA2	Src-like-adaptor 2	0.00109583	−1.5
16	USP20	Ubiquitin-specific peptidase 20	0.00120489	−1.5
17	TTC38	Tetratricopeptide repeat domain 38	0.0013294	−1.5
18	HIST2H3C	Histone cluster 2, H3c	0.00133776	−1.6
19	PI3	Peptidase inhibitor 3, skin-derived	0.00210276	3.1
20	SYT11	Synaptotagmin XI	0.00230888	−1.6
21	ZNF597	Zinc finger protein 597	0.0023228	−1.6
22	CEP78	Centrosomal protein 78 kDa	0.00247458	−1.9
23	TULP3	Tubby-like protein 3	0.00253636	−1.6
24	MRPL49	Mitochondrial ribosomal protein L49	0.0026203	−1.5
25	SCARNA9L	Small Cajal body-specific RNA 9-like	0.00309212	−2.3
26	FUT3	Fucosyltransferase 3 [galactoside 3(4)-L-fucosyltransferase]	0.00316799	1.7
27	MTMR10	Myotubularin-related protein 10	0.00324594	−1.9
28	VNN1	Vanin 1	0.00430811	1.7
29	TLE1	Transducin-like enhancer of split 1 [E(sp1) homolog, Drosophila]	0.0044082	−1.8
30	PRF1	Perforin 1 (pore-forming protein)	0.00460118	−1.6
31	JAZF1	JAZF zinc finger 1	0.00462456	−1.8
32	OPTC	Opticin	0.00503031	1.6
33	LOC100133315	Transient receptor potential cation channel, subfamily C	0.00514394	−1.8
34	EFTUD1	Elongation factor Tu GTP binding domain containing 1	0.00563133	−1.6
35	TOX	Thymocyte selection-associated high-mobility group box	0.00657298	−1.7
36	KRTAP4-3	Keratin-associated protein 4-3	0.00659143	1.7
37	ARHGAP23	Rho GTPase activating protein 23	0.0066427	−1.9
38	PRDX6	Peroxiredoxin 6	0.00668549	−1.8
39	SH2D2A	SH2 domain containing 2A	0.00674759	−1.5
40	OR7G3	Olfactory receptor, family 7, Subfamily G, member 3	0.007437	1.7
41	HIST1H2BH	Histone cluster 1, H2bh	0.00752556	−1.7
42	OR10H2	Olfactory receptor, family 10, Subfamily H, member 2	0.00860143	1.6
43	UBE2F	Ubiquitin-conjugating enzyme E2F (putative)	0.0102957	−1.7
44	ELOF1	Elongation factor 1 homolog (*Saccharomyces cerevisiae*)	0.0108196	−1.6
45	EMC3	ER membrane protein complex subunit 3	0.0113859	−1.6
46	GPR56	G protein-coupled receptor 56	0.0115175	−1.9
47	SNUPN	Snurportin 1	0.0115562	−1.5
48	RPIA	Ribose 5-phosphate isomerase A	0.0116402	−1.7
49	TMEM116	Transmembrane protein	0.0126389	−1.6
50	DEXI	Dexi homolog (mouse)	0.0128963	−1.9
51	SHISA4	Shisa homolog 4 (*Xenopus laevis*)	0.01313	1.6
52	ARHGAP23	Rho GTPase activating protein	0.013844	1.9
53	YOD1	OTU deubiquinating enzyme 1 homolog (*S. cerevisiae*)	0.0142472	−1.6
54	DIP2A	DIP2 disco-interacting protein 2 homolog A (Drosophila)	0.015922	−1.6
55	FAM99A	Family with sequence similarity 99, member A (nonprotein coding)	0.0162297	1.7
56	LRRC18	Leucine-rich repeat containing 18	0.0163249	1.8
57	ZFP90	Zinc finger protein 90 homolog (mouse)	0.0167504	−1.6
58	LINC00299	Long intergenic nonprotein coding RNA	0.0176272	−1.6
59	HIST1H2BC	Histone cluster 1, H2bc	0.0178361	−1.6
60	RPA2	Replication protein A2, 32 kDa	0.0182596	−1.6
61	ACADM	Acyl-CoA dehydrogenase, C-4 to C-12 straight chain	0.0184106	−1.5
62	ASTE1	Asteroid homolog 1 (Drosophila)	0.0184753	−1.6
63	SERPINB3	Serpin peptidase inhibitor, clade B (ovalbumin), member 3	0.0196835	1.6
64	ATP6V1D	ATPase, H+ transporting, lysosomal 34 kDa, V1 subunit D	0.0201942	−1.6
65	SRXN1	Sulfiredoxin 1	0.020326	1.7
66	SCGB1A1	Secretoglobin, family 1A, member 1 (uteroglobin)	0.0204639	1.8
67	RBMX	RNA-binding motif protein, X-linked	0.0206876	−0.2
68	TTI2	TELO2 interacting protein 2	0.0211204	−1.8
69	HARS	Histidyl-tRNA synthetase	0.0215574	−1.6
70	CGB5	Chorionic gonadotropin, beta polypeptide 5	0.0216971	1.5
71	RPSA	Ribosomal protein SA	0.0218604	−1.7
72	HIST2H2AA3	Histone cluster 2, H2aa3	0.0221445	−1.6
73	SLCO4C1	Solute carrier organic anion transporter family, member 4C1	0.02266	−1.6
74	CCR3	Chemokine (C–C motif) receptor 3	0.0227878	−1.8

Table 2 (*continued*)

	Gene symbol	Gene assignment	*P* value (deletion)	Fold change
75	JAKMIP2	Janus kinase and microtubule interacting protein 2	0.0232163	−1.6
76	OR51B4	Olfactory receptor, family 51. Subfamily B, member 4	0.0236548	1.6
77	TBC1D7	TBC1 domain family, member 7	0.0236723	−1.6
78	CGB7	Chorionic gonadotropin, beta polypeptide 7	0.0243057	1.5
79	FAM48B1	Family with sequence similarity 48, member B1	0.024683	1.8
80	ANKRD11	Ankyrin repeat domain 11	0.0251498	−1.9
81	CSDA	Cold shock domain protein A	0.0256404	−1.6
82	CDRT1	CMT1A duplicated region transcript 1	0.0262512	1.6
83	LGALS14	Lectin, galactoside-binding, soluble 14	0.0262856	1.6
84	MUC3B	Mucin 3B, cell surface-associated	0.0265501	1.7
85	MCM8	Minichromosome maintenance complex component 8	0.0268405	−1.6
86	IGKV1D-42	Immunoglobulin kappa variable 1D-42 (nonfunctional)	0.0283412	−1.7
87	SH2D1B	SH2 domain containing 1B	0.0287854	−2.1
88	KRT18	Keratin 18	0.0290164	−1.6
89	OR51E2	Olfactory receptor, family 51. Subfamily E	0.0294379	1.6
90	OR14I1	Olfactory receptor, family 14. Subfamily I, member 1	0.0306603	1.6
91	RFPL4A	Ret finger protein-like 4A	0.031631	1.5
92	RPS12	Ribosomal protein S12	0.0322135	−1.5
93	CHORDC1	Cysteine and histidine-rich domain (CHORD) containing 1	0.0329611	−1.5
94	SNORD38B	Small nucleolar RNA, C/D box 38B	0.0333204	−1.5
95	SLC48A1	Solute carrier family 48 (heme transporter), member 1	0.0343111	−1.5
96	HSPA2	Heat shock 70 kDa protein 2	0.0345332	1.6
97	OR3A1	Olfactory receptor, family 3. Subfamily A, member 1	0.0348752	1.7
98	DHFR	Dihydrofolate reductase	0.0351019	−1.6
99	CYP4Z1	Cytochrome P450, family 4. Subfamily Z, polypeptide 1	0.0353701	1.6
100	PPDPF	Pancreatic progenitor cell differentiation and proliferation factor	0.0355663	−1.6
101	MBNL3	Muscleblind-like splicing regulator 3	0.0361796	−1.9
102	PTPN22	Protein tyrosine phosphatase, nonreceptor type 22 (lymphoid)	0.0362042	−1.6
103	ENC1	Ectodermal-neural cortex 1 (with BTB-like domain)	0.0363468	−1.5
104	MUC12	Mucin 12, cell surface-associated	0.0365138	3.2
105	FCRL6	Fc receptor-like 6	0.0366632	−1.8
106	TPRX1	Tetra-peptide repeat homeobox 1	0.036786	1.8
107	TRAV19	T-cell receptor alpha variable 19	0.0377103	−1.7
108	LCN8	Lipocalin 8	0.0387392	1.9
109	CTSE	Cathepsin E	0.0392981	−1.7
110	TBC1D28	TBC1 domain family, member 28	0.0399368	1.6
111	KRTAP10-5	Keratin-associated protein 10-5	0.0400279	1.6
112	IGSF21	Immunoglobin superfamily, member 21	0.0401894	1.5
113	GRAP	GRB2-related adaptor protein	0.040266	−1.6
114	SCARNA9L	Small Cajal body-specific RNA 9-like	0.0405693	−1.5
115	CMKLR1	Chemokine-like receptor 1	0.0406512	−1.5
116	HIST1H2AJ	Histone cluster 1	0.0409278	−1.7
117	C14orf45	Chromosome 14 open reading frame 45	0.041883	−1.7
118	MICA	MHC class I polypeptide-related sequence A	0.0419817	−1.6
119	CKMT1A	Creatine kinase, mitochondrial 1A	0.0432747	1.7
120	CKMT1A	Creatine kinase, mitochondrial 1A	0.0432747	1.7
121	SRRD	SRR1 domain containing	0.0439037	−1.6
122	GPR128	G protein-coupled receptor 128	0.0440475	2.8
123	MUT	Methylmalonyl CoA mutase	0.0446626	−1.5
124	EFCAB4B	EF-hand calcium-binding domain 4B	0.0461407	−1.6
125	ANKRD50	Ankyrin repeat domain 50	0.0467662	−1.6
126	SRD5A3	Steroid 5 alpha-reductase 3	0.0475235	−1.7
127	ABCE1	ATP-binding cassette. Subfamily E (OABP), member 1	0.0476485	−1.5
128	G6PC2	Glucose-6-phosphatase, catalytic 2	0.0491228	1.6
129	ABCD1	ATP-binding cassette. Subfamily D (ALD), member 1	0.0498771	−1.6

