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SAVE THE DATE - Meeting			
AUDIT PARENT TRAINING E TEACHER TRAINING NELL'AMBITO DEL PROGETTO REGIONALE ADHD.			
c/o IRCCS Istituto Mario Negri di Milano, <b>6 luglio 2017</b> .			

N. 115 anno X - maggio 2017



### BIBLIOGRAFIA ADHD APRILE 2017

### Acad Pediatr. 2017;17:349-55.

Associations Between Adverse Childhood Experiences and ADHD Diagnosis and Severity. Brown NM, Brown SN, Briggs RD, et al.

**OBJECTIVE**: Although identifying adverse childhood experiences (ACEs) among children with behavioral disorders is an important step in providing targeted therapy and support, little is known about the burden of ACEs among children with attention deficit-hyperactivity disorder (ADHD). We described the prevalence of ACEs in children with and without ADHD, and examined associations between ACE type, ACE score, and ADHD diagnosis and severity.

**METHODS**: Using the 2011 to 2012 National Survey of Children's Health, we identified children aged 4 to 17 years whose parents indicated presence and severity of ADHD, and their child's exposure to 9 ACEs. Multivariate logistic regression was used to estimate associations between ACEs, ACE score, and parent-reported ADHD and ADHD severity, adjusted for sociodemographic characteristics.

**RESULTS**: In our sample (N = 76,227, representing 58,029,495 children), children with ADHD had a higher prevalence of each ACE compared with children without ADHD. Children who experienced socioeconomic hardship (adjusted odds ratio [aOR], 1.39; 95% confidence interval [CI], 1.21-1.59), divorce (aOR, 1.34; 95% CI, 1.16-1.55), familial mental illness (aOR, 1.55; 95% CI, 1.26-1.90), neighborhood violence (aOR, 1.47; 95% CI, 1.23-1.75), and incarceration (aOR, 1.39; 95% CI, 1.12-1.72) were more likely to have ADHD. A graded relationship was observed between ACE score and ADHD. Children with ACE scores of 2, 3, and  $\geq$ 4 were significantly more likely to have moderate to severe ADHD.

**CONCLUSIONS**: Children with ADHD have higher ACE exposure compared with children without ADHD. There was a significant association between ACE score, ADHD, and moderate to severe ADHD. Efforts to improve ADHD assessment and management should consider routinely evaluating for ACEs.

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

### Acta Med Iran. 2016;54:503-09.

# A COMPARISON OF EFFECTIVENESS OF PARENT BEHAVIORAL MANAGEMENT TRAINING AND METHYLPHENIDATE ON REDUCTION OF SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

### Mohammadi MR, Soleimani AA, Ahmadi N, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychological disorders of childhood. Methylphenidate is highly effective in the treatment of ADHD. This study aimed to determine the effectiveness of combined Parent behavioral management training (PBMT) and medication treatment (Methylphenidate) in reducing ADHD symptoms in 6-12-year-old children, using randomized sampling. A total of 50 children with ADHD were assigned into two groups: an experimental group of PBMT and a control group of medication treatment (Methylphenidate) without other interventions. Conners  $\Gamma$ ÇÖ Parent Rating Scale (CPRS-48) was employed before and after interventions to determine the effects. Descriptive Statistics method (consisting of Mean and Standard deviation) and Statistical inference method, (including t-test and Levene's Test) were used for data analysis. Findings revealed that the combined behavioral intervention of PBMT and methylphenidate treatment is more effective in reduction of ADHD in children. The difference of means between pre-test and post-test of CPRS in the experimental group was equal to 10.77, and it was equal to 1.88 in the control group. In addition, PBMT was more effective in the case of younger parents (P<0.025). However, parents' education level did not affect the behavioral intervention (P<0.025). The findings suggest that combined intervention of PBMT and methylphenidate is effective in reducing the symptoms of ADHD in children.

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### Acta Paediatr Int J Paediatr. 2017.

# OBSERVER VARIABILITY IDENTIFYING ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN 10-YEAR-OLD CHILDREN BORN EXTREMELY PRETERM.

### Leviton A, Hunter SJ, Scott MN, et al.

**Aim**: A DSM-5 diagnosis of attention deficit/hyperactive disorder (ADHD) requires that symptoms be present in two settings. We wanted to see how teachers and parents compare on their assessments.

**Methods**: We evaluated how well Child Symptom Inventory-4 (CSI-4) reports from 871 parents and 634 teachers of 10-year-old children born before the 28th week of gestation provided information about indicators of school dysfunction.

**Results**: Kappa values for parent and teacher agreement of any ADHD were at best fair to poor (<0.41). Nevertheless, ADHD identified by each alone provided a moderate amount of information about such indicators of school dysfunction as grade repetition. Only occasionally did agreement provide more information than provided by only one reporter. Mother's social class and intelligence level did not discriminate between parents who did and did not agree with the teacher.

**Conclusion**: ADHD identified by a single observer can provide appreciable information about a range of the child's functions needed for success in school and, therefore, should not be discounted when another observer does not consider the child to have ADHD symptoms

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#### Addiction Biology. 2017;22:802-12.

BRAIN CONNECTIVITY AND PSYCHIATRIC COMORBIDITY IN ADOLESCENTS WITH INTERNET GAMING DISORDER. Han DH, Kim SM, Bae S, et al.

Prolonged Internet video game play may have multiple and complex effects on human cognition and brain development in both negative and positive ways. There is not currently a consensus on the principle effects of video game play neither on brain development nor on the relationship to psychiatric comorbidity. In this study, 78 adolescents with Internet gaming disorder (IGD) and 73 comparison subjects without IGD, including subgroups with no other psychiatric comorbid disease, with major depressive disorder and with attention deficit hyperactivity disorder (ADHD), were included in a 3 T resting state functional magnetic resonance imaging analysis. The severity of Internet gaming disorder, depression, anxiety and ADHD symptoms were assessed with the Young Internet Addiction Scale, the Beck Depression Inventory, the Beck Anxiety

Inventory and the Korean ADHD rating scales, respectively. Patients with IGD showed an increased functional correlation between seven pairs of regions, all satisfying q < 0.05 False discovery rates in light of multiple statistical tests: left frontal eye field to dorsal anterior cingulate, left frontal eye field to right anterior insula, left dorsolateral prefrontal cortex (DLPFC) to left temporoparietal junction (TPJ), right DLPFC to right TPJ, right auditory cortex to right motor cortex, right auditory cortex to supplementary motor area and right auditory cortex to dorsal anterior cingulate. These findings may represent a training effect of extended game play and suggest a risk or predisposition in game players for over-connectivity of the default mode and executive control networks that may relate to psychiatric comorbidity

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#### Am J Med Genet A. 2017 May;173:1319-27.

# DE NOVO LOSS-OF-FUNCTION VARIANTS IN **STAG2** ARE ASSOCIATED WITH DEVELOPMENTAL DELAY, MICROCEPHALY, AND CONGENITAL ANOMALIES.

### Mullegama SV, Klein SD, Mulatinho MV, et al.

The cohesin complex is an evolutionarily conserved multi-subunit protein complex which regulates sister chromatid cohesion during mitosis and meiosis. Additionally, the cohesin complex regulates DNA replication, DNA repair, and transcription. The core of the complex consists of four subunits: SMC1A, SMC3, RAD21, and STAG1/2. Loss-of-function mutations in many of these proteins have been implicated in human developmental disorders collectively termed "cohesinopathies." Through clinical exome sequencing (CES) of an 8-year-old girl with a clinical history of global developmental delay, microcephaly, microtia with hearing loss, language delay, ADHD, and dysmorphic features, we describe a heterozygous de novo variant (c.205C>T; p.(Arg69\*)) in the integral cohesin structural protein, STAG2. This variant is associated with decreased STAG2 protein expression. The analyses of metaphase spreads did not exhibit premature sister chromatid separation; however, delayed sister chromatid cohesion was observed. To further support the pathogenicity of STAG2 variants, we identified two additional female cases from the DECIPHER research database with mutations in STAG2 and phenotypes similar to our patient. Interestingly, the clinical features of these three cases are remarkably similar to those observed in other well-established cohesinopathies. Herein, we suggest that STAG2 is a dosage-sensitive gene and that heterozygous loss-of-function variants lead to a cohesinopathy

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Am J Drug Alcohol Abuse. 2017;43:350-59.

### MOTIVES UNDERLYING SMOKING IN COLLEGE STUDENTS WITH ADHD.

### Murphy KG, Flory K.

**Background**. The positive association between attention deficit hyperactivity disorder (ADHD) symptoms and smoking in youth has been well documented. Less research has examined why individuals with ADHD, particularly college students, are at increased risk for smoking.

**Objectives**. This longitudinal study examined whether smoking motives [cognitive enhancement, tolerance, negative reinforcement (smoking to reduce negative affect or stress), craving, social influences, and weight control] helped to explain the relation between ADHD symptoms (inattention and hyperactivity/impulsivity) and cigarette smoking among college students.

**Methods**. Participants were 889 undergraduates (21% men) and their parents who completed online surveys at the beginning and end of the Fall semester regarding their smoking behaviors, ADHD symptoms, and smoking motives. Structural equation modeling was used to analyze data and answer research questions.

**Results**. Nineteen percent of students reported smoking, while 20% reported one or more inattentive symptoms, 35% reported one or more hyperactive/impulsive symptoms, and 3.3% met criteria for ADHD. All smoking motives significantly moderated the relation between inattentive symptoms and smoking, while most smoking motives (negative reinforcement, tolerance, craving, cognitive enhancement, and weight control) moderated the link between hyperactive/impulsive symptoms and smoking. Results remained significant after controlling for stimulant medication use and conduct disorder symptoms.

**Conclusions/Importance**. Addressing negative reinforcement, craving, social influences, and tolerance in prevention and intervention efforts on college campuses may reduce smoking. Results also highlight the importance of assessing a range of ADHD symptoms in college students as ADHD symptoms, even at subthreshold levels, were associated with increased smoking rates among college students

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### Anadolu Psikiyatr Derg. 2017;18:48-50. AN UNUSUAL SIDE EFFECT BY ATOMOXETIN USE: HEMOLYTIC ANEMIA. Canan INCE, Mutlu KARAKUŞ, Sema KANDİL.

Drug-induced autoimmune hemolytic anemia, inducing by antibodies that bind to the erythrocyte surface antigen and resulting by interaction between the immune system and red blood cell membrane, an immunological status characterized by erythrocyte destruction is rare in children. There is enough evidence that about 130 drug caused hemolytic anemia. Hematological side effects due to psychotropic drugs is rare and in the literature there is no case developing hemolytic anemia with the use of atomoxetine. Therefore, this case report is found worthy to be pre-sented and expected to contribute to the literature and possible mechanisms

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### Anadolu Psikiyatr Derg. 2017;18:53-55.

METHYLPHENIDATE-INDUCED VISUAL HALLUCINATIONS IN A CHILD WITH AUTISM SPECTRUM DISORDER AND ADHD: A CASE REPORT.

### Aktepe E, Erdo-fan Y.

Children with autism spectrum disorder (ASD) often exhibit the symptoms of attention-deficit/hyperactivity disorder (ADHD). Methylphenidate (MPH) is commonly used for ADHD symptoms in children with ASD. However, these children are reported to be more sensitive to side effects of MPH. The most common side effects of MPH are insomnia, decreased appetite, nausea, vomiting, headache, and abdominal pain. Visual hallucinations are rarely seen during MPH treatment. In this paper, we report a 10-year-old male patient with ASD who presented with visual hallucinations during treatment with immediate-release MPH. MPH can cause psychotic symptoms especially in the presence of comorbid ASD and ADHD. Clinicians should be aware of this rare side effect in such comorbid cases

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#### Appetite. 2017;116:90-98.

SATIETY REGULATION IN CHILDREN WITH LOSS OF CONTROL EATING AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A TEST MEAL STUDY.

### Kurz S, Schoebi D, Dremmel D, et al.

Children with loss of control (LOC) eating and attention-deficit/hyperactivity disorder (ADHD) are at risk for excessive weight gain. However, it is unclear whether or not these children show disturbances in hunger and satiety regulation. The goal was to examine the food intake and sense of LOC over eating as well as LOC eating-related characteristics during test meal in children with LOC eating and ADHD. Children aged 8ГÇô13-áy with LOC eating (n-á=-á33), ADHD (n-á=-á32), and matched healthy controls (n-á=-á33), consumed a test meal consisting of their chosen lunch food, with the instruction to eat until feeling full. Sense of LOC over eating, desire to eat, feelings of hunger, and liking of food were repeatedly assessed during test meal. Children with LOC eating and ADHD did not show a higher food intake at maximum satiety compared to control children. Sense of LOC over eating was significantly higher in children with LOC eating ate marginally faster than control children. Both children with LOC eating and ADHD reported greater desire to eat, feelings of hounger, and liking of food during test meal than control children. Even though the results did not reveal statistical evidence to support the assumption of a disturbed food intake in children with LOC eating related characteristics were significantly higher in these children compared to cat feelings of hunger, and liking of food during test meal than control children. Even though the results did not reveal statistical evidence to support the assumption of a disturbed food intake in children with LOC eating and ADHD, LOC eating related characteristics were significantly higher in these children compared to

the control children. Sense of LOC over eating was confirmed as a specific characteristic of LOC eating. The examination of behavioral indicators of hunger and satiety dysregulation should be complemented with physiological indicators in future research

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### Arq Neuro-Psiquiatr. 2017;75:204-08.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE IMPACT OF METHYLPHENIDATE ON WORKING MEMORY, INHIBITION CAPACITY AND MENTAL FLEXIBILITY.

### Bolfer C, Pacheco SP, Tsunemi MH, et al.

**Objective**: To compare children with attention-deficit/hyperactivity disorder (ADHD), before and after the use of methylphenidate, and a control group, using tests of working memory, inhibition capacity and mental flexibility.

**Methods**: Neuropsychological tests were administrated to 53 boys, 9-12 years old: the WISC-III digit span backward, and arithmetic; Stroop Color; and Trail Making Tests. The case group included 23 boys with ADHD, who were combined type, treatment-naive, and with normal intelligence without comorbidities. The control group (n = 30) were age and gender matched. After three months on methylphenidate, the ADHD children were retested. The control group was also retested after three months.

**Results**: Before treatment, ADHD children had lower scores than the control group on the tests ( $p \le 0.001$ ) and after methylphenidate had fewer test errors than before ( $p \le 0.001$ )

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

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Asian J Psychiatry. 2017;29:35-38.

DOPAMINE TRANSPORTER GENE POLYMORPHISM IN CHILDREN WITH ADHD: A PILOT STUDY IN INDONESIAN SAMPLES.

### Wiguna T, Ismail RI, Winarsih NS, et al.

**Introduction** Several studies showed that DAT1 polymorphism closed related with ADHD although the results were not consistently found. Studies in China, South Korea, Japan revealed that 10-repeat allele gave a risk for ADHD. Based on that understanding, this study tried to identify whether the similar polymorphism of DAT1 was also apparent in Indonesian children with ADHD.

**Method** This was a case – control study. Case was 50 Indonesian origin children with ADHD and without any other mental disorders and metal retardation. Control is Indonesian origin children without ADHD, other mental disorders and mental retardation. ADHD diagnosis was taken after doing the psychiatric interview and observation based on the DSM-IV TR diagnostic criteria for ADHD at the Child and Adolescent Psychiatry Out-patient Clinic, Dr. Cipto Mangunkusumo National Referral Hospital – Faculty of Medicine Universitas Indonesia. DNA isolation, DNA purity and concentration were measured. PCR was done by using a primer based on Homo sapiens solute carrier family 6 (neurotransmitter transporter), member 3 (SLC6A3), RefSeq Gene on chromosome 5 with accession number NG\_015885.1. To identify the serial of repeated allele, we used the sequencing technique.

**Results** There were 47 children with ADHD and 48 children without ADHD that involved in the final analysis. The mean of age amongst ADHD group was 9.18 (2.42) and 8.10 (2.46) years old in non-ADHD group. The 10-repeated allele of DAT1 was the highest proportion in both.

Conclusion This finding was apparently similar with other studies on DAT1 polymorphism across Asian.

# DIFFERENCES IN BODY DISSATISFACTION AND WEIGHT CONTROL BEHAVIOUR BETWEEN CHILDREN WITH ADHD AND NON-ADHD CONTROLS: A POPULATION-BASED STUDY.

### Bisset M, Rinehart N, Sciberras E.

**Background**: Evidence suggests an association between attention-deficit/hyperactivity disorder (ADHD) and eating disorders/pathology (Levin and Rawana 2016). However, research examining this association has utilized samples across wide age ranges, so it is unknown when these symptoms emerge.

**Objectives**: This study aims to compare risk factors for eating disorders/pathology in children with ADHD and non-ADHD controls at ages 8-9, 10-11 and 12-13 years.

**Methods**: This study uses three waves of data from the nationally representative Longitudinal Study of Australian Children (LSAC) (N = 2792-2979). ADHD was defined by hyperactivity-inattention scores >90th percentile by both parent and teacher report on the Strengths and Difficulties Questionnaire (SDQ) (5.7-7.0% of children at any wave). Eating pathology was assessed via child report.

**Findings**: Although no differences in body dissatisfaction were found by ADHD status at age 8-9 years (p = 0.21), differences emerged at 10-11 years (odds ratio (OR): 1.4; 95% confidence interval (CI): 1.0-1.9; p = 0.03) and 12-13 years (OR: 1.5; 95% CI: 1.0-2.1; p = 0.03). Results held when adjusting for body mass index, gender and maternal education and also when excluding those taking ADHD medication. Engagement in weight control behaviour was associated with ADHD status at ages 10-11 years (p = 0.001) and 12-13 years (p = 0.03). Children with ADHD were more likely to try to lose weight (42% vs 34% and 40% vs 35%, respectively) or gain weight (10% vs 5% and 9% vs 5%, respectively) compared to non-ADHD controls.

**Conclusions**: Findings suggest that two significant risk factors for eating disorders/pathology are more prevalent in children with ADHD from 10 to 11 years, highlighting the importance of assessing for these risk factors throughout pre-adolescence during clinical encounters

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### Aust New Zealand J Psychiatry. 2017;51:106.

# COMPARISON OF PERSONALITY DIMENSIONS IN ADULT ADHD PATIENTS WITH AND WITHOUT A CONFIRMED CHILDHOOD HISTORY.

### Jain U, Jain S.

**Background**: Many patients with attention-deficit hyperactivity disorder (ADHD) are diagnosed only in adulthood and often without collateral history. This is common among females, particularly those experiencing the inattentive subtype.

**Objectives**: To determine if the personality dimensions in adult patients with ADHD with and without a childhood confirmed history are consistent. This may suggest another tool to separate out the conditions from normality.

**Methods**: Ninety-two of 210 participants had a prior diagnosis of ADHD in this study, which included controls (36.9% no prior diagnosis of ADHD; 34.4% controls; 28.7% prior diagnosis of ADHD). The diagnosis of ADHD was based on research criteria including a Structured Clinical Inventory for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, the Adult ADHD Rating Scale and a separate clinical interview including exclusion questionnaires for comorbidity. The Temperament and Character Inventory (TCI) was used as the dependent variable, particularly the components known to stand out in ADHD adults: high novelty seeking, low self-directedness and low persistence dimensions. Comparisons were made using a 2 analysis. **Findings**: There were no significant differences in TCI dimensions (including post hoc comparisons) between the ADHD groups, but the ADHD groups were significantly different from controls (p < 0.005).

**Conclusions**: The TCI may be a very effective way of determining the stability of the personality components within ADHD. The presumption being that if ADHD is genetic, personality dimensions would have been affected, and these features are stable throughout life whether they came to impairment or not in childhood

### Aust New Zealand J Psychiatry. 2017;51:105.

### A NOVEL INTERVENTION FOR THE TREATMENT OF ADHD IN CHILDREN.

### Lee A, Choo C, Lee T, et al.

**Background**: Attention-deficit hyperactivity disorder (ADHD) is one of the most common mental health disorders in children. Limitations of behavioural interventions and pharmacological treatment have led to the development of other novel interventions. Neurofeedback has shown promise in improving not only inattention symptoms but also impulsivity/hyperactivity symptoms. A feed-forward mechanism has been proposed to be more feasible in the treatment of ADHD as it trains individuals to harness their ability to pay attention and also shows promise in improving impulsivity symptoms.

**Objectives**: The aim of the current study is to investigate the impact of a novel intervention using (feedforward) brain-to-computer interface (BCI) technology on an objective measure of attention and impulsivity in children with ADHD.

**Methods**: A total of 172 children aged 6 to 12 years (mean = 8.63, standard deviation = 1.51) with a clinical diagnosis of ADHD, inattentive or combined subtype were recruited. Participants were randomized into the waitlist-control or intervention group. Participants in the intervention group underwent 24 sessions of brain-to-computer interface technology (BCI) intervention over a period of 8 weeks, whereas participants in the control group did not receive any intervention. The Conners' Continuous Performance Test, second edition (CPT-II) was administered to the participants before and after the treatment.

**Findings**: Analysis was conducted for the intervention and control groups at weeks 1 and 8. **Conclusions**: Results will be discussed with a view to inform future research

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### Aust New Zealand J Psychiatry. 2017;51:156.

# **M**ETHYLPHENIDATE IN THE TREATMENT OF AN ADOLESCENT FEMALE WITH OBSESSIVE-COMPULSIVE DISORDER AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A CASE REPORT.

### King J, Dowling N, Leow F.

**Background**: Attention-deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are relatively common neuropsychiatric disorders with respective prevalence rates of 2.5-4% and 2.3%, though their cooccurrence has raised questions about their diagnoses and treatment (Abramovitch et al., 2012). Given the substantial variability in prevalence rates of ADHD-OCD comorbidity, ranging from 0% to 60% in some studies (Abramovitch et al., 2013), it is questioned whether their co-occurrence is genuine, or an artefact of ADHD-like symptoms (i.e. behavioural and / or neuropsychological impairments) being apparent due to the executive system being overloaded by OCD-specific symptoms (Abramovitch et al., 2015). Others have suggested that ADHD- OCD represents a distinct condition or subtype which leads to greater functional impairment (Geller et al., 2000) and a poorer prognosis (Granados and Riddle, 2008). While stimulant medication is regarded first-line treatment for ADHD, its use is cautioned in OCD given the potential to exacerbate symptoms (Kouris 1998). Thus, the effective treatment and management of this complex comorbidity remains unclear.

**Objectives**: We argue that there may be neurobiological connections between the two disorders. We highlight the neurobiological implications and clinical benefit of stimulant treatment on OCD prognosis in a patient with comorbid ADHD-OCD, through a detailed case history and discussion of the relevant literature. **Methods**: We describe a case whereby a 15-year-old female with treatment-resistant OCD was treated with methylphenidate for comorbid ADHD. We describe the patient's treatment history in detail, progress and measurement of OCD symptoms through the Yale-Brown Obsessive-Compulsive Scale (YBOCS) before and after methylphenidate.

**Findings**: In this case, we observed that the adjunctive use of methylphenidate resulted in enhanced treatment response to both psychological and pharmacological interventions for OCD.

**Conclusions**: This case highlights the need to identify and treat comorbid ADHD in OCD cases where progress has stalled

### Aust New Zealand J Psychiatry. 2017;51:89.

### EARLY HIGH SCHOOL ACADEMIC AND NON-ACADEMIC OUTCOMES FOR STUDENTS WITH ADHD.

### Zendarski N, Mensah F, Sciberras E, et al.

**Background**: Despite the transition to high school being a potential 'make or break' period for children with attention-defecit/hyperactivity disorder (ADHD), a limited body of research has examined childrens' functioning during this critical period.

**Objectives**: To describe the academic achievement and school engagement for young people with ADHD in early high school and identify potentially modifiable factors associated with poor transition outcomes.

**Methods**: Students (n = 130) in the first and third year of high school (12-15 years) were recruited from an existing cohort of children with ADHD. Academic outcomes were measured on standardized tests (National Assessment Program - Literacy and Numeracy (NAPLAN)). Measures of engagement included student attitudes to school and suspension. Multivariable regression analyses examined factors associated with academic achievement and engagement, including ADHD symptoms, emotional and behavioural problems, child depression, and family, school and sociodemographic characteristics.

**Findings**: Students with ADHD demonstrated significantly poorer academic functioning, lower school engagement and poorer social-emotional functioning in comparison to state benchmarks and normative data. In comparison to state data, students with ADHD in the first year of high school were less motivated (p < 0.01) and less connected to peers (p < 0.01). There were high rates of suspension in the first and third year of high school (21% versus 6%, p < 0.01). Modifiable factors associated with transition outcomes included behavioural problems, bullying, poor family management and depression.

**Conclusions**: Findings highlight the large achievement gap in this critical period. Interventions targeting child depression, behavioural problems and family management may enable students with ADHD to manage the high school transition period more successfully

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### Aust New Zealand J Psychiatry. 2017;51:106-07.

# COGNITIVE FUNCTION IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER RECEIVING LISDEXAMFETAMINE DIMESYLATE IN A 2-YEAR SAFETY STUDY.

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

**Background**: This phase 4, open-label study (study SPD489-404) was the first 2-year safety study of lisdexamfetamine dimesylate (LDX) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD).

**Objectives**: To measure cognitive function in children and adolescents receiving LDX for 2 years in SPD489-404, using the Cambridge Neuropsychological Test Automated Battery (CANTAB).

**Methods**: Participants aged 6-17 years received doseoptimized, open-label LDX (30, 50 or 70 mg/day) for 104 weeks. Cognition was assessed in the safety population using four selected tests from the CANTAB (delayed matching to sample (DMS), spatial working memory (SWM), stop signal task (SST) and reaction time (RTI)). A groupwise change of >5% from baseline was considered potentially clinically significant.

**Findings**: Of 314 enrolled participants, 314 (100%) received LDX and were included in the safety population and 191 (60.8%) completed the study. Potentially clinically significant improvements from baseline to last ontreatment assessment (LOTA) were observed for DMS median reaction time (mean percent change, -6.5), SWM total between errors (-32.6) and SST reaction time (-25.7). Changes from baseline to LOTA did not reach potential clinical significance for DMS percent correct (mean percent change, -1.3), RTI simple median reaction time (-2.6) or RTI 5-choice median reaction time (-3.1).

**Conclusions**: LDX treatment over 2 years was not associated with deterioration in cognitive function in children and adolescents with ADHD. Although some improvements in cognition were observed, the lack of a control group makes these data difficult to interpret and additional studies are required

# DO EARLY INTERNALIZING AND EXTERNALIZING PROBLEMS PREDICT LATER IRRITABILITY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

### Mulraney M, Zendarski N, Mensah F, et al.

**Objective**: Irritable mood is common in children with attention-deficit/hyperactivity disorder. Research to date has primarily comprised cross-sectional studies; thus, little is known about the antecedents of irritability. Furthermore, existing cross-sectional studies generally focus on the association between irritability and comorbidities and do not examine broader aspects of functioning. Finally, previous research has neglected to include child-report of irritability. This study aimed to address these gaps using data from a longitudinal study of children with attention-deficit/hyperactivity disorder.

**Method**: Children aged 5-13 years (mean = 10.2; standard deviation = 1.9) with attention-deficit/hyperactivity disorder were recruited from pediatric practices across Victoria, Australia. This study reports on those who had reached adolescence (12 years or older, mean = 13.8; standard deviation = 1.2) at the 3-year follow-up (n = 140). Internalizing and externalizing problems were measured using the Strengths and Difficulties Questionnaire. At follow-up, parent-reported and adolescent self-reported irritability was assessed using the Affective Reactivity Index. Parent and adolescent outcomes measured at follow-up included attention-deficit/hyperactivity disorder symptom severity, sleep, behavior and parent mental health.

**Results**: Children with externalizing problems at age 10 had higher parent-reported irritability ( $\pm = 0.31, 95\%$  confidence interval = [0.17,-0.45], p = 0.001) in adolescence. Cross-sectional analyses found that irritability was associated with increased attention-deficit/hyperactivity disorder symptom severity and sleep problems; poorer emotional, behavioral and social functioning; and poorer parent mental health.

**Conclusion**: Our findings highlight the importance of assessing for and managing early conduct problems in children with attention-deficit/hyperactivity disorder, as these predict ongoing irritability which, in turn, is associated with poorer functioning across a number of domains

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### Aust New Zealand J Psychiatry. 2017;51:107.

CORRELATIONS OF SYMPTOMS, FUNCTIONAL IMPAIRMENT AND QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS WITH ADHD.

### Coghill D, Joseph A, Sikirica V, et al.

**Background**: Patients with attention-deficit/hyperactivity disorder (ADHD) experience impaired day-to-day functioning and poor health-related quality of life (HRQoL).

**Objectives**: To assess relationships between ADHD Rating Scale IV (ADHD-RS-IV; symptom-based measure), Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) and Child Health and Illness Profile-Child Edition (CHIPCE:PRF; generic HRQoL instrument) outcomes in children and adolescents receiving ADHD medication.

**Methods**: Pearson correlation coefficients (r) were calculated post hoc for changes in ADHD-RS-IV versus WFIRS-P total scores from baseline to last on-treatment assessment in randomized, placebo-controlled trials of guanfacine extended release (GXR) with an atomoxetine (ATX) reference arm (SPD503-316) and lisdexamfetamine (LDX) with an osmotic-release oral system methylphenidate (OROS-MPH) reference arm (SPD489-325). CHIP-CE:PRF domain T-score changes from baseline were correlated with ADHD-RS-IV and WFIRS-P in SPD489-325.

**Findings**: During pharmacological treatment, correlations between changes in ADHD-RS-IV and WFIRS-P total scores were generally moderate (r = 0.38 to 0.56). Published effect sizes of LDX, OROS-MPH, GXR and ATX versus placebo, respectively, were larger for ADHD-RS-IV total score (1.80, 1.26, 0.76 and 0.32) than WFIRS-P total scores (0.924, 0.772, 0.44 and 0.28). Changes in CHIP-CE:PRF achievement and risk avoidance were correlated moderately with ADHDRS- IV (r = -0.36 to -0.48) and strongly but incompletely correlated with WFIRS-P changes (r = -0.59 to -0.65). Correlation coefficients and effect sizes were both larger in these domains than in resilience, satisfaction and comfort.

**Conclusions**: Symptoms, functional impairment and HRQoL are related, but distinct, constructs in children and adolescents with ADHD. Treatment goals should extend beyond symptom control to include functional and HRQoL improvements

Aust New Zealand J Psychiatry. 2017;51:88-89.

FUNCTIONING IN CHILDREN AND ADOLESCENTS WITH ADHD.

### Mulraney M, Zendarski N, Bisset M.

**Background**: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood, affecting approximately 5% of children worldwide (Polanczyk et al, 2007). Compared to their non-ADHD peers, children with ADHD have impaired functioning across a number of domains including social difficulties, academic underachievement, and mental health comorbidities (Efron et al., 2014). In the long term, children with ADHD are at increased risk for poor educational attainment, substance abuse, adult psychiatric disorders, and unemployment (Sciberras et al., 2009).

**Objectives**: To present findings from three longitudinal studies examining the functioning of children with ADHD over time.

**Findings**: At any given point in time, children with ADHD are functioning more poorly than their non-ADHD peers across a number of domains. Those differences continue over time, and in some cases worsen, despite most children receiving standard ADHD treatments. The presentations will highlight potentially modifiable predictors of outcome that may be targets for intervention to improve children's trajectories.

**Conclusions**: Even when core ADHD symptoms are effectively managed by medication, children with ADHD continue to have significantly poorer quality of life and impaired functioning compared to their non-ADHD peers. Given the high presence of comorbidities in children with ADHD, clinicians should ensure they regularly screen for associated problems. The identification and management of comorbid health and mental health problems in children with ADHD will likely improve their functioning in both the short and long term

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Aust New Zealand J Psychiatry. 2017;51:90.

THE ASSOCIATIONS BETWEEN QUALITY OF LIFE AND ADHD SYMPTOMS OVER A 12-MONTH PERIOD IN CHILDREN WITH ADHD.

### Mulraney M, Giallo R, Sciberras E, et al.

**Background**: Children with attention-deficit/hyperactivity disorder (ADHD) typically have quality of life (QoL) ratings around 1.5-2 standard deviations (SD) below population norms. Although effective interventions that reduce ADHD symptoms also improve QoL, the QoL scores tend to remain at least 1 SD below the population average.

**Objectives**: To describe the relationships between ADHD symptom severity and QoL at three time points over a 12-month period. Methods: Children aged 5-13 years with ADHD were recruited from 21 paediatric practices across Victoria, Australia (N = 392). Child QoL (parent-report using the Pediatric Quality of Life Inventory 4.0) and ADHD symptoms (both parent and teacher-report using the ADHD Rating Scale IV) were assessed at three time points across a 12-month period (0, 6 and 12 months). Data were analysed using Pearson's correlations and autoregressive cross-lagged panel models.

**Findings**: Parent-reported ADHD symptoms and QoL were moderately negatively correlated at each time point (r = -0.38 to -0.53), but teacher-reported ADHD symptoms and QoL were only weakly negatively correlated at 6 months (r = -0.19) and 12 months (r = -0.25). Parentreported ADHD symptoms predicted poorer QoL at each subsequent time point (r = -0.10 to -0.13), and there was a small bidirectional relationship observed between teacher-reported ADHD symptoms and QoL from 6 to 12 months.

**Conclusions**: Change in core ADHD symptoms over time is only one of the influences on change in QoL over time. To improve the QoL in children with ADHD, clinicians need to look beyond symptom control to identify other factors that may be influencing QoL in this population

### Biol Psychiatry. 2017.

# FIRST-DOSE METHYLPHENIDATE-INDUCED CHANGES IN BRAIN FUNCTIONAL CONNECTIVITY ARE CORRELATED WITH 3-MONTH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOM RESPONSE.

### Silberstein RB, Levy F, Pipingas A, et al.

**Background**: Attention-deficit/hyperactivity disorder (ADHD) symptoms are most commonly treated with stimulant medication such as methylphenidate (MPH); however, approximately 25% of patients show little or no symptomatic response. We examined the extent to which initial changes in brain functional connectivity (FC) associated with the first MPH dose in boys newly diagnosed with ADHD predict MPH-associated changes in ADHD inattentiveness and hyperactivity symptoms at 3 months.

**Methods**: Brain FC was estimated using steady-state visual evoked potential partial coherence before and 90 minutes after the administration of the first MPH dose to 40 stimulant drug-na+»ve boys newly diagnosed with ADHD while they performed the AX version of the continuous performance task. The change in parent-rated inattention and hyperactivity scores over the first 3 months of MPH medication was correlated with the initial 90-minute MPH-mediated FC changes.

**Results**: Hyperactivity improvements at 3 months were associated with first-dose MPH-mediated FC reductions restricted to frontal-prefrontal sites following the appearance of the "A" and at frontal and right temporal sites during the appearance of the "X." Corresponding 3-month inattention score improvement was associated with initial MPH-mediated FC reductions restricted to occipitoparietal sites following the appearance of the "A.".

