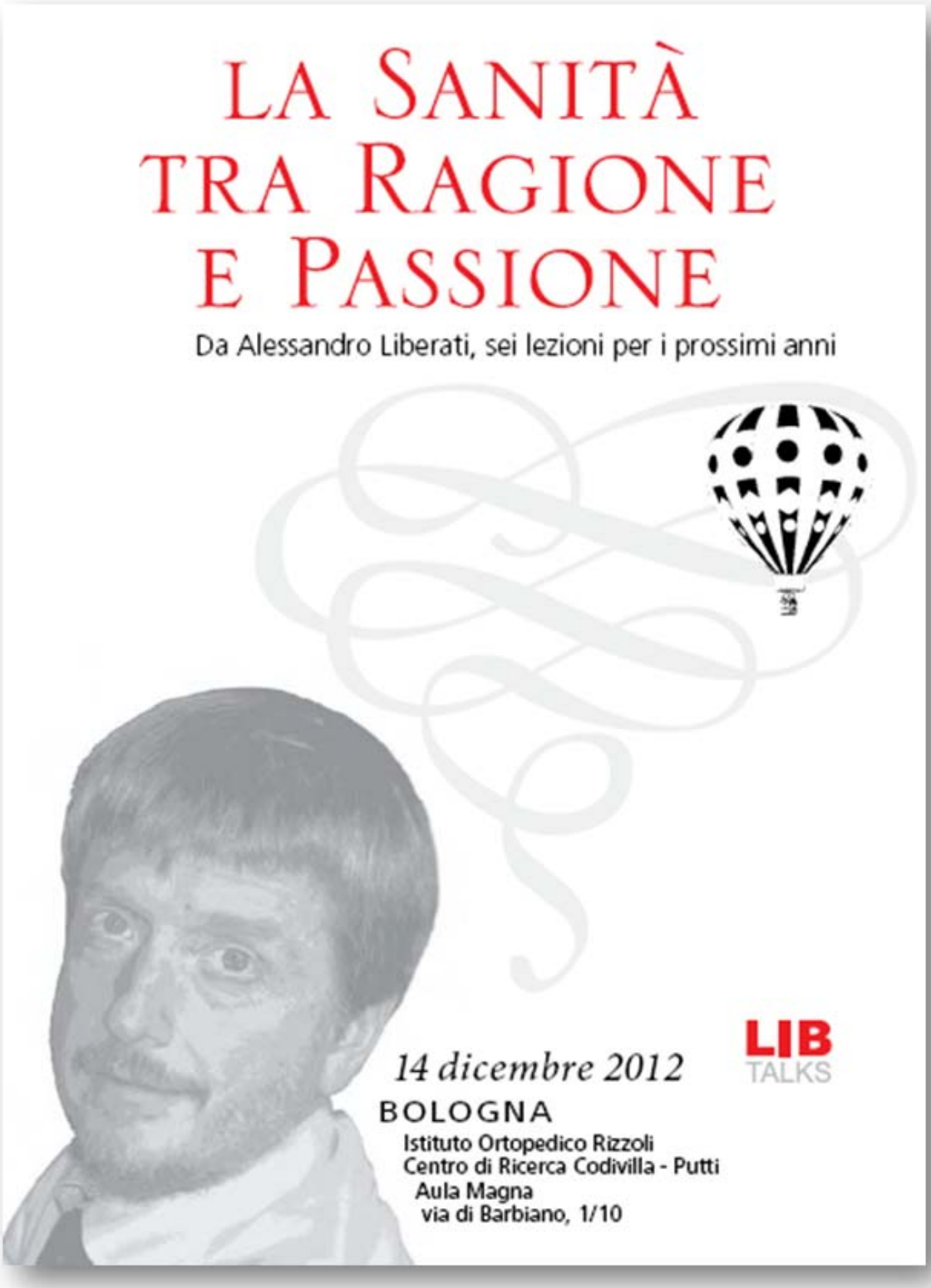
NEWSLETTER

INDICE:

MARIONEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE


LA SANITÀ
TRA RAGIONE
E PASSIONE
Da Alessandro Liberati, sei lezioni per i prossimi anni
14 dicembre 2012
BOLOGNA
Istituto Ortopedico Rizzoli
Centro di Ricerca Codivilla - Putti
Aula Magna
via di Barbiano, 1/10
LIB
TALKS

LIB TALKS

Sei parole non bastano per raccontare una vita.
Soprattutto se intensa e densa di esperienze
come quella di Alessandro Liberati.
Ma forse possono essere sufficienti almeno per evocare
lo spirito che quella vita ha contraddistinto,
per renderne visibili i valori che ne hanno sostenuto
i pensieri e le azioni e per dare a tutti noi
modo di ragionarci intorno, interrogandoci sul senso
del nostro agire da ricercatori dentro il mondo della sanità,
del nostro essere "tecnici" che si occupano di questioni
così delicate per la vita delle persone,
soprattutto del nostro essere parte di un sistema,
quello sanitario, così fortemente evocativo
del tipo di società in cui vorremo vivere
e del mondo che vorremmo:
almeno un po' migliore di come oggi lo vediamo.

A cura di
Mariangela Liberati,
Roberto D'Amico, Marina Davoli,
Luca De Fiore, Roberto Grilli,
Paola Mosconi, Vanna Pistotti,
Francesco Taroni.

8:30 REGISTRAZIONE DEI PARTECIPANTI

9:30 INTRODUZIONE ALLA GIORNATA
ROBERTO GRILLI
Direttore Agenzia Sanitaria e Sociale, Regione Emilia-Romagna

INTERVENTI DI

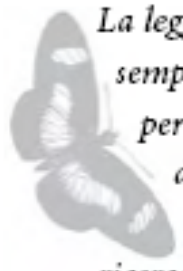
CARLO LUSENTI
Assessore
alle Politiche per la Salute,
Regione Emilia-Romagna

SILVIO GARATTINI
Direttore
dell'Istituto di Ricerche
Farmacologiche Mario Negri

GIOVANNI BISSONI
Presidente
AGENAS

10:00 A cura di Paola Mosconi

LEGGEREZZA | *lightness*



La leggerezza come un valore e non come un difetto. Essere leggeri, cioè semplici e diretti anche di fronte a temi complessi, senza zavorre ideologiche per una visione aperta del mondo. Si può essere leggeri liberandosi dagli orpelli inutili legati al ruolo (essere medico o essere paziente), ai percorsi (accompagnare nella storia di malattia o partecipare alla ricerca clinica) e all'organizzazione (facilitare e coordinare i percorsi di cura).

CON LA PARTECIPAZIONE DI **HAZEL THORNTON** Honorary Visiting Fellow, Dept. Health Sciences, University of Leicester
Interventi di **Alessandra Cerioli** [Lega Italiana per la Lotta contro l'AIDS], **Giuseppe Serravezza** [Unità di Oncologia, Casarano LE]

11:00 A cura di Roberto Grilli

RAPIDITÀ | *quickness*

Quella che dovrebbero avere le risposte che la ricerca offre ai suoi interlocutori per essere tempestiva e rilevante, con una qualche possibilità di incidere sui processi decisionali. Una rapidità che implica evitare di perdersi in percorsi tortuosi, individuando i temi essenziali da affrontare. La rapidità con cui il mondo intorno a noi cambia e la difficoltà del tenerne conto.

CON LA PARTECIPAZIONE DI **TREVOR SHELDON** Professor of Health Services Research and Policy, University of York
Interventi di **Luciana Ballini** [Agenzia Sanitaria e Sociale, Regione Emilia-Romagna], **Gianni Tognoni** [Consorzio Negri Sud, Chieti]

12:00 A cura di Roberto D'Amico

ESATTEZZA | *exactitude*

Il bisogno, umano, di certezze che siano rappresentate anche da risposte "esatte" alle nostre domande, di cittadini, di clinici, di pazienti; bisogno che si scontra con l'intrinseca incertezza probabilistica delle risposte della ricerca, con le tante incertezze determinate per disegno da una cattiva ricerca o da una ricerca assente.

CON LA PARTECIPAZIONE DI **Sir IAIN CHALMERS**
Coordinator, The James Lind Initiative
Interventi di **Salvatore Panico** [Università di Napoli], **Carlo Perucci** [AGENAS, Roma]

13:00 { PAUSA PER IL PRANZO }

14:30 A cura di Marina Davoli

VISIBILITÀ | *visibility*

La necessità di rendere visibili problemi, prospettive e punti di vista che sono sistematicamente trascurati ed omessi dalla ricerca dominante. Visibilità che si traduca anche in trasparenza e in profondità di sguardi.

CON LA PARTECIPAZIONE DI **GIANFRANCO DOMENIGHETTI**
Docente di Comunicazione
e Economia Sanitaria,
Università della Svizzera Italiana

Interventi di **Nicola Magrini** [Agenzia Sanitaria e Sociale, Regione Emilia-Romagna], **Michele Bellone** e **Roberto Satolli** [Zadig, Milano]

{ NEL CORSO DELLA GIORNATA È PREVISTA LA PARTECIPAZIONE DEL MINISTRO DELLA SALUTE **RENATO BALDUZZI** }

15:30 A cura di Luca De Fiore

MOLTEPLICITÀ | *multiplicity*

Quella delle competenze, dei ruoli e delle passioni che devono convergere per poter raggiungere gli obiettivi desiderati. La ricerca come impresa condivisa dove l'essere "metodologo" significa offrire il tessuto connettivo che consente alle tante soggettività di esprimersi in modo coordinato per giungere ad una sintesi possibile. La riduzione della distanza come chiave per vivere di molteplicità senza muri e steccati.

CON LA PARTECIPAZIONE DI **RICHARD SMITH**
Director, Ovation Initiative
Interventi di **Antonio Addis** [Agenzia Sanitaria e Sociale, Regione Emilia-Romagna], **Maurizio Bonati** [Istituto Mario Negri, Milano], **Angelo Stefanini** [Università di Bologna]

16:30

COERENZA | *consistency*

Cinque parole, scelte da Italo Calvino per le sue Lezioni americane, *utili per avviare un dialogo nuovo, fatto di curiosità, di confronto e di disponibilità ad allargare lo sguardo. Parole che diventano sei con quella probabilmente più importante, per molti aspetti "conclusiva": consistency/coerenza. E non potrebbe esserci parola più adatta per ricordare Alessandro.*

CON LA PARTECIPAZIONE DI **RODOLFO SARACCI**
Consiglio Nazionale delle Ricerche, Pisa

17:30 CONCLUSIONI E CHIUSURA DEL CONVEGNO

SEDE DEL CONVEGNO

Istituto Ortopedico Rizzoli
Centro di Ricerca Codivilla - Putti
Aula Magna
via di Barbiano, 1/10
40136 Bologna

La partecipazione al convegno è gratuita
È necessaria l'iscrizione, da effettuare online
http://tinyurl.com/convegno-liberati

Non è previsto
l'accreditamento ECM.

Alcuni relatori svolgeranno
la propria relazione in inglese.
È prevista la traduzione simultanea
in italiano.

Relatori e partecipanti
potranno utilizzare Twitter
per commentare l'evento in diretta
#liberati

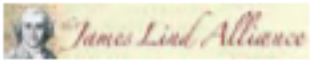
Prima, durante e dopo il convegno,
seguici anche su Facebook
http://tinyurl.com/facebook-liberati

Per informazioni

Agenzia Sanitaria e Sociale – Regione Emilia-Romagna
Leila Mattar – tel. +39 051 527.7405
Vanessa Vivoli – tel. +39 051 527.7182
e-mail: eventisanita@regione.emilia-romagna.it

Il convegno è reso possibile grazie al supporto di


Con il patrocinio di

BIBLIOGRAFIA ADHD NOVEMBRE 2012

Acad Pediatr. 2012;12:523-31.

THE RELATIONSHIP OF REPORTED NEIGHBORHOOD CONDITIONS WITH CHILD MENTAL HEALTH.

Butler AM, Kowalkowski M, Jones HA, et al.

Objective: Although in many studies authors have documented the relationship between neighborhood socioeconomic status and child mental health, few have examined the association between neighborhood conditions and mental health disorders. The objective of this study was to determine whether parent-reported neighborhood conditions are associated with common child mental health disorders.

Methods: We analyzed data on children ages 6 to 17 (N = 64,076) collected through the 2007 National Survey of Children's Health. Primary outcome variables were a child being reported to have a diagnosis of (1) anxiety and/or depression and (2) attention-deficit-hyperactivity disorder (ADHD) and/or disruptive behavior. Main independent variables were parent-reported neighborhood amenities (eg, recreation center), poor physical characteristics (eg, dilapidated housing), social support/trust, neighborhood safety, and school safety. Multivariate logistic regression analyses were conducted to examine associations between neighborhood conditions and (1) anxiety/depression and (2) ADHD/disruptive behavior.

Results: Children living in a neighborhood with 3 poor physical characteristics had greater odds of anxiety/depression (adjusted odds ratio [AOR] 1.58, 95% confidence interval [95% CI] 1.01-2.46) and ADHD/disruptive behavior (AOR 1.44, 95% CI 1.04-1.99) compared with children living in a neighborhood with no poor physical characteristics. Children of parents who reported living in a neighborhood with low social support/trust had greater odds of depression/anxiety (AOR 1.71, 95% CI 1.28-2.30) and ADHD/disruptive behavior (AOR 1.47, 95% CI 1.19-1.81) than children living in a neighborhood with greater social support/trust.

Conclusions: Parent perception of neighborhood social support/trust and physical characteristics may be important to assess in clinical settings and should be examined in future study of child mental health burden.

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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.

Acad Pediatr. 2012;12:502-08.

PARENTAL STRAIN, PARENTAL HEALTH, AND COMMUNITY CHARACTERISTICS AMONG CHILDREN WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Hinojosa MS, Hinojosa R, Fernandez-Baca D, et al.

Objective: It has been documented that parenting a child with attention deficit-hyperactivty disorder (ADHD) can cause family strain, but less is known about the added stress of additional child health diagnoses on levels of strain. This study explores the relationship between family stressors (such as child comorbid conditions) and family resources (such as social support, community charactersitics, and parental health) on parental strain.

Methods: We used the 2007 National Survey of Children's Health (NSCH) to identify children with ADHD and other comorbid mental and physical health conditions (n=5473). Descriptive, bivariate, and multivariate analyses were conducted to explore the association between parental strain, social support, mother's mental health, and neighborhood amenities within groups of children with ADHD and comorbid conditions.

Results: Parental strain was greatest when ADHD was paired with a conduct disorder, physical disorder, or other mental health disorder. Specifically, parental strain was greatest for children with ADHD plus a comorbid conduct disorder compared with ADHD alone. It was also greater for children with other mental and physical health diagnoses compared with children with ADHD alone. Better mental health of mothers in the sample is related to reduced parental strain. Greater access to social support and neighborhood amenities also are related to reduced parental strain.

Conclusions: Greater levels of social support and better mental health of parents is associated with decreased strain. Interventions aimed at relieving stress and building strategies to improve mental health can be beneficial for families with children with ADHD and comorbid conditions.

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Acta Med Iran. 2012;50:547-51.

EFFECT OF ADENOTONSILLECTOMY ON ADHD SYMPTOMS OF CHILDREN WITH ADENOTONSILLAR HYPERTROPHY.

Dadgarnia MH, Baradaranfar MH, Fallah R, et al.

Adenotonsillar hypertrophy and obstructive sleep disordered breathing can lead to attention deficit/hyperactivity disorder (ADHD). The purpose of this study was to evaluate effect of adenotonsillectomy on improvement of ADHD symptoms in a quasi-experimental (before and after) study. The efficacy of adenotonsillectomy on improvement of ADHD symptoms of 35 children aged 5-12 years with adenotonsillar hypertrophy and ADHD was evaluated six months after surgery. Diagnosis of ADHD was based on the DSM-IV criteria in three subtypes (predominantly inattentive type, predominantly hyperactiveimpulsive type and combined type). Seventeen boys (49%) and eighteen girls (51%) with mean ((plus or minus) SD) age of 7.4 (plus or minus) 3.8 years (range: 1-10 years) were evaluated. Frequency of combined type of ADHD decreased significantly six months after adenotonsillectomy (54.3% versus 22.9%, P=0.003). ADHD inattention score (2.26 (plus or minus) 1.93 versus 0.96 (plus or minus) 0.45, P=0.005), hyperactivity score (4.23 (plus or minus)3.57 versus 3.57 (plus or minus)8, P=0.03) as well as ADHD combined score (9.66 (plus or minus)2.58 versus 7.2 (plus or minus)3.67, P=0.0001) improved significantly after surgery. Upper air way obstruction due to adenotonsillar hypertrophy might be an important and treatable cause of ADHD and should be considered in evaluation of affected children. Adenotonsillectomy in these children is associated with improvements in ADHD symptoms.