ADHD, attention-deficit hyperactivity disorder.

Our pathways analyses indicated that apoptosis, oxidative stress, and immune response signaling were the most significantly differentially modulated pathways linked to 15q13 deletions. Interestingly, we found that deletions in *KLF13* and *CHRNA7* genes affected the expression levels of genes implicated in the same immune response signaling, inflammatory as well as stress oxidative pathways. Furthermore, three genes from our list of genes that were significantly altered in ADHD patients with 15q13 deletions [*IL27RA*, interleukin 27 receptor, alpha; *ZAP70*, zeta-chain (TCR)-associated protein kinase 70 kDa; *FUT3*, fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group)] were part of immune/inflammatory response signaling. Similarly, the *PRDX6* (peroxiredoxin 6) gene encoding a thiol-specific antioxidant protein, in our gene list, found to be down-regulated in ADHD patients with 15q13 deletions, belonged to the oxidative stress pathway (Fig. 3).

The *KLF13* gene encodes a transcription factor; it plays an important role in activating *CCL5* (RANTES) gene expression in T lymphocytes (Song *et al.*, 1999). CCL5 is

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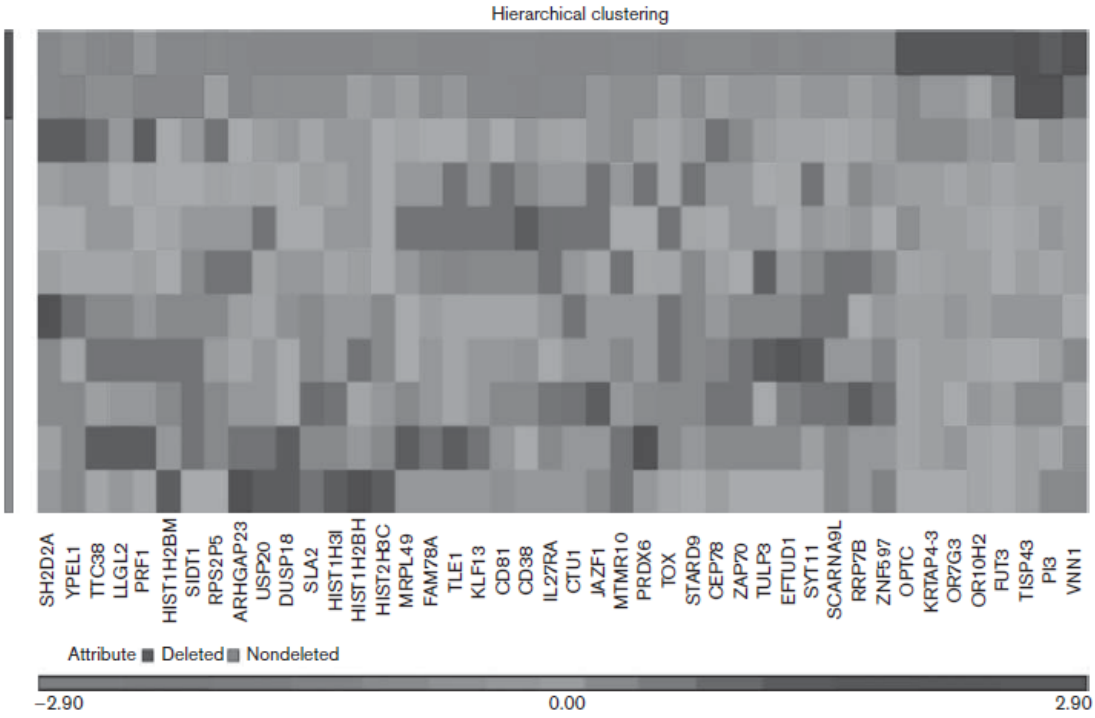
Fig. 2



Heatmap showing the results of hierarchical clustering of our dataset. It identifies two main groups (left side). Black: patients carrying deletions in 15q13; gray: patients without deletions in 15q13. Thirty-five genes are downregulated and 8 genes upregulated in ADHD patients carrying deletions in 15q13 versus ADHD patients without deletions in 15q13. ADHD, attention-deficit hyperactivity disorder.

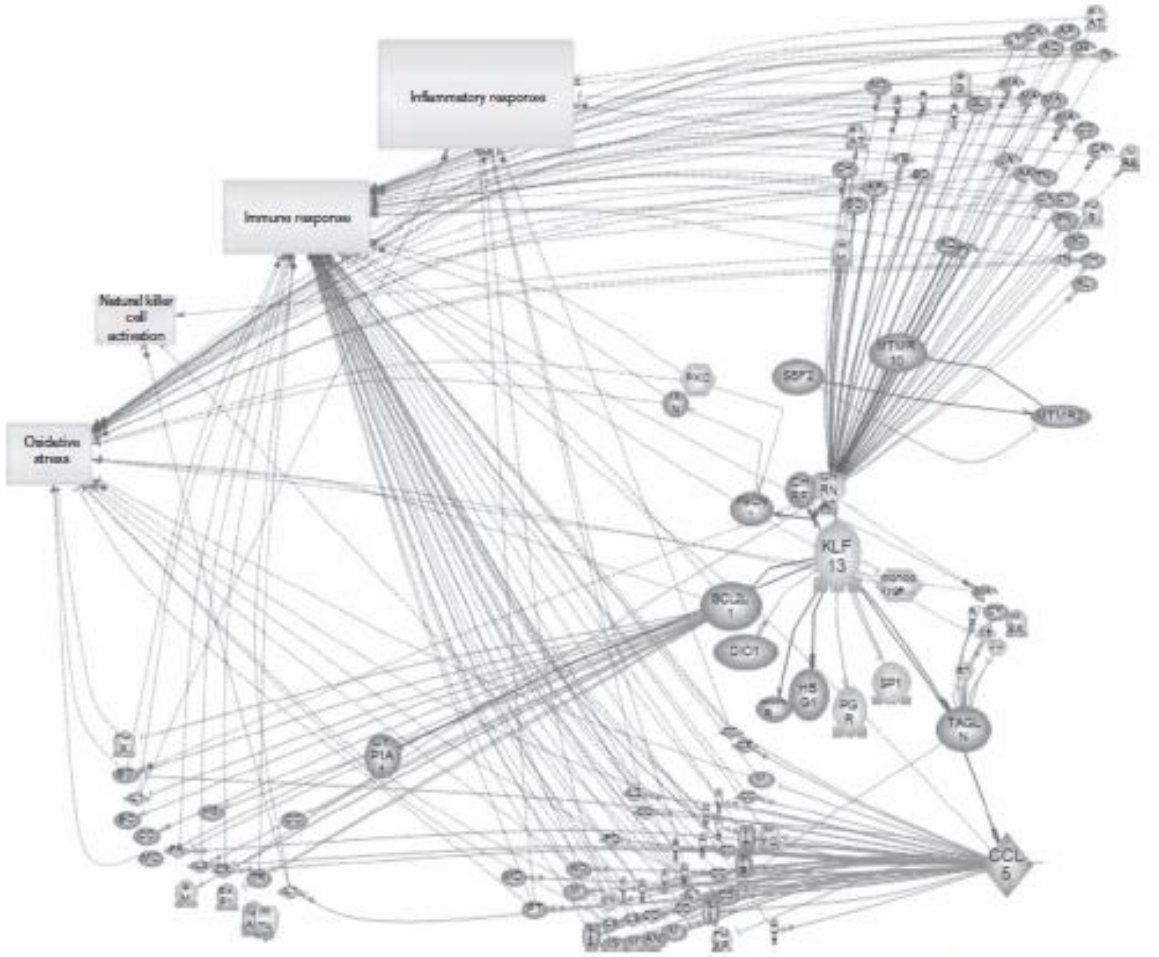
Table 3 Pathways regulated by 15q13 deletion genes