**Conclusions**: These findings are discussed in the context of MPH effects on the default mode network and the possible role of the default mode network in MPH-mediated improvements in inattention and hyperactivity symptom scores

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Child Adolesc Psychiatry Ment Health. 2017;11.

PREVALENCE AND CORRELATES OF ADHD AMONG ADOLESCENTS IN A BEIRUT COMMUNITY SAMPLE: RESULTS FROM THE BEI-PSY STUDY.

### Ghossoub E, Ghandour LA, Halabi F, et al.

**Background**: This study aims to investigate the prevalence, correlates and treatment seeking behavior related to ADHD among adolescents from Lebanon.

**Methods**: Five hundred and ten adolescents were recruited through multistage stratified cluster sampling of households in Beirut, and separately interviewed along with one parent/legal guardian, using the DAWBA. All adolescents completed the PRQ and the SDQ; the parent/legal guardian also completed the SDQ and provided basic demographic information, including attitudes towards seeking mental health services.

**Results**: 10.20% of the adolescents were diagnosed with ADHD. Having ADHD was associated with having academic difficulties and being involved in bullying. Adolescents with ADHD also had higher odds of drinking alcohol, smoking cigarettes, and having comorbid emotional and conduct disorders (compared to those without ADHD). Adolescents with ADHD and their parents reported a higher burden of illness and were more likely to consider seeing a mental health professional than healthy adolescents and their parents.

**Conclusion**: ADHD among adolescents in Lebanon warrants closer attention, mainly increased awareness in the larger public, and stronger commitment to increase treatment resources to the community

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Child Adolesc Psychiatry Ment Health. 2017 May;11.

DIFFERENTIAL THERAPEUTIC EFFECTS OF ATOMOXETINE AND METHYLPHENIDATE IN CHILDHOOD ATTENTION DEFICIT/HYPERACTIVITY DISORDER AS MEASURED BY NEAR-INFRARED SPECTROSCOPY.

### Nakanishi Y, Ota T, lida J, et al.

**Background**: The stimulant methylphenidate (MPH) and the nonstimulant atomoxetine (ATX) are the most commonly-prescribed pharmacological treatments for attention deficit/hyperactivity disorder (ADHD). However, the drug-specific mechanism of action on brain function in ADHD patients is not well known. This

study examined differences in prefrontal hemodynamic activity between MPH and ATX in children with ADHD as measured by near-infrared spectroscopy (NIRS) using the Stroop color-word task.

**Methods**: Thirty children with ADHD participated in the present study. We used 24-channel NIRS (ETG-4000) to measure the relative concentrations of oxyhemoglobin in the frontal lobes of participants in the drugnaïve condition and those who had received MPH (n = 16) or ATX (n = 14) for 12 weeks. Measurements were conducted every 0.1 s during the Stroop color-word task. We used the ADHD RS-IV-J (Home Version) to evaluate ADHD symptoms.

**Results**: Treatment with either MPH or ATX significantly reduced ADHD symptoms, as measured by the ADHD RS-IV-J, and improved performance on the Stroop color-word task in terms of number of correct words. We found significantly higher levels of oxyhemoglobin changes in the prefrontal cortex of participants in the ATX condition compared with the values seen at baseline (pre-ATX). In contrast, we found no oxyhemoglobin changes between pre- and post-treatment with MPH.

**Conclusions**: The present study suggests that MPH and ATX have differential effects on prefrontal hemodynamic activity in children with ADHD

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### Child Neuropsychol. 2017;1-17.

DOES AN ATTENTION BIAS TO APPETITIVE AND AVERSIVE WORDS MODULATE INTERFERENCE CONTROL IN YOUTH WITH ADHD?

### Ma I, Mies GW, Lambregts-Rommelse NNJ, et al.

Interference control refers to the ability to selectively attend to certain information while ignoring distracting information. This ability can vary as a function of distractor relevance. Distractors that are particularly relevant to an individual may attract more attention than less relevant distractors. This is referred to as attention bias. Weak interference control and altered reward sensitivity are both important features of attention deficit hyperactivity disorder (ADHD). However, interference control is typically studied in isolation. This study integrates both. Youths (aged 9 to 17 years) with ADHD (n = 37, 25 boys) and typically-developing controls (n = 38, 20 boys) completed a Stroop task using appetitive words and matched neutral words to assess whether appetitive distractors diminished interference control more in youths with ADHD than controls. In order to test for specificity, aversive words were also included. As expected, appetitive words disrupted interference control but this effect was not stronger for youths with ADHD than the controls. Aversive words, on the other hand, facilitated interference control. Dimensional analyses revealed that this facilitation effect increased substantially as a function of ADHD symptom severity. Possible mechanisms for this effect include up-regulation of interference control as a function of induced negative mood, or as a function of increased effort. In conclusion, appetitive words do not lead to worse interference control in youths with ADHD compared with controls. Interference control was modulated in a valence-specific manner, concurrent with mood-induced effects on cognitive control.

### Clin Pediatr. 2017;56:667-74.

### PSYCHOTHERAPY FOR ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A PEDIATRICIAN'S GUIDE.

### Modesto-Lowe V, Charbonneau V, Farahmand P.

Attention-deficit hyperactivity disorder (ADHD) presents with high levels of inattention, impulsiveness, and hyperactivity. ADHD starts in childhood and results in impairments that continue into adulthood. ADHD symptoms lead to decreased functionality in various life domains and result in poor academics, behavioral challenges, delayed independence, and strained relationships. Despite advances in diagnosis and treatment, persistent residual symptoms are common, highlighting the need for novel treatment strategies. This article aims to provide a review of the psychotherapeutic interventions available for teens that receive pharmacotherapy but continue to struggle with the residual symptoms of ADHD that interfere with academic function, relationship formation, and psychological development

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### Clin Psychopharmacol Neurosci. 2017;15:138-45.

# DIFFERENCES IN RESTING-STATE QUANTITATIVE ELECTROENCEPHALOGRAPHY PATTERNS IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER WITH OR WITHOUT COMORBID SYMPTOMS.

### Kim JW, Kim SY, Choi J-W, et al.

**Objective**: The aim of the present study was to evaluate the role of comorbid psychiatric symptoms on quantitative electroencephalogram (QEEG) activities in boys with the attention deficit/hyperactivity disorder (ADHD).

**Methods**: All participants were male students in the second, third or fourth grade in elementary school. Therefore, there were no significant differences in age or sex. Participants with ADHD were assigned to one of three groups: pure ADHD (n=22), ADHD with depressive symptoms (n=11), or ADHD with problematic internet use (n=19). The Korean version of the Children's Depression Inventory and the Korean Internet Addiction Self-scale were used to assess depressive symptoms and problematic internet use, respectively. Resting-state EEG during eyes closed was recorded, and the absolute power of five frequency bands was analyzed: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-50 Hz).

**Results**: The ADHD with problematic internet use group showed decreased absolute theta power at the central and posterior region compared with the pure ADHD group. However, The ADHD with depressive symptoms group showed no significant differences compared with the other groups.

**Conclusion**: These findings will contribute to a better understanding of brain-based electrophysiological changes in children with ADHD in accordance with comorbid psychiatric symptoms

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Cochrane Database Syst Rev. 2017;2017.

MUSIC THERAPY FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS. Zhang F, Liu K, An P, et al.

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows: To assess the effects of music therapy for ADHD in children and adolescents

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### Community Ment Health J. 2017 May;53:438-44.

YOUTH VIEWS ON COMMUNICATION ABOUT ADHD AND MEDICATION ADHERENCE.

### Sleath B, Carpenter DM, Sayner R, et al.

The purpose of this study was to examine youth perceptions of attention deficit hyperactivity disorder (ADHD) communication with their pediatric providers, their reported adherence to their ADHD medications, and their desired location for an ADHD educational program. Youth ages 7 through 17 with an ADHD diagnosis were recruited. A research associate interviewed the youth. Parents completed demographic questionnaires. Seventy families participated. One-third of the youth wanted more discussion about ADHD with their

providers during visits. The average youth had over eight questions about ADHD and its treatment. Most youth wanted to learn about ADHD at their provider's office. Non-white and older youth were significantly more likely to be less adherent to their ADHD medications. Youth want their providers to engage them more during visits. Providers should take advantage of this interest to engage youth more in discussions regarding ADHD and its treatment during pediatric ADHD visits

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### Dev Med Child Neurol. 2017;59:22-23.

## UNDERSTANDING ADHD AND ASD IN VERY PRETERM CHILDREN FROM A SENSORY PROCESSING PERSPECTIVE: A CONTROLLED NEUROPSYCHOLOGICAL STUDY.

### Bröring T, Oostrom KJ, Van Dijklokkart EM, et al.

**Introduction**: Neurodevelopmental sequelae in very preterm children are generally ascribed to cerebral white matter damage and noxious effects of the neonatal intensive care unit (NICU) environment. Cerebral white matter damage is associated with sensory processing problems in terms of registration, integration and modulation. Literature review confirms that sensory processing problems are common in preterm children. In addition, preterm children have a two to threefold risk on developing attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Interestingly, sensory processing problems are associated with ADHD and ASD. As preterm children are at risk for both cerebral white matter damage and ADHD and ASD, this study tested whether sensory processing problems explain the occurrence of ADHD/ASD symptoms in very preterm children.

**Patients and method**: 57 children aged 7-10 years born very preterm, and 57 gender and age-matched fullterm controls were included. ADHD/ASD symptoms were measured using parent/ teacher behavioural questionnaires and a psychiatric diagnostic interview. Sensory registration, integration and modulation were assessed using neurocognitive tests and a questionnaire.

**Results**: Parents and teachers of very preterms reported more symptoms of ADHD and ASD than parents and teachers of matched controls. Very preterm children performed worse on sensory registration, integration and modulation than term controls. Preliminary data analysis suggests that sensory processing problems mediated the relationship between preterm birth and ADHD/ASD symptoms.

**Conclusion**: Sensory processing problems may play a key role in understanding symptoms of ADHD/ASD in preterm children

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Early Intervent Psychiatry. 2017.

TRANSITIONING FROM CHILD AND ADOLESCENT MENTAL HEALTH SERVICES WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN IRELAND: CASE NOTE REVIEW.

### Tatlow-Golden M, Gavin B, McNamara N, et al.

In a context of international concern about early adult mental health service provision, this study identifies characteristics and service outcomes of young people with attention-deficit hyperactivity disorder (ADHD) reaching the child and adolescent mental health service (CAMHS) transition boundary (TB) in Ireland. The iTRACK study invited all 60 CAMHS teams in Ireland to participate; 8 teams retrospectively identified clinical case files for 62 eligible young people reaching the CAMHS TB in all 4 Health Service Executive Regions. A secondary case note analysis identified characteristics, co-morbidities, referral and service outcomes for iTRACK cases with ADHD (n=20). Two-thirds of young people with ADHD were on psychotropic medication and half had mental health co-morbidities, yet none was directly transferred to public adult mental health services (AMHS) at the TB. Nearly half were retained in CAMHS, for an average of over a year; most either disengaged from services (40%) and/or actively refused transfer to AMHS (35%) at or after the TB. There was a perception by CAMHS clinicians that adult services did not accept ADHD cases or lacked relevant service/expertise. Despite high rates of medication use and co-morbid mental health difficulties, there

appears to be a complete absence of referral to publicly available AMHS for ADHD youth transitioning from CAMHS in Ireland. More understanding of obstacles and optimum service configuration is essential to ensure that care is both available and accessible to young people with ADHD

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### Environ Int. 2017;105:12-19.

EFFECT OF EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS ON BASAL GANGLIA AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN PRIMARY SCHOOL CHILDREN.

### Mortamais M, Pujol J, van Drooge BL, et al.

**BACKGROUND**: Polycyclic aromatic hydrocarbons (PAHs) have been proposed as environmental risk factors for attention deficit hyperactivity disorder (ADHD). The effects of these pollutants on brain structures potentially involved in the pathophysiology of ADHD are unknown.

**OBJECTIVE**: The aim of this study was to investigate the effects of PAHs on basal ganglia volumes and ADHD symptoms in school children.

**METHODS**: We conducted an imaging study in 242 children aged 8-12years, recruited through a set of representative schools of the city of Barcelona, Spain. Indoor and outdoor PAHs and benzo[a]pyrene (BPA) levels were assessed in the school environment, one year before the MRI assessment. Whole-brain volumes and basal ganglia volumes (caudate nucleus, globus pallidus, putamen) were derived from structural MRI scans using automated tissue segmentation. ADHD symptoms (ADHD/DSM-IV Scales, American Psychiatric Association 2002) were reported by teachers, and inattentiveness was evaluated with standard error of hit reaction time in the attention network computer-based test.

**RESULTS**: Total PAHs and BPA were associated with caudate nucleus volume (CNV) (i.e., an interquartile range increase in BPA outdoor level (67pg/m3) and indoor level (76pg/m3) was significantly linked to a decrease in CNV (mm3) ( $\beta$ =-150.6, 95% CI [-259.1, -42.1], p=0.007, and  $\beta$ =-122.4, 95% CI [-232.9, -11.8], p=0.030 respectively) independently of intracranial volume, age, sex, maternal education and socioeconomic vulnerability index at home). ADHD symptoms and inattentiveness increased in children with higher exposure to BPA, but these associations were not statistically significant.

**CONCLUSIONS**: Exposure to PAHs, and in particular to BPA, is associated with subclinical changes on the caudate nucleus, even below the legislated annual target levels established in the European Union. The behavioral consequences of this induced brain change were not identified in this study, but given the caudate nucleus involvement in many crucial cognitive and behavior processes, this volume reduction is concerning for the children's neurodevelopment

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Epilepsy Behav. 2017;71:7-12.

### SLEEP PROBLEMS IN PEDIATRIC EPILEPSY AND ADHD: THE IMPACT OF COMORBIDITY.

### Ekinci O, Okuyaz Ç, Gunes S, et al.

**AIMS**: Attention-deficit hyperactivity disorder (ADHD) is a frequent comorbidity in pediatric epilepsy. Although sleep problems are commonly reported in both children with primary ADHD and epilepsy, those with epilepsy-ADHD comorbidity have not been well studied. This study aimed to compare sleep problems among three groups of children: 1) children with epilepsy, 2) children with epilepsy and ADHD (epilepsy-ADHD), and 3) children with primary ADHD.

**METHODS**: 53 children with epilepsy, 35 children with epilepsy-ADHD, and 52 children with primary ADHD completed the Children's Sleep Habits Questionnaire (CSHQ). Neurology clinic charts were reviewed for the epilepsy-related variables. ADHD subtypes were diagnosed according to the DSM-IV.

**RESULTS**: Children with epilepsy-ADHD had the highest CSHQ total scores, while children with primary ADHD had higher scores than those with epilepsy. Besides the total score, epilepsy-ADHD group differed from the primary ADHD and epilepsy groups with higher CSHQ subscores on sleep onset delay and sleep anxiety. The frequency of moderate-severe sleep problems (CSHQ>56) was 62.9% in children with epilepsy-ADHD, while it was 40.4% and 26.4% in children with primary ADHD and epilepsy, respectively. CSHQ total

scores were not different between ADHD subtypes in both children with epilepsy-ADHD and those with primary ADHD. None of the epilepsy-related variables were found to be associated with CSHQ scores. **DISCUSSION**: Epilepsy-ADHD is associated with a significantly poor sleep quality which is beyond that of primary ADHD and epilepsy

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Ethnicity and Disease. 2017;27:85-94.

HISPANIC RESIDENTIAL ISOLATION, ADHD DIAGNOSIS AND STIMULANT TREATMENT AMONG MEDICAID-INSURED YOUTH.

### Pennap D, Burcu M, Safer DJ, et al.

**OBJECTIVE**: This study aimed to evaluate a conceptual framework that assessed the effect of Hispanic residential isolation on Attention Deficit Hyperactivity Disorder (ADHD) health service utilization among 2.2 million publicly insured youth.

DESIGN: Cross-sectional.

**SETTING**: Medicaid administrative claims data for ambulatory care services from a US Pacific state linked with US census data.

PARTICIPANTS: Youth, aged 2-17 years, continuously enrolled in 2009.

**MAIN OUTCOME MEASURES**: The percent annual prevalence and odds of ADHD diagnosis and stimulant use according to two measures of racial/ethnic residential isolation: 1) the county-level Hispanic isolation index (HI) defined as the population density of Hispanic residents in relation to other racial/ethnic groups in a county (<.5; .5-.64;  $\geq$ .65); and 2) the proportion of Hispanic residents in a ZIP code tabulation area (<25%; 25%-50%; >50%).

**RESULTS**: Among the 47,364 youth with a clinician-reported ADHD diagnosis, 60% received a stimulant treatment (N = 28,334). As the county level HI increased, Hispanic residents of ethnically isolated locales were significantly less likely to receive an ADHD diagnosis (adjusted odds ratio [AOR]=.92 [95% CI=.88-.96]) and stimulant use (AOR=.61 [95% CI=.59-.64]) compared with Hispanic youth in less isolated areas. At the ZIP code level, a similar pattern of reduced ADHD diagnosis (AOR=.81 [95% CI=.77-.86]) and reduced stimulant use (AOR=.65 [95% CI=.61-.69]) was observed as Hispanic residential isolation increased from the least isolated to the most isolated ZIP code areas.

**CONCLUSIONS**: These findings highlight the opportunity for Big Data to advance mental health research on strategies to reduce racial/ethnic health disparities, particularly for poor and vulnerable youth. Further exploration of racial/ethnic residential isolation in other large data sources is needed to guide future policy development and to target culturally sensitive interventions

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Eur Child Adolesc Psychiatry. 2017;1-11.

# TIME-ON-TASK EFFECTS IN CHILDREN WITH AND WITHOUT ADHD: DEPLETION OF EXECUTIVE RESOURCES OR DEPLETION OF MOTIVATION?

### Dekkers TJ, Agelink van Rentergem JA, Koole A, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) are characterized by deficits in their executive functioning and motivation. In addition, these children are characterized by a decline in performance as time-on-task increases (i.e., time-on-task effects). However, it is unknown whether these time-on-task effects should be attributed to deficits in executive functioning or to deficits in motivation. Some studies in typically developing (TD) adults indicated that time-on-task effects should be interpreted as depletion of executive resources, but other studies suggested that they represent depletion of motivation. We, therefore, investigated, in children with and without ADHD, whether there were time-on-task effects on executive functions, such as inhibition and (in)attention, and whether these were best explained by depletion of executive resources or depletion of motivation. The stop-signal task (SST), which generates both indices of inhibition (stop-signal reaction time) and attention (reaction time variability and errors), was administered in 96 children (42 ADHD, 54 TD controls; aged 9FÇô13). To differentiate between depletion of resources and depletion of motivation, the SST was administered twice. Half of the participants was reinforced during

second task performance, potentially counteracting depletion of motivation. Multilevel analyses indicated that children with ADHD were more affected by time-on-task than controls on two measures of inattention, but not on inhibition. In the ADHD group, reinforcement only improved performance on one index of attention (i.e., reaction time variability). The current findings suggest that time-on-task effects in children with ADHD occur specifically in the attentional domain, and seem to originate in both depletion of executive resources and depletion of motivation. Clinical implications for diagnostics, psycho-education, and intervention are discussed

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#### Eur Child Adolesc Psychiatry. 2017;1-9.

### CHANGES IN SERUM LEVELS OF KYNURENINE METABOLITES IN PAEDIATRIC PATIENTS AFFECTED BY ADHD. *Evangelisti M, de RP, Rabasco J, et al.*

This study aims at determining serum levels of tryptophan and other metabolites of the kynurenine pathway in children with attention deficit hyperactivity disorder (ADHD) compared to healthy controls. Such metabolites interact with glutamate receptors in the central nervous system, potentially modulating mechanisms that are pivotal in ADHD and thus potentially representing peripheral biomarkers of the disorder. We measured serum levels of tryptophan and some metabolites of the kynurenine pathway in 102 children with ADHD and 62 healthy controls by liquid chromatography-tandem mass spectrometry (LC-MS/MS). As compared to healthy controls, children with ADHD showed a reduction in serum levels of anthranilic acid (-60%), kynurenic acid (-11.2%), and xanthurenic acid (-12.5%). In contrast, serum levels of tryptophan (+11.0%) and kynurenine (+48.6%) were significantly enhanced, and levels of quinolinic acid were unchanged in children with ADHD. In a logistic regression model, the presence of ADHD was predicted by low anthranilic acid and high tryptophan levels. These findings support the involvement of the kynurenine pathway in the pathophysiology of ADHD and suggest that anthranilic acid and tryptophan levels should be investigated as potential peripheral biomarker for ADHD

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### Eur Child Adolesc Psychiatry. 2017;1-10.

### **P**REDICTING ACADEMIC IMPAIRMENT AND INTERNALIZING PSYCHOPATHOLOGY USING A MULTIDIMENSIONAL FRAMEWORK OF SLUGGISH COGNITIVE TEMPO WITH PARENT- AND ADOLESCENT REPORTS. Smith ZR, Langberg JM.

Adolescents with Sluggish Cognitive Tempo (SCT) exhibit symptoms of slowness, mental confusion, excessive daydreaming, low motivation, and drowsiness/sleepiness. Although many symptoms of SCT reflect internalizing states, no study has evaluated the clinical utility of self-report of SCT in an attentiondeficit/hyperactivity disorder (ADHD) sample. Furthermore, it remains unclear whether SCT is best conceptualized as a unidimensional or multidimensional construct. In a sample of 262 adolescents comprehensively diagnosed with ADHD, the present study used adolescent- and parent reports of SCT to evaluate the predictive utility of a general SCT factor from a bifactor modeling approach compared the utility of three specific SCT factors (slow, sleepy, and daydreamer) for predicting academic impairment and internalizing psychopathology. Overall, a multidimensional framework of SCT was supported, with the three SCT factor did not. Consistent with prior research, SCT slow behaviors appear to be most strongly associated with impairment, predicting both academic impairment and internalizing psychopathology. Parent report of SCT was most useful for predicting academic functioning, whereas youth self-report was important for predicting anxiety and depression. Implications of the findings for the assessment and potential treatment of SCT are discussed

#### Eur Child Adolesc Psychiatry. 2017;1-11.

### SLEEP PROBLEMS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: ASSOCIATIONS WITH PARENTING STYLE AND SLEEP HYGIENE.

### Sciberras E, Song JC, Mulraney M, et al.

We aimed to examine the association between sleep problems and parenting and sleep hygiene in children with attention-deficit/hyperactivity disorder (ADHD). Participants included 5-13-year-old children with DSM 5 defined ADHD and a parent-reported moderate-to-severe sleep problem (N = 361). Sleep was assessed using the parent-reported Children's Sleep Habits Questionnaire. Parents also completed checklists assessing sleep hygiene, parenting consistency, and parenting warmth. Linear regression established prediction models controlling for confounding variables including child age and sex, ADHD symptom severity, comorbidities, medication use, and socio-demographic factors. More consistent parenting was associated with decreased bedtime resistance ( $\beta = -0.16$ ) and decreased sleep anxiety ( $\beta = -0.14$ ), while greater parental warmth was associated with increased parasomnias ( $\beta = +0.18$ ) and sleep anxiety ( $\beta = +0.13$ ). Poorer sleep hygiene was associated with increased bedtime resistance ( $\beta = +0.12$ ), and increased sleep duration problems ( $\beta = +0.13$ ). In conclusion, sleep hygiene and parenting are important modifiable factors independently associated with sleep problems in children with ADHD. These factors should be considered in the management of sleep problems in children with ADHD

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#### Eur Child Adolesc Psychiatry. 2017;1-15.

## COMORBIDITY PREVALENCE AND TREATMENT OUTCOME IN CHILDREN AND ADOLESCENTS WITH ADHD. *Reale L, Bartoli B, Cartabia M, et al.*

Although ADHD comorbidity has been widely studied, some issues remain unsolved. This multicenter observational study aims to examine comorbid psychiatric disorders in a clinical sample of newly diagnosed, treatment naïve children and adolescents with and without ADHD and, to compare treatment efficacy based on the type of comorbidity. We performed an analysis of the medical records of patients identified from the Regional ADHD Registry database, enrolled in 18 ADHD centers in the 2011-2016 period. 1919 of 2861 subjects evaluated (67%) met the diagnostic criteria for ADHD: 650 (34%) had only ADHD, while 1269 (66%) had at least one comorbid psychiatric disorder (learning disorders, 56%; sleep disorders, 23%; oppositional defiant disorder, 20%; anxiety disorders, 12%). Patients with ADHD of combined type and with severe impairment (CGI-S ≥5) were more likely to present comorbidity. 382 of 724 (53%) followed up patients improved after 1 year of treatment. ADHD with comorbidity showed greater improvement when treated with combined interventions or methylphenidate alone. Specifically, combined treatment showed significant superiority for ADHD with learning disorders (ES 0.66) and ODD (ES 0.98), lower for ADHD with sleep or anxiety disorders. Training intervention alone showed only medium efficacy (ES 0.50) for ADHD and learning disorders. This study was the first describing comorbidity patterns of ADHD in Italy, confirming, in a multicenter clinical setting, that ADHD is more often a complex disorder. Findings highlight important diagnostic, therapeutic, and service organization aspects that should be broadly extended to ensure an appropriate and homogenous ADHD management

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### Front Human Neurosci. 2017 Mar;11.

**NEUROFEEDBACK OF SLOW CORTICAL POTENTIALS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY** DISORDER: A MULTICENTER RANDOMIZED TRIAL CONTROLLING FOR UNSPECIFIC EFFECTS. **Strehl U, Aggensteiner P, Wachtlin D, et al.** 

**Background**: Neurofeedback (NF) in children with attention-deficit/hyperactivity disorder (ADHD) has been investigated in a series of studies over the last years. Previous studies did not unanimously support NF as a treatment in ADHD. Most studies did not control for unspecific treatment effects and did not demonstrate that self-regulation took place. The present study examined the efficacy of NF in comparison to electromyographic (EMG) feedback to control for unspecific effects of the treatment, and assessed self-regulation of slow cortical potentials (SCPs).

**Methods**: A total of 150 children aged 7–9 years diagnosed with ADHD (82% male; 43% medicated) were randomized to 25 sessions of feedback of SCPs (NF) or feedback of coordination of the supraspinatus muscles (EMG). The primary endpoint was the change in parents' ratings of ADHD core symptoms 4 weeks after the end of treatment compared to pre-tests.

**Results**: Children in both groups showed reduced ADHD-core symptoms (NF 0.3, 95% CI -0.42 to -0.18; EMG 0.13, 95% CI -0.26 to -0.01). NF showed a significant superiority over EMG (treatment difference 0.17, 95% CI 0.02–0.3, p = 0.02). This yielded an effect size (ES) of d = 0.57 without and 0.40 with baseline observation carried forward (BOCF). The sensitivity analysis confirmed the primary result. Successful self-regulation of brain activity was observed only in NF. As a secondary result teachers reported no superior improvement from NF compared to EMG, but within-group analysis revealed effects of NF on the global ADHD score, inattention, and impulsivity. In contrast, EMG feedback did not result in changes despite more pronounced self-regulation learning.

**Conclusions**: Based on the primary parent-rated outcome NF proved to be superior to a semi-active EMG feedback treatment. The study supports the feasibility and efficacy of NF in a large sample of children with ADHD, based on both specific and unspecific effects

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### Front Human Neurosci. 2017;11.

MULTI-MODAL, MULTI-MEASURE, AND MULTI-CLASS DISCRIMINATION OF **ADHD** WITH HIERARCHICAL FEATURE EXTRACTION AND EXTREME LEARNING MACHINE USING STRUCTURAL AND FUNCTIONAL BRAIN **MRI**.

### **Qureshi MNI, Oh J, Min B, et al.** Structural and functional MRI unveil many hidden properties of the human brain. We performed this multiclass classification study on selected subjects from the publically available attention deficit hyperactivity disorder ADHD-200 dataset of patients and healthy children. The dataset has three groups, namely ADHD

class classification study on selected subjects from the publically available attention deficit hyperactivity disorder ADHD-200 dataset of patients and healthy children. The dataset has three groups, namely, ADHD inattentive, ADHD combined, and typically developing. We calculated the global averaged functional connectivity maps across the whole cortex to extract anatomical atlas parcellation based features from the resting-state fMRI (rs-fMRI) data and cortical parcellation based features from the structural MRI (sMRI) data. In addition, the preprocessed image volumes from both of these modalities followed an ANOVA analysis separately using all the voxels. This study utilized the average measure from the most significant regions acquired from ANOVA as features for classification in addition to the multi-modal and multi-measure features of structural and functional MRI data. We extracted most discriminative features by hierarchical sparse feature elimination and selection algorithm. These features include cortical thickness, image intensity, volume, cortical thickness standard deviation, surface area, and ANOVA based features respectively. An extreme learning machine performed both the binary and multi-class classifications in comparison with support vector machines. This article reports prediction accuracy of both unimodal and multi-modal features from test data. We achieved 76.190% (p < 0.0001) classification accuracy in multi-class settings as well as 92.857% (p < 0.0001) classification accuracy in binary settings. In addition, we found ANOVA-based significant regions of the brain that also play a vital role in the classification of ADHD. Thus, from a clinical perspective, this multi-modal group analysis approach with multi-measure features may improve the accuracy of the ADHD differential diagnosis

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### Front Human Neurosci. 2017;11.

FNIRS STUDIES ON HEMISPHERIC ASYMMETRY IN ATYPICAL NEURAL FUNCTION IN DEVELOPMENTAL DISORDERS. Doi H, Shinohara K.

Functional lateralization is highly replicable trait of human neural system. Many previous studies have indicated the possibility that people with attention-deficits/hyperactivity-disorder (ADHD) and autism spectrum disorder (ASD) show hemispheric asymmetry in atypical neural function. However, despite the abundance of relevant studies, there is still ongoing controversy over this issue. In the present mini-review, we provide an overview of the hemispheric asymmetry in atypical neural function observed in fNIRS studies on people with these conditions. Atypical neural function is defined as group-difference in the task-related

concentration change of oxygenated hemoglobin. The existing fNIRS studies give support to the rightlateralized atypicalty in children with ADHD. At the same time, we did not find clear leftward-lateralization in atypical activation in people with ASD. On the basis of these, we discuss the current states and limitation of the existing studies

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### Front Human Neurosci. 2017;11.

# LIVING IN THE FAST LANE: EVIDENCE FOR A GLOBAL PERCEPTUAL TIMING DEFICIT IN CHILDHOOD ADHD CAUSED BY DISTINCT BUT PARTIALLY OVERLAPPING TASK-DEPENDENT COGNITIVE MECHANISMS.

### Marx I, Weirich S, Berger C, et al.

Dysfunctions in perceptual timing have been reported in children with ADHD, but so far only from studies that have not used the whole set of timing paradigms available from the literature, with the diversity of findings complicating the development of a unified model of timing dysfunctions and its determinants in ADHD. Therefore, we employed a comprehensive set of paradigms (time discrimination, time estimation, time production, and time reproduction) in order to explore the perceptual timing deficit profile in our ADHD sample. Moreover, we aimed to detect predictors responsible for timing task performance deficits in children with ADHD and how the timing deficits might be positively affected by methylphenidate. Male children with ADHD and healthy control children, all aged between 8 and 13 years, participated in this longitudinal study with three experimental sessions, where children with ADHD were medicated with methylphenidate at the second session but discontinued their medication at the remaining sessions. The results of our study reveal that children with ADHD were impaired in all timing tasks, arguing for a general perceptual timing deficit in ADHD. In doing so, our predictor analyses support the notion that distinct but partially overlapping cognitive mechanisms might exist for discriminating, estimating/producing, and reproducing time intervals. In this sense, working memory deficits in terms of an abnormally fast internal counting process might be common to dysfunctions in the time estimation/time production tasks and in the time reproduction task, with attention deficits (e.g., in terms of disruptions of the counting process) additionally contributing to time estimation/time production deficits and motivational alterations additionally contributing to time reproduction deficits. Methylphenidate did not significantly alter performance of the ADHD sample, presumably due to limited statistical power of our study. The findings of our study demonstrate a pivotal role of disturbed working memory processes in perceptual timing task performance in childhood ADHD, at the same time broadening the view for additional attentional and motivational determinants of impaired task performance

Frontiers in Neurology. 2017;8.

ALTERED CERVICAL VESTIBULAR-EVOKED MYOGENIC POTENTIAL IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

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### Isaac V, Olmedo D, Aboitiz F, et al.

**Objective**: Emerging evidence suggests that children with attention deficit and hyperactivity disorder (ADHD) present more difficulties in standing and walking balance than typically developing children. Most of previous studies have assessed these functions using postural and sensory organization tests showing differences in balance performance between control and ADHD children. However, to date, it is unknown whether these balance alterations are accompanied with vestibular dysfunction. The principal aim of this study is to evaluate vestibular otolith function in ADHD and matched control children.

**Methods**: We assessed vestibular otolith function in children with ADHD and controls using the subjective visual vertical (SVV) bucket test and cervical vestibular-evoked myogenic potentials (cVEMPs). In addition, gait and balance were evaluated using the dynamic gait index (DGI) and computerized posturography.

**Results**: Non-significant differences between groups were obtained in SVV evaluation. DGI results show lower scores for overall test performance in children with ADHD (p < 0.001), while computerized postural recordings showed significant differences for the limit of stability between groups (p = 0.02). cVEMPs in response to 500 Hz tone bursts presented at 100 dB were absent or reduced in children with ADHD, as revealed by differences in P1 and N1 peak-to-peak amplitudes between groups (p < 0.01).

**Conclusion**: These findings suggest that vestibular brainstem reflexes are altered in a subset of children with ADHD. We propose to include cVEMP reflexes in the clinical evaluation of ADHD patients

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### Frontiers in Neuroscience. 2017;11.

### NO ASSOCIATION BETWEEN CORTICAL GYRIFICATION OR INTRINSIC CURVATURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADOLESCENTS AND YOUNG ADULTS.