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Addict Disord Treat. 2012.

ADDRESSING DUAL DIAGNOSIS PATIENTS SUFFERING FROM ATTENTION-DEFICIT HYPERACTIVITY DISORDERS AND COMORBID SUBSTANCE USE DISORDERS: A REVIEW OF TREATMENT CONSIDERATIONS.

Martinez-Raga J, Knecht C, de Alvaro R, et al.

OBJECTIVE: To provide an updated, thorough, and critical review of the current status of the pharmacological and psychosocial treatments of patients with attention-deficit hyperactivity disorder (ADHD) and a comorbid substance use disorder (SUD).

METHODS: Comprehensive and systematic search of relevant databases (Medline, PubMed, Embase, and the Cochrane Library of systematic reviews and clinical trials) was carried out until January 31, 2012.
RESULTS: Treatment of patients with ADHD and a comorbid SUD is based on a multimodal and integrated approach, requiring the adequate management of the comorbid disorders, with psychosocial and pharmacological treatments. Regarding the pharmacotherapies for ADHD, prescription psychostimulants, particularly methylphenidate and atomoxetine, have all been assessed in dually diagnosed patients, for treating the symptoms of ADHD or for managing the comorbid SUD. Overall, medications are safe, well tolerated, and provide short-term and long-term benefits in patients with ADHD and comorbid SUD.
CONCLUSIONS: Studies assessing the efficacy of pharmacotherapies for ADHD have shown that they are equally efficacious and well tolerated, generally in combination with psychological interventions, in patients with a comorbid SUD. In addition, psychostimulant treatment of children with ADHD appears to have a protective effect on the subsequent risk for SUD.

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Appl Health Econ Health Policy. 2012;10:381-95.

COST EFFECTIVENESS OF GUANFACINE EXTENDED-RELEASE VERSUS ATOMOXETINE FOR THE TREATMENT OF ATTENTION-DEFICITHYPERACTIVITY DISORDER: APPLICATION OF A MATCHING-ADJUSTED INDIRECT COMPARISON.

Haim Erder M, Xie J, Signorovitch JE, et al.

Background: About 7% of children and adolescents are diagnosed with attention-deficit/hyperactivity disorder (ADHD) in the US. Patients with ADHD who are intolerant of or do not have an optimal response to stimulants often use non-stimulants as alternative therapies. Guanfacine extendedrelease (GXR) and atomoxetine (ATX) are the only non-stimulants approved by the US Food and Drug Administration for once-daily use in the treatment of children and adolescents withADHDin theUS. ATX has been on themarket since 2002 while GXR was recently approved in 2009. To date, there is no comparative effectiveness or cost-effectiveness study comparing the two drugs.
Objectives: The aim of this study was to assess the cost effectiveness of GXR versus ATX for the treatment of ADHD in children and adolescents, using the comparative efficacy results from a matching-adjusted indirect comparison (MAIC).
Methods: The MAIC method was used to compare the efficacy between GXR (target dose and lower doses) and ATX (target dose) in the absence of headto-head clinical trials. Individual patients in the GXR trials were weighted such that the summary baseline characteristics and the efficacy of the placebo arm of the GXR trials matched exactly with those from published ATX trials. After weighting, the efficacy (i.e. change in the ADHD rating scale, fourth edition [ADHD-RS-IV] total score from baseline) was compared between each GXR dosing group and the ATX group. The results from the MAIC analyses were used to populate a 1-year Markov model that is used to compare the cost effectiveness of GXR versus ATX from a US third-party payer perspective. Effectiveness outcomes for each treatment group were estimated as the proportion of responders, defined as patients with (greater-than or equal to)25% reduction in ADHD-RS-IV total score from baseline, and average quality-adjusted life years (QALYs). Utilities associated with response/non-response and disutilities due to adverse events were applied in the model. Costs included drug and medical service costs and were inflated to 2011 US dollars ($US). Incremental cost/QALY and incremental cost/responder were estimated. Univariate sensitivity analyses were conducted by varying all model parameters, including costs, utilities, and response rate.
Results: The target dose of GXR was 0.12mg/kg/day. In match-adjusted populations with balanced baseline characteristics, patients receivingGXR at the dose of 0.09-0.12 (p = 0.0009) and 0.075-0.09 mg/kg/day (p = 0.0248) had better efficacy, while those receiving GXR at the dose of 0.046-0.075mg/kg/day had comparable efficacy (p = 0.0699), compared with patients receiving ATX at the target dose of 1.2mg/kg/day. In the base case of the cost-effectiveness analysis (CEA), GXR had incremental cost-effectiveness ratios of $US10637/QALY and $US853/responder, compared with ATX (incremental costs: $US74; incremental effectiveness: 0.007 QALYs and 86 responders per 1000 patients treated). Results of all univariate sensitivity analyses showed that the model results were robust to changes in model inputs.
Conclusions: To our knowledge, this is the first application of the novel comparative efficacy method ofMAIC to a CEA model. TheMAIC results indicate thatGXR(0.075-0.12mg/kg/day) wasmore effective than

ATX (1.2mg/kg/day) in the trial population. The CEA results indicate that GXR is cost effective compared with ATX for the treatment of ADHD in children and adolescents.

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Arch Dis Child. 2012;97:1027-33.

FAMILY-BASED ASSOCIATION STUDY OF ADHD AND GENES INCREASING THE RISK FOR SMOKING BEHAVIOURS.

Thakur GA, Sengupta SM, Grizenko N, et al .

Objective: To investigate five top single nucleotide polymorphisms (SNPs) located in different genes and loci (CHRNA3, BDNF, DBH and LOC100188947) that were highly associated with different dimensions of smoking behaviour, in relation to attention-deficit hyperactivity disorder (ADHD).
Design: Cohort study consisting of a clinical sample of children with ADHD.
Setting: Douglas Institute ADHD Clinic, Montreal, Canada.
Patients: Families of 454 children with ADHD aged 6-12 years old.
Interventions: Family-based association tests used to study the transmission of risk alleles within these five genetic markers.
Main outcome measures: Clinical diagnosis of ADHD, and a number of behavioural and neurocognitive phenotypes relevant to the disorder.
Results: One SNP (rs1329650) from a non-coding RNA (LOC100188947) was significantly associated with over-all ADHD diagnosis with the C* risk allele being overtransmitted from parents to children with ADHD (p=0.02). It was also over-transmitted to children with higher scores on Conners' Parents (p=0.01) and Conners' Teacher (p=0.002) index scores, and Child Behaviour Checklist withdrawn (p=0.001) and aggressive (p=0.007) behaviours. Children with poorer performances on executive and attention tasks were more likely to inherit the risk allele.
Conclusions: The C* allele of rs1329650 may be increasing the risk for ADHD and smoking behaviour through a common mechanism, possibly externalising behaviours and specific cognitive deficits that manifest as ADHD in childhood and are the gateway to smoking behaviour later in life. This exploratory study illustrates the use of comorbid disorders to investigate ADHD genetics. In spite of its relatively large sample size, replication in future studies is warranted. Trial Registration Number NCT00483106.

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Arch Pediatr Adolesc Med. 2012;166:1074-75.

PRENATAL AND PERINATAL RISK FACTORS FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schmitt J, Romanos M.

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Asia-Pacific Psychiatry. 2012;4:52-53.

THE RELATIONSHIP BETWEEN ASD AND ADHD IN CHILDREN.

Lee S.

Autism spectrum disorders (ASDs) and attention-deficit/ hyperactivity disorder (ADHD) overlap in the core impairments of the disorders (social interaction, communication, and restricted interests). However, the current edition of the DSM precludes making ADHD diagnosis in children with ADSs. Although previous studies indicate high levels of comorbidities between ASDs and ADHD, very little is known about what causes the association between these two disorders. Thus, in this presentation, we will first review the phenotypic overlap of ADHD and ASDs. Then, we will discuss the issue about the DSM precluding a comorbid diagnosis of ADSs and ADHD. As next, neuropsychological, genetic and neuroanatomical findings of ADSs and ADHD in regard to the comorbidity will be summarized.

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Asia-Pacific Psychiatry. 2012;4:9.

ADHD: DISCUSSED FEATURES AND NEW CLINICAL RIDDLES.

Tyano S.

ADHD is a common disorder, existing in all age groups, 6-10% of child and adolescent population and 4-6% of adults. It is getting a lot of attention from several fields of research, and is frequently discussed and studied in many scientific meetings. Hence, we would like to present a course that will last 3 hours, during which we will discuss some of the most important issues today: 1. ADHD etiology, mainly the genetic studies 2. Structural and functional features of ADHD as shown by imaging studies, neuro-cognitive studies, etc. 3. The clinical picture of ADHD in all age groups, including the 'extreme' age groups, i.e. infants and adults 4. The high comorbidity load related to ADHD, its relationship with other chronic disabling disorders such as PDD and psychotic disorders, and its organic comorbidities such as Dysregulation of biological rhythms 5. The dynamic aspects of living with ADHD.

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Asia-Pacific Psychiatry. 2012;4:98.

ABNORMAL FUNCTIONAL CONNECTION AS A BIOLOGICAL MARKER OF INTELLIGENCE IN ADHD.

Jeong B, Choi J.

Purpose: IQ has been known as a phenotype of the developmental delay of overall functioning in attentiondeficit/ hyperactivity disorder (ADHD). However, little has been known of the biological marker of IQ in functional brain network. Here we explored the relationship between IQ and long-range functional connection in medication-naive children with attention-deficit/hyperactivity disorder (ADHD).

Material and method: Twenty medication-naive children with ADHD and 20 age-, gender-matched typically developing control (TDC) children were measured resting state brain activity with functional MRI. Among 12 resting state-related networks (RSICs) extracted using ICA, functional connectivity was calculated using partial correlation analysis. We investigated the relationship of functional connectivity among RSICs with IQ both in each group and across all subjects.

Results: IQ was significantly lower in ADHD than TDC groups and was related with the reduced functional connectivity between anterior and posterior default mode network (DMN) both in each group and across all subjects.

Conclusion: Our results suggest that the deficit in long-range functional connectivity between anterior and posterior DMN is an important biological marker of the developmental delay in ADHD.

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Asia-Pacific Psychiatry. 2012;4:9.

CURRENT PRACTICE FOR THE TREATMENT OF CHILDREN WITH ADHD IN KOREA.

Ahn DH.

ADHD becomes the major problem in psychiatric practice throughout the world since 1990s. The current practice pattern for the treatment of children with ADHD will be reviewed in Korea. We surveyed 76 child and adolescent psychiatrists on the current practice pattern for the treatment of children with ADHD. Additionally we reviewed statistical data on ADHD treatment and published articles in Korea. In according to the National Health Insurance Statistic Data on the ADHD treatment, the number of persons who were treated for ADHD is increased from 18,967 in 2003 to 64,066 in 2009 (237.8%). Especially the number of adults above 20 years-old is increased 7.5 times from 2003 to 2009. This is the first survey the current practice pattern for the treatment of child and adolescent with ADHD in Korea. ADHD and related other disruptive behavior disorders (46.6%) were the most commonly treated disorder in child and adolescent clinical practice, followed by mood and anxiety disorders (21.8%), mental retardation and developmental disorders (14.2%), other disorders including tic and Tourette disorder, psychotic, adjustment, organic, and substance disorders (11.8%), and sleep, elimination, and eating disorders (6.0%). More than 90% of children with ADHD were prescribed medication to school age and adolescents compared with 45.3% to preschool children. Parental psychoeducation or parental training was done to all age groups. The portion of social skills training (SST) and play therapy prescription in school age were 77.3% and 56.0%, which

decreased to 37.3% and 12.0% in adolescents. Cognitive-behavioral therapy (CBT) was constantly conducted from school age (49.3%) through adolescence (45.3%).

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Asia-Pacific Psychiatry. 2012;4:64.

THE RELATION BETWEEN PARENTS' IGNORANCE ON ADHD AND AGE DURING THE FIRST VISIT OF A CHILD TO CHILD & ADOLESCENT PSYCHIATRIC POLYCLINIC IN INDONESIA.

Noor I.

Background: Most of the time, a child with the complaint of emotional and behavioural problems is diagnosed as Attention Deficit Hyperactivity Disorder (ADHD). It is often too late that a child with ADHD is taken to consult to child & adolescent mental health center.

Objective: To explain the relation between parents' ignorance on ADHD and age of their child when first taken to consult to child & adolescent mental health service.

Method: The study is descriptive based on the data obtained from medical records. The samples are children diagnosed to suffer from ADHD in certain time, based on the guidelines of DSM-IV TR. The setting is in a hospital with child & adolescent mental health service in Indonesia.

Results: The number of samples is 65 children who were diagnosed to suffer from ADHD in the period from April 2010 to December 2011. The age varied between 3 to 15 years old. The ratio of gender is 75% men and 25% women. There is a significant relationship between the factor of parents' ignorance on ADHD and age of the child when first taken to consult to child & adolescent mental health service. The children with their parents knowing the information of ADHD will routinely continue the medication and other modalities as follows: remedial (36%), sensory integration (30%), occupation (21%), and group (13%).

Discussion: The study shows that the parents' ignorance on ADHD gives impacts towards child's retardiness to obtain therapy handling which is a combination of psychopharmaca and non-psychopharmaca. As a result, it is necessary to do promotion and information spreading on ADHD which are continuous through a child & adolescent psychiatry program of the community setting

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Asia-Pacific Psychiatry. 2012;4:9-10.

ADHD AND SOCIAL COGNITION.

Shin D.

Many patients with attention deficit/hyperactivity disorder (ADHD) have impairment in social functioning. Impulsivity, hyperactivity and inattention are likely affect adequate tuning of social behavior. Furthermore, oppositional defiant disorder, conduct disorder (CD) which are commonly associated with ADHD are important indicators of social impairment. Several behavioral elements are closely related to the social dysfunction of children with ADHD. Aggressive and negative nature of interactions tends to be associated with rule violation, hostile and controlling behavior. These behaviors may form a direct threat to other children, and result in negative peer nominations. The second element refers to restless and intrusive behaviors that are often inappropriate in the given context. These behaviors may also be related to the peer rejection. Inattention manifests itself in social situation by not listening, being distracted and having trouble switching roles. Predominantly inattentive type of ADHD tends to be dreamier, passive and slow in their behaviors. Results from theory of mind and facial emotion recognition tasks show that children with ADHD are lack of awareness of the feeling of others. Children with ADHD fail in some tests of ToM and display impairments involving emotion, face and prosody perception, and reduced empathy. Social dysfunction may be of crucial importance for the prognosis of children with ADHD on both short and long-term. Social dysfunction predicted later CD and substance abuse after controlling of baseline mood, aggressive behavior and attention problems. Medication-induced reduction of symptoms was the strongest mediator of social skills improvement. Improvement of social cognitive skills and more effective parenting may be helpful. But, research data show inconsistent findings. Optimal treatment strategies for treating social problems in children with ADHD need further development.

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Asia-Pacific Psychiatry. 2012;4:10.

SEARCHING FOR COGNITIVE ENDOPHENOTYPES FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Shang CY.

Attention deficit hyperactivity disorder (ADHD) is a common, early-onset, impairing, clinically and genetically heterogeneous neuropsychiatric disorder. The endophenotype approach has been proposed to reduce the complexity of the phenotype and its potential genetic heterogeneity and to increase linkage or association signals because the endophenotype is proximal to gene products and has the potential to target the possible pathophysiological deficits that combine to create the overall conditions of ADHD. Two of the most striking neuropsychological impairments in ADHD are in executive function and memory. Our recent work showed that the adolescents with ADHD and the unaffected siblings had a significantly shorter backward digit span, more extra-dimensional shift errors, shorter spatial span length, more total errors and poorer strategy use. In addition, the unaffected siblings occupied an intermediate position between ADHD probands and controls in the visual memory tasks. Our findings identified executive function and visual memory as useful endophenotypes for ADHD.

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Autism Res. 2012;5:124-36.

MOTOR LEARNING RELIES ON INTEGRATED SENSORY INPUTS IN ADHD, BUT OVER-SELECTIVELY ON PROPRIOCEPTION IN AUTISM SPECTRUM CONDITIONS.

Izawa J, Pekny SE, Marko MK, et al.