Name	*P* value
Apoptosis	2.44E−76
Oxidation reduction	1.75E−39
Immune response	2.94E−35
Oxidoreductase activity	2.44E−20
Oxidoreductase activity. Acting on single donors with incorporation of molecular oxygen, incorporation of two atoms of oxygen	0.000332
Cell cycle regulation	1.37E−10
Hedgehog pathway	4.12E−06
Nicotinate and nicotinamide metabolism	1.51E−05
Axon guidance	1.76E−05
Guanylate cyclase pathway	0.000134
Apoptosis regulation	0.000191
B-cell activation	0.000305
Gap junction regulation	0.000543
Insulin action	0.000923
Respiratory chain and oxidative phosphorylation	0.001402
Metabolism of triacylglycerols	0.004377
NK-cell activation	0.005798

a member of the chemokines family and is involved in immune/inflammatory events. *KLF13* may regulate multiple stages of both B-cell and T-cell development, in accordance with evidence emerging from murine models (Outram *et al.*, 2008). As expected, we observed down-regulation of this gene, which is further confirmed by another study that reported a decrease in the mRNA levels of this gene in a proband with a homozygous 15q13.3 microdeletion compared with controls (Le Pichon *et al.*, 2013). Thus, because it has been suggested that immune response (Ceylan *et al.*, 2012) as well as inflammation (Donev and Thome, 2010) play a key role in the etiology of ADHD, as well as in autism and schizophrenia (Gibney and Drexhage, 2013), decreased *KLF13* expression could be indirectly involved in these pathologies.

CHRNA7 is located within the deleted region, but shows low expression levels in our blood samples. Our target prediction analysis, however, suggests that it also influences immune response and inflammatory signaling, both of which may be involved in the pathogenesis of ADHD (Donev and Thome, 2010; Ceylan *et al.*, 2012) or other psychiatric disorders (Gibney and Drexhage, 2013). We cannot differentiate the effects of *CHRNA7* from other deleted genes from the same region, but we can speculate that *CHRNA7* is likely to contribute significantly toward immune response and inflammatory signaling pathways. It has been reported that stimulation of *CHRNA7* on human polymorphonuclear neutrophils and

Fig. 3



A target prediction analysis showed the pathways influenced by the genes belonging to the 15q13 deletion (*KLF13*, *MTMR10*, *CHRNA7*). *KLF13* and *CHRNA7* activated inflammatory response, immune response, and oxidative stress networks.

blood mononuclear phagocytes *in vitro* attenuates the expression of leukocyte markers involved in cell recruitment and adhesion, and release of tumor necrosis factor-α and other proinflammatory cytokines (Vukelic *et al.*, 2013).

KLF13 and *CHRNA7* influence the oxidative stress pathway. Some evidence showed that oxidative stress might suppress the expression of the *CHRNA7* at protein and mRNA levels during the early stages of damage in PC12 cells (Guan *et al.*, 2001) as well as in polymorphonuclear neutrophils and blood mononuclear phagocytes *in vitro* (Vukelic *et al.*, 2013). Moreover, several studies have shown the implication of reactive oxygen species in the regulation of RANTES (Lin *et al.*, 2000; Barlic and Murphy, 2007; Tripathy *et al.*, 2007, 2010).

There are findings that support that oxidative metabolism may play a role in the etiopathogenesis of ADHD, with a meta-analysis of extant studies showing increased markers of oxidative stress among unmedicated ADHD patients compared with controls [Joseph *et al.* (in press)]. Alterations in the oxidative stress pathway are also observed for other psychiatric disorders (Ghanizadeh *et al.*, 2013; Wu *et al.*, 2013).

Thus, our results indicate that immune/inflammatory and oxidative stress pathways dysregulated in ADHD patients carrying the 15q13 deletion appear to play a role not only in ADHD but also in other psychiatric disorders such as schizophrenia and autism. This strengthens the issue on the pleiotropic effects of 15q13 deletions and thus on the existence of shared biologic signaling among

multiple neuropsychiatric disorders. Evidence for shared genetic causes among disorders has also been shown for common variants (Cross-Disorder Group of the Psychiatric Genomics Consortium *et al.*, 2013). Furthermore, for inflammatory response, it has also been reported that ADHD patients are at a higher risk for asthma (Fasmer *et al.*, 2011; Mogensen *et al.*, 2011; Kwon *et al.*, 2014). Investigation of the mechanisms associated with deletion could explain the common origin of different psychiatric pathologies.

We acknowledge that this study has some limitations. Because 15q13 CNVs are rare, it is possible that any pathophysiologic insights from CNV carriers may not be generalizable to other ADHD patients. However, it is possible that ADHD CNVs impact the same biological pathways as common variation. If so, our results would be relevant to a larger subset of patients. It is also important to underline that the frequency of 15q13 CNVs observed in our patients is similar to that observed in other European courts. Another limitation is that our gene expression study used ADHD patients without deletions as controls. Although this allows us to differentiate the effects of the deletions from the effects of other sources of ADHD's etiology, it is possible that our power was reduced to detect pathways that have heterogenous etiologies.

Our gene expression study was carried out in leukocytes, a peripheral tissue. Although not all genes expressed in the brain are also expressed in blood, several considerations suggest that peripheral gene expression studies can be useful (Sullivan *et al.*, 2006; Rollins *et al.*, 2010). Moreover, although the brain is clearly the locus for much of psychiatric pathophysiology, numerous studies implicate processes such as inflammation and abnormal immune responses, which are expressed in peripheral tissues (Gladkevich *et al.*, 2004), and would be expected to impact gene expression in blood cells. It is also likely that some gene expression profiles may be epiphenomena of brain activity. A systematic review of the literature shows that peripheral measures of neurotransmitters and their metabolites are associated significantly with brain levels (Marc *et al.*, 2011). Consistent with this, in a recent meta-analysis, we showed that four peripheral measures of monoamine metabolism significantly discriminated ADHD and non-ADHD samples (Scassellati *et al.*, 2012). Although these brain-related changes in neurotransmitters and metabolites in the periphery are not caused by blood cell gene expression, they likely have effects on gene expression that are useful for differentiating ADHD cases from controls.

Finally, a further limitation is linked to *CHRNA7* expression. Despite the importance of this gene in a variety of neuropsychiatric phenotypes (Miller *et al.*, 2009; Shinawi *et al.*, 2009), including ADHD (Stergiakouli *et al.*, 2012; Williams *et al.*, 2012), it is not sufficiently expressed in blood to have been informative for our analyses. However, contrasting results for the expression of this gene in blood have been reported (Sato *et al.*, 1999; Benfante *et al.*, 2011; Van der Zanden *et al.*, 2012; Le Pichon *et al.*, 2013). Higher expression of *CHRNA7* in the brain highlights the potential importance of this gene in the central nervous system (Le Pichon *et al.*, 2013).

Conclusion

Our findings are consistent with the presence of 15q13 deletions in Italian ADHD patients. More interestingly, we show that pathways related to immune/inflammatory response and oxidative stress signaling are affected by the deletion of *KFL13* and *CHRNA7*. Because the phenotypic effects of 15q13 are pleiotropic, our findings imply the existence of shared biologic pathways among multiple neuropsychiatric conditions.

Acknowledgements

The authors thank the patients and their families for their cooperation. Moreover, they also thank the following neuropsychiatrists for sample recruitment: A. Tiberti, P. Effedri, E. Filippini, S. Conte, M. Pezzali, D. Arisi, G. Piccini, and G. Chiarenza. This research was supported by grants from the Fondazione Mariani [RF2006] and from the Italian Ministry of Health [Ricerca Corrente].

Conflicts of interest

In the past year, Dr Faraone received consulting income and/or research support from Shire, Akili interactive Labs, VAYA Pharma, SynapDx, and Alcobra and research support from the National Institutes of Health (NIH). His institution is seeking a patent for the use of sodium–hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. Dr Faraone receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health. For the remaining authors there are no conflicts of interest.