### Forde NJ, Ronan L, Zwiers MP, et al.

Magnetic resonance imaging (MRI) studies have highlighted subcortical, cortical, and structural connectivity abnormalities associated with attention-deficit/hyperactivity disorder (ADHD). Gyrification investigations of the cortex have been inconsistent and largely negative, potentially due to a lack of sensitivity of the previously used morphological parameters. The innovative approach of applying intrinsic curvature analysis, which is predictive of gyrification pattern, to the cortical surface applied herein allowed us greater sensitivity to determine whether the structural connectivity abnormalities thus far identified at a centimeter scale also occur at a millimeter scale within the cortical surface. This could help identify neurodevelopmental processes that contribute to ADHD. Structural MRI datasets from the NeuroIMAGE project were used [n = 306 ADHD, n = 164 controls, and n = 148 healthy siblings of individuals with ADHD (age in years, mean(sd); 17.2 (3.4), 16.8 (3.2), and 17.7 (3.8), respectively)]. Reconstructions of the cortical surfaces were computed with FreeSurfer. Intrinsic curvature (taken as a marker of millimeter-scale surface connectivity) and local gyrification index were calculated for each point on the surface (vertex) with Caret and FreeSurfer, respectively. Intrinsic curvature skew and mean local gyrification index were extracted per region; frontal, parietal, temporal, occipital, cingulate, and insula. A generalized additive model was used to compare the trajectory of these measures between groups over age, with sex, scanner site, total surface area of hemisphere, and familiality accounted for. After correcting for sex, scanner site, and total surface area no group differences were found in the developmental trajectory of intrinsic curvature or local gyrification index. Despite the increased sensitivity of intrinsic curvature, compared to gyrification measures, to subtle morphological abnormalities of the cortical surface we found no milimeter-scale connectivity abnormalities associated with ADHD

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### Frontiers in Physiology. 2017;8.

PERSONALIZED MEDICATION RESPONSE PREDICTION FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER: LEARNING IN THE MODEL SPACE VS. LEARNING IN THE DATA SPACE.

### Wong HK, Tiffin PA, Chappell MJ, et al.

Attention-Deficit Hyperactive Disorder (ADHD) is one of the most common mental health disorders amongst school-aged children with an estimated prevalence of 5% in the global population (American Psychiatric Association, 2013). Stimulants, particularly methylphenidate (MPH), are the first-line option in the treatment of ADHD (Reeves and Schweitzer, 2004; Dopheide and Pliszka, 2009) and are prescribed to an increasing number of children and adolescents in the US and the UK every year (Safer et al., 1996; McCarthy et al., 2009), though recent studies suggest that this is tailing off, e.g., Holden et al. (2013). Around 70% of children demonstrate a clinically significant treatment response to stimulant medication (Spencer et al., 1996; Schachter et al., 2001; Swanson et al., 2001; Barbaresi et al., 2006). However, it is unclear which patient characteristics may moderate treatment effectiveness. As such, most existing research has focused on investigating univariate or multivariate correlations between a set of patient characteristics and the treatment outcome, with respect to dosage of one or several types of medication. The results of such studies are often contradictory and inconclusive due to a combination of small sample sizes, low-quality data, or a lack of available information on covariates. In this paper, feature extraction techniques such as latent trait analysis were applied to reduce the dimension of on a large dataset of patient characteristics, including the responses to symptom-based questionnaires, developmental health factors, demographic variables such as age and gender, and socioeconomic factors such as parental income. We introduce a Bayesian modeling approach in a "learning in the model space" framework that combines existing knowledge in the literature on factors that may potentially affect treatment response, with constraints imposed by a treatment response model. The model is personalized such that the variability among subjects is accounted for by a set of subject-specific parameters. For remission classification, this approach compares favorably with conventional methods such as support vector machines and mixed effect models on a range of performance measures. For instance, the proposed approach achieved an area under receiver operator characteristic curve of 82-84%, compared to 75-77% obtained from conventional regression or machine learning ("learning in the data space") methods

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### Horm Res Paediatr. 2016;86:129.

### ALTERED STRESS SYSTEM ACTIVITY IN CHILDREN WITH ADHD.

### Angeli E, Johnson E, Korpa T, et al.

**Background**: Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder worldwide. Evidence suggests dysfunction of the fronto-subcortical pathways and the dopaminergic and noradrenergic systems, as well as dysregulation of the stress system, i.e., the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS).

**Objective and hypotheses**: The aim of the study was to examine i) the diurnal secretion patterns of salivary Cortisol and salivary alpha (+!)-amylase, as peripheral biomarkers of the HPA axis and the SNS, respectively and ii) the stress response to a physical stressor, the venipuncture, in both ADHD and typically developing children. Our hypothesis is that children with ADHD demonstrate hypo-activity of the stress system. Method: Sixty-two prepubertal children (30.2% girls; mean age 8.63  $\pm$  2.27) with a clinical diagnosis of ADHD were compared with 40 typically developing children (35.9% girls; mean age 8.1  $\pm$  1.7). Saliva was collected at six time points over one weekend day as well as before and 10 min after a scheduled morning venipuncture. Chemilluminescence immunoassay and kinetic-reaction assay were used for the determination of Cortisol and  $\pm$  amylase in saliva, respectively.

**Results**: Both groups demonstrated the typical circadian Cortisol rhythm with highest levels in the morning and lowest in the evening. Significantly lower Cortisol concentrations were observed in children with ADHD across the day compared to controls (P< 0.05). Moreover, children with ADHD had significantly lower CAR and Cortisol AUC (P< 0.001). In both groups, the secretion pattern of a-amylase showed lowest levels in the morning and highest in the afternoon. Venipuncture-induced salivary Cortisol concentrations tended to increase in controls, and decrease in ADHD children. The venipuncture-induced increase in salivary a-amylase tended to be more pronounced in controls

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### Hum Brain Mapp. 2017;38:2359-69.

NETWORK-LEVEL ASSESSMENT OF REWARD-RELATED ACTIVATION IN PATIENTS WITH ADHD AND HEALTHY INDIVIDUALS.

### von RD, Beckmann CF, Franke B, et al.

**Introduction**: Reward processing is a key aspect of cognitive control processes, putatively instantiated by mesolimbic and mesocortical brain circuits. Deficient signaling within these circuits has been associated with psychopathology. We applied a network discovery approach to assess specific functional networks associated with reward processing in participants with attention-deficit/hyperactivity disorder (ADHD).

**Methods**: To describe task-related processes in terms of integrated functional networks, we applied independent component analysis (ICA) to task response maps of 60 healthy participants who performed a monetary incentive delay (MID) task. The resulting components were interpreted on the basis of their similarity with group-level task responses as well as their similarity with brain networks derived from resting state fMRI analyses. ADHD-related effects on network characteristics including functional connectivity and communication between networks were examined in an independent sample comprising 150 participants with ADHD and 48 healthy controls.

**Results**: We identified 23 components to be associated with 4 large-scale functional networks: the defaultmode, visual, executive control, and salience networks. The salience network showed a specific association with reward processing as well as the highest degree of within-network integration. ADHD was associated with decreased functional connectivity between the salience and executive control networks as well as with peripheral brain regions.

**Conclusions**: Reward processing as measured with the MID task involves one reward-specific and three general functional networks. Participants with ADHD exhibited alterations in connectivity of both the salience and executive control networks and associated brain regions during task performanc

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### Int J Ment Health Syst. 2017 Apr;11.

### ITALIAN REGIONAL HEALTH SERVICE COSTS FOR DIAGNOSIS AND 1-YEAR TREATMENT OF ADHD IN CHILDREN AND ADOLESCENTS.

### Casadei G, Cartabia M, Reale L, et al.

The main aim of this study was to estimate the costs associated with diagnostic assessment and 1-year therapy in children and adolescents enrolled in 18 ADHD reference centres. Data concerning 1887 children and adolescents from the mandatory ADHD registry database during the 2012–2014 period were analysed. The overall diagnostic and treatment costs per patient amounts to €574 and €830, respectively. The ADHD centre, the school as sender, and the time to diagnosis constitute cost drivers. Non-pharmacological therapy resulted as being more expensive for patients concomitantly treated with drugs (€929) compared to those treated with psychological interventions alone (€590; p = 0.006). This study gives the first and reliable estimate of the costs associated with both diagnosis and treatment of ADHD in Italy. Although costs associated with mental disorders are difficult to estimate, continuing efforts are need to define costs and resources to guarantee appropriate care, also for ADHD

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### Int J Psychophysiol. 2017;115:86-97.

DEVELOPMENT AND GENETICS OF BRAIN TEMPORAL STABILITY RELATED TO ATTENTION PROBLEMS IN ADOLESCENT TWINS.

### Smit DJA, Anokhin AP.

The brain continuously develops and reorganizes to support an expanding repertoire of behaviors and increasingly complex cognition. These processes may, however, also result in the appearance or disappearance of specific neurodevelopmental disorders such as attention problems. To investigate whether brain activity changed during adolescence, how genetics shape this change, and how these changes were related to attention problems, we measured EEG activity in 759 twins and siblings, assessed longitudinally in four waves (12, 14, 16, and 18-áyears of age). Attention problems were assessed with the SWAN at waves 12, 14, and 16. To characterize functional brain development, we used a measure of temporal stability (TS) of brain oscillations over the recording time of 5-ámin reflecting the tendency of a brain to maintain the same oscillatory state for longer or shorter periods. Increased TS may reflect the brain's tendency to maintain stability, achieve focused attention, and thus reduce  $\Gamma C \pounds mind wandering \Gamma C \emptyset$  and attention problems. The results indicate that brain TS is increased across the scalp from 12 to 18. TS showed large individual differences that were heritable. Change in TS (alpha oscillations) was heritable between 12 and 14 and between 14 and 16 for the frontal brain areas. Absolute levels of brain TS at each wave were positively correlated with attention problems but not significantly. High and low attention problems subjects showed different developmental trajectories in TS, which was significant in a cluster of frontal leads. These results indicate that trajectories in brain TS development are a biomarker for the developing brain. TS in brain oscillations is highly heritable, and age-related change in TS is also heritable in selected brain areas. These results suggest that high and low attention problems subjects are at different stages of brain development

Investigative Ophthalmology and Visual Science. 2015;56:2215. DIGITAL SELF-ASSESSMENT APPLICATION FOR IDENTIFYING ADHD SYMPTOMS.

### Yehezkel O, Sterkin A, Lev M, et al .

**Purpose**: ADHD is a common neurobehavioral disorder. ADHD is diagnosed by clinicians using subjective tools, sometimes supported by a computerized test. However, since this diagnosis requires visiting a clinic and is affected by external factors such as intelligence and fatigue, many cases remain undiagnosed through adulthood. There is a societal burden associated with undiagnosed ADHD, creating a need for objective tools for ADHD preliminary self-assessment, prompting seeking professional clinical diagnosis if relevant. <br/>
here we aimed at testing whether we can manipulate spatial and temporal stimulation to identify ADHD symptoms in adults. To this end, we used a short, self-administered tool based on dynamic crowded visual stimulation to identify ADHD symptoms. Various studies demonstrated the usefulness of crowded conditions for measuring visual performance in aging adults and children.

**Methods**: Measurements using a prototype dynamic digital assessment tool, currently developed by GlassesOff<sup>™</sup>, on smartphones, which reliably measure functional near visual acuity (VA), were compared between diagnosed-ADHD and control groups: 24 ADHD subjects (aged 16-28 years, with an ADHD diagnosis performed by a neurologist or psychiatrist) and 18 controls (aged 20-30 years), all corrected to normal vision (worst binocular VA 0.04 logMAR). Stimuli consisted of matrices composed of 25 letters (5+ù5), each with a randomly chosen orientation having 4 options. Two variations of inter-letter-spacing within the matrix were used (0.4 and 1 letter size). Participants were requested to identify the orientation of the central letter. VA thresholds were determined using a staircase measuring the minimal detectable letter size, under crowding conditions and the stimulus presentation ranged from 34 to 120 msec.

**Results**: Despite normal VA on the clinical static ETDRS chart, our self-administered test showed a large and significant VA reduction in ADHD subjects compared with controls: 62, 79, and 64% for 34, 60, and 120 msec, respectively, equivalent to about 2 ETDRS lines. Similar results were obtained for 0.4-letter spacing. **Conclusions**: Our self-administered dynamic digital tool may be used for objective assessment of ADHD symptoms. We suggest that under-development of visual functions, which is present in children under regular conditions, persist in adults with ADHD symptoms and that this becomes apparent under spatial and temporal

loading conditions

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Iran J Psychiatr Behav Sci. 2014;8:59-65.

### TRIPLE P-POSITIVE PARENTING PROGRAM FOR MOTHERS OF ADHD CHILDREN.

### Aghebati A, Gharraee B, Shoshtari MH, et al.

**Objective**: Attention deficit hyperactivity disorder (ADHD) is a chronic, highly prevalent neurodevelopmental disorder which affects 9% of school-age children. Triple P-Positive Parenting Program is an evidence-based parenting program reported to be useful in the management of this disorder. The aim of this randomized controlled trial was to evaluate the effectiveness of Triple P in mothers of ADHD children.

**Methods**: In this study, 30 mothers with ADHD children aged between 6 to 10 were randomly assigned to two groups (15 participants in each group). Parenting style, mother-child relationship, maternal depression, anxiety and stress, and children's behavioral problems were evaluated. The intervention group received 120 minute sessions for 5 weeks and 15-30 minute telephone contacts for 3 weeks while no intervention was done for the control group.

**Results**: Analysis of covariance revealed that mothers of the Triple P group showed significant (p < 0.01) improvements in parenting style, mother-child relationship, and considerable decrease in depression, anxiety and stress. Women trained in the Triple P group also reported significantly lower rates of child misbehavior than women of the control group.

**Conclusion**: Triple P-Positive Parenting intervention is effective and acceptable for mothers of ADHD children

### Baboli MT, Pasha YZ, Mousavi SS, et al.

**Background**: The exact etiology of attention deficit hyperactivity disorder (ADHD) has not yet been understood. Objectives: The aim of the current study was to investigate the effects of hospitalization at the neonatal intensive care unit (NICU) independent of other variables such as preterm birth and low birth weight on the incidence of ADHD.

**Materials and Method**: This retrospective cohort study was done on an Exposed group of 100 preschool children with a history of NICU hospitalization at Amirkola children's hospital, and an unexposed group of 100 children without such a history. Standard checklist of Diagnostic and statistic manual of mental disorders fourth edition (DSM-IV) was used to diagnose ADHD. Information on gender, current weight, birth weight, gestational age at birth, and type of parturition was also collected and obtained data were statistically analyzed by the SPSS software and unconditional logistic regression analysis.

**Results**: Among the total number of 200 children, 20.5% of children were diagnosed to have ADHD. The incidence of the disorder was more in children with a history of hospitalization in neonatal intensive care unit than children without such a history (27% and 14%, respectively). Lowbirth weightandpreterm birth were associated with the incidence of ADHD(P value=0.001and0.005, respectively). Logistic regression showed that each day of NICU hospitalization was associated with 1.16 times greater risk of developing ADHD in the future when compared to children without a history of hospitalization (P value = 0.006).

Conclusions: The risk of ADHD is independently increased with hospitalization at the NICU

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Isr J Psychiatry Relat Sci. 2016;53:3-8.

PREVALENCE OF ADHD AMONG 7-9-YEAR-OLD CHILDREN IN ISRAEL. A COMPARISON BETWEEN JEWISH AND ARAB POPULATIONS.

### Ornoy A, Ovadia M, Rivkin D, et al.

**INTRODUCTION**: The world prevalence of ADHD ranges between 5-10%. The prevalence in Israel was generally studied from prescriptions of methylphenidate and not from cohorts of children.

**METHODS**: We assessed the prevalence of ADHD among a cohort of early school age children in the Jewish and Arab populations using DSM-IV criteria and evaluated the difference between teachers' and parental assessment. We also studied in the Jewish population the differences in several social-behavioral parameters between children with and without ADHD.

**RESULTS**: The rate of ADHD among the Jewish children was 9.5% and among the Arab children it was significantly lower - 7.35%. Teachers' evaluation in the Jewish population was 2.3 times higher than parental evaluation but in the Arab population it was closer to that of the parents, being only 12% higher. In addition, there were more regulatory, behavioral and learning problems among the Jewish children with ADHD compared to children without ADHD.

**CONCLUSIONS**: The rates of ADHD in school age children among both Jews and Arabs fall within the average rate in other countries. The high difference between teachers' and parental assessment of ADHD in the Jewish population emphasizes that ADHD diagnosis should rely on the joint behavioral assessment of both. The prevalence of ADHD in Jewish early school age children is slightly higher than in Arab children and the inattentive type is the most common. There is a discrepancy between teachers' and parents' evaluation of children's behavior in the Jewish population, but this discrepancy is less in the Arab population

### PROSPECTIVELY OVER TIME.

### McAuley T, Crosbie J, Charach A, et al.

With increasing awareness that ADHD is chronically disabling, a burgeoning literature has examined childhood clinical indicators of ADHD persistence. This study investigates whether childhood factors reflecting biological risk and cognitive reserve have additive predictive value for the persistence of ADHD that is unique beyond childhood indicators of disorder severity. One-hundred thirty children with ADHD (mean age = 8.9 years, 75 % male) were followed into adolescence (mean age = 14.0 years). Childhood ADHD and co-morbidities were assessed via interviews with parents and teachers; parental psychopathology was assessed via parent interview; exposure to neurobiological and psychosocial adversity were indexed by parent questionnaire; and cognitive reserve was evaluated through children's performance on measures of IQ and executive functioning. Univariate analyses identified childhood inattention and hyperactivityimpulsivity, co-morbid oppositional defiant disorder, overall impairment, and paternal anxiety and depression as more prevalent amongst adolescents with persistent compared with remitted ADHD. Only child-level predictors remained significant in a final multivariate model. These results suggest that children who are most likely to experience persistent ADHD have a more severe clinical presentation in childhood, reflected by increased levels of inattention, oppositional behavior, and impairment. They also are more likely to have fathers with internalizing concerns, but these concerns do not uniquely predict ADHD persistence beyond child-level factors. Contrary to expectations, childhood adversity and cognitive functioning did not predict the course of ADHD

J Asthma. 2017;1-7.

THE INFLUENCE OF COMORBID ASTHMA ON THE SEVERITY OF SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

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### Borschuk AP, Rodweller C, Salorio CF.

**Objective:** The current study examined the association between asthma and attention-deficit hyperactivity disorder (ADHD) symptoms in a clinical pediatric sample.

Methods: Demographic and neuropsychological data for children with a billing diagnosis of ADHD were extracted from a clinical database. Families completed standard rating scales. Seventy-one patients with a co-morbid asthma diagnosis were identified and matched by age to a group of 71 patients with only ADHD.

Results: Children with asthma and ADHD were more likely to display clinically elevated levels of hyperactivity, externalizing behaviors, anxiety, and hyperactive/impulsive behaviors compared to children with ADHD alone. Boys with asthma and ADHD had more symptoms than boys with only ADHD of somatization and emotional internalizing, while girls with asthma and ADHD had more symptoms of hyperactivity/impulsivity, conduct problems, anxiety, and emotional internalizing compared to girls with only ADHD.

Conclusions: Findings suggest that in children with ADHD, co-morbid asthma is associated with increased behavioral and internalizing symptoms, with distinct gender differences present. Increased behavioral and internalizing symptoms seen in children with both asthma and ADHD may be due to the burden of their medical condition. No difference was found on cognitive variables, suggesting chronic hypoxia may be less influential in explaining these differences. Future research should determine the specific mechanisms of these differences

### J Autism Dev Disord. 2017;1-7.

DOSE-RESPONSE EFFECTS OF LONG-ACTING LIQUID METHYLPHENIDATE IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND AUTISM SPECTRUM DISORDER (ASD): A PILOT STUDY. *Kim S-J, Shonka S, French WP, et al.* 

Attention deficit/hyperactivity disorder (ADHD) symptoms are common in youth with autism spectrum disorders (ASD) and are frequently treated with stimulant medications. Twenty-seven children were randomized to different dose titration schedules, and ADHD symptoms, tolerability, and aberrant behaviors were assessed weekly during a 6-week trial with long-acting liquid methylphenidate (MPH). MPH at low to moderate doses was effective in reducing ADHD symptoms and was well tolerated in young children with ASD and ADHD. Future studies are needed to assess generalization and maintenance of efficacy

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J Autism Dev Disord. 2017;1-8.

THE PREVALENCE OF INTERNET ADDICTION AMONG A JAPANESE ADDLESCENT PSYCHIATRIC CLINIC SAMPLE WITH AUTISM SPECTRUM DISORDER AND/OR ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A CROSS-SECTIONAL STUDY.

### So R, Makino K, Fujiwara M, et al.

Extant literature suggests that autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are risk factors for internet addiction (IA). The present cross-sectional study explored the prevalence of IA among 132 adolescents with ASD and/or ADHD in a Japanese psychiatric clinic using Young COS Internet Addiction Test. The prevalence of IA among adolescents with ASD alone, with ADHD alone and with comorbid ASD and ADHD were 10.8, 12.5, and 20.0%, respectively. Our results emphasize the clinical importance of screening and intervention for IA when mental health professionals see adolescents with ASD and/or ADHD in psychiatric services

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### Journal of Behavioral Addictions. 2017;6:42-50.

SOCIAL SKILLS DEFICITS AND THEIR ASSOCIATION WITH INTERNET ADDICTION AND ACTIVITIES IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

### Chou W-J, Huang M-F, Chang Y-P, et al.

**Background and aims**: The aims of this study were to examine the association between social skills deficits and Internet addiction and activities in adolescents with attention-deficit/hyperactivity disorder (ADHD) as well as the moderators for this association.

**Methods**: A total of 300 adolescents, aged between 11 and 18 years, who had been diagnosed with ADHD participated in this study. Their Internet addiction levels, social skills deficits, ADHD, parental characteristics, and comorbidities were assessed. The various Internet activities that the participants engaged in were also examined.

**Results**: The associations between social skills deficits and Internet addiction and activities and the moderators of these associations were examined using logistic regression analyses. Social skills deficits were significantly associated with an increased risk of Internet addiction after adjustment for the effects of other factors [odds ratio (OR) = 1.049, 95% confidence interval (CI) = 1.030-1.070]. Social skills deficits were also significantly associated with Internet gaming and watching movies. The maternal occupational socioeconomic levels of the participants moderated the association between social skills deficits and Internet addiction.

**Conclusions**: Social skills deficits should be considered targets in prevention and intervention programs for treating Internet addiction among adolescents with ADHD

J Child Adolesc Psychopharmacol. 2017;27:296-309.

PREDICTORS OF LONG-TERM SCHOOL-BASED BEHAVIORAL OUTCOMES IN THE MULTIMODAL TREATMENT STUDY OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Reed MO, Jakubovski E, Johnson JA, et al.

**Objective**: To explore predictors of 8-year school-based behavioral outcomes in attentiondeficit/hyperactivity disorder (ADHD).

**Methods**: We examined potential baseline predictors of school-based behavioral outcomes in children who completed the 8-year follow-up in the multimodal treatment study of children with ADHD. Stepwise logistic regression and receiver operating characteristic (ROC) analysis identified baseline predictors that were associated with a higher risk of truancy, school discipline, and in-school fights.

**Results**: Stepwise regression analysis explained between 8.1% (in-school fights) and 12.0% (school discipline) of the total variance in school-based behavioral outcomes. Logistic regression identified several baseline characteristics that were associated with school-based behavioral difficulties 8 years later, including being male (associated with truancy and school discipline), African American (school discipline, in-school fights), increased conduct disorder (CD) symptoms (truancy), decreased affection from parents (school discipline), ADHD severity (in-school fights), and study site (truancy and school discipline). ROC analyses identified the most discriminative predictors of truancy, school discipline, and in-school fights, which were Aggression and Conduct Problem Scale Total score, family income, and race, respectively.

**Conclusions**: A modest, but nontrivial portion of school-based behavioral outcomes, was predicted by baseline childhood characteristics. Exploratory analyses identified modifiable (lack of paternal involvement, lower parental knowledge of behavioral principles, and parental use of physical punishment), somewhat modifiable (income and having comorbid CD), and nonmodifiable (African American and male) factors that were associated with school-based behavioral difficulties. Future research should confirm that the associations between earlier specific parenting behaviors and poor subsequent school-based behavioral outcomes are, indeed, causally related and independent cooccurring childhood psychopathology. Future research might target increasing paternal involvement and parental knowledge of behavioral principles and reducing use of physical punishment to improve school-based behavioral outcomes in children with ADHD

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J Child Adolesc Psychopharmacol. 2017;27:383-88.

# BENEFICIAL EFFECTS OF EVEROLIMUS ON AUTISM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN A GROUP OF PATIENTS WITH TUBEROUS SCLEROSIS COMPLEX.

### Kilincaslan A, Kok BE, Tekturk P, et al.

**Objectives**: Such neuropsychiatric symptoms as autism spectrum disorders, attention-deficit/hyperactivity disorder (ADHD), intellectual disability, aggression, and epilepsy are very common in patients with tuberous sclerosis complex (TSC). Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is a recent and effective treatment for TSC patients with giant cell astrocytomas and renal angiomyolipoma, and it has been shown to have a potential to reduce tumor volume. However, there is a paucity of studies on the effects of everolimus on neuropsychiatric symptoms. The aim of the present study is to describe the effects of everolimus on emotional and behavioral symptoms and refractory epilepsy in a group of patients with TSC. **Methods**: Four boys and two girls (median age 16.5; range 7.5-23 years) were included in the study. Information on the clinical and treatment characteristics of the patients was gathered from the medical records.

**Results**: Median everolimus dose was 10 mg/day (range 5-20 mg) and median time for follow-up was 17.5 (range 7-26) months. The drug was well tolerated with mild adverse effects, including stomatitis (three cases), increase in triglycerides and cholesterol (two cases), and constipation (one case). The adverse effects encountered during the course of treatment did not make it necessary to discontinue the drug or decrease its dose. All cases experienced very good to moderate response for controlling epileptic seizures. Besides, improvements in social contact, language, repetitive behavior, inattention, hyperactivity, and depression were observed in some patients.

**Conclusions**: Everolimus was well tolerated without severe adverse effects. It was helpful in controlling seizures and additional improvements were noted in autistic, ADHD, and depressive symptoms

J Child Adolesc Psychopharmacol. 2017;27:366-73.

### PREDICTORS OF NICOTINE DEPENDENCE IN ADOLESCENTS: SYMPTOMS OF BIPOLAR DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

### Yeh T-C, Wang S-C, Chang Y-T, et al.

**Objective**: Bipolar disorder (BD) and attention-deficit/hyperactivity disorder (ADHD) have been associated with the use of cigarettes, but little is known about the impact of the subthreshold symptoms of BD or ADHD on the course of nicotine dependence. Identifying the links is essential for elucidating the pathway and supporting the development of nicotine prevention strategies for adolescents.

**Methods**: Participants (n = 3322) aged 15-17 years completed the Chinese version of the ADHD Self-Report Scale and the Mood Disorder Questionnaire. The modified Fagerstr Tolerance Questionnaire was completed to measure their nicotine use or dependence. Mediation analyses were performed to explore the relationship of two predictors.

**Results**: The prevalence rates of cigarette smoking and nicotine dependence in this study were 14.4% and 2.3%, respectively. Male gender (odds ratio [OR] 2.30; 95% confidence interval [CI] 1.60-3.30), subclinical symptoms of ADHD (OR 1.34; 95% CI 1.04-1.71), clinical symptoms of ADHD (OR 1.69; 95% CI 1.08-2.66), and symptoms of BD (OR 1.59; 95% CI 1.09 to 2.32) were associated with nicotine use. Male gender (OR 4.60; 95% CI 1.41-14.98) and symptoms of BD (OR 6.14; 95% CI 3.37-11.18), but not symptoms of ADHD, were associated with nicotine dependence. In mediation analyses, we found that the effect of ADHD symptoms was no longer significant after controlling for symptoms of BD, and the mediation ratio (PM) was 0.39.

**Conclusions**: Our findings suggest that mood disturbances other than symptoms of ADHD are more likely to be a key predictor of nicotine dependence among adolescents. The conclusions may improve our understanding of the course of nicotine dependence and help to promote potential health policy for nicotine control among youths

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### J Child Psychol Psychiatry. 2017 May;58:555-63.

ANGER-IRRITABILITY AS A MEDIATOR OF ATTENTION DEFICIT HYPERACTIVITY DISORDER RISK FOR ADOLESCENT ALCOHOL USE AND THE CONTRIBUTION OF COPING SKILLS.

### Harty SC, Gnagy EM, Pelham WEJr, et al.

**Background**: Research on susceptibility to alcohol use disorder within the attention deficit/hyperactivity disorder (ADHD) population has begun to expand examination of putative moderators and mediators in order to develop effective treatments. Specific dysregulated emotions have been separately associated with ADHD and with alcohol use difficulties. The current study is the first to conjointly study these variables by testing anger-irritability as a mediator of ADHD risk for adolescent alcohol use.

**Methods**: Frequency of binge drinking, drunkenness, and alcohol problems were examined for 142 children with ADHD followed into adolescence and compared to 100 demographically similar youth without ADHD. Parent-rated anger-irritability was tested as a mediator. Behavioral and cognitive coping skills, which are key clinical treatment targets, were studied as moderators of these associations.

**Results**: Childhood ADHD was positively associated with anger-irritability and the drinking outcomes in adolescence. Anger-irritability mediated the association between ADHD and alcohol use problems, but not binge drinking or drunkenness. Behavioral and cognitive, but not avoidant, coping played a moderating role, but only of the association between childhood ADHD and anger-irritability.

**Conclusions**: Active coping strategies by adolescents with ADHD may reduce the vulnerability to alcohol problems through a reduction of negative emotions. Future research on additional mediators and treatments that target these skills is encouraged

### EFFECT OF TRAIT ANXIETY ON COGNITIVE TEST PERFORMANCE IN ADOLESCENTS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

### Ruf BM, Bessette KL, Pearlson GD, et al.

**Introduction**: Attention-deficit/hyperactivity disorder (ADHD) and anxiety are frequently comorbid disorders associated with different types of abnormal performance on neuropsychological tests. Although some studies have shown that comorbid anxiety alters ADHD test performance, results inconsistently show both improvements and worsening of different abilities, with failures to replicate across different anxiety disorders. Alternatively, trait anxiety may reflect a more stable influence on ADHD test performance than various diagnosable anxiety disorders.

**Method**: To better understand the possible enhancing or deleterious effects of anxiety on ADHD cognitive impairments, this study examined the effect of individual differences in trait anxiety measured by the Multidimensional Anxiety Scale for Children (MASC) on a battery of computerized, rapid-performance tests measuring attention and impulsivity-related performance in 98 Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM–IV) Combined-Subtype ADHD adolescents and 123 healthy controls. It was hypothesized that trait anxiety would attenuate response inhibition and attention deficits in ADHD.

**Results**: ADHD-diagnosed adolescents with higher trait anxiety performed better on indices of sustained attention, reaction time, and motor variability, and had altered overall test-performance strategy, while response inhibition was affected in both ADHD and non-ADHD.

**Conclusions**: This study provides the first evidence that pathological levels of anxiety are not needed to see differences in ADHD neuropsychological test performance. Instead, mildly elevated trait anxiety confers a protective influence by reducing the degree of impairment seen in ADHD. These findings suggest that better performing ADHD adolescents might have optimized levels of cortical arousal, and raise new questions about how best to identify the neurobiological substrates responsible for the beneficial effects

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### J Clin Exp Neuropsychol. 2017 May;39:485-501.

ONLINE INFERENTIAL AND TEXTUAL PROCESSING BY ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING READING COMPREHENSION: EVIDENCE FROM A PROBING METHOD.

### Yeari M, Avramovich A, Schiff R.

**Introduction**: Previous studies have demonstrated that students with attention-deficit/hyperactivity disorder (ADHD) struggle particularly with grasping the implicit, inferential level of narratives that is crucial for story comprehension. However, these studies used offline tasks (i.e., after story presentation), used indirect measurements (e.g., identifying main ideas), and/or yielded inconclusive results using think-aloud techniques. Moreover, most studies were conducted with preschool or elementary school children with ADHD, using listening or televised story comprehension. In this study, we were interested in examining the spontaneous, immediate activation and/or suppression of forward-predictive inferences, backward-explanatory inferences, and inference-evoking textual information, as they occur online during reading comprehension by adolescents with ADHD.

**Method**: Participants with and without ADHD read short narrative texts, each of which included a predictive sentence, a bridging sentence that referred back to the predictive sentence via actualization of the predicted event, and two intervening sentences positioned between the predictive and bridging sentences that introduced a temporary transition from the main (predictive) episode. Activation and suppression of inferential and/or textual information were assessed using naming times of word probes that were implied by the preceding text, explicitly mentioned in it, or neither when following control texts. In some cases, a true–false inferential or textual question followed the probe.

**Results**: Naming facilitations were observed for the control but not for the ADHD group, in responding to inference probes that followed the predictive and bridging sentences, and to text probes that followed the predictive sentences. Participants with ADHD were accurate, albeit slower, than controls in answering the true–false questions.

**Conclusions**: Adolescents with ADHD have difficulties in generating predictive and explanatory inferences and in retaining relevant textual information in working memory while reading, although they can answer

questions after reading when texts are relatively short. These findings are discussed with regard to development of comprehension strategies for individuals with ADHD

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J Consult Clin Psychol. 2017;85:434-46.

COMPARING TREATMENTS FOR CHILDREN WITH ADHD AND WORD READING DIFFICULTIES: A RANDOMIZED CLINICAL TRIAL.

### Tamm L, Denton CA, Epstein JN, et al.

**Objective**: This trial compared attention-deficit/hyperactivity disorder (ADHD) treatment alone, intensive reading intervention alone, and their combination for children with ADHD and word reading difficulties and disabilities (RD).

**Method**: Children (n = 216; predominantly African American males) in Grades 2-5 with ADHD and word reading/decoding deficits were randomized to ADHD treatment (medication + parent training), reading treatment (reading instruction), or combined ADHD + reading treatment. Outcomes were parent and teacher ADHD ratings and measures of word reading/decoding. Analyses utilized a mixed models covariate-adjusted gain score approach with posttest regressed onto pretest.

**Results**: Inattention and hyperactivity/impulsivity outcomes were significantly better in the ADHD (parent Hedges's g = .87/.75; teacher g = .67/.50) and combined (parent g = 1.06/.95; teacher g = .36/41) treatment groups than reading treatment alone; the ADHD and Combined groups did not differ significantly (parent g = .19/.20; teacher g = .31/.09). Word reading and decoding outcomes were significantly better in the reading (word reading g = .23; decoding g = .39) and combined (word reading g = .32; decoding g = .39) treatment groups than ADHD treatment alone; reading and combined groups did not differ (word reading g = .09; decoding g = .00). Significant group differences were maintained at the 3- to 5-month follow-up on all outcomes except word reading.

**Conclusions**: Children with ADHD and RD benefit from specific treatment of each disorder. ADHD treatment is associated with more improvement in ADHD symptoms than RD treatment, and reading instruction is associated with better word reading and decoding outcomes than ADHD treatment. The additive value of combining treatments was not significant within disorder, but the combination allows treating both disorders simultaneously

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J Dev Behav Pediatr. 2017 May;38:249-59.

# NEUROCOGNITIVE CORRELATES OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN BORN AT EXTREMELY LOW GESTATIONAL AGE.