The brain builds an association between action and sensory feedback to predict the sensory consequence of selfgenerated motor commands. This internal model of action is central to our ability to adapt movements and may also play a role in our ability to learn from observing others. Recently, we reported that the spatial generalization patterns that accompany adaptation of reaching movements were distinct in children with autism spectrum disorder (ASD) as compared with typically developing (TD) children. To test whether the generalization patterns are specific to ASD, here, we compared the patterns of adaptation with those in children with attention deficit hyperactivity disorder (ADHD). Consistent with our previous observations, we found that in ASD, the motor memory showed greater than normal generalization in proprioceptive coordinates compared with both TD children and children with ADHD; children with ASD also showed slower rates of adaptation compared with both control groups. Children with ADHD did not show this excessive generalization to the proprioceptive target, but they did show excessive variability in the speed of movements with an increase in the exponential distribution of responses ((tau)) as compared with both TD children and children with ASD. The results suggest that slower rate of adaptation and anomalous bias towards proprioceptive feedback during motor learning are characteristics of autism, whereas increased variability in execution is a characteristic of ADHD.

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BMC Psychiatry. 2012;12.

EXECUTIVE ATTENTION IMPAIRMENT IN FIRST-EPISODE SCHIZOPHRENIA.

Orellana G, Slachevsky A, Pena M.

Background: We compared the attention abilities of a group of first-episode schizophrenia (FES) patients and a group of healthy participants using the Attention Network Test (ANT), a standard procedure that estimates the functional state of three neural networks controlling the efficiency of three different attentional behaviors, i.e., alerting (achieving and maintaining a state of high sensitivity to incoming stimuli), orienting (ability to select information from sensory input), and executive attention (mechanisms for resolving conflict among thoughts, feelings, and actions).

Methods: We evaluated 22 FES patients from 17 to 29 years of age with a recent history of a single psychotic episode treated only with atypical neuroleptics, and 20 healthy persons matched with FES patients by sex, age, and educational level as the control group. Attention was estimated using the ANT in which participants indicate whether a central horizontal arrow is pointing to the left or the right. The central

arrow may be preceded by spatial or temporal cues denoting where and when the arrow will appear, and may be flanked by other arrows (hereafter, flankers) pointing in the same or the opposite direction.
Results: The efficiency of the alerting, orienting, and executive networks was estimated by measuring how reaction time was influenced by congruency between temporal, spatial, and flanker cues. We found that the control group only demonstrated significantly greater attention efficiency than FES patients in the executive attention network.
Conclusions: FES patients are impaired in executive attention but not in alerting or orienting attention, suggesting that executive attention deficit may be a primary impairment during the progression of the disease.

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BMC Psychiatry. 2012;194.

LONG-TERM NEUROCOGNITIVE EFFECTS OF METHYLPHENIDATE IN PATIENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, EVEN AT DRUG-FREE STATUS.

Huang YS, Wang LJ, Chen CK.

Background: Methylphenidate (MPH), a psycho-stimulant, is the most widely administered drug for the pharmacological management of patients with attention deficit hyperactivity disorder (ADHD). This study attempts to determine whether sustainable improvements occur in neurocognitive function among ADHD patients following 12-month treatment with MPH, at drug-free status. Whether age groups, gender or ADHD subtypes differ in neurocognitive performance during MPH treatment is also examined.
Methods: Study participants consisted of 103 ADHD patients (mean age: 9.1 +/- 1.9 years old) who were drug naive or drug free for at least 6 months. The patients were prescribed oral short-acting MPH at each dose range of 0.3--1.0 mg/kg daily. During 12 months of the study, the patients underwent the test of variables of attention (TOVA) at the baseline, month 6 and month12. Patients were instructed to not intake MPH for one week before the second and the third TOVA.
Results: Seventy five patients completed the study. Results of this study indicated that although commission errors and response sensitivity (d') significantly improved during MPH treatment for 12 months, omission errors, response time, response time variability and ADHD score did not. While younger ADHD patients (<9y/o) performed better in response time, response time variability, d' and ADHD score than older ones (>=9y/o), the latter more significantly improved in response time than the former during 12 months of treatment. Additionally, boys improved more than girls in omission error and d'. Moreover, although ADHD subtypes significantly differed in ADHD score during the treatment, MPH treatment and ADHD subtypes did not interact with each other for all TOVA indices.
Conclusions: ADHD patients significantly improved in impulsivity and perceptual sensitivity, determined as TOVA, during MPH treatment for 12 months. Age and gender, yet not ADHD subtypes, appear to influence the MPH treatment effects in some indices of TOVA. A future study containing a comparison group is suggested to confirm whether the neurocognitive improvements are attributed to long-term effects of MPH or natural maturation of patients.

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Brain Struct Funct. 2012;1-12.

STIMULANT DRUGS TRIGGER TRANSIENT VOLUMETRIC CHANGES IN THE HUMAN VENTRAL STRIATUM.

Hoekzema E, Carmona S, Ramos-Quiroga JA, et al.

The ventral striatum (VStr) integrates mesolimbic dopaminergic and corticolimbic glutamatergic afferents and forms an essential component of the neural circuitry regulating impulsive behaviour. This structure represents a primary target of psychostimulant medication, the first-choice treatment for attention-deficit/hyperactivity disorder (ADHD), and is biochemically modified by these drugs in animals. However, the effects of stimulants on the human VStr remain to be determined. We acquired anatomical brain MRI scans from 23 never-medicated adult patients with ADHD, 31 adult patients with a history of stimulant treatment and 32 control subjects, and VStr volumes were determined using individual rater-blinded region of interest delineation on high-resolution neuroanatomical scans. Furthermore, we also extracted VStr volumes before and after methylphenidate treatment in a subsample of the medication-naive adult patients

as well as in 20 never-medicated children with ADHD. We observed smaller VStr volumes in adult patients with a history of stimulant treatment in comparison to never-medicated patients. Moreover, our longitudinal analyses uncovered a reduction of grey matter volume in the bilateral VStr in adult patients after exposure to methylphenidate, which was followed by volumetric recovery to control level. In children, the same pattern of VStr volume changes was observed after treatment with methylphenidate. These findings suggest that the altered VStr volumes previously observed in patients with ADHD may represent a transitory effect of stimulant exposure rather than an intrinsic feature of the disorder. More generally, these data show that stimulant drugs can render plastic volume changes in human VStr neuroanatomy.

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Child Abuse Negl. 2012.

CHILDHOOD MALTREATMENT AND CONDUCT DISORDER: INDEPENDENT PREDICTORS OF CRIMINAL OUTCOMES IN ADHD YOUTH.

De Sanctis VA, Nomura Y, Newcorn JH, et al.

Objective: Children with attention-deficit/hyperactivity disorder (ADHD) are at heightened risk for maltreatment in childhood and criminality as they enter into adolescence and early adulthood. Here, we investigated the effect of moderate to severe childhood maltreatment on later criminality among adolescents/young adults diagnosed with ADHD in childhood while accounting for the contributions of other known risk factors such as early conduct disorder (CD).

Methods: Eighty-eight participants from a longitudinal study of children diagnosed with ADHD and screened for comorbid disorders at age 7-11 years were assessed for maltreatment histories at the time of the 10-year adolescent follow-up. Detailed juvenile and adult criminal records were obtained from the New York State Division of Criminal Justice Services approximately 3-years after commencement of the follow-up study. We used regression analyses to determine predictors of adolescent/young adult criminal behavior.

Results: Moderate to severe childhood maltreatment increased the risk of adolescent/young adult arrest over and above the risk associated with childhood CD, while both childhood maltreatment and childhood CD significantly increased the risk of recidivism. ADHD youth classified as maltreated were three and a half times more likely to be arrested when compared to ADHD youth without a maltreatment classification.

Conclusion: We established maltreatment as a risk factor for criminality in ADHD youth and demonstrated that this relationship was independent of the contributions of CD, and established risk factor for antisocial behavior in this population. The findings highlight the need for maltreatment screening in children with ADHD in order to identify those at heightened risk for criminal activity, and target treatment to improve outcome in this high-risk group of children.

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Child Adolesc Ment Health. 2012;17:238-45.

GENDER DISTINCTIVE IMPACTS OF PREMATURITY AND SMALL FOR GESTATIONAL AGE (SGA) ON AGE-6 ATTENTION PROBLEMS.

Hall J, Jaekel J, Wolke D.

Background: Predictors of attention problems remain uncertain. Here we distinguish prematurity from small (birth weight) for gestational age (SGA).

Method: A total of 1437 children were studied between 0 and 6 years. Gender differences and indirect perinatal effects (via 20-month head circumference and cognition) were considered for age 6 attention problems.

Results: Boys, preterms, and SGA children were all at increased risk for attention problems. Indirect perinatal effects differed between boys and girls.

Conclusions: The routes leading to attention problems seem to differ for SGA and preterm children. SGA appears to reduce brain volume while prematurity alters brain function. Although less frequent, female attention problems are more strongly predicted by prematurity and cognitive dysfunction.

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Child Neuropsychol. 2012 Nov;18:576-85.

RELATIONSHIP BETWEEN REACTION TIME VARIABILITY AND MOTOR SKILL DEVELOPMENT IN ADHD.

Klotz JM, Johnson MD, Wu SW, et al.

Slower and more variable reaction times to computerized tasks have been documented in children diagnosed with attention deficit/hyperactivity disorder (ADHD). Recent research supports a role for attentional lapses in generating abnormally variable and slow responses. However, given the association between ADHD and impairments in motor control, we hypothesized that slower or more variable reaction times might also correlate with motor development. The aim of this case-control study was to explore the relationship between motor function, reaction speed and variability, and ADHD. After comprehensive educational and clinical assessments, motor skill development was evaluated in 35 children ages 9 to 14 (19 with ADHD) using the Physical and Neurological Examination for Subtle Signs (PANESS) test battery. Finger-sequencing speed and variability were quantified with goniometers. Reaction times were measured with 20 trials each of computerized simple and choice (binary) tasks. Compared to healthy controls, children with ADHD had slower and more variable reaction times, and these findings correlated with impaired motor development (PANESS) and slow and variable finger sequencing (goniometers). Further studies of motor development in ADHD may identify factors influencing speed and variability of reaction times.

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Clin Psychol Rev. 2012 Nov;32:605-17.

MODERATORS OF WORKING MEMORY DEFICITS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): A META-ANALYTIC REVIEW.

Kasper LJ, Alderson RM, Hudec KL.

Working memory has assumed a prominent role as a primary neurocognitive deficit or endophenotype in extant models of attention-deficit/hyperactivity disorder (ADHD). The current study updated previous reviews and employed meta-analytic techniques to examine a broad range of moderating variables of effect size heterogeneity across phonological and visuospatial working memory tasks. Collectively, results revealed large between-group effect sizes across both working memory domains. In addition, several sample (percent female) and task (number of experimental trials, recall vs. recognition tasks, and demands on the central executive) moderating variables explained significant effect size variability among phonological and visuospatial studies. These findings suggest that children with ADHD exhibit statistically significant, large magnitude working memory deficits relative to their typically developing peers.

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CNS Spectr. 2012;17:94-99.

THE ROLE OF A LIFETIME HISTORY OF OPPOSITIONAL DEFIANT AND CONDUCT DISORDERS IN ADULTS WITH ADHD: IMPLICATIONS FOR CLINICAL PRACTICE.

Vitola ES, Salgado SAI, Silva KL, et al.

Introduction. Attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) are frequently co-occurring disorders in children and adolescents. However, their clinical status among adults is still under discussion. This study analyzes how the current clinical presentation of adult ADHD might be influenced by a lifetime history of CD and ODD.

Methods. We compared three groups of patients: ADHD without history of CD/ODD (n=178), ADHD1history of ODD (n=184), and ADHD1history of CD (n=96).

Results. A history of CD (and to a lower extent ODD) is associated with a more severe and externalizing profile.

Conclusion. Past CD and ODD entail a significant negative mental health impact on persistent ADHD, reinforcing the importance of actively assessing the developmental history of adult ADHD patients.

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Comput Med Imaging Graph. 2012;36:591-600.

AUTOMATIC BRAIN CAUDATE NUCLEI SEGMENTATION AND CLASSIFICATION IN DIAGNOSTIC OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Igual L, Soliva JC, Escalera S, et al.

We present a fully automatic diagnostic imaging test for Attention-Deficit/Hyperactivity Disorder diagnosis assistance based on previously found evidences of caudate nucleus volumetric abnormalities. The proposed method consists of different steps: a new automatic method for external and internal segmentation of caudate based on Machine Learning methodologies; the definition of a set of new volume relation features, 3D Dissociated Dipoles, used for caudate representation and classification. We separately validate the contributions using real data from a pediatric population and show precise internal caudate segmentation and discrimination power of the diagnostic test, showing significant performance improvements in comparison to other state-of-the-art methods.

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Cortex. 2012.

VISUAL ATTENTIONAL ENGAGEMENT DEFICITS IN CHILDREN WITH SPECIFIC LANGUAGE IMPAIRMENT AND THEIR ROLE IN REAL-TIME LANGUAGE PROCESSING.

Dispaldro M, Leonard LB, Corradi N, et al.

In order to become a proficient user of language, infants must detect temporal cues embedded within the noisy acoustic spectra of ongoing speech by efficient attentional engagement. According to the neuro-constructivist approach, a multi-sensory dysfunction of attentional engagement - hampering the temporal sampling of stimuli - might be responsible for language deficits typically shown in children with Specific Language Impairment (SLI). In the present study, the efficiency of visual attentional engagement was investigated in 22 children with SLI and 22 typically developing (TD) children by measuring attentional masking (AM). AM refers to impaired identification of the first of two sequentially presented masked objects (O1 and O2) in which the O1-O2 interval was manipulated. Lexical and grammatical comprehension abilities were also tested in both groups. Children with SLI showed a sluggish engagement of temporal attention, and individual differences in AM accounted for a significant percentage of unique variance in grammatical performance. Our results suggest that an attentional engagement deficit - probably linked to a dysfunction of the right fronto-parietal attentional network - might be a contributing factor in these children's language impairments.

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Curr Opin Pediatr. 2012.

COMPLEMENTARY AND ALTERNATIVE THERAPIES FOR CHILDREN AND ADOLESCENTS WITH ADHD.

Bader A, Adesman A.

PURPOSE OF REVIEW: To provide a comprehensive review of complementary and alternative medicine (CAM) treatments for children and adolescents with attention deficit hyperactivity disorder (ADHD).

RECENT FINDINGS: Many parents of children with ADHD are reluctant to pursue medication options and unable to access behavioral counseling. CAM therapies are often appealing to families and studies show that a large percentage of children with ADHD are treated with one or more CAM therapy. Most research studies evaluating CAM therapies are methodologically flawed, and often times there are inconsistencies across either study design or results. Although the American Academy of Pediatrics does not recommend any CAM therapies for ADHD, essential fatty acid supplementation is likely well tolerated and modestly effective.

SUMMARY: Most complementary and alternative treatments do not have adequate research to recommend their use in children with ADHD. Physicians should be aware of the many CAM treatment options and the research surrounding them in order to provide their patients with the most current and accurate information available.

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Dev Neuropsychol. 2012 Oct;37:590-600.

THE IMPACT OF ADHD ON THE COGNITIVE AND ACADEMIC FUNCTIONING OF CHILDREN WITH NF1.

Pride NA, Payne JM, North KN.

We compared cognitive functioning, academic ability, and the predictors of academic underachievement in children with neurofibromatosis type 1 (NF1) (n=132), children with NF1 and comorbid attention deficit hyperactivity disorder (NF1+ADHD) (n=60), and unaffected controls (n=52).
Results indicate the presence of ADHD burdens some aspects of cognitive functioning and learning in NF1. Inattention and executive dysfunction are general characteristics of the NF1 cognitive phenotype and significantly undermine academic achievement across children with NF1.

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Dev Neurosci. 2012;34:327-41.

SUBCORTICAL AND CORTICAL STRUCTURAL CENTRAL NERVOUS SYSTEM CHANGES AND ATTENTION PROCESSING DEFICITS IN PRESCHOOL-AGED CHILDREN WITH PRENATAL METHAMPHETAMINE AND TOBACCO EXPOSURE.

Derauf C, Lester BM, Neyzi N, et al.