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Focus

IL REGISTRO ADHD DELLA REGIONE LOMBARDIA

Uno strumento per migliorare i percorsi di cura

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THE LOMBARDY REGION'S ADHD REGISTRY: A TOOL FOR IMPROVING PATHWAYS OF CARE
(Medico e Bambino 2015;34:157-164)

Key words
Attention deficit disorder, Prevalence, Disease registry, Treatment planning, Epidemiology

Summary
Background *- Despite a pooled, worldwide ADHD prevalence of 5.29% in children and adolescents, the rates vary widely between and within countries. Such variability in prevalence rates often corresponds to heterogeneous methodologies used for diagnostic evaluation in the studies. The aim was to estimate the prevalence of ADHD and define the socio-demographic, clinical, and prescription profiles of the subjects enrolled in Italy's Lombardy Region's ADHD Register.*
Method *- Data on patients evaluated by the 18 regional ADHD reference centres in the 2012-2013 period were analysed.*
Results *- 753 of 1.150 (65%) suspected patients received a diagnosis of ADHD (M:F=6:1; range:5-17 yrs). In 24% of cases there was a family history of ADHD. 483 (64%) patients had at least one psychopathological disorder, the more common of which were learning disorders (35%), sleep disturbances (14%), and oppositional defiant disorder (13%), while 68 (9%) patients had other chronic medical conditions. 84% of patients received a prescription for psychoeducational interventions (most commonly parent training, n=428, 82%, child training, n=308, 59%, and teacher training, n=173, 33%), 2% received only pharmacological treatment, and 14% a combination of both. Of the 115 patients receiving drug therapy, 95 (83%) were treated with methylphenidate, 7% (n=8) with atomoxetine, and 10% (n=12) with another drug, especially risperidone. Compared to subjects treated with a psychoeducational intervention alone, patients with drug prescriptions more commonly presented values of CGI-S of 5 or higher (p< .0001), lower cognitive levels (p= .0019), and associated disorders, such as oppositional defiant disorder (p< .0001) and sleep disturbances (p=.0007).*
Conclusions *- The registry has revealed to be an essential tool for a continuous, systematic monitoring of patterns of care, and allows resources to be invested appropriately, based on documented needs, thus promoting progressive, significant improvements in clinical practice and ensuring an efficient and homogeneous quality of care.*

Una chiave di lettura

Circa trenta anni fa fu teorizzata (Basaglia prima; Maccacaro, Panizon e Tognoni dopo) la possibilità di organizzare, nella realtà italiana, un osservatorio sulla pratica della psicofarmacologia in pediatria. Agli inizi degli anni 2000 si avanzò l'ipotesi di utilizzare la reintroduzione del farmaco metilfenidato sul mercato italiano come una occasione irripetibile per un percorso di formazione e integrazione tra le figure responsabili del bambino con vero o presunto ADHD (genitori, insegnanti, pediatra di famiglia, specialista neuropsichiatra ecc.)[1]. Visto sotto questa prospettiva, l'utilizzo dei farmaci per il trattamento dell'ADHD in associazione con interventi di tipo psico-educativo e cognitivo-comportamentale, poteva (e può) assumere il ruolo di un indicatore di bisogni, consentendo di definire il contesto sociale, culturale e diagnostico-assistenziale che riguarda i bambini con ADHD, con l'ovvio obiettivo di migliorare la qualità dell'intervento in generale e naturalmente di precisare il ruolo dei protagonisti della diagnosi e cura di un problema che stime recenti riportano con una prevalenza pari a circa l'1-2% della popolazione pediatrica e adolescenziale.

Nel corso di questi anni la saga italiana dell'ADHD[2] è continuata ed è pressoché unica a livello internazionale. Una serie di opportunità hanno consentito di definire un percorso diagnostico e terapeutico per i pazienti con ADHD basato sulle evidenze e sull'appropriatezza. L'attuazione nella pratica di tale percorso era (ed è) altra cosa, perché necessita di: a) una diversa organizzazione dei Servizi di neuropsichiatria; b) una maggior disponibilità di risorse (anche umane); c) un appropriato e costante aggiornamento degli operatori; d) una valutazione degli interventi; e) una informazione documentata, scientifica e indipendente, per l'intera comunità.

Con queste finalità si è definito "il percorso italiano dell'ADHD" già prima della reintroduzione in commercio del metilfenidato (avvenuta nel 2007), sino all'attuazione del Progetto Regionale Lombardo (punto più avanzato del percorso). Il modello ADHD doveva rappresentare, come detto, anche la fase pilota o il disturbo/pretesto di una valutazione di fattibilità per estenderlo e generalizzarlo (con le dovute migliorie) agli altri disturbi/bisogni che alterano la salute mentale nell'età evolutiva. Non tutti hanno colto il potenziale dell'insieme delle varie iniziative messe in atto, rimanendo vincolati a visioni e modalità di piccolo cabotaggio, invece di affrancarsi con sperimentazioni innovative volte al migliora-

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mento della qualità e appropriatezza delle cure quotidiane. Forse si è chiesto troppo anche alla stessa comunità neuropsichiatrica infantile italiana ancora caratterizzata dall'imprinting dei due procreatori culturali storici (neurologi/epilettologi e psicoanalisti) ed è rimasta, ancora una volta, "una concretissima utopia"[3].

Medico e Bambino è stato, tra i pochi, attento al multimodale svilupparsi del "percorso italiano dell'ADHD"[4-7]. Il presente *Focus*, per forma e contenuto, è parte di questo monitoraggio, con la finalità di stimolare riflessioni e considerazioni anche in ambito pediatrico.

Il *Focus* parte dalla sintesi dei risultati del Registro della Regione Lombardia, con la richiesta di pareri e commenti da parte di quelli che sono i protagonisti della possibile diagnosi, assistenza e cura dei bambini con ADHD. I dati del Registro ci dicono che i bambini che sono stati "intercettati" dai servizi sono molto minori rispetto all'atteso e che quelli che hanno ricevuto un trattamento farmacologico sono pochi. Non crediamo, come è stato detto da parte di alcuni su organismi di stampa nazionale, che i dati del Registro fanno giustizia di diagnosi in eccesso e di sopravvalutazione di un problema molto "americano". Si tratta di una posizione "ideologica", come giustamente sottolineato da Panei nel suo commento. Semmai, possiamo dire, come riporta Zuddas, che può essere vero il contrario, vale a dire che, nonostante il Registro, continua ad esistere una "negazione di un importante bisogno di salute, per il quale da anni sono disponibili strumenti terapeutici altamente efficaci e sicuri".

Il problema non può essere affrontato con una visione che conta i numeri dei pazienti con ADHD ("il poco o il tanto"). La chiave di lettura più giusta, che riguarda gli operatori socio-sanitari che devono porsi la domanda se quel bambino che va male a scuola e ha una condotta iperattiva, può avere o meno un disturbo da deficit di attenzione con iperattività, è quella di chiedersi se siamo sufficientemente in grado di "fare bene" di fronte a situazioni sospette o certe di ADHD che richiedono competenze, professionalità, rete di lavoro. E i commenti che seguono i dati del Registro (da quelli dell'insegnate a quello del genitore, per arrivare a quelli degli specialisti) ci fanno capire chiaramente che la strada da percorrere è ancora lunga, per poter dare voce e contenuto professionale a quello che ci dice e che auspica la sig.ra Occhipinti: "sarebbe utile diffondere un'apertura a questo tipo di disturbo perché, se conosciuto, studiato, approfondito, può essere affrontato e gestito".

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Il Registro della Regione Lombardia sull'ADHD

Il Registro lombardo dell'ADHD è stato attivato a partire da giugno 2011 nell'ambito del progetto "Condivisione dei percorsi diagnostico-terapeutici per l'ADHD in Lombardia", con il contributo della Regione Lombardia. Gli obiettivi principali del progetto sono: monitorare l'attività dei Centri di riferimento regionali per l'ADHD; definire e garantire percorsi diagnostico-terapeutici appropriati e condivisi; intensificare la formazione e l'aggiornamento degli operatori e informare i cittadini. Il Registro, in particolare, è stato concepito come registro di malattia, quindi sono raccolte informazioni relative non solo ai pazienti con diagnosi di ADHD in trattamento farmacologico (come previsto dal Registro Nazionale), ma anche a tutti i pazienti che affe-riscano al Centro di riferimento con sospetto ADHD. Questo studio, realizzato attraverso l'analisi dei dati inseriti nel Registro dai 18 Centri di riferimento regionali per l'ADHD, rappresenta la prima valutazione sistematica dei percorsi di diagnosi e cura dei pazienti con ADHD in Italia in un'ampia popolazione che accede ai Centri di riferimento regionali. Un risultato importante di un progetto ambizioso, a tutt'oggi unico non solo nel panorama nazionale, che ha coinvolto i pazienti, le famiglie, gli insegnanti e gli operatori.

L'articolo completo pubblicato su *Ricerca & Pratica* (2014;30:198-211) ha suscitato interesse, critica, apprezzamento... come atteso. Nel *Box 1* è riportata la sintesi dei risultati dello studio.