### Scott MN, Hunter SJ, Joseph RM, et al.

**Objective**: Compared with children born near term, those born extremely preterm (EP) are at much higher risk for attention-deficit hyperactivity disorder (ADHD). Little information is available about differences in neuropsychological outcomes among EP children with and without ADHD. Our analyses aimed to evaluate the neuropsychological correlates of ADHD symptoms in extremely low gestational age newborns (ELGANs). **Methods**: We obtained Child Symptom Inventory-4 reports from parents (n = 871) and teachers (n = 634) of 10-year-old children born before the 28th week of gestation. Participants completed standardized assessments of neurocognitive and academic functioning.

**Results**: In the total sample, children who screened positive for ADHD symptoms were at increased risk for neurocognitive limitations. These associations were weaker when the sample was limited to those with intelligence quotient (IQ) =70 or =85. Even those with IQ =85 who screened positive for ADHD symptoms were more likely than their peers to have deficits on the DAS-II Working Memory Cluster and the NEPSY-II Auditory Response subtest. The risks for impaired academic performance (Z = -1) on components of the WIAT-III were 2-to-3 times higher in this group than among ELGANs not classified as having ADHD symptoms.

**Conclusion**: Among children born EP, those with ADHD symptoms are more likely to have global neurocognitive impairment. When IQ is within normal limits, ADHD symptoms are associated with deficits in

executive functioning skills. These findings highlight a group at risk for executive functioning deficits and related academic difficulties, even in the absence of intellectual disability

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Journal of Pediatric Hematology/Oncology. 2017.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH SICKLE CELL DISEASE REFERRED FOR AN EVALUATION.

### Acquazzino MA, Miller M, Myrvik M, et al.

Neuropsychological deficits, including difficulties with attention, are well described in children with sickle cell disease (SCD). Very little is known about attention deficit hyperactivity disorder (ADHD) in children with SCD. The objective of this study was to determine the proportion of ADHD in children with SCD referred for neuropsychological evaluation. This prospective, cross-sectional study included patients (age, 4 to 18 y) with SCD and completion of a neuropsychological evaluation between December 2013 and March 2016. Patients were referred for neuropsychological evaluation because of concern regarding school performance, development, and/or behavior. The diagnosis of ADHD was made by a neuropsychologist on the basis of the diagnostic criteria in the Diagnostic Statistical ManualΓÇöFourth or Fifth Editions. ADHD medication usage rate was obtained by medical record review. Of the 89 patients with SCD referred for neuropsychological evaluation, 25% (95% confidence interval, 16%-35%) met diagnostic criteria for ADHD. Only 21% of the patients with SCD and ADHD were prescribed an ADHD medication. Our study supports routine ADHD screening in children with SCD who have poor school performance or behavioral concerns. Despite the benefits of pharmacologic treatment, the majority of patients with SCD and ADHD did not receive a medication for management of their ADHD

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#### J Pediatr. 2017.

PSYCHIATRIC DISORDERS AND FUNCTION IN ADOLESCENTS WITH TETRALOGY OF FALLOT.

### Holland JE, Cassidy AR, Stopp C, et al.

**Objectives**: To assess psychiatric disorders and function in adolescents with repaired tetralogy of Fallot (TOF) without and with a genetic diagnosis and to evaluate associations of functioning with medical factors, IQ, and demographics.

**Study design**: Adolescents with TOF (n = 91) and 87 healthy referents completed a clinician-rated structured psychiatric interview, parent-/self-report measures of psychopathology, and brain magnetic resonance imaging. Twenty-three of the adolescents with TOF had a known genetic diagnosis.

**Results**: The prevalence of anxiety disorders did not differ significantly between adolescents with TOF without genetic diagnosis (n = 68) and referents. Adolescents with TOF and a genetic diagnosis showed an increased lifetime prevalence of anxiety disorder (43%) and lower global psychosocial functioning (median, 70; IQR, 63-75) compared with adolescents with TOF without genetic diagnosis (15% and 83; IQR, 79-87, respectively; P = .04 and <.001, respectively) and referents (6% and 85; IQR, 76-90, respectively; P = .001 and <.001, respectively). Adolescents with TOF without and with a genetic diagnosis had a higher lifetime prevalence of attention deficit-hyperactivity disorder (ADHD) than referents (19% and 39%, respectively, vs 5%; P = .04 and .002, respectively) and worse outcomes on parent-/self-report ratings of anxiety and disruptive behavior compared with referents. Risk factors for anxiety, ADHD, and lower psychosocial functioning for adolescents with TOF without a genetic diagnosis included older age, male sex, and low IQ. Medical variables were not predictive of psychiatric outcomes.

**Conclusion**: Adolescents with TOF, particularly those with a genetic diagnosis, show increased rates of psychiatric disorder and dysfunction. Continued mental health screening and surveillance into young adulthood is warranted for adolescents with TOF

Journal of Pharmacy Research. 2015;9:612-17.

**COMPUTER-BASED ATTENTION TRAINING FOR TREATING A CHILD WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: AN ADJUNCT TO PHARMACOTHERAPY - A CASE REPORT.** 

Saha P, Chakraborty P, Mukhopadhyay P, et al.

**Aim**: The current research aims to understand the efficacy of Captain's log, a computerized training programme, on the EEG parameters, and on attention, working memory, processing speed, hyperactivity of the children with ADHD-combined type.

**Methods**: A computerized cognitive training programme Captains log Brain Train is used for treating the child. The male child performed cognitive tasks 36 minutes twice a week for 35 sessions that focused on improvement of attention, concentration, processing speed, working memory and impulsivity. Pre- and post-treatment differences on the Evoke Related Potential (ERP), Conners Parent Rating Scale, coding was considered as indices of changes.

**Results**: The Scores on Conners Rating Scale revealed a decrease inattention and minimal change in hyperactivity. Electrophysiological testing on Evoke Response Potential (ERP) shows decrease in latency and increase in amplitudes in the few component of ERP.

**Conclusion**: The processing speed, visuomotor coordination, sustained attention and working memory improved in the child after cognitive training but the tasks that recruit higher cognitive functioning such as, planning, organizing and conflict monitoring did not show marked improvement

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J Am Acad Child Adolesc Psychiatry. 2017 May;56:426-35.

BEHAVIORAL AND NEURAL SUSTAINED ATTENTION DEFICITS IN DISRUPTIVE MOOD DYSREGULATION DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

### Pagliaccio D, Wiggins JL, Adleman NE, et al.

**Objective**: Disruptive mood dysregulation disorder (DMDD), characterized by severe irritability, and attention-deficit/hyperactivity disorder (ADHD) are highly comorbid. This is the first study to characterize neural and behavioral similarities and differences in attentional functioning across these disorders.

**Method**: Twenty-seven healthy volunteers, 31 patients with DMDD, and 25 patients with ADHD (8 to 18 years old) completed a functional magnetic resonance imaging attention task. Group differences in intrasubject variability in reaction time (RT) were examined. The present functional magnetic resonance imaging analytic approach precisely quantified trial-wise associations between RT and brain activity.

**Results**: Group differences manifested in the relation between RT and brain activity (all regions: p < .01, F > 2.54, partial eta-squared  $[\eta_p^2] > 0.06$ ). Patients with DMDD showed specific alterations in the right paracentral lobule, superior parietal lobule, fusiform gyrus, and cerebellar culmen. In contrast, patients with DMDD and those with ADHD exhibited blunted compensatory increases in activity on long RT trials. In addition, youth with DMDD exhibited increased activity in the postcentral gyrus, medial frontal gyrus, and cerebellar tonsil and declive (all regions: p < .05, F > 2.46,  $\eta_p^2 > 0.06$ ). Groups in the imaging sample did not differ significantly in intra-subject variability in RT (F<sub>2,79</sub> = 2.664, p = .076,  $\eta_p^2 = 0.063$ ), although intra-subject variability in RT was significantly increased in youth with DMDD and ADHD when including those not meeting strict motion and accuracy criteria for imaging analysis (F<sub>2,96</sub> = 4.283, p = .017,  $\eta_p^2 = 0.083$ ).

**Conclusion**: Patients with DMDD exhibited specific alterations in the relation between pre-stimulus brain activity and RT. Patients with DMDD and those with ADHD exhibited similar blunting of compensatory neural activity in frontal, parietal, and other regions. In addition, patients with DMDD showed increased RT variability compared with healthy youth. This work is the first to identify common and unique behavioral and neural signatures of DMDD and ADHD

J Am Acad Child Adolesc Psychiatry. 2017 May;56:371-72. ROC on WITH ASEBA AND THE ATTENTION PROBLEMS.

### Hamilton J.

Comments on an article by J. S. Raiker et al. (see record [rid]2017-19263-011[/rid]). Raiker et al. bring their expertise in empirically based assessment to a community mental health center (CMHC) context and show how to create feasible infrastructure for attention-deficit/ hyperactivity disorder (ADHD) screening at intake, increasing the odds of busy clinicians being able to get home on time. A public health approach at the community clinic level, including screening, makes sense for ADHD because of the number of children affected. The description of the process of the treatment/no treatment decision as a negotiation among parents, child, and clinician seems important. Using diagnostic likelihood ratios (DLRs) to refine a base rate of probability for ADHD and other disorders can stand as a stake-in-the-ground at busy clinical sites in such discussions, perhaps providing supporting data for the test/no test decision, and still allowing clinicians a decision making process shared with families. The context of an emergency room (ER) provides an interesting comparison: a CBCL T-score of 75 on the Attention Problems subscale generates a DLR of 2.2, a larger effect than the DLR for crushing pain or sweating in diagnosing myocardial infarction in the ER. Just as sweating and crushing pain, especially together, demand a closer look, so do specific high subscale scores at intake on the CBCL and TRF scales

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### J Am Acad Child Adolesc Psychiatry. 2017 May;56:436-44.

IMPACT OF A COMMON GENETIC VARIATION ASSOCIATED WITH PUTAMEN VOLUME ON NEURAL MECHANISMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

### Xu B, Jia T, Macare C, et al.

**Objective**: In a recent genomewide association study of subcortical brain volumes, a common genetic variation at rs945270 was identified as having the strongest effect on putamen volume, a brain measurement linked to familial risk for attention-deficit/hyperactivity disorder (ADHD). To determine whether rs945270 might be a genetic determinant of ADHD, its effects on ADHD-related symptoms and neural mechanisms of ADHD, such as response inhibition and reward sensitivity, were explored.

**Method**: A large population sample of 1,834 14-year-old adolescents was used to test the effects of rs945270 on ADHD symptoms assessed through the Strengths and Difficulties Questionnaire and region-of-interest analyses of putamen activation by functional magnetic resonance imaging using the stop signal and monetary incentive delay tasks, assessing response inhibition and reward sensitivity, respectively.

**Results**: There was a significant link between rs945270 and ADHD symptom scores, with the C allele associated with lower symptom scores, most notably hyperactivity. In addition, there were sex-specific effects of this variant on the brain. In boys, the C allele was associated with lower putamen activity during successful response inhibition, a brain response that was not associated with ADHD symptoms. In girls, putamen activation during reward anticipation increased with the number of C alleles, most significantly in the right putamen. Remarkably, right putamen activation during reward anticipation tended to negatively correlate with ADHD symptoms.

**Conclusion**: These results indicate that rs945270 might contribute to the genetic risk of ADHD partly through its effects on hyperactivity and reward processing in girls

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J Am Acad Child Adolesc Psychiatry. 2017;56:401-09.

ACCURACY OF ACHENBACH SCALES IN THE SCREENING OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A COMMUNITY MENTAL HEALTH CLINIC.

### Raiker JS, Freeman AJ, Perez-Algorta G, et al.

**Objective** To use receiver-operating characteristics analysis to identify multilevel diagnostic likelihood ratios and provide a framework for the diagnosis of attention-deficit/hyperactivity disorder (ADHD) in children (5–10 years old) and adolescents (11–18 years old) in an outpatient setting.

**Method** Caregiver, teacher, and youth reports from the Achenbach System of Empirically Based Assessment (ASEBA) were obtained for 299 children and 321 adolescents with multiple imputation of missing data. The reference standard was diagnosis of ADHD based on case history and a semistructured diagnostic interview masked to the ASEBA measurements.

**Results** In children, caregiver-reported Attention Problems (area under the curve [AUC] = 0.74) outperformed all other subscales of the caregiver and teacher measures (AUCs 0.72). In the older sample, caregiver- and teacher-reported Attention Problems (caregiver AUC = 0.73; teacher AUC = 0.61) were best at identifying ADHD. Inclusion of caregiver and teacher reports significantly (p < .001 for all comparisons) increased prediction of ADHD diagnosis, whereas youth self-report did not.

**Conclusion** Caregiver-reported Attention Problems were more useful than teacher-reports and self-report in identifying ADHD. Combining caregiver and teacher reports improved identification. Multilevel likelihood ratios are provided to facilitate routine clinical use

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### J Am Acad Child Adolesc Psychiatry. 2017;56:483-90.

SPECIFIC COMPONENTS OF PEDIATRICIANS' ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) MEDICATION-RELATED CARE PREDICT ADHD SYMPTOM IMPROVEMENT.

### Epstein JN, Kelleher KJ, Baum R, et al.

**Objective** The development of attention-deficit/hyperactivity disorder (ADHD) care quality measurements is a prerequisite to improving the quality of community-based pediatric care of children with ADHD. Unfortunately, the evidence base for existing ADHD care quality metrics is poor. The objective of this study was to identify which components of ADHD care best predict patient outcomes.

**Method** Parents of 372 medication-na+»ve children in grades 1 to 5 presenting to their community-based pediatrician (N = 195) for an ADHD-related concern and who were subsequently prescribed ADHD medication were identified. Parents completed the Vanderbilt ADHD Parent Rating Scale (VAPRS) at the time ADHD was raised as a concern and then approximately 12 months after starting ADHD medication. Each patient's chart was reviewed to measure 12 different components of ADHD care.

**Results** Across all children, the mean decrease in VAPRS total symptom score during the first year of treatment was 11.6 (standard deviation 10.1). Of the 12 components of ADHD care, shorter times to first contact and more teacher ratings collected in the first year of treatment significantly predicted greater decreases in patient total symptom scores. Notably, it was timeliness of contacts, defined as office visits, phone calls, or email communication, that predicted more ADHD symptom decreases. Office visits alone, in terms of number or timeliness, did not predict patient outcomes.

**Conclusion** The magnitude of ADHD symptom decrease that can be achieved with the use of ADHD medications was associated with specific components of ADHD care. Future development and modifications of ADHD quality care metrics should include these ADHD care components

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### J Med Assoc Thailand. 2017;100:418-26.

# ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): CLINICAL OUTCOMES MEASUREMENT DEVELOPMENT. Santitadakul R, Sithisarankul P, Lertmaharit S, et al.

**Objective**: To develop a reliable and valid treatment outcome checklist for the measurement of ADHD treatment for children in a clinical setting.

**Material and Method**: The behavior indicators to assess the treatment outcomes of ADHD children were researched and developed by using multi-informants perspectives. The present study involved a qualitative study and two rounds of the Modified Delphi Techniques. In the first process, 11 parents/guardians of ADHD children aged 6 to 18 years were given a semi-structured interview on their expectation towards treatment outcomes at the Child and Adolescent Mental Health Rajanagarindra Institute. Items from literature reviews were also added before the first and second round evaluations using the Delphi by five different expert fields (six experts from each field). Final indicators from expert consensus were assessed from 180 ADHD patients,
which were assessed by three child and adolescent psychiatrists. All items were analyzed for internal coefficient reliability. The Receiver Operating Characteristic (ROC) was used to calculate the cut off score. **Results**: Thirteen indicators were assessed by experts as good content validity for clinical outcomes of ADHD treatment with the reliability of 0.60. The optimal cut-off point was 4 (sensitivity: 0.80; specificity: 0.76). The Area under curve (AUC) of total score was considered at a good level (0.83).

**Conclusion**: The ADHD clinical outcome checklist with 13 items has shown good validity and fair reliability. It can be a useful tool for ADHD treatment outcome assessment in clinical setting

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### Kathmandu University Medical Journal. 2016;14:226-30.

### PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG SCHOOL CHILDREN AND ASSOCIATED CO-MORBIDITIES - A HOSPITAL BASED DESCRIPTIVE STUDY.

### Rimal HS, Pokharel A.

**Background** Attention Deficit Hyperactivity Disorder is the most common neuro-developmental disorders of childhood characterized by the core symptoms including inattentiveness and distractibility and frequently involve impairments in executive functioning, increased impulsivity, and restlessness.

**Objective** To find out the prevalence of Attention Deficit Hyperactivity Disorder among school aged children Presented to Pediatric clinic and also to investigate associated co-morbidities.

**Method** This study was conducted at Nobel Medical College Teaching Hospital, Biratnagar during April 2014 - March 2015. Attention Deficit Hyperactivity Disorder was diagnosed by the developmental Pediatrician after taking relevant history and the clinical assessment using Attention Deficit Hyperactivity Disorder rating scale with diagnostic criteria consistent with Diagnostic Statistical Manual - IV classification. Spence anxiety scale child and parent rated version and Strength and Difficulty Questionnaire were also used.

**Result** Result showed the yearly prevalence of Attention Deficit Hyperactivity Disorder being 41(11.7%) with male: female ratio of 4:1. The study reported that Attention Deficit Hyperactivity Disorder combined type was the commonest type that was 26(63%) cases followed by Inattentive type 9(22%) cases and 6(15%) were hyperactive type. The mean age for Attention Deficit Hyperactivity Disorder was 7 years and 5 months. The most common co-morbidities were sleep problem 12(29.3%), Learning difficulty 10(24.4%), Anxiety disorder 10(24.4), Oppositional Defiant Disorder 9(22%), Autism Spectrum Disorder 5(12%), speech delay 6(14.6%), and 4(10%) had associated tics. There was abnormal SDQ prevalence of 29.3% across the area of emotional distress. The mean abnormal SDQ score in total difficulty area 8 (20.7%), socializing with peer 9(22%), behavioral difficulty 11(26.8%), hyperactivity/inattention 23(56.1%) and impact of difficulties in young person $\Gamma$ ÇÖs life being 5(12.2%).

**Conclusion** There is high prevalence of Attention Deficit Hyperactivity Disorder in children and adolescents in Nepal. This study has also looked at co-morbidities associated with Attention Deficit Hyperactivity Disorder and the findings of the study have thrown lights on the mental health and other developmental issues associated with it

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Monatsschr Kinderheilkd. 2017;1-7.

ROLE OF THE PEDIATRICIAN IN LEARNING DISORDERS AND SCHOOL PROBLEMS.

### Rauter L.

At least 10% of school-age children will consult the pediatrician because of problems in connection with learning disorders and school problems. Most of the diagnostic and therapeutic procedures the pediatrician will have to delegate to other professionals but the pediatrician will have to coordinate these procedures. Essential in working with the child should be strengthening his/her self-esteem, and an important aim of the parental work should be that parents adopt realistic expectations regarding the child<sub>3</sub>s school performances and that the respect and appreciation of the child should not depend on the child<sub>3</sub>s school performance. Moreover, parents should be advised to contact the teachers and work in a goal-oriented manner together. The pediatrician too should contact the school to learn how teachers assess the problems of the child. If required, the pediatrician will start and control medical treatment. The aim of the pediatrician<sub>3</sub>s work with the

child, the parents, and school will be that the child likes to attend school again, wants to learn, and will be ready to take exams with self-confidence

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### Mov Disord. 2017;32:601-04.

BASAL GANGLIA STRUCTURE IN TOURETTE'S DISORDER AND/OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. Forde NJ, Zwiers MP, Naaijen J, et al.

**Background**: Tourette's disorder and attention-deficit/hyperactivity disorder often co-occur and have both been associated with structural variation of the basal ganglia. However, findings are inconsistent and comorbidity is often neglected.

**Methods**: T1-weighted magnetic resonance images from children (n = 141, 8 to 12 years) with Tourette's disorder and/or attention-deficit/hyperactivity disorder and controls were processed with the Oxford Centre for Functional MRI [Magnetic resonance imaging] of the Brain (FMRIB) integrated registration and segmentation tool to determine basal ganglia nuclei volume and shape. Across all participants, basal ganglia nuclei volume and shape were estimated in relation to Tourette's disorder (categorical), attention-deficit/hyperactivity disorder severity (continuous across all participants), and their interaction.

**Results**: The analysis revealed no differences in basal ganglia nuclei volumes or shape between children with and without Tourette's disorder, no association with attention-deficit/hyperactivity disorder severity, and no interaction between the two.

**Conclusion**: We found no evidence that Tourette's disorder, attention-deficit/hyperactivity disorder severity, or a combination thereof are associated with structural variation of the basal ganglia in 8- to 12-year-old patients. -® 2016 International Parkinson and Movement Disorder Society

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### NeuroImage Clin. 2017;15:383-90.

# REGIONAL BRAIN NETWORK ORGANIZATION DISTINGUISHES THE COMBINED AND INATTENTIVE SUBTYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

### Saad JF, Griffiths KR, Kohn MR, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is characterized clinically by hyperactive/impulsive and/or inattentive symptoms which determine diagnostic subtypes as Predominantly Hyperactive-Impulsive (ADHD-HI), Predominantly Inattentive (ADHD-I), and Combined (ADHD-C). Neuroanatomically though we do not yet know if these clinical subtypes reflect distinct aberrations in underlying brain organization. We imaged 34 ADHD participants defined using DSM-IV criteria as ADHD-I (n = 16) or as ADHD-C (n = 18) and 28 matched typically developing controls, aged 8<sup>°</sup>Cô17 years, using high-resolution T1 MRI. To quantify neuroanatomical organization we used graph theoretical analysis to assess properties of structural covariance between ADHD subtypes and controls (global network measures: path length, clustering coefficient, and regional network measures: nodal degree). As a context for interpreting network organization differences, we also quantified gray matter volume using voxel-based morphometry. Each ADHD subtype was distinguished by a different organizational profile of the degree to which specific regions were anatomically connected with other regions (i.e., in ГC£nodal degreeГCØ). For ADHD-I (compared to both ADHD-C and controls) the nodal degree was higher in the hippocampus. ADHD-I also had a higher nodal degree in the supramarginal gyrus, calcarine sulcus, and superior occipital cortex compared to ADHD-C and in the amygdala compared to controls. By contrast, the nodal degree was higher in the cerebellum for ADHD-C compared to ADHD-I and in the anterior cingulate, middle frontal gyrus and putamen compared to controls. ADHD-C also had reduced nodal degree in the rolandic operculum and middle temporal pole compared to controls. These regional profiles were observed in the context of no differences in gray matter volume or global network organization. Our results suggest that the clinical distinction between the Inattentive and Combined subtypes of ADHD may also be reflected in distinct aberrations in underlying brain organization

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### NeuroImage Clin. 2017;15:181-93.

# SHARED AND DISORDER-SPECIFIC TASK-POSITIVE AND DEFAULT MODE NETWORK DYSFUNCTIONS DURING SUSTAINED ATTENTION IN PAEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBSESSIVE/COMPULSIVE DISORDER. Norman LJ, Carlisi CO, Christakou A, et al.

Patients with Attention-Deficit/Hyperactivity Disorder (ADHD) and obsessive/compulsive disorder (OCD) share problems with sustained attention, and are proposed to share deficits in switching between default mode and task positive networks. The aim of this study was to investigate shared and disorder-specific brain activation abnormalities during sustained attention in the two disorders. Twenty boys with ADHD, 20 boys with OCD and 20 age-matched healthy controls aged between 12 and 18 years completed a functional magnetic resonance imaging (fMRI) version of a parametrically modulated sustained attention task with a progressively increasing sustained attention load. Performance and brain activation were compared between groups. Only ADHD patients were impaired in performance. Group by sustained attention load interaction effects showed that OCD patients had disorder-specific middle anterior cingulate underactivation relative to controls and ADHD patients, while ADHD patients showed disorder-specific underactivation in left dorsolateral prefrontal cortex/dorsal inferior frontal gyrus (IFG). ADHD and OCD patients shared left insula/ventral IFG underactivation and increased activation in posterior default mode network relative to controls, but had disorder-specific overactivation in anterior default mode regions, in dorsal anterior cingulate for ADHD and in anterior ventromedial prefrontal cortex for OCD. In sum, ADHD and OCD patients showed mostly disorder-specific patterns of brain abnormalities in both task positive salience/ventral attention networks with lateral frontal deficits in ADHD and middle ACC deficits in OCD, as well as in their deactivation patterns in medial frontal DMN regions. The findings suggest that attention performance in the two disorders is underpinned by disorder-specific activation patterns

### Neurology. 2017 Mar;88:1029-36.

MODERATORS AND PREDICTORS OF RESPONSE TO BEHAVIOR THERAPY FOR TICS IN TOURETTE SYNDROME. Sukhodolsky DG, Woods DW, Piacentini J, et al.

**OBJECTIVE**: To examine moderators and predictors of response to behavior therapy for tics in children and adults with Tourette syndrome and chronic tic disorders.

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**METHODS**: Data from 2 10-week, multisite studies (1 in children and 1 in adults; total n = 248) comparing comprehensive behavioral intervention for tics (CBIT) to psychoeducation and supportive therapy (PST) were combined for moderator analyses. Participants (177 male, 71 female) had a mean age of 21.5 +/- 13.9 years (range 9-69). Demographic and clinical characteristics, baseline tic-suppressing medication, and co-occurring psychiatric disorders were tested as potential moderators for CBIT vs PST or predictors of outcome regardless of treatment assignment. Main outcomes measures were the Yale Global Tic Severity Scale Total Tic score and the Clinical Global Impression-Improvement score assessed by masked evaluators.

**RESULTS**: The presence of tic medication significantly moderated response to CBIT vs PST (p = 0.01). Participants showed tic reduction after CBIT regardless of tic medication status, but only participants receiving tic medication showed reduction of tics after PST. Co-occurring psychiatric disorders, age, sex, family functioning, tic characteristics, and treatment expectancy did not moderate response. Across both treatments, greater tic severity (p = 0.005) and positive participant expectancy (p = 0.005) predicted greater tic improvement. Anxiety disorders (p = 0.042) and premonitory urge severity (p = 0.005) predicted lower tic reduction.

**CONCLUSIONS**: Presence of co-occurring attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, or anxiety disorders did not moderate response to CBIT. Although participants on tic medication showed improvement after CBIT, the difference between CBIT and PST was greater for participants who were not on tic-suppressing medication.

**CLINICALTRIALSGOV IDENTIFIERS**: The child and adult CBIT studies are listed on clinical trials.gov (NCT00218777 and NCT00231985, respectively).

**CLASSIFICATION OF EVIDENCE**: This study provides Class I evidence that CBIT is effective in reducing tic severity across subgroups of patients with chronic tic disorders, although the difference between treatments was smaller for participants on tic-suppressing medications, suggesting reduced efficacy in this subgroup

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Neuropsychiatr Dis Treat. 2017;13:1071-80.

# ARE PSYCHIATRIC COMORBIDITIES AND ASSOCIATED COGNITIVE FUNCTIONS RELATED TO TREATMENT RESPONSE TO METHYLPHENIDATE IN BOYS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER?

### Chan MH, Leung PWL, Ho T-P, et al.

**Background**: Methylphenidate (MPH) has been found to be an effective medication for attentiondeficit/hyperactivity disorder (ADHD). However, there are neither consistent nor sufficient findings on whether psychiatric comorbidities and associated cognitive functions of ADHD are related to treatment response to MPH in ADHD children.

**Objectives**: This study investigated whether psychiatric comorbidities, IQ, and neurocognitive deficits are related to treatment response to MPH in ADHD children. In some ways, it is preferable to have a drug that the effectiveness of which to a disorder is not affected by its associated cognitive functions and psychiatric comorbidities. On the other hand, it is likely that the baseline symptom severity of ADHD is associated with the effectiveness of MPH treatment on the symptoms post treatment.

**Methods**: A total of 149 Chinese boys (aged 6ГÇô12 years) with ADHD, combined type, and normal IQ participated in this study. Assessment of ADHD symptom severity was conducted pre and post MPH treatment, while assessment of psychiatric comorbidities, IQ, and neurocognitive deficits was performed in a non-medicated condition. Treatment response was defined as the ADHD symptom severity post MPH treatment.

**Results**: Results indicated that MPH treatment was effective, significantly improving the ADHD condition. Yet, comorbid disorders, IQ, and neurocognitive deficits were not related to MPH treatment response on ADHD symptoms. These findings indicated that the effectiveness of MPH was not affected by psychiatric comorbidities and associated cognitive functions of ADHD. Instead, as expected, it was the baseline symptom severity that was mainly related to the treatment response, ie, the milder the baseline condition, the better the treatment response.

**Conclusion**: The current findings positively endorse the widespread clinical use of MPH for treating ADHD. It improves the behavioral symptoms of ADHD regardless of varying psychiatric comorbidities, IQ, and neurocognitive deficits

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### Neuropsychiatr Dis Treat. 2017;13:1331-39.

# POTENTIAL ROLE OF PRE- AND POSTNATAL TESTOSTERONE LEVELS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: IS THERE A SEX DIFFERENCE?

### Wang L-J, Chou M-C, Chou W-J, et al.

**Objective**: Both prenatal testosterone (T) exposure and postnatal T levels have been associated with developing neural circuitry and behavioral systems. This study examined the potential correlation between pre- and postnatal T levels and behavioral and neurocognitive profiles of children with attention-deficit/hyperactivity disorder (ADHD).

**Methods**: Two hundred ADHD patients with a mean age of 8.7-I2.0 years (158 boys and 42 girls) were recruited. The ratio of the length of the right index finger (2D) to that of the right ring finger (4D) (2D/4D ratio) served as a surrogate of prenatal T exposure, and postnatal T was determined using salivary T concentration. Behavioral symptoms were evaluated using the Swanson, Nolan, and Pelham - Version IV Scale for ADHD (SNAP-IV). Neurocognitive function was assessed using the Wechsler Intelligence Scale for Children  $\Gamma C\hat{C}$  Fourth Edition (WISC-IV) and Conners' Continuous Performance Test (CPT).

**Results**: Lower 2D/4D ratios were associated with comorbid disruptive behavior disorders (t=2.15, P=0.033) in all participants. Among the boys with ADHD, neither 2D/4D ratios nor salivary T levels were associated

with behavioral symptoms or neurocognitive function. Among the girls with ADHD, the salivary T level was positively correlated with the Perceptual Reasoning Index of the WISC-IV (r=0.48, P=0.001) and the Confidence Index (r=0.37, P=0.017) and Omission Errors of the CPT (r=0.62, P,0.001).

**Conclusion**: Findings suggest that a higher prenatal T exposure is associated with a greater risk of developing disruptive behavior disorders, and T may exert differential neurocognitive effects between boys and girls with ADHD. However, the neurobiological mechanisms of T involved in the pathogenesis of ADHD warrant further investigation

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### Neuropsychiatr Dis Treat. 2017;13:947-58.

### ACCESS TO DIAGNOSIS, TREATMENT, AND SUPPORTIVE SERVICES AMONG PHARMACOTHERAPY-TREATED CHILDREN/ ADOLESCENTS WITH ADHD IN EUROPE: DATA FROM THE CAREGIVER PERSPECTIVE ON PEDIATRIC ADHD SURVEY. Fridman M, Banaschewski T, Sikirica V, et al.

**Background**: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders and negatively impacts caregivers lives. Factors including barriers to accessing care, dissatisfaction with support services, and lack of caregiver resources may contribute to this.

**Objectives**: To report caregivers experiences of ADHD diagnosis, behavioral therapy (BT), and supportive care for children/adolescents with ADHD.

**Methods**: The Caregiver Perspective on Pediatric ADHD (CAPPA) survey included caregivers of children/adolescents (6ΓÇô17 years) from ten European countries who were currently receiving/ had received ADHD pharmacotherapy in the previous 6 months. Caregivers reported experiences of obtaining an ADHD diagnosis, access to BT, availability of caregiver resources, and level of health care/school support. Pan-EU and country-specific descriptive statistics are reported; responses were compared across countries. **Results**: Of 3,616 caregivers, 66% were female. Mean age of children/adolescents was 11.5 years; 80% were male. Mean time from the first doctor visit to diagnosis was 10.8 (95% confidence interval 10.2, 11.3) months; 31% of caregivers reported the greatest degrees of difficulty in obtaining an ADHD diagnosis; 44% of children/adolescents did not receive BT. Forty-seven percent of caregivers reported that sufficient resources were available, 44% were very satisfied satisfied with medical care, and 50% found health care providers very supportive som ewhat supportive. Mainstream schools were attended by 82% of children/adolescents ADHD and 48% received extra help/special arrangement. Results varied significantly between countries (P<0.001, all parameters).

**Conclusion**: Almost a third of caregivers reported a high degree of difficulty in obtaining an ADHD diagnosis for their child/adolescent, less than half felt that sufficient resources were available, and gaps in support from health care providers/schools were identified. Findings underscore the need to improve access to diagnosis and provision of supportive services to enable better standards of care, and potentially reduce the impact of child/adolescent ADHD on caregivers lives

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Neuropsychiatry. 2016;6:344-50.

ABNORMAL DEVELOPMENTAL TRAJECTORIES OF AMPLITUDE OF LOW FREQUENCY FLUCTUATIONS WITHIN INTRINSIC CONNECTIVITY NETWORKS FOR SCHOOL-AGE BOYS WITH ADHD.

### Wang X-H, Jiao Y, Li L, et al.

**Background**: ADHD is a prevalent brain disorder in school-age children. To our knowledge, the development of intrinsic connectivity networks (ICNs) remains unclear for children with ADHD. The goals of this paper are two-folds: 1) modeling the ICN-related brain connectivity based on phenotype scores; 2) exploring the altered growth curves of ICNs for ADHD.

**Methods and Findings**: A cohort of boys with ADHD and a cohort of normal controls were recruited from ADHD-200 Consortium. Amplitude of low frequency fluctuations (ALFFs) was applied to measure the brain connectivity within ICNs. Quantic models consisted of age; IQ, behavioral scores and head motion were applied to investigate the relationships between brain developments and intra-ICN ALFFs. The results found

that the lateral visual network and executive control network were nonlinearly correlated to aging in both ADHD group and normal control group. Based on intra-ICN ALFFs, the turning points of brain developments might be 11-12 years old for ADHD.

**Conclusions**: The lateral visual network, cerebellum network, auditory network, and executive control network might play important roles in the brain development of ADHD. The abnormal developmental trajectories of ADHD could be discovered by intra-ICN ALFFs, which could be a potential biomarker for functional connectome

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### Neuropsychiatry. 2016;6:251-63.

IMPACT OF WORKING MEMORY TRAINING ON HOT EXECUTIVE FUNCTIONS (DECISION-MAKING AND THEORY OF MIND) IN CHILDREN WITH ADHD: A RANDOMIZED CONTROLLED TRIAL.

### Bigorra A, Garolera M, Guijarro S, et al.

**Background** Children with attention deficit/hyperactivity disorder (ADHD) have deficits in working memory (WM) and in hot executive functions (EFs) that may be related. The main aim of this study was to analyze the efficacy of computerized Cogmed Working Memory Training (CWMT) on hot EF decision-making and theory of mind (ToM). Correlational analyses between WM and hot EFs at baseline were also performed to better clarify the nature of this interrelationship.