Objective: To examine the independent contributions of prenatal methamphetamine exposure (PME) and prenatal tobacco exposure (PTE) on brain morphology among a sample of nonalcohol-exposed 3-to 5-year-old children followed prospectively since birth.
Study Design: The sample included 20 children with PME (19 with PTE) and 15 comparison children (7 with PTE), matched on race, birth weight, maternal education and type of insurance. Subcortical and cortical volumes and cortical thickness measures were derived through an automated segmentation procedure from T1-weighted structural magnetic resonance images obtained on unsedated children. Attention was assessed using the computerized Conners' Kiddie Continuous Performance Test Version 5 (K-CPT(trademark) V.5). PME effects on subcortical and cortical brain volumes and cortical thickness were tested by general linear model with type III sum of squares, adjusting for PTE, prenatal marijuana exposure, age at time of scan, gender, handedness, pulse sequence and total intracranial volume (for volumetric outcomes). A similar analysis was done for PTE effects on subcortical and cortical brain volumes and thickness, adjusting for PME and the above covariates.
Results: Children with PME had significantly reduced caudate nucleus volumes and cortical thickness increases in perisylvian and orbital-frontal cortices. In contrast, children with PTE showed cortical thinning in perisylvian and lateral occipital cortices and volumetric increases in frontal regions and decreases in anterior cingulate. PME was positively related and caudate volume was inversely related to K-CPT reaction time by inter-stimulus interval, a measure of the ability to adjust to changing task demands, suggesting that children with PME may have subtle attentional deficits mediated by caudate volume reductions.
Conclusions: Our results suggest that PME and PTE may have distinct differential cortical effects on the developing central nervous system. Additionally, PME may be associated with subtle deficits in attention mediated by caudate volume reductions.

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Drug Alcohol Depend. 2012;126:147-55.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND DEPRESSION SYMPTOMS AS MEDIATORS IN THE INTERGENERATIONAL TRANSMISSION OF SMOKING.

Zoloto A, Nagoshi CT, Presson C, et al.

Background: Attention deficit/hyperactivity disorder and depression have been found to be comorbid with smoking behaviors, and all three behavioral syndromes have been shown to be familially transmitted. The present paper reports on the results of analyses testing whether child attention deficit/hyperactivity disorder and depression symptoms were mediators in the intergenerational transmission of cigarette smoking.
Method: Path analyses using bootstrapped mediation procedures were conducted on data from a community sample of 764 families (one or both parents and one adolescent offspring) from the Indiana

University Smoking Survey. Parents reported on their smoking behaviors, ADHD, and depression and their child's ADHD, while offspring reported on their smoking behaviors and depression.
Results: Although fathers' and mothers' smoking status, depression, and ADHD were not significantly correlated with boys' smoking initiation, there was a significant mediated (indirect) pathway from mothers' depression to boys' smoking initiation through boys' depression. Several parental variables were significantly correlated with smoking initiation in girls, and the pathways from mothers' smoking status, mothers' ADHD, and fathers' smoking status to girls' smoking initiation were significantly mediated by girls' ADHD.
Conclusions: For adolescent girls, the intergenerational transmission of ADHD appears to be important in understanding the intergenerational transmission of cigarette smoking. Sex differences in the intergenerational transmission of psychopathology as it leads to smoking initiation were also discussed.

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Dusunen Adam. 2012;25:230-37.
ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND OTHER PSYCHIATRIC SYMPTOMS IN PARENTS OF CHILDREN WITH ADHD.
Simsek S, Gokcen C, Fettahoglu EC.
Objective: The aim of this study is to investigate Attention Deficit Hyperactivity Disorder (ADHD) and other psychiatric symptoms of the parents of children with ADHD.
Method: Mothers (n=34) and fathers (n=29) of 34 children with ADHD were included into the study group. Mothers (n=34) and fathers (n=31) of 34 children with no history of referral to a doctor due to previous psychological problems and for whom diagnoses of ADHD and Disruptive Behavior Disorder (DBD) according to DSM-IV were ruled out were assigned as the controls. The parents were given Symptom Check List (SCL-90-R) and Adult Attention Deficit Hyperactivity Scale (ADHD-A).
Results: Parents from the patient group were found to have significantly more ADHD and psychiatric symptoms compared to parents from the control group.
Conclusion: In the evaluation and treatment process of children with ADHD, it would be beneficial to monitor their parents in terms of adult ADHD and related co-morbid psychiatric conditions. It is suggested that treating parents would benefit in the improvement of ADHD symptoms in children.

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Epilepsy Behav. 2012.
FUNCTIONAL MRI AND STRUCTURAL MRI AS TOOLS FOR UNDERSTANDING COMORBID CONDITIONS IN CHILDREN WITH EPILEPSY.
McDonald BC, Hummer TA, Dunn DW.
Children with epilepsy are at risk for behavioral and cognitive comorbidities. Potential etiologies can be assessed in part by neuroimaging. Functional magnetic resonance imaging (MRI) has a major role in presurgical evaluation and prediction of postoperative outcome by mapping of language and memory. Structural MRI and functional MRI have shown changes in children and adolescents with attention deficit hyperactivity disorder and disruptive behavior, common comorbidities in children with epilepsy. Neuroimaging has the potential for significantly increasing understanding of the basis of cognitive and behavioral problems in children with epilepsy. This article is part of a Special Issue entitled "Translational Epilepsy Research.

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Eur Child Adolesc Psychiatry. 2012;1-14.

HOW EFFECTIVE ARE DRUG TREATMENTS FOR CHILDREN WITH ADHD AT IMPROVING ON-TASK BEHAVIOUR AND ACADEMIC ACHIEVEMENT IN THE SCHOOL CLASSROOM? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Prasad V, Brogan E, Mulvaney C, et al.

Attention-deficit hyperactivity disorder (ADHD) has a significant impact on children's classroom behaviour, daily functioning and experience of school life. However, the effects of drug treatment for ADHD on learning and academic achievement are not fully understood. This review was undertaken to describe the effects of methylphenidate, dexamfetamine, mixed amfetamine salts and atomoxetine on children's on-task behaviour and their academic performance, and to perform a meta-analysis to quantify these effects. Nine electronic databases were systematically searched for randomized controlled trials comparing drug treatment for ADHD against (i) no drug treatment, (ii) baseline (in crossover trials), or (iii) placebo; reporting outcomes encompassing measures of educational achievement within the classroom environment. Forty-three studies involving a pooled total of 2,110 participants were identified for inclusion. Drug treatment benefited children in the amount of school work that they completed, by up to 15 %, and less consistently improved children's accuracy in specific types of academic assignments, such as arithmetic. Similar improvements were seen in classroom behaviour, with up to 14 % more of children's time spent "on task". Methylphenidate, dexamfetamine and mixed amfetamine formulations all showed beneficial effects on children's on-task behaviour and academic work completion. Atomoxetine was examined in two studies, and was found to have no significant effect. These review findings suggest that medication for ADHD has the potential to improve children's learning and academic achievement.

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Eur J Clin Nutr. 2012.

ZINC FOR TREATING OF CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED CLINICAL TRIALS.

Ghanizadeh A, Berk M.

This study systematically reviews the randomized clinical trials examining the effect of zinc on attention-deficit hyperactivity disorder (ADHD), searching the PubMed/Medline and Scholar Google databases. All randomized controlled trials that examined zinc as the intervention, and ADHD as the primary outcome were included. Only three randomized controlled trials, one which included a community sample and two that included clinical samples, met inclusion criteria. The only trial that was well controlled and randomized according to the baseline zinc level showed that using zinc, either alone or in combination with stimulants, did not improve ADHD. Considering the lack of clear evidence for the effect of zinc on ADHD and the possible effect of zinc on the nervous system, more clinical studies are needed to prove or disprove the effect of zinc as a monotherapy or adjuvant therapy. European Journal of Clinical Nutrition advance online publication, 21 November 2012; doi:10.1038/ejcn.2012.177.

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Eur J Health Econ. 2012;1-7.

TREATMENT COSTS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN GERMANY.

Braun S, Zeidler J, Linder R, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioural disorders among children and adolescents. The number of patients as well as prescriptions to treat this disease has continuously increased over the past few years. The aim of the present study was to analyse the costs for treating ADHD patients from the perspective of a major German health insurance fund.

Methodology: Anonymised administrative claims data were available for the study. All services reimbursed by the health fund for the selected ADHD patients were recorded. Apart from the resource use attributed directly to ADHD, co-morbidities as well as incremental costs were described based on a control group design.

Results: A total of 30,264 ADHD patients were diagnosed in 2008. The total costs for these patients were (euro) 3,888, and the incremental costs were (euro) 2,902. The largest proportions of incremental costs were due to therapeutic devices and remedies like occupational therapy amounting to (euro) 1,270.

Proportionate costs of (euro) 263 have been settled for pharmacotherapy with Methylphenidate and Atomoxetine. However, 41 % of the patients were not treated with ADHD-related pharmaceuticals.
Conclusions: ADHD costs are relevant from health insurance perspective. The expenses for occupational therapy constitute the cost driver. Compared to the findings of studies from the United States and contrarily to the backdrop of public discussions about considerably increased prescriptions of ADHD-specific drugs, the significantly higher additional expenses for occupational therapy services are impressing. This kind of therapy is internationally rather unknown and is therefore not acknowledged as a therapeutic standard.

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Eur J Ophthalmol. 2012;22:931-35.

DO CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER HAVE OCULAR ABNORMALITIES?

Mezer E, Wygnanski-Jaffe T.

Purpose. To investigate visual function and ocular features in children with attention deficit hyperactivity disorder (ADHD).
Methods. Fifty-one children underwent a detailed ophthalmologic evaluation. Thirty-two were diagnosed with ADHD, and 19 children with attention deficit disorder (ADD). The mean age was 9.9 (plus or minus) 3.1 years.
Results. The average best-corrected visual acuity of the better-seeing eye was 1 (range 0.9-1.25) and 0.96 (range 0.5-1.25) for the fellow eye. Eighteen percent (10) had amblyopia in one or both eyes (3 had strabismic and 7 had ametropic amblyopia). Heterotropia was found in 5 (10%), and absent stereoacuity was found in 3 (6%). Subnormal convergence amplitude was noted in 2 patients (4%). The mean spherical equivalent (SE) of the eyes in this study was 0.17(plus or minus)1.73 (range -5.5 to +7). Twenty-two subjects (43%) had a myopia of -0.50 D or higher. Hyperopia higher than 3.5 D was seen in 10 cases (20%), and astigmatism larger or equal to 1.0 D was observed in 10 patients (20%). With-the-rule astigmatism was by far most common type in the 29 eyes with an astigmatic refractive error (59%). Significant ametropia was detected in 42 (83%) of the patients. In contrast to other studies, we did not find a higher rate of convergence insufficiency or heterotropia.
Conclusions. Children diagnosed with either ADHD or ADD can present with significant ametropia but infrequent heterotropia.

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Eur Neuropsychopharmacol. 2012;22:S420-S421.

EFFECTS OF OROS METHYLPHENIDATE (OROS MPH) TREATMENT IN CHILDREN AND ADOLESCENTS WITH ADHD, MENTAL RETARDATION AND EPILEPSY.

Kesic A, Lakic A, Dronjak D, et al.

Purpose of the study: Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorder in children. Population studies suggest that the prevalnce of ADHD in childhood epilepsy is between 12 and 17 percent, and some of them also have mental retardation (MR). The treatment of children with MR, epilepsy and ADHD is challenge for doctors who are forced to prescribe drug combinations. The aim of our study is to evaluate effects of OROS MPH on symptoms of ADHD and seizure control in this vulnerable group of children.
Method: We have analyzed a group of 17 children and adolescents with diagnosis of ADHD, mental retardation and epilepsy. Our group included 12 boys and 5 girls, of the age between seven and sixteen years with diagnosis of ADHD. All of them are with mild or moderate mental retaradation and also have epilepsy. They were seizure-free six months or more before we started therapy with OROS MPH. We have evaluated the efficasy of OROS MPH (our patients received 18 mg/day or 36 mg/day) using SNAP IV scale and with clinical observation. Digitalized EEG were recording every three months. The follow up period for at least one year was one of the inclusion criteria for our study.
Results: During a year, we monitored terapeutic effects of drug. We used SNAP IV scale (parents and teachers were asked to complete the scale and doctors also), clinical observation, EEG monitoring. Our study suggest that OROS MPH significantly improved ADHD symptoms by lowering score on SNAP IV

(parents, teachers and the doctor also). Clinical observation also noted a significant improvement of patients (symptoms of ADHD). In our group of patients OROS MPH was well tolerated: Four of our patients (3 boys and one girl) had sleep disturbance (bed time was significantly delayed and total sleep time was decreased), but these problems with sleep stopped during third and fourth week of treatment with OROS MPH. Significant decrease in appetite was observed in five children (all of them boys), in two boys appetite was improved during second week of therapy, one showed improved after 20 days of treatment and two boys had lowered appetite during first and second months of therapy. One boy had both lowered appetite and sleep disturbance. No seizures were observed in our group during the one year study period.
Discussion: Our study has shown that the use of OROS MPH in children and adolescents with ADHD, mental retardation and epilepsy did not lead to deterioration in the control of epilepsy. Also, in this vulnerable group of children and adolescents there has been a significant reduction of symptoms of ADHD. Side effects of OROS MPH were rare and were stopped after a few weeks of taking the drug.

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Eur Neuropsychopharmacol. 2012;22:S419-S420.

DOPAMINERGIC CROSSROADS: CLINICAL IMPLICATIONS IN ADHD AND RESTLESS LEG SYNDROM.

Neu D, Hardy De Buisseret FX, Oswald P, et al.

Introduction: Clinical overlap of adult attention deficit disorder with or without hyperactivity (ADHD) and restless leg syndrome (RLS) might be underestimated in both conditions. ADHD and RLS are associated to suspected physiopathology of dopaminergic brain pathways and in addition they are both clinically related to daytime complaints of sleepiness, fatigue and non-restorative sleep perceptions [1]. The impact of potential overlaps remains currently rather unclear. The clinical assessment of possible overlaps is mostly not performed in daily routine practice. Although specific and different neuropharmacological treatment strategies exist for RLS and ADHD, little is known about the potential benefit of combination therapy in overlapping conditions. Till present L-Dopa for instance has shown to improve RLS symptoms but not ADHD in a co-morbid group presenting with overlaps of both conditions in children [2]. In addition iron deficiency with lower ferritin serum levels has rather been associated to RLS also when combined to ADHD [3]. As first step we propose to assess the clinical dimensions of both symptom clusters in both predefined conditions. Further we suggest investigating associated and potentially shared complaints of impaired sleep, daytime fatigue and sleepiness.
Methods: Within a cross-sectional design, we selected 12 patients addressed to a general University Hospital's sleep laboratory diagnosed with RLS and compared them with a matched outpatient group diagnosed and followed-up for ADHD (n = 12). We similarly assessed chronotype, RLS symptomatology, ADHD symptoms, daytime sleepiness, fatigue levels and sleep quality perception in both groups.
Measurement tools comprised: the Adult ADHD Self-Report Scale (ASRS), the Wender-Utah Rating Scale (WURS), the Epworth Sleepiness Scale (ESS), the Fatigue Severity Scale (FSS), the Horne-Ostberg chronotype scale, the International RLS Scale (IRLS) and the Pittsburgh Sleep Quality Index (PSQI). Whole blood samples were obtained for the measurement of serum ferritin levels.
Results: Sleep quality was worsened in both groups with a trend to a higher severity in RLS patients ($p = 0.06$). Sleepiness levels (ESS) did not show significant differences between RSL and ADHD patients. In contrast the impact of fatigue related symptoms was higher though in the RLS group ($p = 0.011$). Most interestingly, both groups showed similar levels of attention deficit and/or hyperactivity symptom intensities! However in turn, restlessness related motor symptoms of the lower limbs on the IRLS were significantly different between both groups, showing higher levels in the RLS group ($p = 0.013$). Severity of fatigue (FSS) was significantly correlated to sleep quality but not to ADHD symptom intensity in the ADHD group only ($p = 0.009$).
Conclusion: Although that related symptoms in both conditions can be similar and that higher respective prevalence of comorbidity could be expected, it might be that actual overlapping is dissimilar for both groups. Apparently the burden of attentional impairments in RLS patients might be far more underestimated than the restlessness symptoms that can be found in ADHD patients. Currently RLS

patients are not routinely screened for ADHD, hence with respect to the present this might be considered in the future. The potential benefit of combining dopaminergic D2-agonists (pramipexole or ropinirole e.g.) with stimulants like methylphenidate, remains therefore to be explored in clinical trials.