Box 1 - I DATI DEL REGISTRO DELLA REGIONE LOMBARDIA SULL'ADHD

I dati relativi ai nuovi pazienti valutati dai 18 Centri di riferimento lombardi nel periodo 2012-2013 sono stati estrapolati dal database del Registro regionale ADHD e analizzati per descrivere le caratteristiche clinico-diagnostiche e prescrittive del campione.
753 dei 1150 casi sospetti (65%) hanno ricevuto una diagnosi di ADHD (M:F=6:1; età mediana: 9 aa; range: 5-17 aa), nel 24% dei casi era presente familiarità per ADHD. 483 (65%) pazienti presentavano almeno un altro disturbo psicopatologico, più frequentemente disturbi dell'apprendimento (35%), disturbi del sonno (14%) e disturbo oppositivo-provocatorio (13%); mentre 69 (9%) avevano in associazione altra condizione medica cronica, per lo più di tipo neurologico (n=28).
L'85% dei pazienti ha ricevuto una prescrizione di tipo psicologico, più comunemente *Parent training* (n=428, 82%), seguito da *Child training* (n=308, 59%) e *Teacher training* (n=173, 33%); il 2% solo farmacologica, il 13% entrambe. Dei 115 pazienti con terapia farmacologica, 95 (83%) sono stati trattati con metilfenidato, 5 dei quali in associazione con un altro psicofarmaco, il 7% (n=8) con atomoxetina e il restante 10% (n=12) con un altro farmaco, in particolare risperidone. Rispetto ai soggetti cui è stato prescritto solo l'intervento psicologico, i pazienti con prescrizione farmacologica presentavano più frequentemente valori di CGI-S di 5 o superiore (p<0,0001), livello cognitivo inferiore (p=0,0019), la presenza di disturbi associati, quali il disturbo oppositivo-provocatorio (p<0,0001) e i disturbi del sonno (p=0,0007).
Il Registro ha rappresentato un essenziale strumento di monitoraggio continuo e sistematico che ha permesso di programmare e usare in modo appropriato le risorse sulla base dei bisogni (grado e tipo di domanda), attivando progressivi e significativi miglioramenti nella pratica clinica e garantendo un'efficiente e omogenea qualità delle cure.

Il contesto ideale di diagnosi e assistenza del bambino con ADHD

I genitori sono di solito i primi che si accorgono delle difficoltà dei loro figli o, se anche tali difficoltà vengono segnalate dalle insegnanti, sono i genitori che per primi si rivolgono al pediatra. Se si sospetta l'ADHD (disturbo da deficit di attenzione/iperattività) il pediatra dovrebbe indirizzare la famiglia ai Centri di riferimento regionali per la diagnosi e la cura dell'ADHD. La diagnosi di ADHD deve basarsi su una valutazione accurata del bambino condotta da un neuropsichiatra infantile, con esperienza sulla diagnosi e terapia dell'ADHD e sugli altri disturbi che possono mimarne i sintomi (diagnosi differenziale) o che possono associarsi ad esso (comorbilità). Tale valutazione, che può avvalersi delle competenze di altri operatori della salute mentale dell'età evolutiva, deve sempre coinvolgere, oltre al bambino, i suoi genitori e gli insegnanti. Le informazioni diagnostiche devono essere raccolte da fonti multiple al fine di consentire una adeguata definizione del comportamento e della compromissione funzionale del bambino. Inoltre devono sempre essere valutati i fattori socioculturali e l'ambiente di vita. Il trattamento appropriato si basa su un approccio multimodale che combina interventi psicologici di tipo psicoeducativo e cognitivo-comportamentale (effettuati da psicologi con competenze nella terapia dell'ADHD) con terapie farmacologiche, queste ultime per i bambini con sintomatologia tale da compromettere il loro funzionamento, o per coloro che non hanno avuto beneficio dai soli interventi psicologici.

La decisione di intraprendere una terapia farmacologica deve essere presa da un neuropsichiatra. Il percorso di diagnosi e cura più appropriato per l'ADHD, a differenza di altri disturbi psichiatrici dell'età evolutiva, è delineato da linee guida italiane, in accordo con le indicazioni e le evidenze internazionali.

I commenti e le implicazioni

Quando ci capita di avere un problema sentiamo spesso la necessità di condividerlo con gli altri e soprattutto di sentirci confortati ascoltando chi, come noi, ha dovuto affrontare le stesse traversie. Questo accade anche e soprattutto per le famiglie che da anni affrontano la dura battaglia quotidiana, storie di tutti i giorni, con i propri figli affetti da ADHD.

È una lotta con bambini difficili, ma soprattutto contro chi circonda loro e le loro famiglie. Incomprensioni e accuse rivolte a noi genitori per non essere riusciti a educare i nostri figli, accuse che dopo anni spesso si fanno convinzione anche negli stessi genitori, quando nessuno riesce a dare loro una giustificazione plausibile del perché il proprio bambino sia così. Sono le accuse dei parenti, degli amici, dei genitori dei compagni di scuola, talvolta anche degli insegnanti e, non di rado, dei medici.

Nostro figlio è seguito da un'équipe medica da quando aveva sette anni, è stato sottoposto a cure farmacologiche e psicologiche, e devo affermare la verità ogni volta che siamo andati al controllo, oltre ad aiutare mio figlio hanno dato tanto sollievo psicologico anche a noi genitori.

Fin dalla scuola materna, C. aveva grandi difficoltà a portare a termine le consegne date, stare dentro le regole, intessere buone e serene relazioni con i coetanei. Ma la bomba scoppiò quando fece l'ingresso alla scuola elementare. Lì C. rivelò nella sua totalità tutti i bisogni interiori, psicologici, affettivi, relazionali. Un bambino con iperattività, con un deficit dell'attenzione; tutto ciò gli creava grande difficoltà nel comportamento, nelle relazioni con i bambini, con le insegnanti, e tante volte degenerava con aggressività verbale e anche fisica, vivendo grandi conflitti.

Ritengo che lo studio rivolto ai bambini affetti da ADHD sia di fondamentale importanza e sarebbe utile diffondere un'apertura a questo tipo di disturbo perché, se conosciuto, studiato, approfondito, può essere affrontato e gestito.

La nostra esperienza è stata con momenti di alti e bassi, ma sempre pronti a tutte le novità che a volte ci hanno spaventato, ma grazie al supporto di medici competenti li abbiamo affrontati con coraggio. Noi, come genitori, crediamo che accanto al percorso psicoterapico e psicopedagogico che C. continuerà a fare, il contributo del farmaco potrà aiutare nostro figlio nel suo comportamento e nell'attenzione, migliorando a scuola, nel sociale, a casa. Tutto ciò spero possa portare in C. maggiore autostima, serenità, buone relazioni con i compagni, non più rifiuti dai genitori dei compagni, non più paure e difese da parte degli insegnanti. Anche noi genitori, speriamo, respireremo un po' di più. Puntiamo sul positivo. Crediamo che tutto quello che abbiamo vissuto, anche se con fatica e sacrificio, ci ha aiutato a crescere, ci ha fortificato come persone, come coppia, come famiglia; la nostra fede è cresciuta. L'importante in tutto questo è non stare soli, isolati o nell'ignoranza; bisogna chiedere aiuto, e chiederlo alle persone giuste che hanno esperienza e competenza specifica in questo campo, e saper cogliere tutto ciò che c'è di buono e di sano per darlo ai nostri figli, perché diventino persone serene, equilibrate, che vadano incontro al loro futuro con gioia e speranza.

Ringrazio quanti hanno permesso la pubblicazione delle nostre storie, contribuendo così a questo progetto d'amore.

Concetta Occhipinti
Genitore, Ragusa

Tra i risultati dell'attività del Registro ADHD della Lombardia il dato che balza subito agli occhi è la limitata dimensione della popolazione di pazienti con ADHD che accede ai Centri di riferimento rispetto al totale atteso della ipotizzata popolazione generale con ADHD: 3,5 per mille, quindici volte inferiore alla media mondiale (5,3%). Forse questa differenza dipende dal fatto che i casi raccolti comprendono solo i pazienti che hanno un disturbo medio-grave e con maggiore comorbilità. Credo che questa discrepanza meriterebbe di per sé che il Registro continuasse la sua atti-

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vità, se non altro per verificarne le cause. Un'interpretazione possibile: il percorso regionale consente di ridurre il rischio di sovradiagnosi e di ipertrattamento.

Inoltre solo il 15% dei pazienti ha ricevuto un trattamento psicofarmacologico, quasi tutti uno psicologico, e i farmaci sono stati usati solo nei pazienti più gravi. Risultati anche in questo caso piuttosto confortanti, di contrasto alla sopravvalutazione della patologia e al conseguente abuso di prescrizione di psicofarmaci e di terapie inappropriate e piuttosto lontani da quelli di precedenti studi nazionali e internazionali. L'attività del Registro si è rivelata quindi utile per garantire efficienza e qualità delle cure, plausibilmente anche per la metodologia applicata, che oltre all'attività di Registro ha previsto anche formazione di operatori, genitori e insegnanti, e informazione ai cittadini.

Nella mia trentennale esperienza di pediatra di famiglia (PdF) il problema più grande che ho avuto nel prendermi cura dei miei pazienti con ADHD è stato non tanto la diagnosi, quanto l'invio corretto e in tempi brevi e soprattutto un adeguato follow-up del paziente e supporto della famiglia, proprio per la mancanza di un percorso condiviso tra territorio e strutture di riferimento.

Il supporto di un Registro di malattia come quello della Lombardia, che raccoglie informazioni relative non solo ai pazienti con diagnosi di ADHD e in trattamento farmacologico, ma anche a tutti i pazienti che afferiscono ai Centri di riferimento con sospetto ADHD, mi sembra particolarmente utile per la pratica quotidiana di un PdF, perché risponde a tutte queste esigenze, facilitando la realizzazione di un percorso diagnostico terapeutico appropriato e la corretta gestione nel lungo periodo, con prevedibili risparmi anche di costi economici e socio-sanitari.