**Methods** 66 children with combined-Type ADHD, aged 7 to 12 years, were included. Participants were randomized (1:1) to an experimental group (CWMT) (n=36) or a control group (non-Adaptive training). At baseline, 1-2 weeks, and 6 months after the intervention, participants were assessed using performance-based measures of WM (backward digit span, letter-number sequencing of WISC-IV, and backward spatial span of WMS-III), decision-making (Iowa Gambling Task), and ToM (Happe's Strange Stories and Folk Psychology Test).

**Results** Statistically significant correlations were found between WM and ToM measures at baseline, but not between WM and decision-making. On adjusted multiple linear regression analysis, there were no significant improvements in any of the outcome measures at either time point.

**Conclusions** There was no relationship between WM and decision-making in ADHD. A relationship was found between WM and ToM, but CWMT did not show far-Transfer effects on ToM deficits in ADHD. Other implications of these results are discussed

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Neuropsychology. 2017;31:383-94.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND PHONOLOGICAL WORKING MEMORY: METHODOLOGICAL VARIABILITY AFFECTS CLINICAL AND EXPERIMENTAL PERFORMANCE METRICS.

### Tarle SJ, Matt AR, Patros CHG, et al.

**Objective**: Despite promising findings in extant research that suggest impaired working memory (WM) serves as a central neurocognitive deficit or candidate endophenotype of attention-deficit/hyperactivity disorder (ADHD), findings from translational research have been relatively underwhelming. This study aimed to explicate previous equivocal findings by systematically examining the effect of methodological variability on WM performance estimates across experimental and clinical WM measures.

**Method**: Age-matched boys (ages 8-12 years) with (n = 20) and without (n = 20) ADHD completed 1 experimental (phonological) and 2 clinical (digit span, letter-number sequencing) WM measures.

**Results**: The use of partial scoring procedures, administration of greater trial numbers, and high central executive demands yielded moderate-to-large between-groups effect sizes. Moreover, the combination of these best-case procedures, compared to worstcase procedures (i.e., absolute scoring, administration of few trials, use of discontinue rules, and low central executive demands), resulted in a 12.5% increase in correct group classification.

**Conclusion**: Collectively, these findings explain inconsistent ADHD-related WM deficits in previous reports, and highlight the need for revised clinical measures that utilize best-case procedures

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### Pediatr Emerg Care. 2017.

IDENTIFYING UNDIAGNOSED PEDIATRIC MENTAL ILLNESS IN THE EMERGENCY DEPARTMENT. Downey LVA, Zun LS.

**BACKGROUND**: It is well known that pediatric psychiatric patients frequent emergency department (ED), but the number of patients with undiagnosed psychiatric illness presenting to an ED is not well known. Identification and referral of these patients may provide an opportunity for improved patient care. The primary study objective was to identify a tool that can screen for unsuspected psychiatric illness in pediatric patients who present to the ED with non-psychiatric-related complaints.

**METHODS**: The MINI International Neuropsychiatric Interview for Children and Adolescents screening tool was administered to 200 pediatric consenting patients and guardians. The inclusion criteria were English-speaking patients who presented in the ED with a nonpsychiatric complaint who were stable and able to communicate. The study was conducted in a level 1 trauma center ED of an inner-city hospital that serves a predominantly African American and Hispanic population. This study was institutional review board approved.

**RESULTS**: The study populations consisted of 53% African American (107), 45% Hispanic (90), 1% white (2), and 0.5% Asian (1). Their age range was divided, with 49% between 12 and 14 years (98) and 51% between 15 and 17 years (102). The sex was evenly split, with 50% male (100) and 50% female (100). The 41% who did screen positive for an undiagnosed mental illness had a range of diagnoses. The top modules with positive results were oppositional defiant (13.5%, 27), attention-deficit/hyperactivity disorder (13%, 25), depression (10%, 11), conduct disorder (9%, 19), and anxiety (5%, 11).

**CONCLUSIONS**: The pediatric Mini International Neuropsychiatric Interview was effective in screening for undiagnosed mental illness in pediatric patients who presented to the ED with no psychiatric-related illness. The screening tool indicated that 41% of pediatric patients screened positive for an undiagnosed mental illness, with attention deficit-related disorders being the most widely seen. Further study should be conducted to test the tools used in a range of ED settings

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Pediatric Transplantation. 2017;21:95.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN CHILDS WHO UNDERWENT LIVER TRANSPLANTATION.

### Marangoz Y, Bari+f Z, Sari BA, et al.

**INTRODUCTION**: We planned to investigate the frequency of ADHD in children with liver transplantation and the possible causes of this disorder.

**METHODS**: Sixty-two children aged between six and eighteen years, who had liver transplantation between 2003 and 2015 in B+£TF Hospital was participated in the study. Primary diagnoses, age of transplantation, duration of pretransplantation illness, duration of hospitalization and intensive care unit before and after transplantation, Child Pugh and PELD scores, donor type, prematurity, history of low birth weight, convulsion, familial epilepsy and maternal smoking during pregnancy was recorded. K-SADS (Schedule for Affective Disorders and Schizophrenia for School Aged Children-Kiddie- SADS-Present and Lifetime Version) was performed on all children and their parents by the clinical interviewer who is a specialist in child and adolescent mental health and DSM IV Axis 1 diagnosis was determined. Patients were evaluated with Conners' Parent-Teacher Rating Scale (CPRS-CPTS).

**RESULTS**: Six of the 62 patients (9.7%) were diagnosed with ADHD. Two of these patients' primary diagnosis was Alagille syndrome, two patients had familial hypercholesterolemia, one had biliary atresia and one patient had tyrosinemia. 4% of the girls in the sample (1/25); 13.5% of men (5/37) were diagnosed with ADHD. The only patient who was diagnosed with inattentive type of ADHD was female, while the other five were male. Four patients had combined type of ADHD and one patient had hyperactive-impulsive type of

ADHD. As the duration and number of post-transplantation hospitalization during the following years increased, hyperactivity scores increased in the Conners test conducted by teachers. (r: 0.273 p: 0.046) **CONCLUSION**: In our study the rate of ADHD was slightly higher than the proportion of community-based studies and lower than studies conducted with children with liver transplants. This suggests the effects of hepatic transplantation on cognitive function and attention. This study is the first study to investigate ADHD in children with liver transplants in our country. We suggest simultaneous consideration of physical health and mental health in patients with organ transplantation and problems should be intervened in time

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### Percept Mot Skills. 2017 Apr;124:425-40.

### ATTENTION DEFICIT HYPERACTIVITY DISORDER AND MOTOR IMPAIRMENT.

### Goulardins JB, Marques JC, De Oliveira JA.

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder during childhood, affecting approximately 3-6% of school-aged children; its cardinal symptoms of high activity, impulsivity, and behavioral distractibility might be assumed to have close relationships to interferences with motor skills. A separate body of literature attests to ways that motor problems can severely impact children's daily lives, as motor problems may occur in 30-50% of children with ADHD. This article critically reviews research on motor impairment in children with ADHD, notable differences in motor performance of individuals with ADHD compared with age-matched controls, and possible neural underpinnings of this impairment. We discuss the highly prevalent link between ADHD and developmental coordination disorder (DCD) and the lack of a clear research consensus about motor difficulties in ADHD. Despite increasing evidence and diagnostic classifications that define DCD by motor impairment, the role of ADHD symptoms in DCD has not been delineated. Similarly, while ADHD may predispose children to motor problems, it is unclear whether any such motor difficulties observed in this population are inherent to ADHD or are mediated by comorbid DCD. Future research should address the exact nature and long-term consequences of motor impairment in children with ADHD and elucidate effective treatment strategies for these disorders together and apart

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### PLoS ONE. 2017;12.

# SHARED AND DIFFERENTIATED MOTOR SKILL IMPAIRMENTS IN CHILDREN WITH DYSLEXIA AND/OR ATTENTION DEFICIT DISORDER: FROM SIMPLE TO COMPLEX SEQUENTIAL COORDINATION.

### Marchand-Krynski M-E, Morin-Moncet O, B+®langer A-M, et al.

Dyslexia and Attention deficit disorder (AD) are prevalent neurodevelopmental conditions in children and adolescents. They have high comorbidity rates and have both been associated with motor difficulties. Little is known, however, about what is shared or differentiated in dyslexia and AD in terms of motor abilities. Even when motor skill problems are identified, few studies have used the same measurement tools, resulting in inconstant findings. The present study assessed increasingly complex gross motor skills in children and adolescents with dyslexia, AD, and with both Dyslexia and AD. Our results suggest normal performance on simple motor-speed tests, whereas all three groups share a common impairment on unimanual and bimanual sequential motor tasks. Children in these groups generally improve with practice to the same level as normal subjects, though they make more errors. In addition, children with AD are the most impaired on complex bimanual out-of-phase movements and with manual dexterity. These latter findings are examined in light of the Multiple Deficit Model

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Psychiatric Bulletin. 2015;39:136-40.

SPECIALIST ADULT ADHD CLINICS IN EAST ANGLIA: SERVICE EVALUATION AND AUDIT OF NICE GUIDELINE COMPLIANCE.

### Magon RK, et al.

**Aims and method**: To measure compliance with National Institute for Health and Care Excellence (NICE) recommendations in two adult attention-deficit hyperactivity disorder (ADHD) clinics and to guide further service development. We audited the case notes of 150 patients referred to adult ADHD clinics in East Anglia in 2010-2011 against NICE standards using an adapted version of the ADHD audit support tool.

**Results**: We found good compliance with NICE standards for diagnosis, assessment and pharmacological treatment of adult ADHD. There was a failure in smooth transitional arrangements from child and adolescent mental health to adult ADHD services. Comprehensive treatment programmes addressing psychological, behavioural, educational and occupational needs were not well developed. Deficiencies were observed in conducting recommended physical examinations. Substance use was prevalent in almost half of ADHD patients.

**Clinical implications**: Greater attention is needed in delivering better transitional arrangements and comprehensive treatment programmes for adult ADHD. More structured training with emphasis on ADHD-specific psychological interventions, physical examination and treatment of complex cases, especially with comorbid substance misuse, should be offered to clinicians

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### Psychiatric Bulletin. 2015;39:140-43.

SERVICES FOR ADULTS WITH ADHD: WORK IN PROGRESS - COMMENTARY ON ... SPECIALIST ADULT ADHD CLINICS IN EAST ANGLIA.

### Coghill D.

Magon and colleagues highlight a number of relative strengths and weaknesses very reminiscent of those we have seen over the years in the development of similar services for children and adolescents. It is clear that we all have a lot of work to do to improve our approach to the transition from child to adult services. There was clear evidence that adult services can adapt to manage ADHD, but there is also a clear need for increased upskilling of clinicians in the practical management of medication and other treatments. I disagree with Magon and colleagues about the role of primary care and believe that treatment initiation and ongoing monitoring should, for the time being, remain in secondary care and that, because of the volume of work that will come our way, this will need to become a core rather than specialist task. As with other aspects of psychiatric care, there is a clear role for specialist nurses in delivering a significant proportion of the core care

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### Psychiatry Clin Neurosci. 2017.

PHARMACOTHERAPY FOR THE TREATMENT OF AGGRESSION IN PEDIATRIC AND ADOLESCENT PATIENTS WITH AUTISM SPECTRUM DISORDER COMORBID WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A QUESTIONNAIRE SURVEY OF 571 PSYCHIATRISTS.

### Yamamuro K, Tsujii N, Ota T, et al.

**Aim**: Both attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are frequently accompanied by serious aggression that requires psychiatric treatment. However, little is known about the experiences psychiatrists have had using pharmacotherapy to treat aggression in patients who have both ASD and ADHD (ASD/ADHD). The purpose of this study was to examine the experiences of Japanese child and adolescent psychiatrists in prescribing medication for aggression in patients with ASD/ADHD.

**Methods**: A prospective questionnaire was mailed to 2001 psychiatrists affiliated with the Japanese Society for Child and Adolescent Psychiatry. Multivariate logistic regression analysis was used to identify factors predicting the outcome of pharmacotherapeutic treatment of aggression in pediatric and adolescent patients with ASD/ADHD.

**Results**: Of 2001 psychiatrists, 571 (28.5%) completed the full questionnaire (final sample). Of these, 488 (85.4%) prescribed psychotropic medication in treating pediatric and adolescent patients with ASD/ADHD, 299 (61.3%) of them doing so to treat aggression. Prescribers' duration of practice (odds ratio, 1.055; P=0.038) and patient symptoms of residual impulsivity (odds ratio, 2.479; P=0.039) increased the odds of prescribing psychotropic medications to treat aggression in these patients. The respondents reported a similar effect for patients with ADHD/ASD compared with those with ADHD only in treating aggression. **Conclusion**: Japanese psychiatrists tended to prescribe psychotropic medication for aggression in pediatric and adolescent patients with ASD/ADHD. Future studies examining aggression in pediatric and adolescent patients with ASD/ADHD. Future studies evidence for the use of psychotropic medications, which could help clinicians make better decisions

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### Psychiatr Invest. 2017;14:260-70.

THE BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION AND CONTINUOUS PERFORMANCE TEST IN PRESCHOOLERS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

### Çak HT, et al.

**Objective** The aim of this study is to examine performance-based measures and behavioral ratings of executive functions (EF) as a component of preschool attention deficit hyperactivity disorder (ADHD).

**Methods** Twenty-one 4-to-6-year-old children with ADHD and 52 children with no psychopathology, matched on age, gender, socioeconomic status, and parental education, were enrolled. Parents were interviewed with the use of The Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version. The Conners Kiddie Continuous Performance Test (K-CPT) was administered to the children, and the Behavior Rating Inventory of Executive Function-Preschool version (BRIEF-P) and the Conners Parent Rating Scale-Revised/Short Form (CPRS-R/S) were filled out by the parents.

**Results** All BRIEF-P and CPRS-R/S scores, the K-CPT measures of inattention and impulsivity were higher in the ADHD group. The CPRS-R/S ADHD index was strongly correlated with inhibition and related indexes in the BRIEF-P and was moderately correlated with inattention measures in the K-CPT.

**Conclusion** The current study is one of the few to investigate the features of preschool ADHD with the use of behavioral ratings of EF and a performance-based measure. Our results suggest that the BRIEF-P was able to identify behavioral difficulties in inhibition and working memory and that the K-CPT identified difficulties indicating inattention. The findings of this study support the use of a combination of methods for a complete evaluation of preschoolers with inattentive and hyperactive/impulsive behavior, the application of rating scales for screening ADHD symptoms, and the measurement of behavioral correlates of EF, along with performance-based measures

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Psychiatry Res. 2017;254:1-7.

ATTENTIONAL CONTROL OF EMOTIONAL INTERFERENCE IN CHILDREN WITH ADHD AND TYPICALLY DEVELOPING CHILDREN: AN EMOTIONAL N-BACK STUDY.

### Villemonteix T, Marx I, Septier M, et al.

Emotional interference control refers to the ability to remain focused on goal-oriented processes when confronted with disrupting but irrelevant emotional stimuli, a process that may be impaired in children and adults with attention deficit/hyperactivity disorder (ADHD). However, emotional interference levels are known to be associated with trait anxiety, and patients with ADHD often display elevated levels of trait anxiety, such as these may have confounded previous findings of decreased emotional interference control in this population. In the present study, male and female 8-13 years old (mean =11.0 years) children with ADHD (n=33) and typically developing (TD) children (n=24) performed a visual emotional working memory (n-back) task with 2 memory loads and three different background pictures (neutral/positive/negative), and trait anxiety measures were obtained. Children with ADHD performed less well, and displayed increased emotional interference in the presence of aversive distractors when compared with TD children. Contrary to our expectations, trait anxiety did not mediate the association between diagnostic group membership and the

degree of emotional interference control; however, co-morbid ODD was associated with decreased levels of emotional interference in ADHD. Future research should aim at characterizing the mechanisms subtending decreased emotional interference control in the ADHD population

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### Res Autism Spectr Disord. 2017;39:20-32.

# PARENT-REPORTED PROBLEMATIC SLEEP BEHAVIORS IN CHILDREN WITH COMORBID AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

### Reynolds KC, Patriquin M, Alfano CA, et al.

**Background** Sleep problems are frequent and well documented in children with Autism Spectrum Disorders (ASD), children with Attention Deficit/Hyperactivity Disorder (ADHD) and children with internalizing problems, however limited work has examined sleep problems in children presenting with comorbid ASD/ADHD. In healthy children, sleep problems negatively impact social, emotional, and academic functioning. The current study sought to examine diagnostic severity as predictors of sleep problems in children with comorbid ASD/ADHD. Additionally, the association between sleep and real-life functional domains (i.e., intellectual functioning, academic achievement, and executive functioning) were assessed.

**Method** Sleep, internalizing difficulties, intellectual functioning, academic achievement and executive functioning were assessed in 85 children with who carried the dual diagnoses of ASD and ADHD.

**Results** Internalizing difficulties, rather than ASD or ADHD symptom severity, was the most consistent predictor of problematic sleep behaviors (i.e., nightmares overtiredness, sleeping less than other children, trouble sleeping, and Total Problematic Sleep Behaviors) in this sample. Further, parent report of problematic sleep behaviors was significantly associated with functional domains after controlling for ASD, ADHD, and internalizing symptoms.

**Conclusions** Results suggest that internalizing symptoms are associated with problematic sleep behaviors in children with comorbid ASD/ADHD and may have implications for the real-life functioning among children with comorbid ASD/ADHD

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Res Dev Disabil. 2017;65:46-56.

# WHAT DOES HANDEDNESS REVEAL ABOUT ADHD? AN ANALYSIS BASED ON CPT PERFORMANCE. Simes EN, Carvalho ALN, Schmidt SL.

**Background** Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder. Continuous performance Tests (CPTs) aid the diagnosis. Handedness is linked to disabilities.

**Objectives** 1-To study the association between handedness and ADHD; 2-To verify the usefulness of the CPT in school settings; 3-To exam the relationship between handedness and CPT performance.

**Method** Each child was classified as right-consistent, left-consistent, or non-consistent. From the sample, 171 controls and 68 ADHDs fulfilled the inclusion criteria. The effect of handedness on the CPT was studied using a paired-sample that matched handedness by age, grade, gender, and ADHD.

**Results** Left-handed students had a probability of suffering from ADHD 2.88 greater than right-handers. ANOVAs on standardized scores indicated that the ADHD students exhibited higher number of errors and higher variability of reaction times as compared to the controls. Discriminant analysis indicated that these CPT parameters could discriminate ADHD from controls. Repeated ANOVAs showed a significant effect of handedness on commission errors (CE) because left-handers made more CEs than right-handers.

**Conclusions** 1-The association between ADHD and handedness reflects that left-handers are less lateralized and have decreased interhemispheric connections; 2-The CPT can be used to measure different attention domains in school settings; 3- Left-handers have problems in the impulsive/hyperactivity domain

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### Schweiz Arch Neurol Psychiatr. 2017;168:41-47. ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN SWISS PRIMARY CARE.

### Gamma A, et al.

In 2012, the "Sentinella" survey of Swiss primary care physicians (PCPs) examined the frequency and treatment of attention deficit hyperactivity disorder (ADHD) in Swiss primary care, the differences between pediatricians and general practitioners (GPs) in handling ADHD, as well as the needs of PCPs regarding management of ADHD in practice. An average of 1 out of every 1000 consultations concerned suspected or confirmed ADHD, with pediatricians reporting 18x more consultations per 1000 than GPs. Male patients aged 7-12 represented the majority of consultations. Overall, 54% of pediatricians vs. 17% of GPs diagnosed ADHD themselves, and 88% of pediatricians vs. 40% of GPs treated the condition themselves. Both used medication in almost two-thirds of cases, with no gender-correlated differences observed in stimulant use. A lack of competence for diagnosing and treating ADHD was frequently reported, especially among GPs, and a corresponding need for better practical training and education was expressed. The self-reported lack of diagnostic and therapeutic expertise regarding ADHD among Swiss PCPs underscores the need for more training programs, better information on the disorder, and reliable easyto-use testing aids

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### Sleep. 2017;40:A347.

ROLE OF PERIODIC LIMB MOVEMENTS DURING SLEEP IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: DIFFERENTIAL ASSOCIATION WITH INTERNALIZING VS. EXTERNALIZING BEHAVIORS. *Frye S, Fernandez-Mendoza J, Calhoun SL, et al.* 

**Introduction**: Attention deficit hyperactivity disorder (ADHD) in children has been associated with sleep disordered breathing (SDB), insomnia, and periodic limb movement disorder (PLMD). However, there is lack of data examining the association of ADHD and PLMD with internalizing and externalizing behavioral outcomes, particularly in adolescents from the general population.

**Methods**: Data from the Penn State Child Cohort, a random sample of 421 adolescents (12-23y) who underwent 9-hour polysomnography was used. The presence of ADHD was ascertained by parent- or self-report of receiving treatment for the disorder during the clinical history and physical examination. PLMD was defined as a PLM index (PLMI) greater or equal to 5 events per hour of sleep. The Child or Adult Behavior Checklist were used to ascertain internalizing and externalizing behaviors. We adjusted for sex, race, age, eveningness, insomnia symptoms, total sleep time, awakenings, daytime sleepiness, SDB, and body mass index in our analyses.

**Results**: Adolescents with ADHD had a significantly higher PLMI ( $5.4 \pm 7.3$ ) and prevalence of PLMD (35%) as compared to controls ( $3.4 \pm 5.6$ , p = 0.006 and 21%, p = 0.004). Significant interactions between ADHD and PLMD showed that adolescents with both disorders had significantly elevated internalizing (e.g., anxious-depressed), attention and externalizing (i.e., rule-breaking, aggression) problems, while adolescents with ADHD-alone had the expected significant elevations in attention and externalizing problems. Adolescents with PLMD-alone did not have significantly elevated internalizing or externalizing problems.

**Conclusion**: PLMD is significantly more frequent in adolescents with ADHD. Importantly, adolescents with both disorders have worse behavioral outcomes than adolescents with ADHD-alone, particularly in terms of anxiety and depression. Interestingly, PLMD in the absence of ADHD is not significantly associated with behavioral problems. These data suggest that PLMD, rather than comorbid with or causally related to ADHD, is a marker of more severe underlying neurobiological deficits in ADHD

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Soc Psychiatry Psychiatr Epidemiol. 2017 Apr;52:457-64.

AN EPIDEMIOLOGICAL STUDY OF ADHD AND CONDUCT DISORDER: DOES FAMILY CONFLICT MODERATE THE ASSOCIATION?

Sigfusdottir ID, Asgeirsdottir BB, Hall HA, et al.

**Purpose**: To examine the role of family conflict in the relationship between attention deficit hyperactivity disorder (ADHD) and conduct disorder (CD).

**Methods**: A cross-sectional national population survey was carried out among 10,838 14–16 year old students in all secondary schools in Iceland. Three latent measures, financial status, ADHD and CD, and one observed measure, family structure, were included in the study. A structural equation model was used to evaluate direct effects between ADHD and CD for four different groups; females and males, experiencing family conflict and those not experiencing family conflict.

**Results**: ADHD was significantly and positively associated with CD for all groups. When controlling for financial status and family structure it was found that ADHD was positively and significantly associated with CD for adolescent females and males not experiencing family conflict as well as for those experiencing family conflict. The link between ADHD and CD was significantly stronger for those adolescents who had experienced family conflict compared to those who had not experienced family conflict. These results suggest that family conflict moderates the association between ADHD and CD for both girls and boys.

**Conclusions**: The results of this study indicate that family environment and ADHD symptoms are important when predicting CD among adolescent youth. Most notably, family conflict exacerbates the effects of ADHD symptoms on CD among both females and males

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### Transl Psychiatry. 2017;7.

### CROWDSOURCED VALIDATION OF A MACHINE-LEARNING CLASSIFICATION SYSTEM FOR AUTISM AND ADHD. Duda M, Haber N, Daniels J, et al.

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) together affect >10% of the children in the United States, but considerable behavioral overlaps between the two disorders can often complicate differential diagnosis. Currently, there is no screening test designed to differentiate between the two disorders, and with waiting times from initial suspicion to diagnosis upwards of a year, methods to quickly and accurately assess risk for these and other developmental disorders are desperately needed. In a previous study, we found that four machine-learning algorithms were able to accurately (area under the curve (AUC)>0.96) distinguish ASD from ADHD using only a small subset of items from the Social Responsiveness Scale (SRS). Here, we expand upon our prior work by including a novel crowdsourced data set of responses to our predefined top 15 SRS-derived questions from parents of children with ASD (n=248) or ADHD (n=174) to improve our model's capability to generalize to new, 'real-world' data. By mixing these novel survey data with our initial archival sample (n=3417) and performing repeated cross-validation with subsampling, we created a classification algorithm that performs with AUC=0.89-i0.01 using only 15 questions

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ORIGINAL CONTRIBUTION

# CrossMark

# Changes in serum levels of kynurenine metabolites in paediatric patients affected by ADHD

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Abstract This study aims at determining serum levels of tryptophan and other metabolites of the kynurenine pathway in children with attention deficit hyperactivity disorder (ADHD) compared to healthy controls. Such metabolites interact with glutamate receptors in the central nervous system, potentially modulating mechanisms that are pivotal in ADHD and thus potentially representing peripheral biomarkers of the disorder. We measured serum levels of tryptophan and some metabolites of the kynurenine pathway in 102 children with ADHD and 62 healthy controls by liquid chromatography-tandem mass spectrometry (LC-MS/MS). As compared to healthy controls, children with ADHD showed a reduction in serum levels of anthranilic acid (-60%), kynurenic acid (-11.2%), and xanthurenic acid (-12.5%). In contrast, serum levels of tryptophan (+11.0%) and kynurenine (+48.6%) were significantly enhanced, and levels of quinolinic acid were unchanged in children with ADHD. In a logistic regression model, the presence of ADHD was predicted by low anthranilic acid

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and high tryptophan levels. These findings support the involvement of the kynurenine pathway in the pathophysiology of ADHD and suggest that anthranilic acid and tryptophan levels should be investigated as potential peripheral biomarker for ADHD.

Keywords ADHD  $\cdot$  Biomarker  $\cdot$  Kynurenines  $\cdot$  Children  $\cdot$  Neurobiology

### Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral childhood disorder characterized by inattention, hyperactivity, impulsivity, or a combination of these symptoms. The disorder is typically diagnosed in childhood, but affected persons frequently remain symptomatic in adulthood [1].

The world-wide prevalence in developmental age is 5.29% and is higher in boys than girls [2].

The diagnosis in children focuses on behavioural symptoms and, according to DSM-5 criteria, is based on the presence of at least six out of nine symptoms in the two domains of inattention and hyperactivity–impulsivity [3].

The aetiology of ADHD can be explained by a combination of inherited and environmental factors that critically influence the developmental trajectory of the prefrontal cortex [4]. In fact, Shaw and colleagues have found that persistence of ADHD is associated with divergence away from typical developmental trajectories [5].

Several studies from genomics to metabolomics as well as measurements of plasma levels of monoamines, hormones (e.g., corticol and oxytocin), and neurotrophic factors have been performed in an attempt to elucidate the biological mechanisms involved in ADHD and to identify potentially predictive peripheral and genetic markers [6-10]. These studies, however, are not conclusive and further investigation is needed.

The kynurenine pathway of tryptophan metabolism generates neuro-active compounds that are able to interact with neurotransmitters receptors in the central nervous system (CNS). The pathway is activated by either indolamine-2,3-dioxygenase or tryptophan-2,3-dioxygenase, which catalyzes the conversion of L-tryptophan into N-formylkynurenine. L-Kynurenine generated from N-formylkynurenine can be (1) transaminated into kynurenic acid by types 1 and 2 kynurenine aminotransferases (KATs); (2) hydroxylated into 3-hydroxykynurenine by kynurenine mono-oxygenase (KMO); or (3) converted into anthranilic acid by kynureninase. 3-Hydroxykynurenine is sequentially metabolized into 3-hydroxyantranylic acid and quinolinic acid, which is the direct precursor of nicotinamide. Xanturenic acid and cinnabarinic acid are by-products of the kynurenine pathway, generated from 3-hydroxykynurenine and 3-hydroxyanthranilic acid, respectively [11]. Kynurenic acid acts as a competitive antagonist at the glycine site on the GluN1 NMDA receptor subunit, thereby inhibiting NMDA receptor activation [12]. In contrast, quinolinic acid acts as an orthosteric agonist at the GluN2 NMDA receptor subunits [13]. Recent evidence suggests that xanthurenic acid activates mGlu2 and mGlu3 metabotropic glutamate receptors [14], although it has been argued that xanthurenic acid acts primarily by inhibiting the vesicular glutamate transporters, thereby enhancing non-vesicular release of glutamate from nerve endings [15]. Cinnabarinic acid acts as a weak orthosteric agonist of mGlu4 receptors [16]. Given the involvement of glutamatergic system (especially with respect to NMDA receptor-related genetic variants) in the development of ADHD [17] and the at least partial inconsistency of studies that have tried to shed light on biological mechanisms underlying ADHD, a study on kynurenine metabolites levels in this disorder is warranted.

To the best of our knowledge, only two research groups have examined serum levels of kynurenine metabolites in patients affected by ADHD with contrasting results [18, 19]. On one hand, Aarsland and colleagues found that ADHD in adults is associated with lower serum concentrations of tryptophan, kynurenic acid, xanthurenic acid, and 3-hydroxyanthranilic acid [18].

On the other hand, Oades and colleagues describe lower levels of 3-hydroxykynurenine in children with ADHD and interpret this finding as consistent with the delayed brain maturation peculiar to the disorder [19]. However, the study by Oades and colleagues is based on a rather small sample, while Aarsland and colleagues focused on adults, a population where age-related changes might have occurred. The aim of our study was to investigate the serum levels of tryptophan and several metabolites of the kynurenine pathway in children with ADHD and healthy controls.

### Methods

One hundred and two drug-naïve children, referred to the Clinic for Developmental Neurology and Psychiatry of the S. Pertini Hospital in Rome and to the Paediatric Department of Sant'Andrea Hospital in Rome, and diagnosed with ADHD according to DSM-5 criteria, were enrolled. Children, as well as their parents, underwent a semi-structured psychiatric interview, i.e., the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [20]. In addition, parents filled out the ADHD Rating Scale, adapted for the Italian population [21].

A detailed medical history was obtained for all subjects. All participants to the study underwent a neurological and physical examination to detect co-morbid medical and neurological conditions. Children with genetic disorders, cerebral palsy, autism, neuromuscular disease, and associated chromosomal syndromes were excluded.

Serum samples from fasting patients and controls were obtained between 10 am and 12 am. Blood was sampled in anticoagulant-free tubes and kept at room temperature for 1 h before the serum was separated (centrifugation at 2000g for 10 min). Aliquots of serum were stored at -80 °C until analysis.

A control group of 62 healthy Caucasian children, age and sex matched, were randomly recruited from a community-based survey in the same area of children with ADHD, in Rome. A diagnosis of ADHD or other disorders was subsequently ruled out through the ADHD Rating Scale and the K-SADS-PL as previously described for children diagnosed with ADHD.

All children underwent a cognitive assessment by the Italian validated version of the Wechsler Intelligence Scale for Children—Third Edition Revised [22], and a full-scale intelligence quotient was obtained. Any child with an Intelligence Quotient (IQ) <70 was excluded.

None of the subjects showed any signs of topic eczema or other allergic or rheumatic diseases. Parents of all children gave written informed consent to the study. The study was approved by the local ethical committee of S. Andrea Hospital in Rome, on the basis of the Helsinki criteria.

### **Clinical assessment**

Parents filled out the ADHD Rating Scale, consisting of 18 items divided into two subgroups of nine questions that investigate inattention and hyperactive-impulsive symptoms. Parents were requested to record the frequency of symptoms (0 = no symptoms; up to 3 = mostof the time). The presence of at least six out of nine symptoms in either or both of the two subgroups (inattention and hyperactivity–impulsivity) was considered positive. The clinical diagnosis was subsequently confirmed by the K-SADS-PL administered by an experienced clinician (R. D.).

### **Cognitive assessment**

IQ was obtained using the Wechsler Intelligence Scale for Children—Third Edition Revised [22]. This is a validated intelligence test for children between 6 and 16 years of age, which is usually administered in 75–80 min.

The test comprises ten core subtests and two supplemental tests. These subtests generate a full scale score, Total-IQ (T-IQ), and two composite scores known as indexes: the Verbal-IQ (V-IQ) (including Vocabulary, Similarities, Comprehension, Information, Arithmetic, and Digit Span as supplemental test) and the Performance-IQ (P-IQ) (including Block Design, Picture Stories, Picture Completion, Puzzle, Coding, and Mazes as supplemental test).

# Analysis of serum levels of tryptophan and selected metabolites of the kynurenine pathway

We assessed serum levels of tryptophan, kynurenine, kynurenic acid, anthranilic acid, 3-hydroxyanthraniclic acid, xanthurenic acid, and quinolinic acid by a liquid chromatography-tandem mass spectrometry (LC-MS/ MS) method, as described previously [14]. In brief, serum samples were collected and stored at -80 °C until analysis. One hundred  $\mu l$  of serum samples were deproteinized using 100 µl of Internal Standard (IS) working solution (50 µM in TCA 4%). Samples were vortex-mixed centrifuged at 14,000 rpm for 5 min. Fifty µl of clean upper layer were injected into chromatographic system. The HPLC analysis was performed using an Agilent Liquid Chromatography System series 1100 (Agilent Technologies, USA) which included a binary pump, an auto-sampler, a solvent degasser, and a column oven. Chromatographic separation was performed on a pentafluorophenyl column ( $100 \times 2.1 \text{ mm}$ , Kinetex PFP, 2.6 µm, 100 Å pore size, Phenomenex, CA, USA) equipped with a security guard precolumn (Phenomenex, Torrance, CA, USA) containing the same packing material. The mobile phase consisted of a solution of 0.1%aqueous formic acid (eluent A) and 100% methanol (eluent B); elution was performed at flow rate of 300 µl/min, using an elution gradient. The mass spectrometry method was performed on a 3200 triple quadrupole system (Applied Biosystems, Foster City, CA, USA) equipped with a Turbo Ion Spray source. The detector was set in the positive ion mode. The ion spray voltage was set at 5000 V and the source temperature was 300 °C. The instrument was set in the Multiple Reaction Monitoring (MRM) mode. Data were acquired and processed by the Analyst 1.5.1 Software. The inter- and intra-assay coefficients were always lower than 20%.

The Kynurenine/tryptophan ratio was used as an index of tryptophan-2,3-dioxygenase/indoleamine 2,3-dioxygenase (TPO/IDO) activity.