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Eur Neuropsychopharmacol. 2012;22:S362-S363.
Adult attention deficit hyperactivity disorder and anxiety disorder comorbidity: Prevalence in a clinical sample.
Van Ameringen M, Simpson W, Patterson B.
Purpose: Adult Attention Deficit Hyperactivity Disorder (ADHD) is a life-long, chronic disorder, affecting 8.1% of the US population [1]. Until recently, it was believed that ADHD was mainly a disorder of childhood, however a large proportion of children continue to experience symptoms of ADHD through adolescence and into adulthood. Clinical presentation of ADHD differs substantially between children and adults. While children will often be referred due to conduct problems or academic difficulties, adults present with social or work impairments, antisocial behaviours or problems with substance abuse [2]. ADHD appears to be highly comorbid with other psychiatric disorders [3], however little is known about the prevalence of ADHD in anxiety disorder clinical samples.
Method: Consecutive patients referred to an anxiety disorders clinic in Hamilton Canada, completed the Adult ADHD self-report scale and were assessed with a Structured Clinical Interview for DSM-IV (SCID), and the ADHD module of the Mini International Neuropsychiatric Interview (MINI). Baseline global severity was assessed by clinicians using the Clinical Global Impression Severity Scale (CGI-S). Patients completed a series of self report symptom severity measures.
Results: Of the 264 patients, the rate of lifetime ADHD was 37.5% (48.5% male, 51.5% female, $p<0.05$). ADHD was significantly associated with a primary diagnosis of impulse control disorder and bipolar disorder, and most commonly associated with social phobia (57.6%, NS) and Major Depressive Disorder (56.6%, NS). Those with ADHD had a significantly higher number of comorbid disorders than those without ADHD, (3.8(plus or minus)1.8 vs. 3.1(plus or minus)1.5, $p<0.001$.). Symptom severity measure scores on the Padua Inventory, Yale-Brown Obsessive Compulsive Scale ($p<0.05$), Sheehan Disability Scale (SDS) ($p<0.05$), Anxiety Sensitivity Index (ASI) ($p<0.05$), the QUIDS depression rating scale ($p<0.001$), the Penn State Worry Questionnaire ($p<0.05$) and the Davidson Trauma Scale ($p<0.001$) were significantly higher in the ADHD group. Individuals with ADHD, plus comorbid generalized anxiety disorder, had higher CGI-S ($p <0.05$) and those with ADHD and comorbid panic disorder with agoraphobia had higher CGI-S, SDS and Quality of Life and Enjoyment Scale scores ($p<0.001$). High ADHD severity (defined by symptom count on the MINI), was associated with a higher number of lifetime comorbid diagnoses ($p<0.05$), and higher scores on the CGI-S, QUIDS and ASI. Males were more likely than females to have received ADHD treatment in the past. Seventy-six percent (75/99) of those diagnosed with Adult ADHD on the MINI had never received the diagnosis previously, and 17.2% had received ADHD treatment in the past. Of the patients who had received previous ADHD diagnoses, 25% were diagnosed in childhood.
Conclusions: The prevalence of lifetime ADHD was higher in our anxiety disorders clinic sample than that found in the general population. Individuals with ADHD had more severe OCD, depressive, generalized anxiety, and disability symptoms than those without ADHD. Despite meeting DSM-IV criteria for lifetime ADHD, most patients in this sample had never been diagnosed or treated. The presence of comorbid ADHD appears to have a significant impact on the severity and impact of comorbid anxiety disorders.

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Eur Neuropsychopharmacol. 2012;22:S426-S427.
Treatment adherence and parents' characteristics in children with attention deficit hyperactivity disorder.
Lee S, Seo H, Lim H, et al.
Objective: The importance of early medication adherence in Attention Deficit Hyperactivity Disorder (ADHD) is being emphasized due to the benefit in reducing the development of comorbid mental health conditions and the sequelae from poor academic outcomes. Considering patients' ages, parents'

understanding and attitude to the disorder and medication may significantly influence on the treatment adherence in ADHD. This study was conducted to find out parents' factor associated with adherence to treatment in ADHD children.
Methods: 271 School-aged children (6-18 years) diagnosed with ADHD according to Diagnostic and Statistical manual of Mental Disorders (DSM-IV) criteria were included in this study. They were classified into 2 groups according to their adherence to treatment with long acting methylphenidate; early dropout group (N = 117, treatments discontinue within 3 months) and continuous treatment group (N = 154, treatments continue more than 3 months). Child Behavior Checklist (CBCL), Personality Inventory for Children (PIC), Minnesota Multiphasic Personality Inventory (MMPI), Parenting Sense of Competence (PSOC), Parenting Stress Index-Short Form (PSI-SF), and Parental Acceptance Rejection Questionnaire (PARQ) were applied to parents of the participants and compared between two groups with controlling for severity of ADHD symptoms.
Results: The mean age of the participants was 10.6 years and majority of the samples was male (81%). The mean educational year of mother and father was 12.8 and 13.4 years, respectively. There was no significant difference in socioeconomic data between early dropout group and continuous treatment group except for more male in continuous treatment group (85.1% vs. 75.2%, P = 0.044). When comparing PIC between two groups with controlling for gender and severity of ADHD symptoms, we found that the parents of early dropout group considered their children had a higher tendency of 'somatization' and 'delinquency' compared with those of continuous treatment groups (P = 0.048 and 0.046, respectively), but there was no difference in 'depression', 'anxiety' and 'hyperactivity' subscales. Comparing MMPI data revealed that the parents of early dropout group had the higher scores of 'Hypochondriasis' and 'Psychasthenia' subscales in MMPI compared with those of continuous treatment groups (P = 0.024 and 0.017, respectively). The parents of early dropout group perceived lower sense of parenting competence than those of continuous treatment groups (P = 0.047). However, we found no significant difference between the two groups in parenting stress and parental acceptance and rejection attitude.
Conclusion: In the current study, we found that the parents of early dropout group may have the characteristics of high anxiety and somatization tendency and consider their children's symptoms as somatization or delinquency. They may also have low competence in parenting and these variables all may be attributable to hesitancy in sticking to their decision of initiating treatment. Our findings suggested that parents' characteristics and perspectives on children's symptoms could be possible factors associated with treatment adherence in ADHD. Further recognition and researches on these issues may provide opportunities to improve treatment adherence in children with ADHD.

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Eur Neuropsychopharmacol. 2012;22:S431-S432.
Maintenance of efficacy of lisdexamfetamine dimesylate in children and adolescents with ADHD: Randomised withdrawal design.
Coghill D, Banaschewski T, Lecendreux M, et al.
Purpose: Lisdexamfetamine dimesylate (LDX), a prodrug stimulant, was shown to be an effective, once-daily treatment for children and adolescents with attention-deficit/hyperactivity disorder (ADHD) in a 7-week, European phase 3 trial (SPD489-325) [1]. This study (SPD489-326) evaluated the long-term maintenance of efficacy and safety of LDX using a randomized-withdrawal study design.
Methods: SPD489-325 was a randomized, double-blind, placebo-controlled study that enrolled children and adolescents (aged 6-17 years) diagnosed with ADHD of at least moderate severity (baseline ADHD rating scale IV [ADHD-RS-IV] total score (greater-than or equal to)28). Patients who received (greater-than or equal to)4 weeks of doubleblind treatment, reached visit 4, and completed the 1-week posttreatment washout in SPD489-325 were assessed for entry into SPD489-326, where they received open-label LDX (30, 50, or 70 mg/day). Patients from US sites were evaluated for direct entry into SPD489-326. After (greater-than or equal to)26 weeks of open-label LDX, patients whose responder status was confirmed during a fixed-dose, 2-week period, were randomized (1:1) to continue receiving their optimal dose of LDX, or to switch to placebo, for a 6-week, doubleblind, randomized-withdrawal period (RWP). The primary efficacy outcome was the proportion of patients meeting treatment failure criteria during the RWP ((greater-than or equal to)50% increase in ADHD-RS-IV score and (greater-than or equal to)2-point increase in

Clinical Global Impression-Severity of Illness rating). Secondary efficacy outcomes included maintenance of efficacy during the open-label phase (OLP), as assessed using ADHD-RS-IV and Clinical Global Impression-Improvement (CGI-I). Safety and tolerability assessments included treatmentemergent adverse events (TEAEs) and vital signs.
Results: Of 276 patients enrolled in the OLP, 157 (LDX, n = 78; placebo, n = 79) were randomized in the RWP and 76 (LDX, n = 60; placebo, n = 16) completed the RWP. At endpoint of the RWP, the proportion (95% CI) of patients meeting treatment failure criteria was greater for placebo [67.5% (57.1, 78.0)] than for LDX [15.8% (7.6, 24.0)] (p<0.001). The majority of treatment failures occurred within the first 2 weeks of the RWP (LDX, 6/12; placebo, 39/52). At endpoint of the OLP, the mean change (95% CI) from baseline in ADHD-RS-IV total score was -26.6 (-28.0, -25.2) (p<0.001); 79.8% (95% CI, 74.9, 84.7) of patients showed improvement (CGI-I of 1 or 2). During the RWP, TEAEs were reported in 31/78 (39.7%) and 20/79 (25.3%) of patients receiving LDX and placebo, respectively. No serious TEAEs were reported during the RWP; one patient receiving placebo reported a TEAE leading to discontinuation of study drug. During the OLP, TEAEs with an incidence >10% were decreased appetite (27.5%), headache (21.0%), decreased weight (16.7%), nasopharyngitis (15.6%), anorexia (14.9%), insomnia (14.1%) and vomiting (11.6%). Serious TEAEs occurred in 12/276 (4.3%) patients; 45/276 (16.3%) patients reported TEAEs leading to discontinuation of LDX.
Discussion: In children and adolescents with ADHD treated for at least 26 weeks with LDX, continued LDX treatment was associated with maintenance of efficacy compared with placebo. The rapid return of symptoms after discontinuation of LDX demonstrates the need for continued treatment. The safety profile of LDX during the OLP was generally consistent with that of stimulant therapy, and there were no concerning trends during the RWP.

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Eur Neuropsychopharmacol. 2012;22:S415.

METHYLPHENIDATE-OSMOTIC RELEASE ORAL DELIVERY SYSTEM REDUCES PARENTING STRESS IN PARENTS OF CHILDREN AND ADOLESCENTS WITH ADHD IN KOREA.

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

Purpose: Until now, many associated changes that are actually relevant to the everyday lives of ADHD children themselves and their family members have not been investigated thoroughly [1]. The aim of the current study was to investigate how methylphenidateosmotic release oral delivery system (MPH-OROS) treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) would affect parenting stress in their parents.
Methods: Four hundred and ninety-five children and adolescents (391 boys and 104 girls), aged 7 to 18 years who met DSM-IV criteria for ADHD were recruited at 48 psychiatric outpatient clinics across South Korea. Children's symptoms, parenting stress, and parental depression [2] were assessed at baseline, week 4 and week 8 of MPH-OROS treatment using the Korean version of the DuPaul's ADHD Rating Scale (ARS), the Beck's Depression Inventory (BDI), and the Parenting Stress Index, Short Form (PSI-SF).
Results: In accordance with the result of past study [3], the total score of the ARS was decreased from baseline to week 4 and from week 4 to week 8 during treatment period. In addition, parental BDI and PSI-SF score were also significantly decreased from baseline to week 4 and from week 4 to week 8, respectively. Post-hoc comparison using the Bonferroni adjustment indicated that the changes in children's ARS and CGI-S and parental BDI and PSI-SF were significant from baseline to week 4 and from week 4 to week 8 (Table 1). (Table presented) Stepwise multiple regression analyses revealed that baseline PSI-SF score was significantly affected by baseline BDI (t = 12.985, p<0.001) and ARS scores (t = 9.155, p<0.001). These two clinical factors accounted for 29.1% and 10.4% of the total variance of baseline PSI-SF score, respectively. In addition, the decreased score in PSI-SF was significantly predicted by score changes in the ARS and PSI-SF and the sex of their children (R2=0.308, p<0.001). Tests of the individual predictors revealed that children's sex (t = 2.118, p = 0.035) and the score changes in the BDI (t = 10.276, p<0.001) and the ARS (t = 8.532, p<0.001) had significant contributions to the regression equation.

Conclusions: We suggest that the increased parenting stress and depression in parents of children and adolescents with ADHD can be improved following the treatment of their children.

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Eur Neuropsychopharmacol. 2012;22:S422.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN EARLY CHILDHOOD.

Cak HT, Gokler B, Oktem F, et al.

Objective: ADHD is a neurodevelopmental disorder characterized with persistent symptoms of inattention, impulsivity or hyperactivity outside the expected range for typically developing individuals. ADHD diagnosis is still most commonly made in middle childhood. However recently, there has been a noticeable increase in the number of preschool children diagnosed and treated for ADHD in early childhood. The aim of the study is to determine age-specific behavioral and cognitive characteristics of ADHD symptoms, distribution of ADHD symptoms and comorbid disorders of early childhood ADHD and their frequencies.

Method: 21 children, aged between 4-6 years old, admitted to Hacettepe University Child and Adolescent Psychiatry Outpatient Clinic and diagnosed as ADHD were enrolled to form the study group. 25 children admitted to the Hacettepe University Pediatric Outpatient Clinic with no psychopathology identified, matched for age, gender, socioeconomic status and parental education were enrolled to form the control group. Children with any kind of chronic or neurological disease, mental retardation, attending any kind of special education program, and who could not complete the psychiatric assessments required, were excluded from the study. All 46 children were evaluated with Stanford-Binet V Intelligence Scale and computer based Conners' Continuous Performance Test for Windows(registered trademark): Kiddie Version (K-CPT). Parents were asked to fill Sociodemografic Data Form, Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF), and Conners' Parent Rating Scale (CPRS). Parents and children were also interviewed with Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL).

Results: Mean age of the whole study group was 60 months. The study and the control group did not significantly differ for sociodemograpfic features such as parental age and occupation, parental health status, pregnancy and birth history and motor and mental development history. In the ADHD group, male to female ratio was 6/1 and the comorbidity rate was 76%. Most common comorbid psychiatric disorders were oppositional defiant disorder (42%), enuresis nocturne (25%) and separation anxiety disorder (14%). All BRIEF and CPRS subscale scores were significantly higher in the ADHD group. Omissions, hit reaction time standard error, variability of standard errors, hit reaction time inter-stimulus interval change and hit standard error inter-stimulus interval change scores were significantly higher in the ADHD group in K-CPT results. Mean IQ scores on Stanford-Binet V Intelligence Scale were 98 and 109 for the study and the control groups respectively. Children in the ADHD group scored significantly lower on the cognition, visio-spatial processing and working memory subscales on Stanford-Binet V Intelligence Scale. All CPRS subscale scores were correlated with BRIEF inhibit scale scores. CPRS oppositional subscale scores were correlated with BRIEF inhibitory self-control index, flexibility index and global executive composite. CPRS cognitive problems/inattention subscale scores were correlated with BRIEF emergent metacognition index and global executive composite. CPRS hyperactivity subscale scores were correlated with BRIEF inhibitory self-control index. When compared for gender in the ADHD group only CPRS hyperactivity subscale score were significantly higher for boys. There were no significant differences in any subtest scores when compared for the presence of psychiatric comorbidity in the ADHD group.

Conclusions: These findings confirm the validity of the diagnosis of ADHD using K-SADS-PL in early childhood, supported by the neurocognitive profiles. Moreover preschoolers with ADHD seem to show similar neurocognitive impairment patterns as school age children and adolescent with ADHD.

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Eur Neuropsychopharmacol. 2012;22:S435.

ADULT OUTCOME OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CONTROLLED 16-YEAR FOLLOW-UP STUDY.

Biederman J, Petty C, Faraone SV.

Purpose: The main purpose of this long term, 16-year follow-up study was to estimate the burden of psychopathology and functional impairments associated with ADHD into adulthood, and to investigate whether the morbidity of ADHD is due to ADHD or its associated psychiatric comorbidity. We tested the hypothesis that participants who had ADHD in childhood would manifest greater impairment and dysfunction in adulthood when compared with non-ADHD controls of the same age and sex. We further hypothesized that patterns of impairments in ADHD children grown up would be independent of psychiatric comorbidity. To the best of our knowledge, this is one of the most comprehensive and longest follow-up studies of children with ADHD reaching adult years.