Questi aspetti sono rilevanti non solo nella cura del paziente con ADHD e della sua famiglia, ma di tutti i disturbi neuropsichiatrici più gravi dell'età evolutiva. Pertanto, invece che chiudere il Registro per l'ADHD, io vedrei bene di aprire anche un Registro di malattia ad esempio per l'autismo, proprio per diffondere la cultura della corretta "care" di malattie così complesse.

Laura Reali
Pediatra di libera scelta, Roma

Le evidenze in Medicina si basano sui risultati di osservazioni metodologicamente rigorose, sul confronto di tali risultati con quelli di altre osservazioni caratterizzate dallo stesso rigore metodologico e dall'analisi delle rispettive similitudini e delle differenze. Le più recenti e rigorose meta-analisi sulla prevalenza mondiale dell'ADHD riportano tassi intorno al 2,2% dei maschi (0,7 % per le femmine) tra i 4 e i 19 anni, con significative variazioni a seconda dell'età (più frequente nei bambini che negli adolescenti), del genere, del tipo di informatori (genitori, insegnanti o entrambi), e di metodologie (questionari, interviste, fasi di raccolta e screening) ma, a parità di metodologia, con minime variazioni geografiche negli ultimi 30 anni[1]. Anche i pochi dati epidemiologici di popolazione, raccolti in Italia con informatori multipli, confermano tale prevalenza[2,3]. L'epidemiologia di Servizio riportata dal Registro lombardo per l'ADHD (0,035%)[4] indica con chiarezza che i Centri di riferimento di quella Regione (come praticamente in ogni Regione d'Italia) non riescono a intercettare in maniera adeguata i pazienti con tale disturbo. Una possibile spiegazione di tale disparità tra atteso e osservato, avanzata anche dagli Autori dello studio, è che ai Centri di riferimento vengano riferiti, e inseriti nel Registro, solo i casi più gravi: la bassa percentuale di pazienti con disturbo oppositivo provocatorio (10% contro il 60% delle classiche casistiche europee che includono anche bambini e adolescenti italiani[5]) sembra però contraddire questa ipotesi. Lascia peraltro stupiti soprattutto il bassissimo numero di pazienti inseriti in terapia farmacologica. I dati del Registro lombardo riportano che tra i pazienti con sottotipo combinato solo il 20% riceve una terapia farmacologica, l'80% un intervento psicologico, il 20%, in apparenza, nessun intervento. Recenti meta-analisi indicano un modesto *effect size* (ES) per gli interventi di *parent/child /teacher training* sui sintomi *core* di inattenzione, iperattività e impulsività (ES < 0,4); tale modesto ES sembra annullarsi quando l'efficacia viene valutata da osservatori verosimilmente ignari degli interventi messi in atto (*probably blind*: ES 0,02[6]), sebbene con un significativo effetto sui sintomi di condotta (ES 0,3) e sul *parenting* (ES 0,6) anche quando misurato da osservatori ignari dell'intervento[7]. Al contrario, tutte le meta-analisi riportano un ES tra 0,7 e 1 per i diversi farmaci con indicazione specifica per i sintomi *core*[8] dell'ADHD, con elevato profilo di tollerabilità[9,10]. Studi registrativi europei su specifici nuovi farmaci o preparazioni con indicazione specifica per l'ADHD, non in commercio in Italia, mostrano ES tra 1,3 e 1,8[11], con significativo e persistente miglioramento anche della qualità della vita[12]. Crescenti evidenze suggeriscono un effetto preventivo delle terapie farmacologiche per l'ADHD sulle conseguenze a lungo termine del disturbo[13,14], specie per quelli, come il disturbo di condotta, per i quali non esistono attualmente valide terapie[15]. Nel loro insieme, i dati del Registro lombardo suggeriscono che l'atteggiamento clinico di molti operatori non si è significativamente modificato rispetto a quello prevalente a prima della reintroduzione di farmaci specifici per l'ADHD, nonostante l'intensa e meritoria attività di formazione resa possibile dalle risorse economiche che, unica in Italia, la Regione Lombardia ha dedicato al disturbo. L'analisi anche "qualitativa" delle diversità osservabili tra i diversi Centri lombardi (alcuni di essi partecipano con successo a studi europei sull'ADHD) potrebbe essere utile per verificare tale ipotesi.

La maggiore differenza tra l'Italia e gli altri Paesi europei nella gestione dell'ADHD è costituita dall'esistenza del Registro Nazionale, di cui il Registro della Regione Lombardia è una meritoria evoluzione: la complessità delle modalità di prescrizione e di monitoraggio obbligatorio delle prescrizioni farmacologiche correlate ai Registri sembra rendere difficoltosa, in Italia, la diagnosi e la gestione corretta dell'ADHD: tali strumenti, ideati per migliorare appropriatezza e corretta gestione di un disturbo frequente e invalidante, sembrano aver contribuito in maniera significativa a una sorta di mascheramento diagnostico (in alcuni stimolato forse dalla conseguente possibilità di poter così *non prescrivere* un farmaco ritenuto forse utile ma *difficile* da gestire) e alla conseguente negazione di un importante bisogno di salute, per il quale da anni sono disponibili strumenti terapeutici altamente efficaci e sicuri.

Per essendo stato uno dei promotori del Registro Nazionale, a sette anni dalla sua istituzione (che peraltro doveva durare due anni) penso sia giunto il momento di riconsiderarne sia le modalità che la sua stessa utilità.

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Cosa poter dire di più dopo la partecipazione al Convegno a Milano, del 28-29 maggio 2013, "ADHD: per una condivisione dei percorsi diagnostico-terapeutici". Mi si è rivelato un mondo parallelo al mio professionale. Consentitemi di fare qualche riflessione da un osservatorio privilegiato: quello della quotidianità scolastica, cioè otto ore di osservazione continuativa, forse non finalizzata e ben strutturata, ma pur sempre significativa: tempi, modi e ambiti che monitorizzano una persona, il bambino, nella sua specificità, a volte patologica, socio-relazionale-cognitiva.

Quando si considera un caso, possibile ADHD, complicato, misterioso, che si incontra e scontra con una realtà spesso altrettanto complessa, tipica una classe prima di 25, con altri alunni diversamente abili (DVA), e poi con alcuni con bisogni educativi speciali (BES), con una possibile percentuale di stranieri pari al 20%, allora emerge la consapevolezza di non avere strumenti e riferimenti per gestire la portata complessiva del groviglio psichiatrico-psicologico e pedagogico della situazione.

Le difficoltà maggiori che incontriamo come docenti sono innanzitutto:

- definizione del caso nei diversi ambiti: famiglia, scuola, extrascuola; la descrizione e la narrazione della sintomatologia sono frequentemente fraintesi e mal interpretati e ricondotti ad altri fattori;
- tempi del percorso di valutazione diagnostica;
- tempi e modalità delle indicazioni terapeutiche.

In ambito scolastico recentemente si è creata una sovrastruttura normativa che pone in essere i problemi e le strategie di interventi, ratificando sigle, acronimi e procedure formali; purtroppo però l'apparato burocratico spesso non vede una significativa ricaduta didattica attraverso strategie di intervento appropriate, lasciate ai singoli docenti, ai team spesso variamente composti quanto a background formativo, raramente supportati nella maturazione di competenze utili al riconoscimento delle anomalie tipiche dell'ADHD, atto fondamentale per le diagnosi precoci.

Ciò che vorrei sottolineare è il gap (nel suo peculiare significato grafico) temporale e operativo che esiste tra assunti normativi, clinici, diagnostici e terapeutici e l'ordinaria attività quotidiana in ambito scolastico, fatta di estreme privazioni riguardo a organico e gestione logistico-finanziaria.

Mentre nel tempo si è consolidata in ambito sanitario una prospettiva diagnostico-terapeutica adeguata e condivisa, grazie anche alla costituzione del Registro Regionale e dei Centri di riferimento, in ambito scolastico i processi di riconoscimento, segnalazione e presa in carico del caso, a seguito di avvenuta prassi di valutazione e certificazione, sono troppo lunghi, e altrettanto difficili e lunghe le liste di attesa. Se poi si considera la variabile famiglia, nella sua tipologia socio-economica-culturale, a cui si riconosce la facoltà esclusiva di procedere secondo le indicazioni della scuola, spesso si determina un quadro consapevole verso la terza o la quarta primaria, dove altri aspetti, soprattutto cognitivi, perché compromessi da altri fattori, amplificano un'evidenza non più gestibile.

Un altro anello debole della rete, sovrastruttura tutelante, è il passaggio delle comunicazioni e delle indicazioni specialistiche tra i diversi enti preposti, meglio tra le diverse figure che gestiscono un caso.

Mancano linearità e continuità, per cui cade la tempestività dell'intervento.