### Statistical analysis

The normal distribution of data was assessed by means of the Kolmogorov-Smirnov test. Continuous variables were expressed as arithmetic mean  $\pm$  SD or median (IQR) depending on their distribution. In our study, the results analysed with a Student t test revealed that group 1 (children with ADHD, N = 102) had a mean tryptophan and kynurenine metabolite serum levels of 1343.0 ng/ml (SD 279.5) and that group 2 (healthy children, N = 62) had a mean of 1199.7 ng/ml (SD 341.3). The calculated p value was 0.004. The calculated effect size was 0.5, which is considered "medium" according to Cohen. To test our hypothesis and determine if this finding was real or due to chance (i.e., to find a significant difference), with an effect size of 0.5 and p of <0.05, we considered a sample size of approximately N = 60 in each group with a power 0.80.

Pearson's correlation was used to correlate the characteristics of ADHD children (age, sex, comorbidity presence, ADHD Rating Scale, and IQ scores) with tryptophan and kynurenine metabolites levels.

Comparisons between the socio-demographic characteristics of ADHD and healthy children were performed using Student's *t* test and Chi-square test. Student's *t* test was also used for comparisons of the levels of tryptophan and kynurenine metabolites between healthy children and children affected by ADHD. Multiple testing was corrected using the Benjamini–Hochberg method to control the falsediscovery rate (FDR).

Multiple logistic regression analysis, stepwise method was used to assess the effect of potential confounders on the presence of ADHD between patients and healthy controls.

Receiver operating characteristic (ROC) curves were performed and the area under curve (AUC) was calculated to assess the diagnostic value of anthranilic acid (ng/ml) for the prediction of ADHD. Optimal cut-off values were obtained from the Youden's index. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at the optimal cut-off value for anthranilic acid.

**Table 1** Differences in socio-demographic characteristics and IQ scores between ADHD and healthy children

	ADHD ( $n = 102$ )	Controls $(n = 62)$	р
Age (years)	$9.3 \pm 2.7$	$9.60 \pm 1.74$	NS
Sex (males)	75 (73.5%)	48 (77.4%)	NS
Total IQ	$101.14\pm15.28$	$109.56\pm12.99$	0.001*
Performance IQ	$100.43\pm16.03$	$117.68\pm10.24$	0.001*
Verbal IQ	$102.46\pm15.22$	$114.91\pm10.31$	0.001*

Data are expressed as mean  $\pm$  standard deviation

ADHD attention deficit hyperactivity disorder, IQ intelligence quotient, NS not significant

\* Student's t Test

 Table 2
 Comorbities in children with attention deficit hyperactivity disorder (ADHD)

	ADHD children ( $n = 102$ )
Comorbitity	53/102 (52%)
Oppositional defiant disorder (ODD)	20/102 (19.6%)
Anxiety disorders	12/102 (11.8%)
Language impairment	11/102 (10.8%)
Dyslexia	9/102 (8.8%)
Dysorthography	8/102 (7.8%)
Learning disability	8/102 (7.8%)
Bipolar disorder	7/102 (6.9%)
Mood disorders	6/10 (5.9%)
Deficit emotional self-regulation (DESR)	5/102 (4.9%)
Dyscalculia	5/102 (4.9%)
Tourette syndrome	3/102 (2.9%)

An SPSS software (Version 19, SPSS Inc., Chicago II, USA) was used for the analyses. "p" values of <0.05 were considered to be statistically significant.

### Results

One hundred and two children with ADHD (mean age of ADHD diagnosis  $9.3 \pm 2.7$  years, 75 males and 27 females, BMI:  $18.0 \pm 3.7$  kg/m<sup>2</sup>) and 62 healthy controls (mean age  $9.60 \pm 1.74$  years, 48 males and 14 females, BMI:  $17.4 \pm 2.4$  kg/m<sup>2</sup>), all of Caucasian origin, were enrolled.

V-IQ, P-IQ, and T-IQ scores fell within the normal range in both groups (Table 1), with higher values in healthy children (p < 0.001).

The ADHD Rating Scale Total Score in children with ADHD was  $37.13 \pm 9.16$ . In 53/102 (52.0%), children with ADHD at least one comorbid condition was present (Table 2).

Serum levels of tryptophan and kynurenine metabolites and kynurenine/tryptophan ratio are shown in Table 3.

Children with ADHD showed a substantial reduction in anthranilic acid levels (-60%; p < 0.001), slight reductions in kynurenic acid (-11%; p = 0.03) and xanturenic acid (-12.5%; p = 0.04) levels, and no changes in 3-hydroxyanthranilic acid levels. In contrast, kynurenine levels were largely increased in children with ADHD (+49%; p < 0.001). We also found a slight increase in L-tryptophan levels (+11%; p < 0.01) and values for the kynurenine/tryptophan ratio (+25%; p < 0.001) in children with ADHD with respect to healthy controls. We divided the ADHD children into two subgroups, which differed by the extent of changes in the kynurenine/tryptophan ratio with respect to healthy controls. ADHD children with values of the kynurenine/tryptophan ratio >1.5 SDS (Standard Deviation Score) with respect to the mean value of healthy controls were those in which-presumably-the kynurenine pathway was highly activated. In spite of this, these children (n = 17) showed lower levels of anthranilic acid with respect to the other ADHD children (5.5  $\pm$  3.6 vs  $10.4 \pm 7.6$  ng/ml, p < 0.02) and to healthy controls. This

	ADHD ( $n = 102$ )	Controls $(n = 62)$	р	FDR
Tryptophan (ng/ml)	$8914.9 \pm 1776.3$	8038.6 ± 2219.6	0.01*	0.025
Kynurenic acid (ng/ml)	$3.2 \pm 0.9$	$3.6 \pm 1.4$	0.03*	0.031
Xanthurenic acid (ng/ml)	$1.4 \pm 0.5$	$1.6 \pm 0.6$	0.04*	0.037
Anthranilic acid (ng/ml)	$9.6 \pm 7.3$	$24.0\pm8.9$	< 0.001*	0.006
3-Hydroxyanthranilic acid (ng/ml)	$4.57\pm3.01$	$3.62\pm2.02$	0.15	0.050
Kynurenine (ng/ml)	$440.3 \pm 158.6$	$296.0 \pm 148.7$	< 0.001*	0.012
Quinolinic acid (ng/ml)	$33.8 \pm 10.1$	$31.3\pm8.6$	0.10	0.044
Kynurenine/Tryptophan Ratio	$0.05 \pm 0.02$	$0.04 \pm 0.02$	< 0.001*	0.019

Data are expressed as mean  $\pm$  standard deviation

ADHD attention deficit hyperactivity disorder, FDR p value from Benjamini–Hochberg method control for false-discovery rate (FDR)

\* Student's t Test

controls

 Table 3
 Serum levels

 of L-tryptophan, selected
 metabolites of the kynurenine

 pathway and kynurenine/
 tryptophan ratio in children

 with ADHD and age-matched
 the compared of t

interesting finding suggests that the reduction in anthranilic acid is observed even in those cases in which large amounts of its metabolic precursor, L-kynurenine, are generated from tryptophan metabolism.

Changes in kynurenine metabolites observed in ADHD children were not influenced by comorbid conditions, as shown in Table 4.

We performed a Pearson's correlation analysis between serum levels of L-tryptophan and kynurenine metabolites in children with ADHD, and either IQ or ADHD Rating Scale scores. Kynurenic acid levels positively correlated with IQ V score (p = 0.01, r = 0.31) and negatively correlated with both Total (p = 0.047, r = -0.22) and hyperactivity (p = 0.04, r = -0.23) scores of the ADHD Rating Scale. Levels of anthranilic acid showed a negative correlation with the IQ performance score (p = 0.02, r = -0.30). Levels of kynurenine positively correlated with the IQ performance score (p = 0.047, r = 0.25) and ADHD Rating Scale Inattention Score (p = 0.05, r = 0.21). No correlations were found in healthy children (Table 5). In a regression logistic model, the presence of ADHD was predicted by low anthranilic acid levels and higher tryptophan levels (Table 6).

We performed ROC analysis to evaluate the diagnostic performance of anthranilic acid (Fig. 1). The AUC of anthranilic acid was 0.88 (95% CI = 0.83-0.94).

In ADHD group, an optimal anthranilic acid cut-off value of 10.4 ng/ml generated a sensitivity of 66.3%, a specificity of 96.8%, a PPV of 98.1%, and an NPV of 49.2% according to Youden's index.

### Discussion

We examined blood levels of metabolites of the kynurenine pathway in paediatric patients affected by ADHD. An obvious limitation of our study (and in all studies measuring blood levels of kynurenine metabolites) is that the kynurenine pathway is not confined to the CNS, and the liver and other peripheral organs are an important source

Table 4Serum levelsof L-tryptophan, selectedmetabolites of the kynureninepathway, and kynurenine/tryptophan ratio in childrenwith ADHD and at least onecomorbidity

	ADHD comorbidity $(n = 53)$	ADHD no comorbidity $(n = 49)$	р
Tryptophan (ng/ml)	9131.8 ± 2067.5	8680.4 ± 1350.9	0.2
Kynurenic acid (ng/ml)	$3.1 \pm 0.9$	$3.2 \pm 0.8$	0.3
Xanthurenic acid (ng/ml)	$1.4 \pm 0.5$	$1.3 \pm 0.4$	0.6
Anthranilic acid (ng/ml)	$9.3 \pm 7.3$	$9.8 \pm 7.3$	0.7
3-Hydroxyanthranilic acid (ng/ml)	$4.06 \pm 2.5$	$4.34 \pm 2.6$	0.6
Kynurenine (ng/ml)	$445.7 \pm 139.8$	$434.4 \pm 178.05$	0.7
Quinolinic acid (ng/ml)	$33.2 \pm 9.7$	$34.3 \pm 10.6$	0.6
Kynurenine/Tryptophan ratio	$0.05\pm0.02$	$0.05\pm0.02$	0.9

Data are expressed as mean  $\pm$  standard deviation

ADHD attention deficit hyperactivity disorder

\* Student's t Test

 Table 5
 Pearson's correlation analysis between serum levels of L-tryptophan and kynurenine metabolites in children with ADHD, and either IQ or ADHD Rating Scale scores

	IQ Performance score	IQ Verbal score	IQ Total score	ADHD Rating Scale Hyperactivity Score	ADHD Rating Scale Inattention Score	ADHD Rating Scale Total score
Tryptophan (ng/ml)	NS	NS	NS	NS	NS	NS
Xanthurenic acid (ng/ml)	NS	NS	NS	NS	NS	NS
3-Hydroxyanthranilic acid (ng/ml)	NS	NS	NS	NS	NS	NS
Anthranilic acid (ng/ml)	p = 0.02 $r = -0.30$	NS	NS	NS	NS	NS
Kynurenine (ng/ml)	p = 0.047 r = 0.25	NS	NS	NS	p = 0.05 r = 0.21	NS
Kynurenic acid (ng/ml)	NS	p = 0.014 r = 0.31	NS	p = 0.04 r = -0.23	NS	p = 0.047 r = -0.22
Quinolinic acid (ng/ml)	NS	NS	NS	NS	NS	NS

ADHD attention deficit hyperactivity disorder, NS not significant

**Table 6**Multiple logisticregression analysis

Model		В	Std. error	Wald	Sig.	Exp (B)	95% CI Exp (B)		
							Lower limit	Upper limit	
1	Anthranilic acid (ng/ml)	-0.21	0.032	42.561	0.000	0.814	0.765	0.866	
	Constant	3.9	0.601	44.165	0.000	54.171			
2	Tryptophan (ng/ml)	0.000	0.000	9.863	0.002	1.000	1.000	1.001	
	Anthranilic acid (ng/ml)	-0.237	0.036	40.590	0.000	0.797	0.743	0.855	
	Constant	1.204	1.019	1.396	0.237	3.333			



Fig. 1 Receiver operating characteristic (ROC) curves to assess the diagnostic value of anthranilic acid (ng/ml) for the prediction of ADHD

of blood kynurenine metabolites. Peripheral kynurenine and 3-hydroxykynurenine may cross the blood-brain barrier in significant amounts, and in the CNS, are metabolized by either KMO and kynureninase present in microglia or KATII present in astrocytes [11, 23]. In particular, astrocytes account for the biosynthesis of kynurenic acid, which is regulated by intracellular metabolic events, while 3-hydroxykynurenine and its major downstream metabolites are synthesized in microglia and other cells of monocytic origin [11]. Xanthurenic acid can also enter the brain [24]. It is generally believed that peripheral levels of kynurenine metabolites reflect CNS levels, perhaps with the exception of quinolinic acid [11, 23].

We found increased serum levels of tryptophan and kynurenine, reduced levels of kynurenic acid, anthranilic acid, and xanthurenic acid, and no changes in 3-hydroxyanthranilic acid and quinolinic acid levels in children with ADHD. These data are only partially consistent with those reported in adult ADHD patients, who showed lower levels of kynurenic acid, xanthurenic acid, and 3-hydroxyanthranilic acids, but no changes in anthranilic acid levels [18]. Possible explanations for these differences are that neurochemical modifications associated with ADHD are age dependent or that comparison of data in different studies is made difficult by a number of variables, such as comorbid conditions or drug treatments.

Interestingly, the tryptophan breakdown index (i.e., the kynurenine/tryptophan ratio) was significantly higher in children affected by ADHD, suggesting that a greater proportion of tryptophan is metabolized by IDO/TDO in ADHD. An increase of this index is definitely expected in the presence of pathology, as stated by Oades and colleagues who, in spite of this hypothesis, found a reduced breakdown index in their ADHD sample [19]. They interpret their own result as unexpected and meriting further attention in future studies. We believe that our result represents a piece of evidence contributing to clarifying this point. Data of kynurenine and its downstream metabolites are not easy to interpret. The higher levels of kynurenine associated with lower levels of kynurenic and anthranilic acids suggest that KAT and kynureninase are defective in ADHD. A defect of KAT may also explain the lower levels of xanthurenic acid found in children affected by ADHD. The lack of changes in 3-hydroxyanthanylic and quinolinic acid levels suggests that hydroxylation of kynurenine into 3-hydroxykynurenine (the precursor of 3-hydroxyantranilic acid) is not altered in ADHD. However, a reduction in 3-hydroxykynurenine levels has been reported in a small cohort of ADHD patients [19].

Kynurenic acid, quinolinic acid, and xanthurenic acid are neuroactive compounds that interact with different types of glutamate receptors. Kynurenic acid activates AMPA receptors at nanomolar concentrations, and inhibits AMPA receptors at micromolar concentrations [25]. In addition, kynurenic acid acts as a competitive antagonist at the glycine site of NMDA receptors, thereby inhibiting the activity of the NMDA-gated ion channel [26]. Owing to this mechanism, kynurenic acid exerts neuroprotective and anticonvulsant activities [27]. In contrast, quinolinic acid is an agonist of NMDA receptors and may cause seizures and excitotoxic neuronal death at pharmacological doses [23, 25]. Xanthurenic acid interacts at multiple levels with glutamatergic neurotransmission by inhibiting vesicular glutamate transporters [28] and activating mGlu2 and mGlu3 metabotropic glutamate receptors [29]. These receptors are coupled to Gi proteins and negatively modulate glutamate release from presynaptic terminals [30].

Changes in kynurenic and xanthurenic acid levels we have found in our sample of ADHD children may have an impact on the activity of NMDA and mGlu2/3 receptors, and therefore, our findings are in line with the hypothesis of an abnormal glutamatergic transmission in ADHD [31]. Glutamate plays a crucial role in cognitive processes, as well as in mechanisms of developmental plasticity that shape neuronal circuitries and network activity across the entire lifespan. During development, abnormalities in glutamatergic neurotransmission might alter the process of synaptic pruning, which refers to a progressive synaptic elimination that is completed at the time of sexual maturation [32]. Interestingly, synaptic pruning is believed to be abnormal in ADHD, and this may underlie the observed morphological changes in brain regions that are involved in cognitive functions, attention, executive functions, and emotions, such as the dorsolateral prefrontal cortex, anterior cingulate cortex, and insular cortex [33, 34].

It is difficult to predict in which direction a reduction in kynurenic acid levels influences excitatory neurotransmission. Lower levels of kynurenic acid may limit endogenous inhibition of NMDA receptors, thereby facilitating receptor activation by the endogenous glutamate in the ADHD brain. However, at least in the prefrontal cortex, NMDA receptors are predominantly expressed by GABAergic interneurons, as shown by the evidence that systemic administration of NMDA receptor antagonists enhances the firing rate of glutamatergic pyramidal neurons [35, 36]. In ADHD, we expect that the reduction in kynurenic acid levels reinforces NMDA-mediated excitation of GABAergic interneurons, thereby restraining the activity of pyramidal neurons. Of note, genetic and animal studies suggest that a dysregulation of NMDA receptors is involved in the pathophysiology of ADHD [17, 37], and anti-ADHD drugs, such as methylphenidate and atomoxetine, cause changes in the expression or function of NMDA receptors [38]. An interesting question is whether these changes in kynurenine metabolites are specific for ADHD or not. ADHD is frequently comorbid with other diagnoses and it has been proposed that the association between ADHD and certain comorbidities (especially conduct problems) may represent a distinct nosographic entity [39]. For this reason, we compared levels of kynurenine metabolites in ADHD subjects with

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and without comorbidities. No significant differences were found in our sample. This provides preliminary evidence that ADHD is associated with specific neurobiological features even in the presence of comorbidities.

Furthermore, in favour of an "ADHD specificity" of our findings, a different scenario is found in patients affected by schizophrenia, in which levels of the NMDA receptor antagonist, kynurenic acid, are increased, and levels of the NMDA receptor agonist, quinolinic acid, are reduced because of a defective conversion of kynurenine into 3-hydroxykynurenine [14, 40]. The resulting hypoactivity of NMDA receptors in GABAergic interneurons is expected to enhance the overall firing rate of pyramidal neurons and to severely impair neuronal synchronization and network oscillations in schizophrenia [41]. Where ADHD and schizophrenia converge is in the reduction of xanthurenic acid levels, which, however, is more prominent in patients affected by schizophrenia (compare our data with data reported by Fazio et al. [14]). The reduction of xanthurenic acid levels raises the interesting hypothesis that the function of mGlu2 and/or mGlu3 receptors is abnormal in ADHD. This hypothesis warrants further investigation, because mGlu2 receptor ligands are under clinical development for the treatment of psychiatric disorders [42].

Perhaps, the most striking finding of our study is the large reduction of anthranilic acid, which was associated with a two-fold increase in kynurenine levels. Again, this strongly suggests that the activity of kynureninase-the enzyme that converts kynurenine into anthranilic acidis defective in ADHD. The biological relevance of this finding is unknown, because neither kynurenine nor anthranilic acid is so far considered as neuroactive compounds. However, the large reduction in the ratio between anthranilic acid and kynurenine levels we have found in children affected by ADHD suggests that this ratio can be investigated as a potential peripheral biomarker of ADHD. This requires further studies with large cohorts of ADHD patients in which the influence of age and drug treatment on the ratio between anthranilic acid and kynurenine should be specifically investigated.

### Compliance with ethical standards

**Conflict of interest** MelaniaEvangelisti—Reports no disclosures. JoleRabasco—Reports no disclosures. Renato Donfrancesco—Reports no disclosures. Pietro De Rossi—Reports no disclosures. LuanaLionetto—Reports no disclosures. MatildeCapi—Reports no disclosures. Gabriele Sani—Reports no disclosures. Maurizio Simmaco—Reports no disclosures. Ferdinando Nicoletti—Reports no disclosures. Maria Pia Villa—Reports no disclosures.

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ORIGINAL CONTRIBUTION



# Comorbidity prevalence and treatment outcome in children and adolescents with ADHD

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Abstract Although ADHD comorbidity has been widely studied, some issues remain unsolved. This multicenter observational study aims to examine comorbid psychiatric disorders in a clinical sample of newly diagnosed, treatment naïve children and adolescents with and without ADHD and, to compare treatment efficacy based on the type of comorbidity. We performed an analysis of the medical records of patients identified from the Regional ADHD Registry database, enrolled in 18 ADHD centers in the 2011-2016 period. 1919 of 2861 subjects evaluated (67%) met the diagnostic criteria for ADHD: 650 (34%) had only ADHD, while 1269 (66%) had at least one comorbid psychiatric disorder (learning disorders, 56%; sleep disorders, 23%; oppositional defiant disorder, 20%; anxiety disorders, 12%). Patients with ADHD of combined type and with severe impairment (CGI-S  $\geq$ 5) were more likely to

Lombardy ADHD Group members are moved to Acknowledgement.

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present comorbidity. 382 of 724 (53%) followed up patients improved after 1 year of treatment. ADHD with comorbidity showed greater improvement when treated with combined interventions or methylphenidate alone. Specifically, combined treatment showed significant superiority for ADHD with learning disorders (ES 0.66) and ODD (ES 0.98), lower for ADHD with sleep or anxiety disorders. Training intervention alone showed only medium efficacy (ES 0.50) for ADHD and learning disorders. This study was the first describing comorbidity patterns of ADHD in Italy, confirming, in a multicenter clinical setting, that ADHD is more often a complex disorder. Findings highlight important diagnostic, therapeutic, and service organization aspects that should be broadly extended to ensure an appropriate and homogenous ADHD management.

**Keywords** Comorbidity · Attention deficit hyperactivity disorder · Treatment outcome · Children · Adolescents

### Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurobiological condition characterized by developmentally inappropriate and impairing patterns of inattention, hyperactivity, and impulsivity [1]. ADHD symptoms usually become more evident in school aged children, are more frequent in boys than girls and tend to persist into adulthood [2]. As for other psychiatric disorders occurring during the developmental age, the categorical and relatively simple symptomatological core of ADHD often does not appear alone. Frequently, a wide variety of concurrent psychiatric disorders contribute to the psychopathological status of children and adolescents with ADHD, with a well-established consensus among authors that the presence of

overlapping psychiatric disorders is more likely to be the rule than the exception [3].

The medical term commonly used for this concurrence is comorbidity, even though the early meaning of the word as a "distinct additional clinical entity occurring during the clinical course of a patient having an index disease" [4] is clearly not fully applicable and appropriate to most psychiatric diagnoses. Indeed, the majority of those listed as comorbid conditions represents disorders, multifunctional impairments, and symptom constellations whose clustering together characterizes the clinical condition [5-7]. The first study evaluating a broad range of comorbid conditions in children with ADHD was published more than 30 years ago [8], and its main findings simply highlighted that ADHD is very often associated with other disorders, particularly depression and anxiety disorders, oppositional and conduct problems, and developmental disorders. No considerable evidence followed the study until more than 10 years later, when the emerging understanding of attention deficit disorders and comorbidities was summarized by Brown et coll. in a comprehensive manual [9]. It is now largely agreed that comorbidities are often one of the most important aspects of ADHD [10-15] and this has led, at least for ADHD, to the consideration of their impact on the outcome of the individual child in the longer term [16].

The overall prevalence of psychiatric disorders associated with ADHD in children and adolescents ranges from about 40 to 80% depending on the sample [11, 17–20], with higher rates in clinically referred ADHD children (67–87%) [3]. Thus, it seems rather clear that, in addition to an ADHD diagnosis, a clinician should consider a whole range of possible psychiatric conditions. The main disorders likely to co-occur with ADHD are: oppositional defiant disorder (ODD) (50–60%), conduct disorder (CD) (20–50% in children and 40–50% in adolescents), depression (16–26%) and anxiety (10–40%) disorders, bipolar disorders (11–75%), tic disorders (20%), obsessive compulsive disorders (6–15%), and autism spectrum disorders (65–80%) [11–13, 15, 21–23].

Other comorbidities, however, have also been observed in ADHD children and adolescents. A wide variety of learning difficulties are associated with ADHD, with over 45% having at least one or more significant impairments in reading, arithmetic or spelling [3, 24]. Several other problems, including, for example, social problems [25] or sleep disturbances [26], may be more common in ADHD than in the population without this condition. Comorbidity involving ADHD and learning disorders is frequent, ranging from 25 to 40% [3, 24]. A few studies point out the possibility of there being a specific learning disorder at first, which could later be complicated by a behavioral pattern of ADHD [27, 28]. Other authors note that learning disorders are almost a constant in ADHD children and adolescents; this may be due to the fact that inattention and hyperactivity, alone, could encourage the emergence of specific learning difficulties [29, 30]. Others, yet, claim that learning disorders and ADHD may occur together because of a shared genetic etiology and that a genetically mediated comorbid subtype may exist [29]. This hypothesis has been suggested also for many other neurodevelopmental disorders [31, 32]. Pennington proposed a probabilistic and multifactorial etiopathogenetical model to explain the high rate of overlap between different neurodevelopmental disorders [33]. Based on this dimensional perspective, ADHD was placed in the DSM-V section "neurodevelopmental disorders", including different disorders with high rates of comorbidity among them and with common onset in the developmental age [1]. These different explanations proposed are not mutually exclusive, but can be used as causal models of pathogenic pathways [29]. Literature data reveal that about 70% of children with ADHD show mild to severe sleep disorders [34]. In particular, ADHD patients experience much higher rates of sleep problems than their peers without ADHD [35]. The reported prevalence rates differ according to the subtype of ADHD, with a higher prevalence in the combined subtype and in patients with psychiatric comorbidity, which increase the risk of occurrence of sleep disorders [36]. On the other hand, some authors suggest that patients with severe sleep disorders develop subsequent ADHD symptoms [35], but more studies are needed to define the neurobiological basis of this possible casual relationship.

Despite the fact that ADHD comorbidity has been widely studied [11, 17–20], some issues remain unsolved. In fact, in clinical practice, comorbidities may mask the core symptoms of ADHD, or ADHD may be masked by comorbid conditions, thereby confusing the diagnostic process [37]. When making an ADHD diagnosis, it is important to exclude other disorders that might overlap with ADHD or mimic ADHD symptoms. Comorbid disorders, recognized or unrecognized, may also complicate the treatment process [11, 38] since most children with ADHD have co-occurring conditions that may complicate not only the clinical presentation, but also the choice of the most appropriate treatment strategy. A specific practice guideline pathway has been proposed by the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance to identify the key comorbidities and the different treatments priorities they require [39], simply suggesting that outcome is generally determined by the most serious comorbid condition. However, very little systematic research exists on sequencing of treatment for comorbidities, and this is generally handled on a case-by-case basis.

What is known about comorbidity is largely confined to ADHD of combined type [3]. Furthermore, to date, literature data are also sometimes inconsistent because of differences in patients' age, sample selection (clinical or community) and size [40], and diagnostic instruments used to assess comorbid conditions. Moreover, only a few studies have been conducted with a multidimensional and multicenter approach [41, 42] analyzing the entire spectrum of psychiatric comorbidities and outcomes according to treatments received [12, 20].

The importance of recognizing the psychopathological profile of the comorbidities in ADHD has been patchily documented, but there is a limited amount of research addressing concerns on treatments efficacy remaining in need of exploration. This study aims to evaluate the prevalence rate of psychiatric comorbidity and treatment outcomes in children and adolescents with ADHD, aged 5–17 years, enrolled in the 18 ADHD reference centers of the Lombardy Region between June 2011 and August 2016. The objectives related to scope achievement specifically analyzing, documenting and evaluating co-occurring disorders in ADHD were expected to be achieved according to four specific aspects: prevalence rate and, prescribed and performed treatments, improved subjects rates and treatment efficacy related to the therapeutic approaches.

### Methods

This study was designed as a review of patient medical records identified from the Regional ADHD Registry database. The research was approved by the Institutional Review Board of the IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri" in Milan, Italy, and written informed consent was obtained for all patients.

### The local health setting

In the Lombardy Region, during the study period, a network of 34 Child and Adolescent Neuropsychiatric Services (CANPS) provides care at the hospital (tier three) and community (tier two) levels for children and adolescents with neurologic, neuropsychologic and/or psychiatric disorders, and for their families. About 15% of the Italian pediatric population live in this region. Regional health authorities are responsible for the accreditation of the ADHD reference centers in regional hospitals ("ADHD centers"), as specialized ADHD hubs (tier three) of the CANPS network. All CANPS community centers (tier two) take care of children with ADHD and their families, whereas ADHD centers are responsible for confirming the diagnosis and verifying the appropriateness of the therapeutic plan prescribed. ADHD centers are also responsible for the prescription of pharmacological therapies, their monitoring over time, and for inputting data into the registry. Moreover, ADHD centers ensure the interface with the family pediatricians for children on pharmacological therapy, guarantee the periodic visit and the management of the drug prescriptions, provide parent, teacher and child training directly.

### The lombardy ADHD registry project

Following a previous, national, drug-oriented ADHD registry set up in 2007 [43, 44], in June 2011 an official, alternative regional registry was activated in the Lombardy Region. The Regional ADHD Registry was designed as a disease-oriented registry collecting information not only on ADHD patients treated with pharmacological therapy (as provided by the National Registry) but also on all patients who access ADHD centers for a diagnosis of suspected ADHD. Italian legislation [45] requires data on all ADHD patients receiving methylphenidate or atomoxetine treatment to be reported in the registry. The Regional Registry is part of a more general project aimed to ensure appropriate ADHD management for every child and adolescent once the disorder is suspected and reported, and includes commonly acknowledged diagnostic and therapeutic procedures as well as educational initiatives for health care workers (child neuropsychiatrists and psychologists) of the Lombardy Region's health care system who provide assistance to ADHD patients and their families. Initiatives focused on increasing knowledge on ADHD in parents, teachers, and family pediatricians were also part of the regional project [46-48].

The Regional ADHD Registry represents a distinctive tool, internationally, aimed to ensure the appropriate care of, and the safety of drug use in, ADHD children [46-48]. In practice, a strict diagnostic assessment of the disorder prior to treatment, as well as its systematic monitoring during both pharmacological treatment and behavioral interventions, must be guaranteed to ADHD patients who come to the attention of the 18 local ADHD centers. To define an optimal, evidence-based, shared strategy for diagnostic evaluation, an ad hoc assessment working group was created, involving a child neuropsychiatrist and a psychologist from each participating ADHD center and a group of researchers of the registry coordinating center (IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"). More specifically, this strategy consisted of seven mandatory steps to be applied at the time of diagnostic evaluation: (1) the clinical anamnestic and psychiatric interview; (2) the neurological examination; (3) the evaluation of cognitive level by Wechsler Scales [49-51]; (4) the Schedule for affective disorders and schizophrenia for school-age children (K-SADS) [52] for a complete psychopathology overview and comorbidity assessment; (5) the child behavior checklist (CBCL) and/or the conners' parent rating scale-revised (CPRS-R)

rated by parents; (6) the conners' teacher rating scalerevised (CTRS-R) rated by teachers [53–55]; and 7) the clinical global impressions-severity scale (CGI-S) [56] to quantify symptom severity. This diagnostic pathway was agreed on, approved, and shared by all participating ADHD centers.

Following a diagnosis of ADHD, the registry was designed to guide the user by providing several, differently structured types of follow-up visits at periodic intervals to monitor the clinical outcome of the treatment strategies. These were carried out at 3 and 6 months after the diagnosis, and every 6 months afterward. Patients given methylphenidate were also monitored at 1 week and 1 month after the diagnosis (only after 1 month if they received atomoxetine).

All collected data, i.e., those concerning the diagnostic evaluation and the systematic monitoring assessments described above, were analyzed monthly, and the findings were reported and periodically discussed with all 18 ADHD centers belonging to the Lombardy ADHD Group. In this study, to evaluate clinical outcome evaluation we used the improved subject rates and the treatment efficacy as measured by the CGI-Improvement and the CGI-Severity (preto post-treatment change,  $\Delta$  Mean) scales, respectively.

This is a clinical multicenter study, in which all patients received a rigorous diagnostic assessment (according to national and international guidelines) [57, 58], approved by all involved clinicians and monitored by a registry-based data collection method. Here, we report clinical evaluation and treatment outcome data on new, treatment naïve patients who accessed the ADHD centers between June 2011 and August 2016 and were followed up for 1 year ( $12 \pm 3$  months) according to their comorbidity profile.

### Data analysis

Descriptive statistics were summarized. We used Kruskal-Wallis or Chi-square tests to determine differences in population characteristics and between groups of subjects. Statistically significant differences were assessed at an alpha level of 0.05. We applied logistic regression analyses with stepwise selection and a significance level of 0.05 to, first, identify risk factors associated with ADHD and, secondly, with comorbidity, considering sociodemographic and anamnestic characteristics, ADHD subtypes, and symptom severity (only for the second step) as independent variables. To evaluate treatment efficacy, we also calculated standardized residuals (Std. Res) [59] and the Cohen's d effect size [60]. A standardized residual is the difference between the observed and expected values for a single treatment group: the larger the residual, the greater the contribution of the group to the magnitude of the resulting Chi-square obtained value. All statistical analyses were performed using SAS software (version 9.2).

### Results

Diagnostic and therapeutic pathways of the sample are summarily presented in Fig. 1.

### **Prevalence** rate

In all, 3030 children and adolescents from the 18 ADHD centers were evaluated for suspected ADHD, the majority (2861, 94%) had completed the diagnostic procedure at the time of data extraction (September 1, 2016) and were included in this study (Fig. 1). 1919 of 2861 new subjects evaluated (67%) met the diagnostic criteria for ADHD (M: 1635, 85%; F: 284, 16%). Of these, 650 (34%) received a diagnosis of ADHD only, while 1269 (66%) had at least one comorbid psychiatric disorder. 1106 of 1919 ADHD patients (58%) had ADHD of combined type (ADHD-C), 633 (33%) of inattentive type (ADHD-I), and 180 (9%) of hyperactive/impulsive type (ADHD-H). Comorbid psychiatric disorders were more frequent in patients with ADHD-C subtype (OR 1.54, IC 1.28-1.85) and in those with a CGI-S score equal to or greater than 5 (OR 2.46, IC 1.92-3.14).

Using logistic regression analyses with stepwise selection to determine differences in population characteristics and between groups, some anamnestic characteristics showed a statistically significant association (p < 0.05) with comorbidity in ADHD: lower age at diagnosis, having a family history of ADHD, and not being breastfed (Table 1).

Of the 2447 patients with at least one psychiatric disorder, 650 (27%) were diagnosed only with ADHD and 401 (16%) only with another psychiatric disorder, while 1396 (57%) had two or more mental disorders (1269 also ADHD). The rate of sleep disorders (23 vs. 13%;  $p \le 0.0001$ ) and oppositional defiant disorder (20 vs. 11%;  $p \le 0.0001$ ) was significantly higher in ADHD patients, while inverse data proportion was observed for anxiety disorders (12 vs. 19%; p = <0.0001) (Fig. 2). Overall, learning disorders (56%), sleep disorders (26%), oppositional defiant disorder (20%), and anxiety disorders (12%) were the more frequent disorders in ADHD subjects (Fig. 2).