Method: This was a case-control, 16-year (15-19 years) prospective follow-up study of ADHD. Subjects were derived from a longitudinal case-control family study of Caucasian boys 6-17 years with (N = 140) and without (N = 120) DSM-III-R ADHD ascertained from pediatric and psychiatric clinics. At baseline, subjects were 6-18 years old. At the 16-year follow-up, 79 (56%) and 90 (75%) of the ADHD and control children, respectively, were re-assessed (mean age 27.4 years). The main outcome measures were structured diagnostic interviews, and measures of psychosocial, educational, and neuropsychological functioning.

Results: At the 16-year follow-up, subjects with ADHD continued to significantly differ from controls in lifetime rates of antisocial, mood, anxiety, and addictive disorders, but with the exception of a higher interval prevalence of anxiety disorders (20% versus 8%, z = 2.32, p = 0.02) and smoking dependence (27% versus 11%, z = 2.30, p = 0.02), the incidence of individual disorders in the six year interval between the current and prior follow-up did not differ from controls. At follow-up, compared with controls, the ADHD subjects were significantly more impaired in psychosocial, educational, and neuropsychological functioning, differences that could not be accounted for by active comorbid psychopathology.

Conclusion: This 16-year follow-up found that ADHD boys grown up were at higher risk than controls for a wide range of adverse psychosocial, educational, occupational and cognitive outcomes, even after controlling for psychiatric comorbidity. ADHD boys grown up had statistically indistinguishable rates of antisocial, mood and alcohol and drug addictions in the sixyear interval since their prior assessment, compared with age and sex compared with age and sex matched controls. These longterm prospective findings provide further evidence for the high morbidity associated with ADHD across the lifecycle, stressing the importance of early recognition of this disorder for prevention and early intervention strategies. These results indicate that the many impairments associated with ADHD in adult life are due to ADHD itself and not to associated psychiatric disorders. The consistency in findings between these prospective results with those derived from retrospective studies of adults with ADHD [1] and [2], strongly support the syndromatic continuity between pediatric and adult ADHD.

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Eur Neuropsychopharmacol. 2012;22:S421-S422.

METHYLPHENIDATE EFFECTS ON SOCIAL FUNCTIONING IN CHILDREN WITH ADHD.

Carucci S, Anchisi L, Ambu G, et al.

Background: Although their interest in social relations, ADHD children show problems to attune their behavior to other people and to the environment, apparently presenting a deficit of comprehension of the consequences of their behaviors to other. These features may show some overlap with Autism Spectrum Disorders (ASD) symptoms, such as lack of reciprocity. Recent literature suggests that Methylphenidate (MPH) can improve joint attention initiations, self-regulation, and regulated affective state, consequently having positive effects on social behaviors.

Objectives: The main aim of the study was to explore, by using the Italian Version of the Social Responsiveness Scale (SRS [1]), the social functioning of a sample of ADHD children and to compare it to ASD patients and healthy controls and preliminarily investigate the effects of MPH on social impairment in the ADHD group.

Methods: SRS was administered to 234 drug-naive children aged 4-13 and IQ >70. According to DSM-IV criteria, 93 children were ADHD, 32 ASD, and 109 matched Children with Typical Development (CTD). Conner's Parent Rating Scale (CPRS), C-GAS and CGI were also administered. SRS Constantino's

Symptom domains [1], and the four Grzadzinski's categories (Reciprocal Social Interaction (S), Communication (C), Restricted, Repetitive and Stereotyped Patterns of Behaviour/Interests (R) and Non-SCR [2]), were used to investigate the relation between social responsiveness and Conner's ADHD indices and dimensions. 38 ADHD patients were then treated with methylphenidate, (0.3 to 0.5 mg/kg/dose, bid or tid): SRS and CPRS administered again after 9-12 months of therapy.
Results: ADHD patients significantly differed from ASD in global impairment assessed by C-GAS (49.1(plus or minus)5.7 vs 45.6(plus or minus)5.4, p = 0.008) and in rate of comorbid diagnosis with ODD (p<0.001). SRS Total T score in ADHD and in ASD were comparable and significantly higher than CTD (p<0.001). 81.7% of ADHD showed a total SRS score >60 (ADHD+) and 18.2% <60 (ADHD-). SRS total and subscales scores in ADHD- were comparable to CTD and significantly different from ASD except for Social Awareness. ADHD+ and ASD mean scores at each SRS subscale were similar. ADHD+ Total SRS scores significantly correlated to all Conners subscales except for Psychosomatic; SRS Social Motivation did not correlate with CPRS Oppositional and Hyperactivity. ADHD+ significantly differed from CTD in all CPRS subscale, while ADHD- revealed CPRS mean scores comparable to CTD on subscales Anxious/shy, Perfectionism and Social Problems. MPH treatment for 9-12 months in the ADHD sample induced a significant improvement in total SRS score and each subscale apart from social cognition. A significant improvement was also shown in all SRS categories [2] apart from R category.
Discussion: This study highlights a significant impairment in social responsive behavior in ADHD children and adolescents. A subgroup of ADHD patients shows a SRS profile similar to ASD: in these patients methylphenidate appears affective not only on CPRS-measured ADHD symptoms but also on SRSmeasured social impairment. This confirm the opportunity of considering a ADHD as a complex disorder, with the deficit in social responsiveness as a specific targets for a comprehensive therapeutic intervention.

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Eur Neuropsychopharmacol. 2012.

MR IMAGING OF THE EFFECTS OF METHYLPHENIDATE ON BRAIN STRUCTURE AND FUNCTION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schweren LJS, De Zeeuw P, Durston S.

Methylphenidate is the first-choice pharmacological intervention for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The pharmacological and behavioral effects of methylphenidate are well described, but less is known about neurochemical brain changes induced by methylphenidate. This level of analysis may be informative on how the behavioral effects of methylphenidate are established. This paper reviews structural and functional MRI studies that have investigated effects of methylphenidate in children with ADHD. Structural MRI studies provide evidence that long-term stimulant treatment may normalize structural brain changes found in the white matter, the anterior cingulate cortex, the thalamus, and the cerebellum in ADHD. Moreover, preliminary evidence suggests that methylphenidate treatment may normalize the trajectory of cortical development in ADHD. Functional MRI has provided evidence that methylphenidate administration has acute effects on brain functioning, and even suggests that methylphenidate may normalize brain activation patterns as well as functional connectivity in children with ADHD during cognitive control, attention, and during rest. The effects of methylphenidate on the developing brain appear highly specific and dependent on numerous factors, including biological factors such as genetic predispositions, subject-related factors such as age and symptom severity, and task-related factors such as task difficulty. Future studies on structural and functional brain changes in ADHD may benefit from inclusion strategies guided by current medication status and medication history. Further studies on the effects of methylphenidate treatment on structural and functional MRI parameters are needed to address unresolved issues of the long-term effects of treatment, as well as the mechanism through which medication-induced brain changes bring about clinical improvement.

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Eur Neuropsychopharmacol. 2012;22:S431.

CLINICAL EFFICACY OF LISDEXAMFETAMINE DIMESYLATE IN CHILDREN AND ADOLESCENTS WITH ADHD: A POST-HOC ANALYSIS.

Zuddas A, Banaschewski T, Lecendreux M, et al.

Purpose: Lisdexamfetamine dimesylate (LDX), a long-acting prodrug stimulant, was shown to be an effective, once-daily treatment for children and adolescents diagnosed with at least moderately symptomatic attention-deficit/hyperactivity disorder (ADHD) in a phase 3 trial in Europe (SPD489-325) [1]. Patients treated with LDX showed significantly greater improvement in ADHD core symptoms than placebo, as indicated by a decrease in ADHD Rating Scale version IV (ADHD-RS-IV) score. This post-hoc analysis assessed the proportion of patients showing a clinical response at each study visit.

Methods: In this 7-week, multicentre, double-blind, parallelgroup, dose-optimized study, children and adolescents (6-17 years) with ADHD were randomized (1:1:1) to a once-daily dose of LDX (30, 50, or 70 mg), osmotic-release oral-system methylphenidate (OROS-MPH, 18, 36, or 54 mg; reference arm) or placebo. ADHD-RS-IV total score was assessed at weekly, onsite visits with reference to baseline. Endpoint was the last ontreatment, post-randomization visit at which a valid ADHD-RSIV total score was observed. In this post-hoc analysis, clinical response was predefined as (greater-than or equal to)25% or (greater-than or equal to)30% reduction from baseline in ADHD-RS-IV total score. P values were based on a Cochran-Mantel-Haenszel test controlling for country and age group. Number needed to treat (NNT) to achieve one responder was calculated as the inverse of the difference in proportions between the active treatment and placebo.

Results: Of 336 patients randomized, 196 completed the study. At baseline, mean (SD) ADHD-RS-IV total scores were similar across treatment groups [LDX, 40.7 (7.3); placebo, 41.0 (7.1); OROS-MPH, 40.5 (6.7)]. At endpoint, differences between LDX and placebo in the percentages of patients (95% CI) with (greater-than or equal to) 25% or (greater-than or equal to) 30% reduction in ADHD-RS-IV total score from baseline were 62.0 (51.6, 72.4; p<0.001; NNT, 2) and 65.7 (55.5, 75.9; p<0.001; NNT, 2), respectively. Differences between LDX and placebo in the proportions of patients (95% CI) with (greater-than or equal to)25% or (greater-than or equal to)30% reduction in ADHD-RS-IV total score from baseline were significant by the first on-treatment visit [(greater-than or equal to)25% reduction, 30.0 (17.7, 42.2), p<0.001, NNT, 4; (greater-than or equal to)30% reduction, 26.9 (15.0, 38.9), p<0.001, NNT, 4] and every visit thereafter. At endpoint, differences between OROS-MPH and placebo in the percentages of patients (95% CI) with (greater-than or equal to)25% or (greater-than or equal to)30% reduction in ADHD-RS-IV total score from baseline were 44.9 (32.8, 57.1; p<0.001; NNT, 3) and 47.8 (35.9, 59.7; p <0.001; NNT, 3), respectively. Differences between OROS-MPH and placebo in the proportions of patients (95% CI) with (greater-than or equal to)25% or (greater-than or equal to)30% reduction in ADHD-RS-IV total score from baseline were significant by the first on-treatment visit [(greater-than or equal to)25% reduction, 13.0 (1.4, 24.7), p<0.05, NNT, 8; (greater-than or equal to)30% reduction, 13.1 (1.9, 24.2), p<0.05, NNT, 8) and every visit thereafter.

Conclusions: LDX was more effective than placebo in improving core symptoms in children and adolescents with ADHD, as assessed by the proportions of patients with (greater-than or equal to)25% or (greater-than or equal to)30% reductions in ADHD-RS-IV total score from baseline at each study visit. Improvements in ADHD core symptoms were also observed for OROS-MPH.

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Eur Neuropsychopharmacol. 2012;22:S415-S416.

OBESITY IS ASSOCIATED WITH NON-RESPONSE TO PROLONGED-RELEASE METHYLPHENIDATE TREATMENT IN ADHD.

Yook KH, Kim YW, Suh HS.

Purpose: Attention-deficit/hyperactivity disorder (ADHD) is a common, life-long condition associated with major functional impairment, and remission is the primary goal of treatment. Osmotic release oral system (OROS)-methylphenidate (MPH) has been recommended as the first line treatment modality for ADHD We examined whether clinical characteristics become potential predictors of clinical response to OROS-MPH in children and adolescents with ADHD.

Methods: 90 children and adolescents, 6-15 years old, diagnosed with ADHD according to the Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version-Korean Version were included in this study. It is an 8-week, open-label trial of OROS-MPH. The subjects were assessed using the ADHD Rating Scale, Korean version (KARS), Conners parent rating scale, Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), and the Barkley Stimulant Side Effect Rating Scale at baseline, 1, 2, 4, and 8 weeks of OROS-MPH trial. They were evaluated for IQ with Wechsler Intelligence Scale for Children (K-WAIS-III) at baseline. The subjects were titrated to the next dose level at the investigators' discretion (up to 54 mg). The definition of drug responder used in this study was much or very much improvement on the CGI plus > 30% reduction in symptoms on the K-ARS at 8 week of the trial. We examined the differences in the clinical characteristics between responders and non-responders.
Results: The response rate at 8 week of this trial was 80.2% (N = 73). At the end of the 8 week study, there was statistically difference in the reduction of the K-ARS score between responders and non-responders groups (Responders; 22.1(plus or minus)7.8, Nonresponders; 13.2(plus or minus)6.2, p = 0.00) Reduction in the CGI-S score was statistically different for responders and non-responders groups (Responders; 2.2(plus or minus)0.8, Non-responders 1.0(plus or minus)0.6, p = 0.00). No differences were observed in the age, sex, severity of ADHD symptoms, IQ, comorbidities at baseline, or doses of OROSMPH at each evaluation point between the two groups. There were statistical differences in weight and body mass index (BMI) between the two groups (p = 0.00). The non-responders had higher BMI at baseline than the responders. The responders were more likely to have more side effects at first week of trial.
Conclusion: Some study suggests that the impulsivity and poor behavioral regulation in patients with ADHD may lead to the development of eating patterns that put youth at increased risk for obesity. Impulsivity and delay dissatisfaction as behavioral manifestations of ADHD may also play an important role in the relationship between ADHD and overweight and obesity. Nonresponder group in our study is more likely to has obesity and high BMI. Non-responder group may be more impulsive and poorly regulates their eating behavior. At initial treatment period of OROS-MPH, responders may experience more side effects. Responders may have to tolerate side effects of OROS-MPH.

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Eur Neuropsychopharmacol. 2012;22:S374-S375.

THE FREQUENCY OF ANXIETY DISORDERS IN PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Karamustafalioglu K, Sertcelik S, Bakim B, et al.

Purpose of the study: This is a cross-sectional study designed to assess the frequency of adult anxiety disorders in parents of children between 6 and 12 years old with attention deficit hyperactivity disorder (ADHD) and parents of non-ADHD children.
Methods used: 132 parents (67 mothers and 65 fathers) of 90 ADHD children aged between 6 and 12 years, and 67 parents (34 mothers and 33 fathers) of 45 non-ADHD children aged between 6 and 12 years, were recruited. All children were assessed by child psychiatrists using Conners' teacher and parent rating scales adapted for DSM-IV. Control parents were matched to parents of ADHD children according to age, gender and educational status. The Spielberger State Trait Anxiety Inventory was administered to the participants. SCID-I/CV (Structured Clinical Interview for DSM-IV Axis I Disorder, Clinical Version) was used to evaluate the psychopathology in probands and control parents.
Summary of results containing real data and Appropriate statistical assessments: The rate of generalized anxiety disorder was significantly higher among parents of ADHD children compared to the control group (25.0% vs 6.0%) (p = 0.001); it was significantly higher among mothers of ADHD children compared to control mothers (32.8% vs 8.8%) (p = 0.006). The rate of simple fobia was significantly higher among mothers of ADHD children compared to control mothers (41.8% vs 17.6%) (p = 0.015). In parents of ADHD children, the rates of generalized anxiety disorder (32.8% vs 16.9%) (p = 0.045) and simple fobia (41.8% vs 18.5%) (p = 0.004) were significantly higher among mothers than among fathers. The rates of repeating a year in school (19.7% vs 7.5%) (p = 0.025) and having trouble with the police (11.4% vs 3.0%) (p = 0.046) were significantly higher among parents of ADHD children than in the control group.

Conclusions: In a family study of girls with DSM-III-R ADHD, Faraone found the rate of generalized anxiety disorder to be 9% in proband's parents and siblings and 3% in a control group (p = 0.005) [1]. In a family study of boys with DSM-III-R ADHD, Biederman found the rate of generalized anxiety disorder to be 15% in proband's parents and siblings and 5% in a control group (p = 0.000) [2]. Our study is the first family study to use the DSM-IV-TR ADHD criterion. In another study by Faraone, the relatives of ADHD probands were more likely to have required extra help in school and to have been placed in special classes than relatives of normal children [3]. The rate of generalized anxiety disorder was significantly higher among parents of ADHD children than in the control parent group. In parents of ADHD children, the rates of generalized anxiety disorder and simple fobia were significantly higher among mothers than among fathers. In view of our findings, assessing anxiety disorders in patients having a child with ADHD is important for treatment and prognosis. Parents of children with ADHD might have a history of criminal behavior.

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Eur Neuropsychopharmacol. 2012;22:S428-S429.

TC-99M TRODAT BRAIN SPECT CHANGES IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AFTER 2 MONTHS OF METHYLPHENIDATE THERAPY.

Ozek H, Akay A, Kaya Capa G, et al.