Sostanzialmente sono ancora carenti la regia e la condivisione delle strategie tra l'ambito sanitario, altamente specialistico, e l'ambito scolastico, il terreno più fertile per la modificazione dei contesti socio-relazionali e cognitivi del bambino, dove esiste invece una consapevolezza generica, lasciata alla motivazione e alla disponibilità del singolo.

Concludo con semplici e forse scontate prospettive finalizzate al supporto del mondo scolastico e familiare:

- formazione capillare dei docenti e degli operatori;
- maggiore prossimità territoriale dei Centri di riferimento; le famiglie faticano a percorrere le lunghe strade che conducono ad appropriati supporti, anche e non da ultimo per condizioni socio-economiche difficili;
- prevedere figure professionali intermedie, magari a livello interscolastico, che gestiscano la trama della rete di relazioni e di scambi di informazioni fondamentali alle strategie di intervento didattico.

È l'auspicio per un ponte di sinergie produttive tra due mondi: socio-sanitario e scolastico!

Maria Teresa Foà
Insegnante di scuola primaria, Vimercate

Focus

Lo studio svolto sull'attività del Registro ADHD della Regione Lombardia è un lavoro per noi tecnici importante, in quanto ci permette di avere dati recenti sulla prevalenza del disturbo e promuove un confronto tra strutture specializzate in merito ai protocolli di valutazione e riabilitazione.

In ambito valutativo, come riportato dai colleghi del gruppo lombardo, una diagnosi corretta, precoce aggiungerei, è il punto di partenza per poter rendere davvero efficace il lavoro riabilitativo. Nonostante la maggior parte dei Centri specializzati si riferiscano alle Linee Guida della SINPIA, ad oggi non c'è un vero e proprio confronto sui protocolli che meglio descrivano il funzionamento di questi pazienti. A mio avviso risulta necessario un lavoro di confronto permanente su questo tema con il compito, destinato ai Centri clinici, di sperimentare batterie di test sempre più "raffinate". Nello specifico si potrebbero approfondire test che valutino le funzioni esecutive nei due ambiti: le funzioni esecutive calde (legate all'elaborazione rapida, automatica ed emozionale degli stimoli) che diventano preponderanti nelle situazioni di stress, e le funzioni esecutive fredde (basate su una elaborazione complessa, cognitiva, controllata e quindi più lenta).

In ambito riabilitativo, nell'articolo viene riportata la distribuzione del campione in relazione al tipo di intervento a cui sono stati sottoposti i pazienti coinvolti e, in merito alla prescrizione psicologica, quella più frequente corrisponde a: *Parent training, Child training* e *Teacher training*. Su questo possiamo confermare che l'indicazione preferenziale, per ottenere risultati clinicamente rilevanti, è quella della terapia multimodale (ossia che comprenda contemporaneamente tutti e tre i lavori citati) che viene attuata mediante protocolli tacitamente condivisi.

In questo momento storico, in cui l'ADHD inizia ad essere un tema affrontato a trecentosessanta gradi dalla comunità scientifica, è necessario, soprattutto per tutelare i pazienti e le loro famiglie, rendere maggiormente espliciti i percorsi riabilitativi aprendo un confronto tra clinici in merito alle tecniche più efficaci. Ci si riferisce, dunque, all'importanza, sollevata anche nell'articolo, di fare formazione e dare informazioni corrette sull'ADHD, con lo scopo di condividere i punti cardine della patologia onde "normalizzare" la quantità delle diagnosi. La stessa necessità si rileva anche per l'area dell'intervento psicoterapeutico, in cui è fondamentale condividere informazioni e protocolli tra specialisti così da poter fornire un servizio omogeneo ed efficace agli utenti.

In questo ruolo di servizio formativo e informativo della nostra Associazione (AIDAI - Associazione Italiana Disturbo da Deficit di Attenzione/Iperattività) è protagonista attiva da anni, poiché si condivide l'idea che una rete di informazioni corrette è già di per sé un importante anello del più corretto iter diagnostico e terapeutico.

Erica Menotti
Psicologa e Psicoterapeuta familiare
Roma

Il Registro regionale lombardo dell'ADHD ha diffuso il rapporto sui primi due anni di attività. Si tratta di un documento importante perché riguarda la regione più popolosa e produttiva del Paese e per le peculiarità del Registro: raccoglie i dati su tutti i soggetti affetti da ADHD a prescindere dal tipo di trattamento ricevuto, psicosociale o multimodale.

Il Registro di cui si è dotata la Lombardia rappresenta, perciò, un oggettivo arricchimento rispetto a quello nazionale che resta, comunque, un prezioso strumento di sanità pubblica. L'aspetto più importante del rapporto è rappresentato dalla descrizione del percorso che porta dalla percezione "generica" del problema all'esatto inquadramento diagnostico e alla presa in carico: chi bussa alla porta dei servizi di NPIA che tipo di accoglienza (liste di attesa) e di risposta riceve (presa in carico). Il Registro lombardo focalizza la sua attività su chi vive un disagio reale e perciò cerca aiuto. Ritengo che questo tipo di approccio al problema dell'ADHD sia corretto almeno finché non sarà dimostrato che la ricerca di fattori predittivi di un futuro ADHD nella popolazione in età evolutiva possa cambiare la storia naturale della malattia: questo è il primo requisito che la WHO prescrive per poter parlare di utilità di uno screening. Dato questo tipo di approccio, ne discende che la prevalenza della sindrome è risultata sensibilmente inferiore all'atteso, in base ai dati della letteratura, così come l'esposizione al trattamento farmacologico. Intorno a questi dati osservazionali, purtroppo, si è sviluppato un dibattito, a mio avviso, fuorviante e, talora, "ideologico". Si sta perdendo l'occasione di discutere, partendo dai dati italiani, regionali e nazionali, dei bisogni della popolazione in età evolutiva, delle risposte date finora a chi "bussa" alla porta dei servizi, del vuoto istituzionale e normativo (i Livelli Essenziali di Assistenza, LEA).

Se ci poniamo nell'ottica di rispondere ai bisogni della popolazione, un punto percentuale, in più o in meno, di prevalenza di questa come di altre malattie resta importante per dimensionare i servizi ma perde ogni connotazione "ideologica". I dati osservati vanno accettati, poi si interpretano usando sempre il metodo scientifico: revisioni sistematiche e meta-analisi innanzitutto. Peraltro, gli estensori del rapporto del Registro lombardo, nel descrivere i loro risultati, hanno accuratamente definito il loro ambito d'indagine e le similitudini e differenze con altri studi osservazionali.

Tornando al merito del rapporto, caratteristiche salienti, ancillari alla descrizione del percorso diagnostico-terapeutico, sono l'accuratezza della diagnosi, la distribuzione delle risorse in base ai bisogni reali, il miglioramento indotto della pratica clinica.

Certamente ci sono ampi margini di miglioramento che vanno dal maggior coinvolgimento dei pediatri alla formazione/informazione delle famiglie e degli insegnanti, ma la strada intrapresa è quella giusta.

Pietro Panei
Istituto Superiore di Sanità, Roma

GLI STRUMENTI UTILI PER LA DIAGNOSI

Riportiamo di seguito due strumenti clinici utili al pediatra: il primo, un questionario sui punti di forza e di debolezza (SDQ), utile per identificare in modo appropriato i bambini le cui difficoltà comportamentali potrebbero essere espressione di un disturbo psicopatologico e che quindi necessitano di una valutazione specialistica; il secondo, invece, è una scala che focalizza l'osservazione sui tipi di comportamento che risultano più specificamente connessi con la disattenzione, l'iperattività e l'impulsività caratteristiche dell'ADHD. Riportiamo infine una scheda informativa per i genitori.

IL QUESTIONARIO SDQ

Il questionario sui punti di forza e di debolezza (*Strength and Difficulties Questionnaire*, SDQ) di Goodman, è uno strumento che permette di valutare i problemi comportamentali dei bambini e degli adolescenti di età compresa tra i 3 e i 17 anni, e può essere utile anche come strumento di screening allo scopo di individuare bambini a rischio di disturbi psicopatologici. Il questionario è composto da 25 item suddivisi in 5 dimensioni: sintomi emotivi (item n. 3, 8, 13, 16, 24); problemi della condotta (item n. 5, 7, 12, 18, 22); iperattività/disattenzione (item n. 2, 10, 15, 21, 25); problemi di relazione con i coetanei (item n. 6, 11, 14, 19, 23); comportamento prosociale (item n. 1, 4, 9, 17, 20). Il genitore deve rispondere dando una valutazione secondo una scala di Likert a 3 punti in base a quanto un certo attributo è descrittivo del comportamento del bambino. Si otterranno quindi 5 punteggi separati per ogni dimensione, dati dalla somma dei rispettivi item, e un punteggio totale ottenuto sommando i punteggi di tutti i gruppi eccetto il gruppo sui comportamenti prosociali. Di seguito i punteggi che rappresentano bambini i cui comportamenti risultano tali da poter necessitare e beneficiare di una valutazione specialistica da parte di un neuropsichiatra infantile: *Punteggio totale* maggiore di 16; *sintomi emotivi* maggiore di 4; *problemi della condotta* maggiore di 3; *iperattività/disattenzione* maggiore di 6; *problemi di relazione con i coetanei* maggiore di 3; *comportamento prosociale* minore di 5.