Odds ratios and goodness-of-fit tests from logistic regression models for comorbid disorders with a statistically significant association (sleep disorders, oppositional defiant disorder, anxiety disorder) (Fig. 2) and sociodemographic and anamnestic variables (Table 1) in patients with ADHD and with other psychiatric disorders were performed to calculate the relative risk, excluding association bias related to differences on sociodemographic Fig. 1 Diagnostic and therapeutic pathways of the sample. \*Subjects treated with pharmacological treatment alone or with associated psychological interventions; <sup>a</sup>methylphenidate; <sup>b</sup>atomoxetine; <sup>c</sup>risperidone; <sup>d</sup>valproic acid; <sup>e</sup>sertraline; <sup>f</sup>haloperidol



variables: an ADHD diagnosis was a significant risk factor for sleep disorders (OR 1.81, CI 95%: 1.31–2.51) and oppositional defiant disorder (OR 1.93, CI 95%: 1.37–2.72), while it was not a significant risk factor for the other mental disorders when all significant statistical variables in the bivariate model were controlled for. Moreover, the Hosmer–Lemeshow Chi-square test indicated that the observed data were not significantly different from expected values derived from each model (p > 0.05). Most models had a good estimation of predicted variables (concordance  $\geq 0.57$ ).

### **Therapeutic approaches**

Data concerning the assessment and outcome of the therapeutic approaches were analyzed only for ADHD patients receiving care continuity at the ADHD center within a 1-year period ( $12 \pm 3$  months). Among patients receiving pharmacological treatment, with or without an associated psychological intervention, we chose to consider only those treated with methylphenidate (n = 168, 85%), thus, excluding those who received other psychotropic drugs or polytherapy (n = 29) to ensure a homogeneous treatment outcome evaluation (Fig. 1).

### Prescribed and performed treatments

The rates of the different treatments prescribed (at the time of the diagnosis) and those received (during the 1-year period after the diagnosis) in 724 ADHD patients with and without psychiatric comorbidities were compared. The rate of psychological therapies (Psy) provided, i.e., training (Psy-Training) and other psychological (Psy-Other) interventions, decreased in both ADHD groups (with and without comorbidity) compared to what was prescribed upon diagnosis. ADHD patients with comorbidity, compared to those without, showed a slight increase in the rate of combined treatment received than that prescribed (from 25 to 26%), while a higher rate of ADHD patients without comorbidity (20%) did not receive any treatment compared to those with comorbidity (12%). The rate of the treatments prescribed and received in ADHD patients according to the more frequent comorbidities showed similar trends, except for the ODD group showing a lower decrease between the rate of the treatments prescribed and received

Table 1 Sociodem	ographic and anamnes	stic characteristics of the	e sample					
Characteristics	ADHD ( $N = 1919$ )			NO ADHD ( $N = 94$ )	2)		Total $N = 2861$	Bivariate model
	ADHD only N = 650 n (%)	ADHD with comor- bidity $N = 1269$ n (%)	ADHD total $N = 1919 n (\%)$	No psyc disorders N = 414 n (%)	Other psyc disorders $N = 528 n (\%)$	NO ADHD total $N = 942 n (\%)$	n (%) n	$p^*$
Mean age (SD) median	8.7 (2.4) 8	9.3 (2.5) 9	9.1 (2.5) 9	9.3 (2.5) 9	9.8 (2.5) 9	9.5 (2.5) 9	9.2 (2.5) 9	<0.0001
12-17 years	98 (15)	268 (21)	366 (19)	84 (20)	131 (25)	215 (23)	581 (20)	0.0071
Male	556 (86)	1.079 (85)	1.635 (85)	338 (82)	429 (81)	767 (81)	2.402 (84)	0.0091
Only child	167 (26)	307 (24)	474 (25)	92 (22)	120 (23)	212 (23)	686 (24)	0.1723
Born abroad	23 (4)	87 (7)	110(6)	13 (3)	29 (5)	42 (4)	152 (5)	0.2704
Adopted	19 (3)	58 (5)	77 (4)	9 (2)	12 (2)	21 (2)	98 (3)	0.0205
School failures	19 (3)	78 (6)	97 (5)	16 (4)	36 (7)	52 (6)	149 (5)	0.3777
Employed parents	395 (61)	730 (58)	1125 (59)	261 (63)	307 (58)	568 (60)	1693 (59)	0.5119
Family history of ADHD	147 (23)	270 (21)	417 (22)	45 (11)	63 (12)	108 (11)	525 (18)	<0.0001
Dystocic delivery	166 (27)	322 (27)	488 (27)	92 (23)	128 (25)	220 (24)	708 (26)	0.1513
Preterm/low weight <sup>b</sup>	89 (15)	185 (16)	274 (16)	59 (15)	76 (16)	135 (16)	409 (16)	0.8788
Breastfeeding <sup>c</sup>	339 (65)	607 (62)	946 (63)	246 (69)	288 (66)	534 (68)	1480 (64)	0.0387
Motor delay	17 (3)	76 (6)	93 (5)	16 (4)	18 (3)	34 (4)	127 (5)	0.1699
Language delay	106 (17)	280 (23)	386 (21)	62 (15)	106 (21)	168 (18)	554 (20)	0.2230
*Test v <sup>2</sup> used for c	ategorical variables an	d Kruskal-Wallis for c	ontinuous variables					

. , - 14 -. Ű -Tabla

# \*Lest $\chi^{*}$ used for categorical variables and K <sup>a</sup> Preterm (<37 sett), low weight (<2500 gr) <sup>b</sup> $\geq$ 3 months





compared to other groups. Only treatments that were actually received in the clinical practice and during the study period (12  $\pm$  3 months) were considered in the outcome evaluation.

### Improved subject rates

Clinical outcome evaluation of ADHD patients after one year of therapy, as measured by the CGI-Improvement scale, was evaluated. Overall, in the ADHD group (N = 724), 141 (20%) and 241 (33%) patients showed great and minimal improvement, respectively, while 299 (41%) showed no significant clinical change and 43 (6%) worsened. Results show similar rates in both ADHD with and without comorbidity groups, while, when considering each type of psychiatric comorbidity as a separate group, some differences arose. The ADHD group with an associated sleep disorder showed a higher rate of much improved subjects (28%), while the groups with ADHD with a comorbid ODD or anxiety disorder showed higher rates of worsened subjects of 11 and 13%, respectively.

Findings of the Chi-square test for each treatment (counting the number of improved patients, CGII <3) in these following ADHD groups: only ADHD, ADHD with comorbidity, ADHD with most frequent comorbidities, i.e., learning, sleep, ODD, and anxiety disorders, and ADHD Total, are shown in Fig. 3. A statistical difference between treatment groups was found in ADHD with comorbidity (p < 0.001), ADHD + Learning disability (p = 0.004), ADHD + ODD (p = 0.019) groups and in all ADHD (p < 0.001). Residual analysis was then applied to identify which specific treatment made the greatest contribution to the Chi-square test's significance (Fig. 3). Overall, combined treatment proved superior, showing a significant

value in the overall ADHD group (ADHD Total), which is equivalent to stating that subjects who received MPH + Psy were significantly more likely to improve compared to other treatment groups. In ADHD with comorbidity, subjects treated with combined treatment (MPH + Psy) and those treated with MPH alone had positive values, indicating that there were more improved subjects in these groups than would be expected by chance. Although other treatments showed positive residual values, no significant findings were found.

Moreover, we evaluated whether a more severe symptomatology could have acted as moderator for the improvement rate: no differences were observed in the improvement rates for all treatment groups after stratifying for CGI-Severity at the baseline evaluation (CGIS <5 vs  $\geq$ 5) (*p* > 0.05).

### Treatment efficacy

We also analyzed outcome data as measured by the CGI-Severity scale (pre- to post-treatment change,  $\Delta$  Mean). Figure 4 includes the effect sizes (ES) for each treatment group relative to a control condition, such as those subjects who did not receive any treatment. A common way to interpret effect sizes proposed by Cohen (1969) [60] considers an ES of 0.2 as "small", 0.5 as "medium" and "large enough to be visible to the naked eye", and an ES of 0.8 or more as "large" and "grossly perceptible and therefore large".

Comparing only ADHD with ADHD with comorbidity groups, pharmacological treatment alone (MPH) showed a medium ES (0.63) for patients with only ADHD and a large ES (0.89) for ADHD with comorbidity, while the combined treatment (X) shows a large, and statistically significant,



Fig. 3 Clinical improvement (CGI-I  $\leq$ 3) in ADHD with and without comorbidities according to treatment received (Std. Res). \*Statistically significant

	Т	reatme	nt		Contro	l							
Subgroup	∆ Mean	SD	Total	∆ Mean	SD	Total	Weight	Effect Size [95% Cl	[]	Effec	ct Size [95%	6 CI]	
PSY – TRAINING													
Only ADHD	0.4	1	120	0.3	0.9	49	46.1%	0.10 [-0.23, 0.43]					
ADHD with comorbidity	0.5	1	184	0.1	1	62	53.9%	0.40 [0.11, 0.69]				-	
												-	
Total (95 % CD			304			111	100.0%	0.26 [-0.03, 0.55]				•	
Heterogeneity: $Tau^2 = 0.02$ : Chi	$i^2 = 1.73$ , df	r = 1 (P = 1)	$0.19$ ): $I^2 =$	42%. Test	for over	all effect: 7	z = 1.77 (P =	= 0.08)	<b>—</b>		-		
,,		- (-	,, .					)	-2	-1	0	1	2
More frequent comorbiditie	S												
ADHD + ODD	0.3	1.1	28	0.2	0.8	6	10.2%	0.09 [-0.79, 0.97]			-		
ADHD + Sleep	0.5	1.1	36	0.2	1	14	20.6%	0.27 [-0.34, 0.89]					
ADHD + Learning	0.7	1	97	0.2	1	44	60.7%	0.50 [0.14, 0.86]*					
ADHD + Anxiety	0.5	1	28	0	0.5	5	8.6%	0.51 [-0.45, 1.47]				•	-
Total (95 % CI)			189			69	100.0%	0.41 [0.13, 0.69]					
Heterogeneity: $Tau^2 = 0.00$ ; Chi	$i^2 = 0.95$ , df	r = 3 (P =	0.81); I <sup>2</sup> =	0%. Test f	or overal	ll effect: Z	= 2.87 (P =	0.004)					
NERV - DOV									-2	-1	0	1	2
MPH + PSY													
Only ADHD	0.7	1.1	17	0.3	0.9	49	25.9%	0.41 [-0.14, 0.97]				_	
ADHD with comorbidity	0.9	1.1	109	0.1	1	62	74.1%	0.75 [0.43, 1.07]*			· · ·		
												-	
Total (95 % CI)			126			111	100.0%	0.66 [0.38, 0.95]*					
Heterogeneity: $Tau^2 = 0.00$ ; Chi	$f^2 = 1.03$ , df	f = 1 (P =	0.31); I <sup>2</sup> =	= 3%. Test f	or overal	ll effect: Z	= 4.53 (P <	0.00001)	-2	-1	0	1	2
More frequent comorbiditie	c								-2		0		2
ADUD + Sloop	0.0	1.2	21	0.2	1	14	22 20/	0.57[0.08]1.211			+	-	
ADHD + Learning	0.9	1.5	59	0.2	1	14	22.370 57.00/	0.57 [-0.06, 1.21]			_	_	
ADID + Aurista	0.9	1.1	20	0.2	1	44	37.0% 0.20/	0.00[0.23, 1.00]					
ADHD + Anxiety	0.6	0.9	21	0	0.5	3	9.5%	0.09 [-0.31, 1.08]				1.00	
ADHD + ODD	I	0.8	32	0.2	0.8	6	11.3%	0.98 [0.08, 1.88]*					
						~ 0							
Total (95 % CI)			142			69	100.0%	0.68 [0.37, 0.98]*					
Heterogeneity: $Tau^2 = 0.00$ ; Chi	$f^2 = 0.56, df$	= 3 (P =	0.91); I <sup>2</sup> =	= 0%. Test f	or overa	Il effect: Z	= 4.36 (P <	0.0001)	-2	-1	0	1	2
COUNSEL INC									-2	-	0		2
Only ADHD	0.2	1.1	3/	0.3	0.0	/0	30.6%	0 10 [ 0 54 0 34]					
ADHD with comorbidity	0.2	1.1	62	0.5	1	62	60.4%	0.10[0.16]0.54]				_	
ADITD with comorbidity	0.5	1.1	02	0.1	1	02	00.470	0.19 [-0.10, 0.54]					
Total (05.9/ CD			06			111	100.00/	0.07 [ 0.20 0.25]					
101a1 (95 % C1)	2 - 1.02.46	- 1 (D -	90 0 21): 1 <sup>2</sup> -	- 20/ Teat 6		III 11 offects 7	100.070	0.07 [-0.20, 0.35]					
Helefogeneity: Tau – 0.00; Chi	– 1.02, di	– 1 (P –	0.51); 1 -	- 270. Test I	or overa	II effect. Z	– 0.33 (P –	0.00)	-2	-1	ò	1	2
More frequent comorbiditie	s												
ADHD + ODD	0.1	0.9	11	0.2	0.8	6	11.4%	-0.11 [-1.10, 0.89]		_		_	
ADHD + Learning	0.2	1.2	37	0.2	1	44	59.3%	0.00 [-0.44, 0.44]					
ADHD + Sleen	0.3	0.9	17	0.2	1	14	22.6%	0 10 [-0 60 0 81]		-			
ADHD + Anxiety	0.5	0.5	5	0	0.5	5	6.7%	0.72 [-0.58, 2.03]		-			<b></b>
Tibilib + Tilikiety	0.1	0.5	5	0	0.5	5	0.770	0.72 [ 0.50, 2.05]					<i>.</i>
Total (95 % CD			70			69	100.0%	0.06 [-0.28 0.40]					
Heterogeneity: $Tau^2 = 0.00$ . Chi	$i^2 = 1.19$ df	r = 3 (P =	$0.76$ ) · $I^2 =$	0% Test f	or overa	ll effect: Z	= 0.34 (P = 1)	0.73)	<b>—</b>				
neterogeneny: rua oloo, en	·, u	5 (1	0.70), 1	0,0. 10001	or oreru		0.5 (1		-2	-1	ò	1	2
PSY – OTHER													
Only ADHD	0.3	0.9	12	0.3	0.9	49	31.0%	0.00 [-0.63, 0.63]		-	-	_	
ADHD with comorbidity	0.3	1.2	33	0.1	1	62	69.0%	0.18 [-0.24, 0.61]					
-													
Total (95 % CI)			45			111	100.0%	0.13 [-0.22, 0.48]			-		
Heterogeneity: $Tau^2 = 0.00$ ; Chi	$i^2 = 0.23$ , df	r = 1 (P = 1)	0.63); I <sup>2</sup> =	0%. Test f	or overa	ll effect: Z	= 0.71 (P =	0.48)	<u> </u>	<u>     t     </u>		<u> </u>	<u> </u>
									-2	-1	0	1	2
More frequent comorbiditie	\$												
ADHD + Sleep	0	1.2	3	0.2	1	14	22.9%	0.18 [-1.43, 1.06]					
ADHD + ODD	0	0	1	0.2	0.8	6	-	Not estimable			1		
ADHD + Learning	0.2	1.2	20	0.2	1	44	64.2%	0.00 [-0.53, 0.53]				-	
ADHD + Anxiety	0.7	0.1	3	0	0.5	5	13.0%	1.48 [-0.28, 3.23]			_		<b></b> →
Total (95 % CI)			27			69	100.0%	0.15 [-0.53, 0.82]					
Heterogeneity: $Tau^2 = 0.11$ ; Chi	$i^2 = 2.69$ , df	f = 2 (P =	0.26); I <sup>2</sup> =	26%. Test	for over	all effect: Z	z = 0.43 (P =	= 0.66)	<u> </u>				<u> </u>
MDU									-2	-1	0	1	2
MPH													
Only ADHD	0.9	1.1	11	0.3	0.9	49	31.5%	0.63 [-0.03, 1.30]			1	·	
ADHD with comorbidity	1	1	31	0.1	1	62	68.5%	0.89 [0.44, 1.34]*					
Total (95 % CI)	2		42			111	100.0%	0.81 [0.44, 1.18]*					
Heterogeneity: $Tau^2 = 0.00$ ; Chi	$d^2 = 0.41 \text{ df}$	= 1 (P =	$0.52$ ; $I^2 =$	0%. Test fo	or overal	l effect: Z =	= 4.26 (P < 0)	0.0001)	-2	-1			
More frequent comorbiditio	c								-2	- 1	0		2
ADUD + ODD	<u> </u>	1 1	17	0.2	1	4.4	55 20/	0.50 [ 0.01 1 1/7			L		
	0.8	1.1	10	0.2	1	44	33.2%	0.38 [-0.01, 1.16]					
	1.3	1.1	11	0.2	1	14	20.0%	$1.02 [0.17, 1.87]^*$					
ADID + Learning	1.5	1./	3	0	0.5	5	/.2%	1.00 [-0.54, 2.6/]					
ADHD + Anxiety	1.9	1.1	8	0.2	0.8	6	11.6%	1.61 [0.34, 2.89]*					
						<i>c</i> <b>2</b>	100 00						
Total (95 % CI)	2		38			69	100.0%	0.85 [0.41, 1.28]*					
Heterogeneity: $Tau^2 = 0.00$ ; Chi	r = 2.45, df	= 3 (P =	0.48); I <sup>2</sup> =	= 0%. Test f	or overa	II effect: Z	= 3.84 (P =	0.0001)	-2	-1		1	
									-2	-1	U		2

Fig. 4 Treatment outcomes (Effect size) on global functional impairment (CGI-S mean pre-post) of ADHD patients with and without comorbidities according to treatment received

ES (0.75) for ADHD with comorbidity. Other treatments showed lower ES values for these groups. According to more frequent comorbidities (ODD, anxiety, learning and sleep disorders), on the other hand, we found: for subjects with comorbid learning disorders, medium ESs of the Psy—Training treatment alone (0.50) and of the combined treatment (MPH + Psy, 0.66); for those with ODD, a large ES (0.98) of the MPH + Psy treatment; and very large ESs for ADHD with anxiety (1.61) and with sleep (1.02) disorders when they received MPH alone (Fig. 4).

### Discussion

### **Prevalence** rate

In our sample of Italian children and adolescents with ADHD, most of the patients (66%) resulted as having one or more comorbid psychiatric disorders, in strong agreement with previous studies [6, 13, 14, 21, 61-65]. This rate is consistent with studies that found that ADHD without comorbidity is rare [66], even in the general population sample [14]. Among the sociodemographic and anamnestic characteristics, the variables that resulted significantly associated with a higher risk of presenting a co-occurring disorder in ADHD were a lower age at diagnosis, having a family history of ADHD, and not being breastfed. These results were somewhat expected following data from previous reports evaluating risk factors for psychiatric disorders in a large population sample [67-70]. Moreover, ADHD patients show a higher risk of presenting two or more psychiatric comorbidities compared to subjects with other psychiatric disorders, although with lower rates than those reported in the MTA study [13] (21% in our study vs 40% in the MTA study).

Consistently with other reports, most of our patients with ADHD had other psychiatric conditions more frequently compared to subjects with other mental disorders. On the broad spectrum of possible co-existing problems likely to occur in individuals diagnosed with ADHD [3], in our ADHD sample the most common comorbid conditions were specific learning disorder, sleep problems, oppositional defiant disorder and anxiety disorders, with slightly different prevalence rates compared to previous reports [6, 15, 24, 34, 36, 64, 71]. In particular, in our ADHD sample ODD co-occured in 20% of cases; this rate was slightly lower than that of other studies showing association rates varying from 25 to 50% [10, 61, 62, 65], with a higher prevalence in population studies (61%) compared to clinical sample studies (39%) [63]. This difference may be related to the Italian context, based on the findings of previous studies that found an overall lower rate of externalizing disorders (1%) in the developmental age compared to those estimated in other countries [72]. The general population prevalence in children and adolescents is 6.5% for anxiety disorders and 2.6% for depressive disorders [73]; similar results emerged from our study's entire sample. The association between anxiety disorders and ADHD, on the other hand, ranges from 10 to 40% [13, 14, 74] in clinic-referred children and is consistent with our results. Moreover, consistent with our findings, perspective, longitudinal studies across the lifespan show that the risk of anxiety disorders in ADHD children and adolescents is no greater than in control groups, but, in young adulthood, shows a large rise in those whose ADHD persists to age 27 [75]. This inconsistence in the literature data is probably due to the fact that most research merges all types of anxiety disorders together.

The co-occurrence of other psychiatric comorbidities is less frequent. The prevalence rate of depressive disorder associated with ADHD (5%), e.g., was lower than expected, based on other reports that indicated association rates of between 20 and 30% [13, 75–77]. Our finding, however, may be explained by the fact that the risk of depression among ADHD patients seems to be largely mediated by the co-occurrence of conduct disorders [78– 80] whose incidence is very low in our sample (3%).

In all the children with two or more psychiatric disorders, the ADHD group showed two age peaks, at 8 and 12 years, compared to a single peak in subjects without ADHD. This data could be explained by the fact that the onset of most comorbid disorders occurred earlier when an ADHD diagnosis was present. This issue has been reported previously, for example in obsessive compulsive [81] and bipolar disorders [82]. In our sample, subjects with ADHD-C subtype showed higher rates of psychiatric comorbidity, more significant global functional impairment, and higher drug prescription rates. The overlap between the presence of comorbid conditions and clinical global severity is consistent with recent data confirming that comorbidity strongly impacts on the level of functional impairment [83]. Moreover, subjects with comorbidity, and who therefore show higher impairment, also more frequently receive a prescription of pharmacological treatment in combination with psychological intervention, as is to be expected given the Italian National guidelines [58].

### **Therapeutic approaches**

Among ADHD patients receiving care continuity for 1 year, the performed treatment rate changed according to the type of prescribed treatment and to the presence and type of psychiatric comorbidity.

### Prescribed and performed treatments

Overall, training and other psychological treatments were performed less frequently than prescribed at the time of diagnosis in, both, patients with and without comorbidity. While ADHD without comorbidity had a higher rate of subjects not receiving any treatment, ADHD with comorbidity showed an increase in the rate of subjects treated with combined therapy and, more specifically, ADHD with ODD was the group that more frequently received the treatment prescribed. These results were expected, not only for the above-mentioned reasons concerning the clinicians' compliance to guidelines, but also for the existing, and well known, critical issues related to the services organization and their sustainability in responding to care needs [84]. It is known worldwide that only a very limited number of children and adolescents with mental health needs has access to care, and Italy is no exception: access to services occurs only in 1 case every 4 for children with a neuropsychiatric disorder [85]. The waiting lists for diagnosis and treatment represent a major issue to be resolved in clinical practice and could be a possible explanation of the difference found between prescribed and received treatments [84].

Our data also show that patients with ADHD and ODD more frequently receive the treatment prescribed. This could be explained by the fact that ODD symptoms are largely known to increase the clinical severity and to worsen long-term outcomes [86], but also to be the major reason for difficulties in the daily management of patients at school and in other life contexts. This, in turn, could result in a priority need to be answered from different perspectives. It is, in fact, clinically reasonable that patients with high comorbidity and impairment are considered a priority for intervention and, therefore, show a greater correspondence between received and prescribed treatments, and a lower percentage of no treatment when compared to ADHD alone. Moreover, a higher rate of ADHD subjects with comorbidity receive a pharmacological therapy alone compared to those with only ADHD, probably related to the fact that clinical service resources fail to ensure all psychological treatments prescribed. Despite this, it is important to note that not all clinical and environmental factors that could be playing a substantial role in the therapeutic strategy, nor a possible change in these factors during the 1-year period, could be considered in our study because, in order to increase the number of variables considered, a higher number of enrolled patients would have been needed.

### Improved subject rates

ADHD subjects, with and without comorbidity, receiving combined treatment had a higher subject improvement rate

compared to that of the other treatment groups. Interestingly, the improvement rate did not seem to be related to clinical severity at baseline, which could mean that appropriate and different therapeutic choices were made according to the different severity levels at the time of diagnosis. Defining specific, different therapeutic approaches according to CGI-Severity at baseline was one of the objectives of the Lombardy ADHD treatment group, and, thus, seems to have been achieved. Nonetheless, this aspect needs to be verified with larger numbers.

The clinical improvement rate according to specific comorbidities showed that combined therapy was superior for ADHD with learning disorders and with sleep disorders compared to training intervention alone, as expected considering the effect of the pharmacological treatment on sleep [26] and on learning disorders—improving attention allows improvement in learning skills [39].

On the other hand, according to our results, subjects with ADHD and anxiety disorders need to be treated with psychological interventions other than training, rather than with combined therapy, in order to reach a greater improvement. In this case, our data seem to be in contrast with previous findings: March and coll. [87]—MTA study—indeed, show that the increase in treatment effect size is relatively greater for behavioral and, more robustly, for combined treatment, when comparing ADHD with and without anxiety disorders. The findings, however, are not fully comparable because in our study "other psychological treatment" is a heterogeneous treatment group including not only behavioral treatment, but also psychoanalytic, psychodynamic, and familiar psychological approaches.

### **Treatment efficacy**

Our results are in line with the main results of the most important study on the efficacy of treatments for ADHDthe MTA study [88]—according to which the combined treatment did not yield significantly greater advantages than pharmacological therapy alone for core ADHD symptoms, but may have provided advantages for positive functioning outcomes. In our sample, we considered the improvement rate in clinical global functioning, as measured by CGI scales (CGIs), to measure treatment outcomes. In the interpretation of our findings, however, we need to consider not only the strengths of CGI scales (overall clinician-determined summary measures taking into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function) [89], but also their weaknesses, i.e., clinician only, subjectivity, and heterogeneous confidence intrinsic to the use of these scales.

Nonetheless, taking into account these limitations, and consistently with the results of previous reviews [89–92] we could also conclude that, in our sample, combined treatment and pharmacological therapy are well-established interventions for ADHD also in an observational clinical practice context, with a large ES, followed by training treatments, with an almost medium effect size. However, a lower ES for pharmacological treatment alone was found in the group with ADHD only, but this could probably be due to the lower number of subjects with ADHD only that have been treated with pharmacological therapy alone, since it is known, indeed, that small samples are particularly susceptible to inflated effect size estimates [93].

Finally, these results should be considered with caution considering to some limitations related to the specific methodological study design, which was not a randomized controlled trial (RCT), but an observational study conducted in the clinical practice context. The service organization variables may have had an impact on the possibility to ensure treatments prescribed and to fully follow clinical guidelines, and this may, in turn, be a bias in estimating the efficacy and efficiency of the treatments performed. Moreover, an important aspect that would require to be investigated is the clinical outcome of each specific comorbidity through the collection, i.e., change in symptoms severity, clinical evaluation over the time (chronicity, improvement, recovery,...). But this is another analysis we expect to perform further and according to database adjustment. Lastly, although the Regional ADHD Registry, as part of a larger, multimodal project, represents a distinctive tool for ensuring appropriate diagnostic and therapeutic pathways of care in ADHD children, our findings refer specifically to the population with ADHD accessing ADHD centers since only these hubs input data into the Registry.

### Conclusion

Our findings confirm, in a multicenter observational study involving a large sample of children and adolescents, that ADHD is more often a complex disorder with a high rate of associated comorbid conditions [94]. This study was the first to describe the comorbidity patterns of ADHD in the Italian context and to highlight certain important clinical and service organization aspects that should be extended to other national ADHD centers to ensure an appropriate and homogenous care management of ADHD in Italy. First, the high prevalence of associated psychiatric conditions warrants that these problems be systematically and specifically investigated, diagnosed, and, especially, taken into consideration as the main guide for choosing among the available therapeutic options. Secondly, as parents

are frequently not aware of the longitudinal course of the ADHD disorder, especially when complicated by psychiatric comorbidity, clinicians should consider the best evidence-based treatment to improve outcome, informing and actively involving families and patients (if possible) in the decision making process. Third, given the demonstration of this relevant rate of co-existing psychiatric conditions in ADHD, it would be appropriate that clinicians working in ADHD centers not only have expertise in ADHD, but also have clinical skills in most neuropsychiatric disorders, as previously reported [9, 95]. Finally, clinicians should consider the full spectrum of neurodevelopmental disorders, anxiety, and mood disorders as possible differential diagnoses of ADHD. Neurodevelopment disorders in children and adolescents, such as ADHD, are multifactorial disorders and have shared characteristics and several risk factors in common [96]. This raises the need for accurate clinical evaluations regarding the specificity of underlying etiological factors, the degree of functional impairment of the core symptoms and different comorbidities, and, consequently, of appropriate treatment. In our opinion, this will be the challenge for future clinical care and research in the area.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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### RESEARCH



### Italian regional health service costs for diagnosis and 1-year treatment of ADHD in children and adolescents

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### Abstract

The main aim of this study was to estimate the costs associated with diagnostic assessment and 1-year therapy in children and adolescents enrolled in 18 ADHD reference centres. Data concerning 1887 children and adolescents from the mandatory ADHD registry database during the 2012–2014 period were analysed. The overall diagnostic and treatment costs per patient amounts to €574 and €830, respectively. The ADHD centre, the school as sender, and the time to diagnosis constitute cost drivers. Non-pharmacological therapy resulted as being more expensive for patients concomitantly treated with drugs (€929) compared to those treated with psychological interventions alone (€590; p = 0.006). This study gives the first and reliable estimate of the costs associated with both diagnosis and treatment of ADHD in Italy. Although costs associated with mental disorders are difficult to estimate, continuing efforts are need to define costs and resources to guarantee appropriate care, also for ADHD.

Keywords: Health care costs, Child and adolescent health, Mental health, Ambulatory/outpatient care

### Background

The costs of psychiatric disorders have been scantly investigated, particularly with regard to those that affect children and adolescents [1, 2]. Methodological complexities justified the lack of comprehensive estimates of the economic impact associated with the burden of psychiatric disorders [3, 4]. World-wide up to 20% of children and adolescents suffer from a neuro-psychiatric condition; in developed countries, both mental and neurological disorders account for the 40% of the burden of all brain diseases and for the 35% in Europe only [5–8].

Attention deficit hyperactivity disorder (ADHD) is a neurobiological disorder [9] characterized mainly by clinical manifestations such as difficulty in paying attention, impulsive behaviour, and a heightened level of physical activity, occurring more frequently and intensely than in other children of the same age or developmental level

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[10]. ADHD symptoms usually become more evident in school aged children, are more frequent in boys than girls (ratio 3:1), and tend to persist into adulthood [11]. ADHD accounts as the third most common mental disorders in children and adolescents [12].

Despite a pooled worldwide ADHD prevalence in children and adolescents of 5.3%, there is wide variability between and within countries [13]. Such variability in prevalence rates may be explained by the different methodologies, diagnostic procedures, and criteria used in the studies [14, 15] as well as by the different settings and cultural approaches considered [16, 17]. However, when standardized diagnostic and impairment assessment procedures are followed, prevalence does not seem to have changed over time nor to have differed in the geographic locations considered [18]. According to national and international guidelines [19-22], ADHD treatment should be based on a multimodal approach combining psychosocial interventions with pharmacological therapies, and should take into consideration the subject's characteristics, including age, symptom severity,



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co-morbid disorders, cognitive level, and social and family context.

The impairments of ADHD are multi-faceted and occur in multiple settings, as costs associated with ADHD impact multiple societal costs within and outside the healthcare sector [23, 24]. Studies on the economic burden of ADHD within Italy, where healthcare is provided to all citizens, are currently lacking [25, 26]. An understanding of the costs associated with ADHD in children and adolescents is important for public policy makers as a rationale for improving and planning public services for both diagnosis and treatment [27].

Overall, in addition to the human suffering they cause, psychiatric disorders are among the most expensive of all health problems in adults [24, 28], even if evidence regarding the costs of psychiatric disorders has been slow to accumulate, particularly with regard to those that affect children and adolescents [29]. Literature review of the health care and treatment-related ADHD economic impact estimates an annual cost, specifically for children and adolescents, at \$14,576 per individual, with a comprehensive range from \$36 billion to \$52.4 billion considering an ADHD prevalence rate of 5% [30]. However, these estimates are incomplete and inaccurate due to the fact that the majority of the existing studies did not fully assess all the potential costs related to an ADHD diagnosis [31]. A few reviews covering the attempts made at defining economic impact of ADHD by the limited number of available, country-based studies, highlighted a wide range in the magnitude of the societal cost estimates [30, 32-38].

In June 2011 an official ADHD regional registry was activated in the Lombardy Region, designed as a disease oriented registry collecting information on all subjects who access ADHD centres for a suspected ADHD diagnosis [39-41], as part of a regional project aimed to define a common approach to, and improve, ADHD diagnosis and therapy. In the Lombardy Region, during the study period, a network of 34 Child and Adolescent Neuropsychiatric Services (CANPS) provide care at the hospital (tier three) and community (tier two) levels for children and adolescents with neurologic, neuropsychologic and/or psychiatric disorders, and for their families. About 15% of the Italian pediatric population live in this region. Regional health authorities are responsible for the accreditation of the ADHD reference centers in regional hospitals ("ADHD centers"), as specialized ADHD hubs (tier three) of the CANPS network.

In such a context, the objective of this study was to estimate the costs, from the National Health Service (NHS) perspective, associated with diagnostic assessment and 1-year therapy in children and adolescents aged 5–17 years enrolled in any of the 18 ADHD reference centres of the Lombardy Region between January 2012 and December 2014 for suspected ADHD.

### Methods

This study was designed as a review of patient medical records identified from the Regional ADHD Registry database, to estimate the costs of the diagnostic assessment and 1-year therapy for subjects with a suspected ADHD diagnosis. The research was approved by the Institutional Review Board of the IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri" Milan, Italy. Written informed consent was obtained for all patients to put information in the registry database and analyze them anonymously.

### Setting

This study is part of a specific project supported by the Regional Health Ministry and aimed to ensure appropriate ADHD management for every child and adolescent once the disorder is suspected and reported, and includes commonly acknowledged diagnostic and therapeutic procedures as well as educational initiatives for health care workers (child psychiatrists and psychologists) of the Lombardy Region's health care system. The project's participants are all the 18 ADHD centres of the Lombardy Region, the most economically important and populated Italian region with 1.690.127 citizens under 18 years old, and with an average income earned per person equal to  $\notin$  24.005 in the study period. The ADHD centres, accredited by regional health authorities, are the hubs specialised in ADHD (Tier 3) of the Child and Adolescent Neuropsychiatric Services (CANPS) network and provide diagnosis and treatment care free, or at a nominal charge, working mainly on an outpatient basis and in close connection with educational and social services. ADHD centres are also responsible for the prescription of pharmacological therapies and their monitoring over time. Moreover, ADHD centres are responsible for inputting data into the official ADHD registry and for providing parent, teacher, and child training treatments [39-41].

### Study population and pathways of care

Anonymized, updated data of the official ADHD registry of the Lombardy Region (as of 31 August 2015) were available, with 3163 subjects enrolled in the June 2011– August 2015 period. The study population includes children and adolescents from January 2012 to December 2014 who had both a first outpatient visit at one of the 18 ADHD centres for a suspected ADHD diagnosis in the same period and had a complete diagnostic evaluation and treatment prescription at the time of data extraction. Our goal was to identify only children who had never been evaluated and treated before for ADHD. We further required that all of the study children with a confirmed ADHD diagnosis were received a care continuity at the ADHD centre within a 1-year period.