Tc-99m TRODAT-1 has high affinity and specifity as an agent for presynaptic DAT in the striatum dopamine nerve terminal. Effectivity of Tc-99m TRODAT-1 for assessment of the existence of DAT in striatum was determined in most of the previous studies. Tc-99m TRODAT-1 brain SPECT studies found various results. Although some studies found increase of DAT receptor attachment in patients with attention deficit hyperactivity disorder (ADHD) compared to the normal controls, some of them did not find any increase. Methylphenidate as first line treatment of ADHD blockades DAT receptors strongly. In Tc-99m TRODAT-1 brain SPECT studies, some patients had more frequent DAT attachment compared to the controls and these results hypothesized that the response to stimulants was related to DAT attachment. Purpose: The aim of this study is to assess Tc-99m TRODAT-1 brain SPECT changes in adolescents with ADHD after 2 months methylphenidate (MPH) therapy. Method: Eighteen adolescents aged between 13-18 years, diagnosed with ADHD participated in the study. None of them had comorbid neurological disease or psychiatric disorders other than oppositional defiant disorder. All patients were right handed. ADHD diagnoses were made by two experienced child psychiatrists, based on ADHD criteria listed in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). For inclusion of the patients in this study, K-SADS-PL semistructured clinical interview was carried out and ADHD diagnosis should be confirmed and CGI-ADHD-severity scale should be (greater-than or equal to)3 at visit 1. DuPaul ADHD Questionnaire and Conner's Teacher Rating Scale-Short Form were used. Tc-99m TRODAT-1 was obtained by the Institute of Nuclear Energy Research (INERTaipei, Taiwan). Regions of interest (ROIs) were drawn on the right basal ganglia, left basal ganglia and the localization of cerebellum as the background. The two consecutive transverse slices showing the highest uptake in the basal ganglia were selected. Mean counts per pixel were used. While comparing cerebellar activity, mean corrected activity in the basal ganglia was calculated as follows: (basal ganglia - background)/background. Before and after treatment, the results of clinical parameters and striatal DAT density in patients diagnosed with ADHD were compared analysis of Wilcoxon test. Results: There was a statistically significant decrease in pretherapy availability of DAT assessed by brain SPECT and after 2 months MPH treatment in both right and left basal ganglia (pre; 1.23(plus or minus)0.29 and post; 0.49(plus or minus)0.36, p = 0.000, for right, pre; 1.15(plus or minus)0.27 and post; 0.49(plus or minus)0.35, p = 0.000 for left). The mean score on the CGI was 5.1(plus or minus)0.6 (range: 4-6) at baseline, 3.4(plus or minus)1.0 (range: 2-5) at the second visit (p = 0.000 for visit 1-2). Also, there was a statistically significant improvement in behavior at the second visit, as indicated by the scores in DuPaul and Conner's Rating scales. Conclusion: The decreased availability of DAT in basal ganglia under treatment with MPH correlates well with the improvement in clinical parameter like previous studies.

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Eur Neuropsychopharmacol. 2012;22:S123-S124.

POTENTIAL BIOMARKERS AND GENETIC FINDINGS IN ADHD.

Taurines R, Renner TJ, Schecklmann M, et al.

Objectives: In absence of objective clinical characteristics, the identification of disease markers/ biomarkers in neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), is highly relevant for the diagnostic process, an individualized therapy and assessment of prognosis. After a brief overview on major genetic findings in ADHD from the literature, potential biomarker candidates are discussed.

Methods: Gene and protein expression in the blood as well as odor sensitivity analyses were performed in children and adolescents with ADHD, diagnosed according to ICD-10 criteria, in minors with another neurodevelopmental disorder - autism spectrum disorder (ASD) - and in healthy developing control subjects. mRNA expression was determined via quantitative realtime polymerase chain reaction (qRT-PCR), serum protein profiling via proteomic techniques (matrix-assisted laser desorption/ionization time of flight mass spectrometry, MALDI-ToF MS).

Results: Subjects with ADHD respectively ASD showed altered MALDI-ToF-MS peak patterns in the low molecular range (at 4.4kDa, 5.15kDa, 10.38 kDa). Children and adolescents with ADHD presented with significantly decreased DRD4-mRNA concentrations in the whole blood as well as with a lowered odor sensitivity threshold in comparison to healthy developing children.

Conclusions: Alterations in the peripheral expression of mRNA and proteins and an increased odor sensitivity as potential biomarker candidates might support an early (differential-) diagnosis and a more personalized therapy of ADHD. However, sensitivity and specificity of these potential disease markers have to be further probed in future studies comprising larger cohorts and patients with further neuropsychiatric disorders, such as e. g. affective disorders or schizophrenia.

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Eur Neuropsychopharmacol. 2012;22:S423.

ASSOCIATION BETWEEN HTR1A GENE POLYMORPHISMS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN KOREAN CHILDREN.

Lee KK, Kwon HJ, Ha MINA, et al.

Objectives: Attention deficit hyperactivity disorder (ADHD) is common disorder of the school-age population. ADHD has been shown to be familial and genetic studies estimate its heritability at 80-90%. The aim of the present study was to investigate the association between the genetic type and alleles for the HTR1A gene in Korean children with Attention deficit hyperactivity disorder.

Methods: A questionnaire was conducted with about 16,000 elementary school students in a city whose population is about 500,000 from September 2007 and August 2008. A telephone interview was performed randomly with the children whose Korean version of the Dupaul ADHD Rating Sales (K-ARS) score was 19 or higher, and 142 ADHD children who consented to the genetic study were selected. For the control group, 139 children in the same area were selected by matching the sex and age of the subjects in the patient group. For both of the patient and control groups, a clinical evaluation and the DSM-IV diagnosis were performed by child psychiatrists. The number of ADHD children was 142, including 101 boys (71.1%) and 41 girls (28.9%), and the mean age was 8.67(plus or minus)0.84. The number of the children in the control group was 139, including 93 boys (66.9%) and 46 girls (33.1%), and the mean age was 8.65(plus or minus)0.81. There was no significant difference in the sex and age between two groups. Subjects were excluded from the study if there was any evidence of conduct disorder, mood disorder, anxiety disorder, Tourette's disorder, pervasive development disorder, mental retardation (IQ<70) and neurological disorders. None of the children who participated in the study has ever undergone drug treatment. Each subject and caregivers were provided adequate counseling on the study and the associated investigations. Informed consent was obtained prior to study entry. The study was also approved by the Hospital Ethics Committee. None of the children was taking psychostimulants at the time of the study. On the day of visiting the hospital, the child psychiatrist performed a clinical interview as well as Kovac's Children's Depression Inventory, State Anxiety Inventory, Trait Anxiety Inventory and Dupaul ADHD Rating Sales (K-ARS), computerized ADS as well as completing a questionnaire survey regarding the pregnancy, infancy, developmental history and anamnesis of the children with their parents. A professional clinical psychologist

performed a comprehensive psychological test, including an intelligence test. A child psychiatrist evaluated ADHD symptoms and co-existing illnesses through personal interviews with each subject. DNA was extracted from leukocytes using a commercial DNA extraction kit, the Wizard Genomic DNA purification kit. The HTR1A SNP was genotyped by polymerase chain reaction (PCR). HTR1A rs10042486(T/C), rs1423691(T/C), rs6295(G/C), rs878567(T/C) were genotyped by Illumina, Inc. through the use of their Integrated Bead Array System. We supplied Illumina with barcoded DNA microtiter plates containing the DNA quantified with Pico Green to be at 100 ng/ml and Illumina delivered genotypes with quality scores calculated by proprietary Illumina algorithms. Genotyping methods for the Korean samples were previously reported.
Results: This study showed that there was a significant correlation among the frequencies of the rs10042486 (OR = 1.55, 95% CI = 1.02-2.30, p = 0.041), rs1423691 (OR = 1.55, 95% CI = 1.02-2.30, p = 0.041), and rs878567 (OR = 1.60, 95% CI = 1.06- 2.43, p = 0.027) of alleles of HTR1A, but the final conclusions are not definite.

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Eur Neuropsychopharmacol. 2012;22:S425-S426.

DECREASED SERUM LEVELS OF BRAIN DERIVED NEUROTROPHIC FACTOR IN ADULTS WITH ADHD.

Ramos-Quiroga J, Margarida Corominas MC, Marta Ribases MR, et al.

Purpose of the study: Brain derived neurotrophic factor (BDNF) has been hypothesized of being involved in the pathogenesis of ADHD although experimental data regarding the contribution of BDNF gene polymorphisms to this psychiatric disorder, are controversial. Recently, changes in BDNF serum levels have been reported in children with ADHD, but there are no studies about the possible role of this neurotrophin in adults. 54 caucasoid patients with combine or inattentive ADHD diagnosis (age 33.43(plus or minus)8.99 years) and 59 caucasoid unrelated healthy controls (aged 35.52(plus or minus)9.37 years), were included in a study to evaluate BDNF levels in serum.
Methods: The clinical sampled consisted of 54 caucasoid adults with ADHD recruited from the Program for adults with ADHD in the Department of Psychiatry of the Hospital Universitari Vall d'Hebron, between 2008 and 2010. All patients met the diagnostic of ADHD, according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria. Exclusion criteria for both groups included the following: 1) lifetime and current history of mood, psychotic, anxiety, substance abuse disorders or DSM-IV axis II disorders; 2) history of neurological, metabolic, cardiac or any medical illness that can interfere with the expression of BDNF; 3) IQ below 70. The control sample consisted of 59 caucasoid-unrelated adults recruited from the Blood and Tissue Bank at Hospital Universitari Vall d'Hebron, matched with the patients for sex and age and in whom DSM-IV ADHD diagnosis was excluded. The diagnosis of ADHD was evaluated the Conners' Adult ADHD Diagnostic Interview for DSM-IV and the comorbidity was evaluated with the Structured Clinical Interview for DSM-IV axis I and Axis II Dirsorders. Severity of ADHD symptoms was evaluated with the long version of the Conners' ADHD Rating, self-report. The Wender Utah Rating Scale was also used to assess retrospective symptomatology. To exclude current symptoms of depression and anxiety, often present in ADHD, patients fulfilled the Beck Depression Inventory and the State and Trait Anxiety Inventory. IQ was estimated with the Vocabulary and Block Design subtest of the Wais-III. All patients were naive of psychopharmacological treatment. The study was approved by the ethics committee of Vall d'Hebron University Hospital and written informed consent was obtained from all adult subjects, patients and controls. Medical, neurological and psychiatric comorbidities were excluded. Clinical data concerning ADHD diagnosis and blood samples for patients and controls were collected.
Results: BDNF serum levels were significantly lower in adults with ADHD compared to healthy controls ($p<0.0003$). Although the combine subgroup displayed lower BDNF serum levels than the inattentive subgroup, differences did not reach statistical significance. No significant correlations were found between serum BDNF levels and scores of CAARS subscales.
Conclusions: These results suggest a role for BDNF in ADHD at least in those patients whose disorder persists throughout life. Low BDNF levels may contribute to the neurodevelopmental deficits of ADHD and

to the persistence of the disorder into adulthood. BDNF differences between ADHD subtypes should be further studied. Our data point toward a role for the epigenetic mechanisms as inducers of the decrease of serum BDNF levels in adults with ADHD.

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Eur Neuropsychopharmacol. 2012;22:S144.

COMORBIDITY BETWEEN ADHD AND BIPOLAR DISORDER.

Yazgan Y.

One of the most controversial issues in the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD) is the cooccurence of bipolar disorder. Disordered attention, activity and speech overlap between the two disorders. In addition, children with bipolar disorder are often irritable during and between mood episodes, which can be attributed in part to presence of ADHD or oppositional defiant disorder (ODD), depression and generalized anxiety disorder, that are often comorbid with ADHD [1]. The rates of bipolar disorder in children with ADHD vary widely - from less than 2% to 23% [2] - and depend in part on how the diagnosis of bipolar disorder is made. In samples of children with bipolar disorder, the rate of ADHD has been reported to vary between 4% and 98% [1,3]. Some of the controversies associated with the identification of this comorbidity become evident with these variations in prevalence estimates. Moreover, a recognizable feature of children with ADHD is affective lability which can be challenging for the clinician. Subjective states of elation and grandiosity, the primary characteristics of mania are not readily apparent in pre-adolescent children and symptoms are expressed as extreme excitement and driven behavior. The key to the bipolar diagnosis is the episodic nature of the illness, however some cases exhibit a non-episodic chronic presentation with irritability which overlaps with symptoms of ADHD and especially ODD. This pattern of behavior, named as severe mood dysregulation, is found to predict anxiety and depression rather than being a developmental presentation of bipolar disorder [1].

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Front Syst Neurosci. 2012.

EXPLOITING THE BRAIN'S NETWORK STRUCTURE IN IDENTIFYING ADHD SUBJECTS.

Dey S, Ravishankar Rao A, Shah M.

Attention Deficit Hyperactive Disorder (ADHD) is a common behavioral problem affecting children. In this work, we investigate the automatic classification of ADHD subjects using the resting state Functional Magnetic Resonance Imaging (fMRI) sequences of the brain. We show that brain can be modeled as a functional network, and certain properties of the networks differ in ADHD subjects from control subjects. We compute the pairwise correlation of brain voxels' activity over the time frame of the experimental protocol which helps to model the function of a brain as a network. Different network features are computed for each of the voxels constructing the network. The concatenation of the network features of all the voxels in a brain serves as the feature vector. Feature vectors from a set of subjects are then used to train a PCA-LDA (principal component analysis-linear discriminant analysis) based classifier. We hypothesized that ADHD related differences lie in some specific regions of brain and using features only from those regions are sufficient to discriminate ADHD and control subjects. We propose a method to create a brain mask which includes the useful regions only and demonstrate that using the feature from the masked regions improves classification accuracy on the test data set. We train our classifier with 776 subjects, and test on 171 subjects provided by The Neuro Bureau for the ADHD-200 challenge. We demonstrate the utility of graph-motif features, specifically the maps that represent the frequency of participation of voxels in network cycles of length 3. The best classification performance (69.59%) is achieved using 3-cycle map features with masking. Our proposed approach holds promise in being able to diagnose and understand the disorder

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Front Syst Neurosci. 2012;1-10.

ADHD DIAGNOSIS FROM MULTIPLE DATA SOURCES WITH BATCH EFFECTS.

Olivetti E, Greiner S, Avesani P.

The Attention Deficit Hyperactivity Disorder (ADHD) affects the school-age population and has large social costs. The scientific community is still lacking a pathophysiological model of the disorder and there are no objective biomarkers to support the diagnosis. In 2011 the ADHD-200 Consortium provided a rich, heterogeneous neuroimaging dataset aimed at studying neural correlates of ADHD and to promote the development of systems for automated diagnosis. Concurrently a competition was set up with the goal of addressing the wide range of different types of data for the accurate prediction of the presence of ADHD. Phenotypic information, structural magnetic resonance imaging (MRI) scans and resting state fMRI recordings were provided for nearly 1000 typical and non-typical young individuals. Data were collected by eight different research centers in the consortium. This work is not concerned with the main task of the contest, i.e., achieving a high prediction accuracy on the competition dataset, but we rather address the proper handling of such a heterogeneous dataset when performing classification-based analysis. Our interest lies in the clustered structure of the data causing the so-called batch effects which have strong impact when assessing the performance of classifiers built on the ADHD-200 dataset. We propose a method to eliminate the biases introduced by such batch effects. Its application on the ADHD-200 dataset generates such a significant drop in prediction accuracy that most of the conclusions from a standard analysis had to be revised. In addition we propose to adopt the dissimilarity representation to set up effective representation spaces for the heterogeneous ADHD-200 dataset. Moreover we propose to evaluate the quality of predictions through a recently proposed test of independence in order to cope with the unbalancedness of the dataset.

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HealthMED. 2012;6:3008-11.

EFFECTS OF HYPEROXIC AIR ON SIMPLE VISUAL MATCHING TASK PERFORMANCE AND BLOOD OXYGEN SATURATION OF ADHD CHILDREN.

Choi MH, Kim HJ, Chung YS, et al.

This study attempted to identify the effect of hyperoxic air on simple visual matching task performance and blood oxygen saturation (SpO2 (%)) of Attention Deficit Hyperactivity Disorder (ADHD) children. Sixteen boys (mean age=12.8, SD=1.4 year) who were diagnosed as ADHD and are under treatment, participated in the study. Two subsets of simple visual matching tasks with similar difficulties were developed. The experiment consisted of visual matching tasks performed under two conditions: normal air (21% oxygen) and hyperoxic air (92% oxygen). The experiment consisted of three phases, which included the Adaptation phase (1 min.) after oxygen administration, the Control phase (2 min.) that maintained a stable condition before the task, and the Task phase (2 min.) that performed simple visual matching task. SpO2 was measured during all the phases. There was a significant increase in accuracy rate in the presence of 92% oxygen compared with the 21% oxygen condition. When 92% oxygen in the air was supplied, the SpO2 increased compared to that under the 21% oxygen condition. This result supports the hypothesis that hyperoxic air increase oxygen saturation level in the blood, lead to more available oxygen to the brain, thus increase cognitive performance of ADHD children.