Questionario sui punti di forza e di debolezza (SDQ) *Per ciascuna domanda mettere una crocetta su una delle tre caselle: non vero, parzialmente vero, assolutamente vero.*	**Non vero**	**Parzialmente vero**	**Assolutamente vero**
1. Rispettoso dei sentimenti degli altri	0	1	2
2. Irrequieto, iperattivo, incapace di stare fermo per molto tempo	0	1	2
3. Si lamenta spesso per mal di testa, mal di stomaco o nausea	0	1	2
4. Condivide volentieri con gli altri bambini (dolci, giocattoli, matite ecc.)	0	1	2
5. Spesso ha crisi di collera o è di cattivo umore	0	1	2
6. Piuttosto solitario, tende a giocare da solo	0	1	2
7. Generalmente obbediente, esegue di solito le richieste degli adulti	0	1	2
8. Ha molte preoccupazioni, spesso sembra preoccupato	0	1	2
9. È di aiuto se qualcuno si fa male, è arrabbiato o malato	0	1	2
10. Costantemente in movimento o a disagio	0	1	2
11. Ha almeno un buon amico o una buona amica	2	1	0
12. Spesso litiga con gli altri bambini o li infastidisce di proposito	0	1	2
13. Spesso infelice, triste o in lacrime	0	1	2
14. Generalmente ben accetto dagli altri bambini	2	1	0
15. Facilmente distratto, incapace di concentrarsi	0	1	2
16. È nervoso o a disagio in situazioni nuove, si sente poco sicuro di sé	0	1	2
17. Gentile con i bambini più piccoli	0	1	2
18. Spesso dice bugie o inganna	0	1	2
19. Preso di mira e preso in giro dagli altri bambini	0	1	2
20. Si offre spesso volontario per aiutare gli altri (genitori, insegnanti, altri bambini)	0	1	2
21. Pensa prima di fare qualcosa	2	1	0
22. Ruba a casa, a scuola o in altri posti	0	1	2
23. Ha migliori rapporti con gli adulti che con i bambini	0	1	2
24. Ha molte paure, si spaventa facilmente	0	1	2
25. È in grado di portare a termine ciò che gli viene richiesto, rimanendo concentrato per il tempo necessario	2	1	0

Focus

LA SCALA SDAG

La scala SDAG (Cornoldi, 1995), scala diretta ai genitori per l'individuazione di comportamenti di disattenzione e iperattività del bambino, è uno strumento di rapido utilizzo per raccogliere informazioni dai genitori sulla presenza di sintomi di disattenzione e iperattività. La scala è composta da 18 item, basati sui sintomi descritti dal DSM-IV, ai quali il genitore deve rispondere dando una valutazione da 0 a 3 in base alla frequenza con cui si manifesta un comportamento. Gli item dispari sono relativi alla dimensione della disattenzione, mentre quelli pari alla dimensione iperattività/impulsività. Si otterranno quindi due punteggi separati: uno per la *subscale* disattenzione (somma degli item dispari) e uno per la *subscale* iperattività/impulsività (somma degli item pari). Il punteggio massimo che un bambino può ottenere è 27 per ogni *subscale*; un punteggio pari o superiore a 14 in almeno una delle due dimensioni rappresenta un bambino il cui comportamento risulta tale da poter necessitare e beneficiare di una valutazione specialistica da parte di un neuropsichiatra infantile.

	Mai	Qualche volta	Spesso	Molto spesso
1. Incontra difficoltà nell'esecuzione di attività che richiedono una certa cura	0	1	2	3
2. Spesso a tavola o alla scrivania, durante lo svolgimento dei compiti, si agita con le mani (ad esempio, giocherellando con gli oggetti che gli sono vicini), o con i piedi, o si dimena sulla sedia	0	1	2	3
3. Incontra difficoltà nel mantenere l'attenzione sui compiti o sui giochi in cui è impegnato, interrompendosi ripetutamente o passando di frequente ad attività differenti	0	1	2	3
4. Non riesce a stare seduto quando le circostanze lo richiedono	0	1	2	3
5. Quando gli si parla non sembra ascoltare	0	1	2	3
6. Manifesta una irrequietezza interna, correndo o arrampicandosi dappertutto	0	1	2	3
7. Non esegue ciò che gli viene richiesto o fatica a portarlo a compimento	0	1	2	3
8. Incontra difficoltà a impegnarsi in giochi o attività tranquille	0	1	2	3
9. Incontra difficoltà a organizzarsi nei compiti e nelle sue attività	0	1	2	3
10. È in movimento continuo come se avesse dentro un motorino che non si ferma	0	1	2	3
11. Evita o è poco disposto a impegnarsi in attività che richiedono uno sforzo continuato	0	1	2	3
12. Non riesce a stare in silenzio; parla eccessivamente	0	1	2	3
13. Non tiene in ordine le sue cose e di conseguenza le perde	0	1	2	3
14. Spesso risponde precipitosamente	0	1	2	3
15. Viene distratto facilmente da stimoli esterni	0	1	2	3
16. Incontra difficoltà ad aspettare il suo turno	0	1	2	3
17. Trascura o dimentica le incombenze o i compiti di ogni giorno	0	1	2	3
18. Spesso interrompe o si comporta in modo invadente con altre persone impegnate in un gioco o in una conversazione	0	1	2	3

ADHD - SCHEDA INFORMATIVA PER I GENITORI

Cos'è? I genitori sono spesso in difficoltà quando ricevono frequenti comunicazioni dalla scuola perché il loro bambino non ascolta l'insegnante o disturba in classe. Una possibile ragione per questo tipo di comportamento è il disturbo da deficit di attenzione e iperattività, l'ADHD (acronimo per l'inglese *Attention Deficit Hyperactivity Disorder*).

Quali sono i sintomi/segni? Anche se il bambino con ADHD spesso vorrebbe essere un bravo alunno, il comportamento impulsivo e le difficoltà a prestare attenzione interferiscono e causano problemi nel contesto della classe. Tutti i bambini possono a volte mostrare disattenzione, impulsività e/o iperattività, ma il bambino con ADHD presenta questi sintomi e comportamenti più frequentemente e in maniera più intensa di altri bambini della stessa età. L'ADHD si verifica in circa l'1% dei bambini italiani in età scolare. I sintomi sono solitamente evidenti all'età di circa 5-6 anni e possono persistere fino all'età adulta. Nel 25% dei casi uno dei genitori ha, o ha presentato, difficoltà simili. Un bambino con ADHD spesso:

- ha difficoltà a mantenere la concentrazione su un'attività, anche se si tratta di un gioco;
- commette errori di distrazione e ha una scarsa attenzione ai dettagli;
- viene distratto facilmente da stimoli esterni;
- perde il materiale scolastico o dimentica in giro i suoi giocattoli;
- non riesce a portare a termine un compito o un gioco;
- sembra non ascoltare quando gli si parla;
- ha difficoltà a seguire le istruzioni ricevute pur avendole capite, non avendo intenzioni oppositive;
- spesso risponde precipitosamente;
- non riesce a rispettare il proprio turno;
- spesso si agita con le mani o i piedi o si dimena sulla sedia;
- è sempre in movimento, corre e si arrampica dappertutto;
- parla eccessivamente;
- incontra difficoltà a impegnarsi in attività o in giochi tranquilli (ad esempio giochi da tavolo);
- spesso interrompe o si comporta in modo invadente con gli altri.

Alcuni bambini hanno soprattutto difficoltà di attenzione e organizzazione. Altri hanno per lo più sintomi iperattivi e impulsivi. In alcuni casi possono essere presenti entrambi questi gruppi di sintomi.
Un bambino che presenta sintomi di ADHD dovrebbe avere una valutazione completa da parte di un neuropsichiatra infantile. Un bambino con ADHD potrebbe avere anche altri disturbi psichiatrici e/o difficoltà di apprendimento.

Come si cura? Se l'ADHD non viene riconosciuto tempestivamente, il bambino spesso viene rimproverato a causa del suo comportamento e questo può portare a bassa autostima e depressione. Senza un adeguato trattamento il bambino sperimenta inoltre continui insuccessi scolastici e importanti difficoltà relazionali con i compagni e con gli adulti. Il trattamento migliore prevede interventi di tipo psicologico, educativo e comportamentale rivolti al bambino, ai genitori e agli insegnanti per fornire strumenti utili a gestire i sintomi del disturbo. Nei casi di ADHD di grado grave e in coloro che non abbiano risposto in modo efficace agli interventi psicologici è indicato il trattamento farmacologico. Se si sospetta l'ADHD, il pediatra dovrebbe indirizzare la famiglia ai Centri di riferimento regionali per la diagnosi e la cura dell'ADHD.

Tratto da: Bonati M (a cura di). Per un uso razionale degli psicofarmaci nell'età evolutiva. Il Pensiero Scientifico Editore, Roma 2015, in press.


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