The guideline for all clinicians at the ADHD centres is to use the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [42] criteria for diagnosing ADHD. Moreover, to define an optimal, evidence-based, shared strategy for diagnostic evaluation, an ad hoc assessment working group was created, involving a child neuropsychiatrist and a psychologist from each participating ADHD center and a group of researchers of the registry coordinating center (IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri"). More specifically, also according to the recommendations of the Italian guidelines [22, 43], this strategy consisted of seven mandatory steps to be applied at the time of diagnostic evaluation: (1) a clinical anamnestic and psychiatric interview; (2) the neurological examination; (3) the evaluation of cognitive level by Wechsler Scales [44]; (4) the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) [45] for a complete psychopathology overview and comorbidity assessment; (5) the Child Behavior Checklist (CBCL) and/or the Conners' Parent Rating Scale-Revised (CPRS-R) rated by parents; (6) the Conners' Teacher Rating Scale-Revised (CTRS-R) rated by teachers; [46-48] and (7) the Clinical Global Impressions-Severity scale (CGI-S) [49] to quantify symptom severity. This diagnostic pathway was agreed on, approved, and shared by all participating ADHD centers.

Once a patient receives a diagnosis of ADHD and a treatment prescription, the registry is designed to provide differently structured types of follow-up visits at periodic intervals: at 3 and 6 months after the diagnosis, and every 6 months afterward for all patients; while for those given methylphenidate at 1 week and 1 month after the diagnosis also (after only 1 month if they received atomoxetine or other psychotropic drugs). Moreover, patients that receive a methylphenidate prescription need to perform a visit called "dose-test" which is carried out in day hospital regimen before starting the drug treatment.

### Data analytic procedures

Complete data of all eligible patients were extracted. Besides anamnestic and clinical information regarding age, gender, diagnosis and comorbidity, detailed information was available on a patient medical records basis for the following cost domains:

 Diagnostic pathway: all services supplied to patients with a suspected ADHD diagnosis, whether or not confirmed, by an agreed and shared child and adolescent neuropsychiatrists' and psychologists' assessment. In addition, the working days elapsed from the request a diagnosis of ADHD were calculated. In line with the regional health service perspective, only direct healthcare costs were estimated. Unit costs related to diagnostic tests were derived from tariffs reimbursed by the Lombardy Region in 2014. Detailed information is presented in Additional file 1: Table S1.

- Non-pharmacological therapies: Prescribed by physicians specialised in child and adolescent neuropsychiatry working in one of the 18 ADHD centres and provided by other therapists for example psychologists, also working within the ADHD centre. The direct health cost of non-pharmacological therapies was assessed by multiplying the estimated number of annual visits per patient by the unit costs derived from tariffs reimbursed by the Lombardy Region in 2014. Detailed information is presented in Additional file 1: Table S2.
- Pharmacological treatments: Prescribed by medical doctors specialised in child and adolescent neuropsychiatry working in one of the 18 ADHD centres (only prescriptions filled by patients). Drug utilization data were also derived from the Regional ADHD registry [39, 40]. Detailed information is presented in Additional file 1: Table S3.

Data on the total annual consumption of ADHD medications that require a therapeutic plan prescription form were evaluated over 1 year after the date of the diagnosis. The trends in total consumption of ADHD drugs were also analysed based on changing patterns of the drugs' prescription practices, dosages, and formulations.

The unit costs of prescribed drugs were assessed based on: (a) price to public of medicines fully reimbursed by the Italian NHS and supplied through retail pharmacies (class A); or (b) sum of ex-factory price and 10.2% distribution margin of fully reimbursed drugs under direct distribution. Patient co-payment was not considered as it impacted a minority (<10%) of patients under drug treatment. The cost per milligram was calculated on the basis of the prescribed formulation (immediate- or extendedrelease, tablet, capsule, drops) by selecting the generic, when marketed. Annual drug consumption was estimated for each patient by multiplying the daily dosage prescribed at each visit by the number days until the following visit.

Laboratory tests,—including blood count, blood sugar, haemoglobin, ferritin, albumin, bilirubin, transaminases, gamma-glutamyl transpeptidase, erythrocyte sedimentation rate, thyroid hormones, uric acid, BUN, creatinine, urine—and EKG were carried out in day hospital (DH) setting only in patients undergoing pharmacological treatments, according to the Italian guidelines [22]. Hence, they were considered as pharmacological treatment-related expenditures. A DH unit cost of  $\in$ 232.00 was derived from DRG code 431 reimbursed by the Lombardy Region in 2014. Hospitalization (inpatient regimen) costs were been estimated as no patient was hospitalized.

All data were analysed with SAS Version 9.2, (SAS Institute, Inc., Cary, NC, USA). Descriptive statistics were computed for the entire study population and for subgroups. As costs of diagnostic pathways (recommended, optional, and total), time to diagnosis, and treatment costs were not normally distributed, median and inter quartile ranges were analysed. The Student's t test was used to compare continuous variables (baseline clinical and anamnestic data), while  $\chi^2$  (baseline clinical and anamnestic data), Wilcoxon-Mann-Whitney (diagnosis related costs, time to diagnosis evaluation), and Kruskal-Wallis (treatment and diagnosis related costs) tests were used to compare categorical variables. A multivariate logistic regression analysis with stepwise selection was carried out to assess the socio-demographic (baseline personnel and familiar data) and clinical, service models' characteristics (clinical and organizational determinants). Moreover, a multivariate linear regression analysis was performed to assess the drivers of diagnostic costs and time to diagnosis.

### Results

### **Baseline characteristics**

Data concerning 1887 children and adolescents who accessed 1 of the 18 ADHD centres for the first time during the 2011-2015 period and. completed the diagnostic evaluation at the time of data extraction (September 1, 2015; Table 1) were analysed. These patients had a median age of 9 years (range: 5–17 years) at their first visit, and 1597 (85%) were males and 290 (15%) were females. In all, 1276 patients (68%) met DSM-IV-TR criteria (43) for ADHD: 1099 (86%) males and 177 (14%) females. In all, 1189 of 1887 (63%) enrolled patients had one or more psychiatric disorders (346 without ADHD) (learning disorders, 56%; sleep disorders, 19%; anxiety and mood disorders, 19%; oppositional defiant disorder, 17%; other, 13%), whereas 163 (9%) had a concomitant chronic diseases (neurological, 31%; respiratory, 30%; gastrointestinal, 7%; other, 19%). As shown in Table 1, the main anamnestic characteristics significantly associated with ADHD diagnosis were: lower age, presence of support teacher (at the time of assessment), ADHD familiarity, and an associated psychiatric disorder.

### Diagnosis related costs

Total diagnostic cost per patient to complete the diagnostic evaluation amounted to  $\notin$ 574.00, of which  $\notin$ 510.00 was related to recommended procedures and tests and  $\notin$ 105.60 to optional examinations (Fig. 1; Additional

file 1: Table 4). The multivariate analysis highlighted the following cost drivers: ADHD centre, sender, and time to diagnosis (Table 2). Concomitant psychiatric disorders, as well as other clinical and anamnestic variables, didn't affect diagnosis costs (Table 2).

Statistically significant (Kruskal–Wallis, p < 0.001) inter-centre variability was related to the completion rate of the recommended set of assessments (Additional file 1: Table S5). The total cost of the diagnosis also varied in relation to the sender and was highest for patients referred from CANPS (€615.60). However, the relative increase was only 7.4% over the total median cost (Additional file 1: Table S6).

Globally, it took 119 days to complete the diagnostic pathway, with a wide variability mainly due to the centres (range from 51 to 302 days; Kruskal–Wallis, p < 0.0001) and the senders, with median time-to-diagnosis markedly reduced when the patient was referred by CANPS (91 days) or increased if referred by GPs (162 days), or by other specialist neuropsychiatrists practicing in agreement with the NHS (169.5 days; Kruskal–Wallis, p < 0.0001; Additional file 1: Table S7.

Whether or not the diagnosis of ADHD was confirmed on elapsed time was not statistical significative: 123 days if positive compared to 108 days if negative (Wilcoxon– Mann–Whitney, p = 0.0871). However, the time to diagnosis was slightly greater for patients receiving all the recommended tests (122 working days) compared to those who did not complete the assessment (111.5 days; Wilcoxon–Mann–Whitney, p = 0.0086).

Assuming that the time to diagnosis could be considered as a measure of efficiency by the regional health service (and by patients, too), Fig. 2 shows the wide variability among centres of the ratio of costs reimbursed by the health service and median time to diagnosis. This ratio varies significantly also in relation to the sending unit (Fig. 3).

### **Treatment costs**

The following annual treatment costs were assessed for patients with an ADHD diagnosis (n = 753):

- Non-pharmacological interventions: 1092 patients (86%), of whom 903 received a non-pharmacological intervention only (71%) and 189 (15%) combined with drugs;
- Drug treatments: 199 patients (16%), of whom 10 (1%) received drug treatment alone and 189 (90%) combined with non-pharmacological treatments.

The remaining 174 patients (14%) were not included because they were still being monitored (watchful-waiting) at the time of data extraction. Detailed information is presented in Additional file.

Characteristics	Total sample ( $N = 1887$ )	With ADHD ( <i>n</i> = 1276)	Without ADHD ( $n = 611$ )	p*
Age M (SD); median	9.3 (2.5); 9	9.1 (2.4); 9	9.7 (2.5); 9	<0.0001
5–11, n (%)	1506 (80)	1038 (81)	468 (77)	0.0161
12–17, n (%)	381 (20)	238 (19)	143 (23)	
Male: female	1597:290	1099:177	498:113	0.0092
Only child, n (%)	453 (24)	328 (26)	125 (20)	0.0116
Born abroad, <i>n</i> (%)	99 (5)	76 (6)	23 (4)	0.0453
Adopted, n (%)	63 (3)	54 (4)	9 (1)	0.0018
School variables, n (%)				
Grade				
Primary	1417 (75)	980 (77)	437 (72)	0.0139
Middle	465 (25)	293 (23)	172 (28)	
Repeaters	99 (5)	61 (5)	38 (6)	ns
Support teacher	142 (8)	123 (10)	19 (3)	<0.0001
Parent/family variables, n (%)				
High school graduate				
Mother	1070 (64)	694 (63)	376 (66)	ns
Father	871 (53)	562 (52)	309 (55)	ns
Employed				
Mother	1235 (72)	840 (74)	395 (67)	0.0028
Father	1584 (95)	1046 (95)	538 (94)	ns
Family history of ADHD	375 (20)	293 (23)	82 (13)	<0.0001
Anamnestic data, n (%)				
Pregnancy				
Cesarean section	465 (26)	333 (28)	132 (23)	0.0207
Preterm (<37 weeks)	168 (9)	120 (10)	48 (8)	ns
Low weight (<2500 g)	149 (9)	107 (9)	42 (7)	ns
Motor delay	85 (5)	60 (5)	25 (4)	ns
Language delay	366 (20)	266 (22)	100 (17)	0.0167
Psychiatric disorders, n (%)				
One or more	1189 (63)	843 (66)	346 (57)	<0.0001
Other chronic medical condit	tions, <i>n</i> (%)			
One or more	163 (9)	110 (9)	53 (9)	ns

Table 1 Demographic and clinical characteristics of the sample population

\* t test for continuous and  $\chi^2$  for categorical variables

The median total treatment cost per patient, including laboratory and instrumental assessment needed to begin the drug therapy, was €830.00 (Additional file 1: Table S8), and resulted due mainly to the non-pharmacological therapy cost per patient. In addition to marked variability among centres (Kruskal–Wallis, p < 0.0001; Additional file 1: Table S9), non-pharmacological therapy resulted as being more expensive for patients concomitantly treated with drugs (€929) compared to those treated with psychological interventions alone (€590; Wilcoxon–Mann–Whitney p = 0.0064).

Pharmacological treatments were prescribed in 14 out of 18 centres. Methylphenidate was the most used drug, prescribed in 170 patients (85.4%), followed by

atomoxetine (10.1%). Median drug cost for 1 year was  $\notin$ 97.60, of which  $\notin$ 65.36 covered by stimulant treatment and  $\notin$ 32.34 by non-stimulant treatment. Inter-centre variability (Fig. 4) was not statistically significant (Additional file 1: Table S10).

A total of 331 adverse events associated with drug treatments were reported, of which 9 (3%), 99 (30%), and 222 (67%) were classified as severe, moderate and mild, respectively. No action was required for 208 adverse events, while, for the remaining events, patients recovered upon drug discontinuation (n = 77, 23%) or dose changing (n = 46, 14%). No patient was treated or hospitalised due to adverse events so no adjunctive cost estimation was needed.





Table 2 Drivers of the diagnostic costs: multivariate analyses

Constant	Coefficient	CI 95%	<b>p</b> *
	378.55	(348.43–408.66)	<0.0001
Center			
A	66 24	(48 05-84 42)	< 0.0001
В	20.25	(2.42-38.08)	0.0260
C	77.75	(59.81–95.69)	< 0.0001
D	51.21	(30.99–71.42)	< 0.0001
E	70.33	(48.53-92.12)	< 0.0001
F	79.40	(58.18–100.62)	< 0.0001
G	75.76	(55.44–96.108)	< 0.0001
Н	72.11	(54.92-89.31)	< 0.0001
1	79.72	(58.63–100.8)	< 0.0001
J	93.36	(75.5–111.22)	< 0.0001
К	38.67	(15.63–61.71)	0.0010
L	-		
Μ	87.82	(13.78–161.86)	0.0201
Ν	46.85	(25.86–67.84)	< 0.0001
0	84.22	(67.35–101.09)	< 0.0001
Р	82.20	(61.25–103.15)	< 0.0001
Q	59.44	(32.61-86.28)	< 0.0001
R	77.65	(56.14–99.15)	< 0.0001
Gender			
Female	4.41	(-2.79 to 11.61)	ns
Male	-		
Age at diagnosis			
Years	0.70	(-1.14 to 2.54)	ns
Scholarship			
Primary	6.71	(-3.66 to 17.08)	ns
Middle	-		
Scholar support			
Yes	-		
None	9.56	(-0.84 to 19.97)	ns
Sender			
GP	8.70	(-5.78 to 23.19)	ns
Relatives	-		
School	9.47	(1.52–17.43)	0.0196
Neuropsychiatric (private)	5.38	(-5.89 to 16.65)	ns
Neuropsychiatric (NHS)	5.65	(-8.08 to 19.38)	ns
CANS	5.11	(-3.77 to 14)	ns
Familiar history of ADHD			
Positive	2.10	(-4.99 to 9.18)	ns
Negative	-		
Diagnosis of ADHD			
Yes	2.70	(-3.55 to 8.94)	ns
None	-		
Psychiatric concomitant	disorders		
Yes	-		
None	0.66	(-5.02 to 6.33)	ns

### Table 2 continued

Constant	Coefficient 378.55	CI 95% (348.43-408.66)	<i>p</i> * <0.0001
CGIS			
<5	3.74	(-3.15 to 10.64)	ns
≥5	-		
Fime to diagnosis			
Working days	0.05	(0.02–0.09)	0.0033

\* Multivariate linear regression model

### Discussion

This study presents the first, and most comprehensive, estimate to date of the costs, from the NHS perspective, associated with both the diagnostic assessment and a 12-month therapy in children and adolescents with ADHD in Italy. The overall diagnostic and treatment costs per patient amounts to  $\notin$ 574 and  $\notin$ 830, respectively (median total:  $\notin$ 1404). In our opinion, this is a reliable and representative estimate of ADHD health costs in Italy. Indeed, in our country, the management of ADHD patients was provided mainly by a network of specialized hubs on ADHD (Tier 3)-the Regional ADHD centreswho are responsible for following the most appropriate diagnostic procedures and treatment prescriptions according to the Italian guidelines [22, 43]. This process, in the Lombardy Region, was strictly monitored by the official Regional ADHD registry [40, 41] thus we can therefore expect that it accurately represents a cost estimate that is consistent with that of the management of ADHD in real clinical practice. The evaluation of ADHD costs presented in this article was calculated through a retrospective analysis of data inputted in this registry. Moreover, neuropsychiatrists working at the ADHD centres are also the only clinicians who, according to existing Italian legislation, can prescribe drug therapies for ADHD. This, in turn, gave us the possibility of calculating a reliable estimate also of the total treatment costs.

These costs are consistent, in some cases, and not, in others, with those previously suggested in other countries [32, 35, 50–56]. Such variability in ADHD costs reported may be explained by the different methodologies, especially diagnostic procedures, and criteria used in the studies, as well as by the different settings considered, and, for some authors, also the different cultural approaches [17]. In particular, psychopharmacological treatment in Italian children and adolescents is not the norm, and prescription rates for mental disorders are relatively low. A recent Italian study [40] shows that only 16% of ADHD patients are treated pharmacologically, compared with higher rates reported in other countries, suggesting that also for ADHD, the cultural education and disposition, and the professional attitude of the majority of the child



psychiatrists of the Lombardy Region's mental health services, are more inclined toward behavioural treatments than the use of drugs. To date, a cost analysis on ADHD in Italy has not yet been performed and published. An abstract presented in a conference contribution shows similar costs compared to those estimated in the present study [25]. This study, however, was methodologically different and did not calculate the diagnostic versus the therapeutic costs separately, and this does not allow us to make a more critical comparison with our findings.

Our cost analysis is relevant from the perspective of the Italian NHS not only for ADHD [27]. Indeed, the ADHD centre, the sender, and the time to diagnosis, but not the ADHD diagnosis itself, constitute cost drivers. We can thus expect these drivers to be common to other mental health disorders. Moreover, assuming that the time to diagnosis is a moderator measure of care efficiency, and considering the wide inter-centre variability in both the relationship between cost and time to diagnosis, and between cost and diagnosis completeness according to the National recommended guidelines, these data could serve as a measure for monitoring and reassessing the accreditation over time of the 18 regional centres as specialized hubs on ADHD.

Interestingly, when community CANPS (Tier 2) was the sender, time to diagnosis markedly decreased (1 month), with a relative increase (7%) over the total cost. As such, the recommended pathway of care by the Italian National Institute of Health (*Istituto Superiore di Sanità*, ISS) [57] when a child has a suspected diagnosis of ADHD states that the paediatrician should refer the child to the CANPS, and that the CANPS, after a psychiatric screening assessment (if necessary) should refer the patient to the ADHD centre (Tier 3). Our findings confirm that this suggested model of transition of care is likely to be a positive, cost-effective pathway, given that it ensures a more prompt response to care needs in exchange for an acceptable increase of direct health costs.

There is public concern that the more rapid efficacy, in symptomatic terms, of pharmacological therapy, combined with its lower cost compared to non-pharmacological interventions, could favour an increased use of drugs



alone for the ADHD management [58]. As previously reported [16, 39, 40] this study showed a significantly higher prescription of non-pharmacological treatments, thus confirming that this alarming risk is absolutely not present in the Italian context. Indeed, the majority of the children with ADHD were not currently receiving medication. This is due, in part, to an Italian tradition that drug treatment should be reserved for those with more severe symptoms and impairments [59]. To some extent, the modest incremental cost of the combination of drug and behavioural interventions, compared to behaviour therapies alone resulting in the present study, representing for more effective, versus less effective, management strategies, as widely suggested, should be considered in terms of the best choice for each patient.

Moreover, it has also become apparent from our analysis that the cost of the non-pharmacological therapies is higher whether these are combined with drug treatment. This finding is probably related to the fact that patients requiring a combined treatment more often present greater severity in terms of both symptomatology and functional impairment. We can thus expect that, for these patients, not only is a more intensive (in terms of frequency) psychoeducational approach needed, but there is also a need that this approach be carried out in several different settings in the children's life [58].

Finally, the ADHD project of the Lombardy Region ensured that the diagnostic and therapeutic protocol followed by the ADHD centres, on which the cost analysis was based, was strictly monitored by the official registry, that it has been established according to the main recommendations of the national guidelines and that it is representative of the real clinical practice of an entire region. Indeed, the compliance to the shared diagnostic and therapeutic evaluation, according to the project guidelines, estimated by the analysis of data recorded by all 18 ADHD centers is very high and homogeneous in the Regional context (total completeness: 93.6%; range: 81.7-99.1%). We can't expect similar conclusions assuming to analyze ADHD health care differences and similarities between the Italian regions: various socioeconomic and service organization characteristics, i.e., may be explain



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a part of these differences and highlighting an important and broader issue, but not specific to the ADHD management. Limited literature data available from the Italian context are not enough to reach useful comparisons and comments about regional differences among ADHD management.

However, the Regional ADHD Registry, as the main tool to monitor the ADHD project, was designed as a disease-oriented registry collecting information not only on ADHD patients treated with pharmacological therapy (as provided by the National Registry) but also on all patients who access ADHD centers for a diagnosis of suspected ADHD.

These reasons strengthen the potential use of our findings as a proxy model to estimate the cost of the implementation of the guidelines in clinical practice for the development of similar projects in other Italian regions or for other mental health disorders.

### Limitations

A few study limitations should be mentioned. First, our estimate was based on tariffs reimbursed by the Regional Health Service that does reflect the direct medical costs and not all costs of care provided. Furthermore, the estimates did not include other perspectives considered in cost studies, such as societal and caregiver perspectives. Subjects with mental health problems, including ADHD patients, require support from several dimensions in life, not only from the healthcare system, i.e. social care, housing, and employment [27, 60]. Service utilization, outpatient care, and medications, however, are described as the main components of the economic impact of a disorder in mental health [3]. Second, although the Lombardy Region is the most populated region in Italy, representing about 17% of the national health care costs, all data originated from a single region of Italy, and this may affect the generalizability and comparability of the reported findings. However, studies evaluating costs of mental health problems are not easily generalisable from one country to another because service systems, funding arrangements, and relative prices can vary considerably. Third, the clinical effect of the treatments was not explored. It was therefore not possible to perform a costeffectiveness evaluation, although, to our knowledge, this is the first study that estimates the ADHD costs for both diagnosis and therapeutic pathways, with previous studies typically focusing only on economic evaluation of the treatment.

### Implications for behavioral health

This study gives a reliable indication of the economic effect of both diagnosis and treatment of ADHD in Italy from the NHS perspective. There is clearly a need, however, for a comprehensive picture of the total health and societal costs of ADHD. There also is an urgent need for studies on cost-effectiveness of interventions and for consequent support arrangements for specialised ADHD services that address the needs of patients and their families so as geographically equitable and efficient as to the best evidence care management.

The costs associated with mental disorders are difficult to estimate, but continuing efforts to do so increase available evidence as well as the understanding of the struggles of the individuals and families who need appropriate and adequate care.

### **Additional file**

Additional file 1. Additional tables.

### Authors' contributions

MB coordinated the study. GC and MC analysed the data and prepared the results. MB and LR wrote the first draft of the report. All authors participated in the design and establishment of the study, and edited the report. MB is the guarantor. All authors read and approved the final manuscript.

### Author details

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### **Competing interests**

All authors declare no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear have influenced the submitted work.

### Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

The research was approved by the Institutional Review Board of the IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy; and written informed consent was obtained for all patients when enrolled in the regional registry.

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# AIFA. Comunicazione sull'utilizzo degli antidepressivi Pillole dal Mondo n. 1217

18/05/2017

L'Agenzia Italiana del Farmaco ritiene utile richiamare l'attenzione dei medici prescrittori circa l'utilizzo dei medicinali antidepressivi ed in particolare sulla pericolosità in bambini ed adolescenti.

Si ricorda che nelle informazioni relative a questi medicinali (Riassunto delle Caratteristiche del Prodotto e Foglio Illustrativo) è stato segnalato che la paroxetina non deve essere usata per il trattamento di bambini e adolescenti al di sotto dei 18 anni di età per mancanza di significativi dati di efficacia a fronte di un aumentato rischio di comportamento suicidario e atteggiamento ostile. Questa informazione è stata inserita a seguito della revisione europea in merito alla sicurezza di Paroxetina ed altri antidepressivi in età pediatrica conclusa nel marzo 2005.

Si sottolinea che nel corso della revisione periodica della sicurezza dei medicinali a base di Paroxetina, condotta a livello europeo nel marzo 2014, il rischio suicidario in bambini e adolescenti è stato inserito come rischio potenziale importante da approfondire e monitorare nel tempo, considerato che il medicinale non è indicato in tale popolazione. Da un'analisi della letteratura, inoltre, nell'anno 2016 sono state pubblicate due metanalisi dei dati provenienti dai trial clinici randomizzati sull'efficacia e la sicurezza degli antidepressivi in età pediatrica. Una prima metanalisi dei dati relativi al rischio suicidario e all'aggressività provenienti dai principali studi sulla rispetto agli adulti. Una seconda metanalisi dei dati relativi all'efficacia ed alla sicurezza degli antidepressivi in età pediatrica per il trattamento della depressione paroxetina ed altri inibitori della ricaptazione della serotonina e della serotonina/noradrenalina, ha evidenziato un rischio doppio nei bambini e negli adolescenti Pertanto, si raccomanda di attenersi scrupolosamente a quanto già riportato nel foglio illustrativo e nel Riassunto delle caratteristiche del Prodotto dei medicinali contenenti paroxetina, come ribadito dal Tavolo Tecnico sugli antidepressivi nei bambini e negli adolescenti istituito dal Ministro della Salute Lorenzin nel maggiore, ha osservato come solo la fluoxetina abbia raggiunto la significatività per i parametri di efficacia confermando le problematiche di sicurezza. novembre 2015.





IRCCS Istituto di Ricerche Farmacologiche Mario Negri Via G. La Masa 19 - 20156 Milano

### Milano, 21 giugno, 2017 Ore 8.30-14.00 - Aula Guasti



### Audit su Child Training nell'ambito del Progetto Regionale ADHD



FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO





L'IRCCS – Istituto di Ricerche Farmacologiche Mario Negri si trova a Milano in zona Bovisa nelle vicinanze del Campus Politecnico (Ingegneria) e della Triennale Bovisa.

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E' facilmente raggiungibile con il passante ferroviario, scendendo alle fermate di Bovisa (FNM) o Villapizzone (FS).

Se fermate a Bovisa ricordatevi di scendere le scale che si trovano sul lato destro della stazione.

Con il patrocinio della:



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Segreteria scientifica: M. Antonella Costantino – Direttore UONPIA\* Segreteria organizzativa: Jessica Babboni – Centro ADHD – UONPIA\* \* Fondazione IRCCS Ca' Granda – Osp. Maggiore Policlinico, via Fanti, 6 – Milano

La partecipazione è gratuita ed è stato richiesto l'accreditamento ECM (Regione Lombardia) per le seguenti figure professionali: medici, psicologi, educatori professionali, terapisti

LOMDATCIA) PET le Seguenti figure professionani: medici, psicologi, educatori professionani, terapisu della neuro e psicomotricità dell'età evolutiva, assistenti sanitari, infermieri ed infermieri pediatrici, tecnici della riabilitazione pediatrica, farmacisti, fisioterapisti, logopedisti. Per l'iscrizione al corso è necessario accedere e redistrarsi a TOM attraverso il sito:

Per l'iscrizione al corso è necessario accedere e registrarsi a TOM attraverso il sito: https://tom.policlinico.mi.it

PRESENTAZIONE	PROGRAMMA
L'Audit Clinico è l'iniziativa condotta da clinici, che si pone l'obiettivo di migliorare la qualità e gli outcomes dell'assistenza attraverso una revisione strutturata fra pari, per mezzo della quale i clinici esaminano la propria attività e i propri risultati in confronto a standard espliciti e la modificano se necessario, sottoponendo i risultati di tali modifiche a nuove verifiche.	08:30 – 09:00 Registrazione 09:00 – 10:00 Il Child Training nell'ambito del registro regionale
Il nuovo Progetto <i>Percorsi diagnostici-terapeutici in rete per l'ADHD</i> si è posto un nuovo importante obiettivo per rafforzare il lavoro e l'impegno degli ultimi anni: consolidare la struttura della rete curante per l'ADHD in Lombardia, ampliarla alla partecipazione di nuovi servizi e garantire risposte terapeutiche e interventi formativi e informativi omogenei ed appropriati in tutto il territorio regionale. Nello specifico si prefigge di implementare l'adesione dei Centri al monitoraggio strutturato e programmato dei percorsi di cura e diffondere modalità di audit clinico. I Centri ADHD nell'ambito del Progetto dovranno assumere un ruolo attivo all'interno della rete UONPIA per implementare e diffondere e coordinare gli obiettivi previsti a livello regionale e garantire un percorso di audit ad essi relativi.	10:00 – 12:00 TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO: I PERCORSI DI CHILD TRAINING: MODELLI E APPLICAZIONI NEI CENTRI PER ADHD LOMBARDI Coordinano: Ottaviano Martinelli e Umberto Balottin Presentano: i Referenti dei Centri ADHD
Relativamente al Child Training il percorso di audit è ancora molto iniziale, e si focalizzerà sul confronto formalizzato tra i Centri relativo alle modalità con le quali sono stati attivati i percorsi sia individuali che di gruppo e sulle differenze di indicazione tra i due, per giungere alla condivisione di un percorso di riferimento per il CT analogamente a quanto è stato fatto per il Parent Training e per il Teacher Training.	12:00 – 13:30 TAVOLA ROTONDA CON DISCUSSIONE CON IL PUBBLICO: STRUTTURAZIONE DI PRATICHE COLLABORATIVE TRA I CENTRI PER IL CHILD
RELATORI Umberto Balottin UONPIA IRRCS Mondino, Pavia Maurizio Bonati Dipartimento Salute Pubblica, IRCCS Istituto "Mario Negri" di Milano	<b>TRAINING</b> Coordinano: <b>Davide Villani e Antonella Costantino</b> Presentano: <b>i Referenti dei Centri ADHD</b>
UONPIA RECES Fondazione Policifinico UONPIA, ASST di Lecco Massimo Molteni	13:30 Conclusioni
IRCCS, Istituto Scientifico Eugenio Medea di Bosisio Parini Laura Reale Dipartimento Salute Pubblica, IRCCS Istituto "Mario Negri" di Milano Monica Saccani UONPIA ASST SS Paolo e Carlo Davide Villani UONPIA ASST di Lecco Edda Zametti UONPIA ASST Spedali Civili di Brescia Referenti dei Centri ADHD	Umberto Balottin, Maurizio Bonati, Antonella Costantino, Ottaviano Martinelli, Massimo Molteni, Monica Saccani, Edda Zanetti

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RegioneLombardia

Il Progetto: "Condivisione dei percorsi diagnostico-terapeutici per l'ADHD in Lombardia" è stato finanziato dalla Regione Lombardia con Decreto della Dg Welfare N. 1077 del 02 febbraio 2017. Il progetto coinvolge 18 Centri di Riferimento per l'ADHD e il Laboratorio per la Salute Materno Infantile dell'IRCCS - Istituto di Ricerche Farmacologiche Mario Negri. Coordinatore del Progetto è la UONPIA dell'ASST di Brescia.

Con il patrocinio:



**Centro per l'Età Evolutiva** Studio Associato di Psicologia



### **CONVEGNO SCIENTIFICO**

### Diagnosi differenziale e comorbilità in adolescenza

Milano, venerdì 22 settembre 2017

Edificio U6 Aula Martini - Università di Milano Bicocca

### PROGRAMMA

8.15 - Registrazione dei partecipanti

### 9.20 – Dati epidemiologici in Psicopatologia dell'adolescenza

<u>Gian Marco Marzocchi</u> – Università di Milano Bicocca & Centro per l'Età Evolutiva, Bergamo

### 9.40 – La psicopatologia e i disturbi del neurosviluppo. Quali linee per il futuro dei servizi?

<u>Massimo Molteni</u> – Dipartimento di Psicopatologia dello Sviluppo, Associazione La Nostra Famiglia - IRCCS E. Medea, Bosisio Parini (LC)

**10.30 – Disregolazione emotiva come predittore per i disturbi dell'umore in adolescenza ed età adulta** Gabriele Masi – *IRCCS Stella Maris, Calambrone (PI)* 

### 11.30 – Disturbi dirompenti del comportamento: approccio evolutivo, dimensionale, fattori di rischio e prognosi

Dino Maschietto – UOC NPI, San Donà di Piave (VE)

12.30 - 14.00 Pranzo

### 14.00 – Conoscere e Ri-conoscere i disturbi d'ansia e depressivi attraverso l'adolescenza

<u>Maria Nobile</u> – Associazione La Nostra Famiglia – IRCCS E. Medea, Bosisio Parini (LC)

### 15.00 – La valutazione diagnostica dei DSA nell'adolescente e nel giovane adulto

<u>Enrico Ghidoni</u> – Fondazione Italiana Dislessia, Centro di Neuroscienze Anemos, Reggio Emilia

### 16.00 – Diagnosticare e comprendere la Sindrome di Asperger durante l'Adolescenza

<u>Davide Moscone</u> – Direttore clinico di CuoreMenteLab, Roma. Presidente dell'Associazione Spazio Asperger ONLUS



### Per raggiungere la sede del Convegno:

- In auto (parcheggio): raggiungere zona Bicocca Greco Pirelli.
- In treno: fermata Milano Greco Pirelli. L'edificio U6 dell'Università di Milano Bicocca dista 5 minuti a piedi.
- In metro: Linea 5 Lilla, fermata Ponale

### Per iscriversi:

Compilare la scheda di iscrizione sul sito http://www.centroetaevolutiva.it/formazione/giornatestudio/diagnosi-differenziale-comorbilita-adolescenza

### Costo di partecipazione

Il costo per partecipare alla Giornata di Studio è di:

- € 80,00 (iva compresa) senza ECM
- € 100,00 (iva compresa) con ECM

Erickson



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http://adhd.marionegri.it/index.php/eventi/conclusi/2017/audit-clinico-di-maggio



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## AUDIT CLINICO DI MAGGIO

## Audit Clinico di Maggio

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Per scaricare le presentazioni cliccare il simbolo 🖿 vicino ad ogni relatore

LA METODOLOGIA DELL'AUDIT CLINICO NELL'AMBITO DEL PROGETTO Laura Reale (520 KB) L

AUDIT SULL'APPROPRIATEZZA DELL'INDICAZIONE AL TRATTAMENTO FARMACOLOGICO

Monica Saccani (315 KB) 🖺

Per ricevere la newsletter iscriversi al seguente indirizzo: http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-newsletter

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza (Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI) Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia (in attuazione della D.G. sanità n. 3798 del 08/05/2014, n. 778 del 05/02/2015, n. 5954 del 05/12/2016 e N. 1077 del 02/02/2017) Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia" "*Percorsi diagnostico-terapeutici per l'ADHD*".

### IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI DIPARTIMENTO DI SALUTE PUBBLICA Laboratorio per la Salute Materno Infantile

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