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Hum Mov Sci. 2012.

MOTOR IMAGERY SKILLS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND DEVELOPMENTAL COORDINATION DISORDER.

Williams J, Omizzolo C, Galea MP, et al.

Up to 50% of children with ADHD experience motor impairment consistent with DCD. Debate continues as to whether this impairment is linked to inattention or is a genuine motor deficit. This study aimed to determine whether (1) inattention was greater in ADHD + DCD than in ADHD alone and (2) motor imagery deficits observed in DCD were present in ADHD + DCD. Four groups aged 7-12 years-ADHD, combined type, with motor impairment (ADHD + DCD; N = 16) and alone (ADHD; N = 14), DCD (N = 10) and typically

developing comparison children (N = 18) participated. Levels of inattention did not differ between ADHD groups. On an imagined pointing task, children with DCD did not conform to speed accuracy trade-offs during imagined movements, but all other groups did. However, on a hand rotation task, both the ADHD + DCD and DCD groups were less accurate than the non-motor impaired groups, a finding not explained by differences in IQ, age, or working memory capacity. Overall, there was evidence that children with ADHD + DCD experience genuine motor control impairments indicating the impact of motor impairment in ADHD and its causal risk factors require more study. Motor impairment in ADHD should not be dismissed as a by-product of inattention.

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Int J Behav Dev. 2012 Nov;36:413-19.

SUSTAINED ATTENTION AT AGE 5 PREDICTS ATTENTION-RELATED PROBLEMS AT AGE 9.

Martin A, Razza RA, Brooks-Gunn J.

This study tested whether two aspects of sustained attention (focused attention and lack of impulsivity) measured at child age 5 predicted attention problems reported by mothers and teachers at age 9. Because lack of impulsivity reflects the executive control network, and ADHD is commonly characterized as a deficit in executive function, it was expected to have more predictive power than focused attention. Data were drawn from the Fragile Families and Child Wellbeing Study. Focused attention and lack of impulsivity, measured in a laboratory task at age 5, were equally predictive of attention problems at age 9, including the mother's report of whether the child had been diagnosed with ADHD. However, age 9 teacher-reported hyperactivity was not predicted by focused attention, and only marginally predicted by lack of impulsivity. Results complement an earlier study by Razza, Martin, and Brooks-Gunn showing that both focused attention and lack of impulsivity at age 5 predicted children's approaches to learning at age 9.

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J Abnorm Psychol. 2012 Nov;121:922-35.

CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND GROWTH IN ADOLESCENT ALCOHOL USE: THE ROLES OF FUNCTIONAL IMPAIRMENTS, ADHD SYMPTOM PERSISTENCE, AND PARENTAL KNOWLEDGE.

Molina BSG, Pelham WEJr, Cheong J, et al.

Research on the relation between childhood attention-deficit/hyperactivity disorder (ADHD) and adolescent alcohol use has found mixed results. Studies are needed that operationalize alcohol use in developmentally appropriate ways and that test theoretically plausible moderators and mediators in a longitudinal framework. The current study tested childhood ADHD as a predictor of alcohol use frequency at age 17 and age-related increases in alcohol use frequency, through adolescence for 163 adolescents with ADHD diagnosed in childhood and 120 adolescents without ADHD histories. Childhood ADHD did not predict either alcohol outcome. However, parental knowledge of the teen's friendships, activities, and whereabouts moderated the association such that childhood ADHD predicted alcohol use frequency at age 17 when parental knowledge was below median levels for the sample. Mediational pathways that explained this risk included social impairment, persistence of ADHD symptoms, grade point average, and delinquency. Social impairment was positively associated with alcohol use frequency through delinquency; it was negatively associated with alcohol use frequency as a direct effect independent of delinquency. These nuanced moderated-mediation findings help to explain previously inconsistent results for the ADHD-adolescent alcohol use association. The findings also imply that future research and intervention efforts should focus on ADHD-related social and academic impairments as well as symptom persistence and parenting efforts.

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J Abnorm Psychol. 2012 Nov;121:1011-23.

DOUBLE DISSOCIATION BETWEEN LAB MEASURES OF INATTENTION AND IMPULSIVITY AND THE DOPAMINE TRANSPORTER GENE (DAT1) AND DOPAMINE D4 RECEPTOR GENE (DRD4).

Gizer IR, Waldman ID.

Studies examining the biological and neuropsychological processes underlying attention-deficit/hyperactivity disorder (ADHD) suggest that error indices from the A-X Continuous Performance Test (A-X CPT) might represent useful endophenotypes for ADHD. The current study extended such findings by evaluating the utility of these putative endophenotypes in the context of a molecular genetic study. One hundred and forty-eight clinic-referred ADHD probands and 56 siblings were recruited as part of an ongoing study. Between- and within-family tests of association were conducted to test for relations between polymorphisms in two candidate genes, the dopamine transporter gene (DAT1) and the dopamine D4 receptor gene (DRD4), and indices of inattention and impulsivity derived from the A-X CPT. Association analyses of these polymorphisms with the A-X CPT indices suggested a double dissociation such that an index of inattention was associated with DRD4 but not DAT1, and an index of impulsivity was associated with DAT1 but not DRD4. Further analyses suggested that an A-X CPT index of impulsivity partially mediated previously observed associations between hyperactive-impulsive ADHD symptoms and DAT1. Additionally, an A-X CPT index of inattention moderated the relation between inattentive ADHD symptoms and DRD4 such that children with high levels of the endophenotype showed a stronger association between inattentive symptoms and DRD4. The potential utility of endophenotypes derived from the A-X CPT in molecular genetic studies of ADHD is discussed.

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Journal of Attention Disorders. 2012 Nov;16:685-96.

EFFECTS OF SYMPTOMS OF ADHD, ODD, AND COGNITIVE FUNCTIONING ON SOCIAL ACCEPTANCE AND THE POSITIVE ILLUSORY BIAS IN CHILDREN.

Scholtens S, Diamantopoulou S, Tillman CM, et al.

Objective: To examine the effects of symptoms of ADHD and ODD and cognitive functioning on social acceptance and positive bias in children.

Method: The sample consisted of 86 children (49 girls) between 7 and 13 years old, recruited to reflect a wide range of ADHD symptoms. Parents and teachers reported on ADHD and ODD symptoms and social acceptance. Children reported on social acceptance and were given tasks measuring working memory, inhibition and reaction-time variability. A discrepancy score between child and adult reports of social acceptance was used as a measure of positive bias.

Results: Inattention independently explained variance in social acceptance. The cognitive factors were related to social acceptance and the positive bias, but not beyond the ADHD and ODD symptoms.

Conclusion: It is primarily disruptive behavior that contributes to external reports of children's social acceptance.

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Journal of Attention Disorders. 2012 Nov;16:675-84.

PUTTING FAMILIES IN THE CENTER: FAMILY PERSPECTIVES ON DECISION MAKING AND ADHD AND IMPLICATIONS FOR ADHD CARE.

Davis CC, Claudius M, Palinkas LA, et al.

Objective: To examine components of family-centered care in families' stories about treatment decision making for their child with ADHD.

Method: Twenty-eight families participated in qualitative interviews that addressed families' perspectives on (a) the treatment decision-making process, (b) the cause and impact of their child's symptoms, and (c) treatment goals and preferences.

Results: The majority of families preferred to be primary or shared decision makers regarding treatment decisions. Families' perspectives on the cause of the child's symptoms varied and often were not consistent with a biomedical framework. Families described multiple areas of impairment on child, family relationships, and family functioning. Perspectives toward evidence-based treatments were mixed, with

families also expressing interest in and pursuing interventions not delineated in current treatment guidelines.
Conclusion: These findings reinforce the importance of eliciting families' perspectives and involving these important stakeholders in shared decision making as critical components of family-centered care for children with ADHD.

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Journal of Attention Disorders. 2012 Nov;16:697-705.
TIME COURSE OF TREATMENT EFFECT OF OROS® METHYLPHENIDATE IN CHILDREN WITH ADHD.
Armstrong RB, Damaraju CV, Ascher S, et al.
Objective: The authors evaluated the time course of the treatment effect of Osmotic-Release Oral System methylphenidate (OROS® MPH) HCl (Concerta®, Raritan, NJ) CII in children with ADHD.
Method: Data were combined from two double-blind, randomized, placebo-controlled, cross-over, analog classroom studies in children (9-12 years) with ADHD. Participants received an individualized dose of placebo or OROS® MPH on two laboratory school days. Permanent Product Math Test and Swanson, Kotkin, Agler, M-Flynn, and Pelham scores were evaluated 0.5 hr before dosing and 1, 2, 4, 10, 11, and 12.5 hr post dose. Analysis used a repeated-measures mixed model.
Results: Treatment effects were present at all postdose assessment points ($p < .0001$ for all comparisons, $n = 139$). Adverse events were similar to previous reports for OROS® MPH.
Conclusion: A robust treatment effect occurred with OROS® MPH; onset was at 1 hr and persisted for at least 12.5 hr after dosing.

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J Child Adolesc Psychopharmacol. 2012;22:388-92.
ONSET OF ABNORMAL MOVEMENTS AND CARDIOVASCULAR SYMPTOMS AFTER ACUTE CHANGE IN COMPLEX POLYPHARMACY IN A CHILD WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND MOOD SYMPTOMS.
Potter O, John N, Coffey BJ.

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J Child Adolesc Psychopharmacol. 2012;22:343-52.
DOPAMINERGIC AND NORADRENERGIC GENE POLYMORPHISMS AND RESPONSE TO METHYLPHENIDATE IN KOREAN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: IS THERE AN INTERACTION?
Hong SB, Kim JW, Cho SC, et al.
Objective: We aimed to investigate the independent and interaction effects of dopamine transporter gene (DAT1), dopamine D4 receptor gene (DRD4), alpha-2A adrenergic receptor gene (ADRA2A), and norepinephrine transporter gene (NET1), with regard to treatment response to methylphenidate (MPH) in attention-deficit/hyperactivity disorder (ADHD).
Methods: The participants of the study were 103 children and adolescents (ages 9.1(plus or minus)2.1 years) diagnosed as having ADHD according to American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria. They were enrolled in an 8-week, open-label trial of MPH. The good responder group was defined as subjects having an (greater-than or equal to)50% decrease in the ADHD Rating Scale-IV (ADHD-RS) total score from the baseline, and at the same time a Clinical Global Impressions-Improvement Scale (CGI-I) score of 1 or 2, both at the 8th week of MPH treatment. Multivariate stepwise logistic regression was performed to examine the independent and interaction effects of genotypes on the dichotomized MPH treatment response.
Results: Significant interaction effects on MPH response were detected between the genotypes of the DRD4 variable number of tandem repeat (VNTR) polymorphisms and those of either the ADRA2A DraI or the NET1 -3081(A/T) polymorphisms; significant interaction effects were also detected between the genotypes of the ADRA2A DraI polymorphisms and those of either the NET1 G1287A or the NET1 -

3081(A/T) polymorphisms (Nagelkerke R 2=0.40). No significant independent effect of a genotype was detected according to the stepwise logistic regression results.
Conclusion: The results suggest that genes involved in the dopaminergic and noradrenergic systems might interact to form important predictors of short-term response to MPH.

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J Child Adolesc Psychopharmacol. 2012;22:353-63.

IMPROVING VISUAL MEMORY, ATTENTION, AND SCHOOL FUNCTION WITH ATOMOXETINE IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shang CY, Gau SSF.

Objective: Atomoxetine is efficacious in reducing symptoms of attention- deficit/hyperactivity disorder (ADHD), but its effect on visual memory and attention needs more investigation. This study aimed to assess the effect of atomoxetine on visual memory, attention, and school function in boys with ADHD in Taiwan.
Method: This was an open-label 12 week atomoxetine treatment trial among 30 drug-naive boys with ADHD, aged 8-16 years. Before administration of atomoxetine, the participants were assessed using psychiatric interviews, the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III), the school function of the Chinese version of the Social Adjustment Inventory for Children and Adolescents (SAICA), the Conners' Continuous Performance Test (CPT), and the tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB) involving visual memory and attention: Pattern Recognition Memory, Spatial Recognition Memory, and Reaction Time, which were reassessed at weeks 4 and 12.
Results: Our results showed there was significant improvement in pattern recognition memory and spatial recognition memory as measured by the CANTAB tasks, sustained attention and response inhibition as measured by the CPT, and reaction time as measured by the CANTAB after treatment with atomoxetine for 4 weeks or 12 weeks. In addition, atomoxetine significantly enhanced school functioning in children with ADHD.
Conclusion: Our findings suggested that atomoxetine was associated with significant improvement in visual memory, attention, and school functioning in boys with ADHD.

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J Child Adolesc Psychopharmacol. 2012;22:375-84.

SURVEY OF UNITED STATES CHILD AND ADOLESCENT PSYCHIATRISTS' CARDIAC SCREENING PRACTICES PRIOR TO STARTING PATIENTS ON STIMULANTS.

Leslie LK, Rodday AM, Saunders TS, et al.

Objective: The purpose of this study was to determine psychiatrists' barriers, attitudes, and practices regarding cardiac screening prior to initiating stimulants in children with attention-deficit/hyperactivity disorder.
Background: Professional and federal oversight organizations recently have debated the evidence regarding sudden cardiac death (SCD) risk with stimulants, and have published guidelines recommending cardiac screening. It is not known how psychiatrists have responded.
Methods: This study was a cross-sectional survey of 1,600 randomly-selected U.S. members of the American Academy of Child and Adolescent Psychiatry. Analyses included descriptive statistics and logistic regression.
Results: Response rate was 40%; 96% met eligibility criteria. Barriers to identifying cardiac disorders in general included ability to perform a routine physical examination (74%) and care coordination with primary care providers (35%). Only 27% agreed that SCD risk warranted cardiac assessment. Prior to starting a patient on stimulants, 95% of psychiatrists obtained a routine history. The majority either conducted (9%), or relied on primary care providers to conduct (67%) a physical examination; 26% did not obtain a physical examination. Nineteen percent of psychiatrists ordered an electrocardiogram (ECG), of those, non-mutually exclusive reasons for ordering an ECG included standard practice procedure (62%), clinical findings (27%), medicolegal considerations (25%), and guideline adherence (24%). On multivariate modeling, psychiatrists were less likely to conduct cardiac screening themselves if in private practice (referent: academic medical

center), if >50% of their patients had private insurance, or if they believed their ability to perform a physical examination to be a barrier. When modeling cardiac screening performed by any healthcare professional (e.g., psychiatrist, primary care practitioner), screening was less likely if the psychiatrist was practicing in a community mental health center (referent: academic medical center), was male, or if >50% of that psychiatrist's patients had private insurance.
Conclusion: Findings suggest the tacit interplay between primary care and psychiatry for the assessment and management of medical risks associated with psychotropic medications should be improved, and solutions prioritized.

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Journal of Child and Family Studies. 2012 Oct;21:775-87.

THE EFFECTIVENESS OF MINDFULNESS TRAINING ON BEHAVIORAL PROBLEMS AND ATTENTIONAL FUNCTIONING IN ADOLESCENTS WITH ADHD.

van de Weijer-Bergsma E, Formsma AR, Bruin EI, et al.

The effectiveness of an 8-week mindfulness training for adolescents aged 11–15 years with ADHD and parallel Mindful Parenting training for their parents was evaluated, using questionnaires as well as computerized attention tests. Adolescents (N=10), their parents (N=19) and tutors (N=7) completed measurements before, immediately after, 8 weeks after and 16 weeks after training. Adolescents reported on their attention and behavioral problems and mindful awareness, and were administered two computerized sustained attention tasks. Parents as well as tutors reported on adolescents' attention and behavioral problems and executive functioning. Parents further reported on their own parenting, parenting stress and mindful awareness. Both the mindfulness training for the adolescents and their parents was delivered in group format. First, after mindfulness training, adolescents' attention and behavior problems reduced, while their executive functioning improved, as indicated by self-report measures as well as by father and teacher report. Second, improvements in adolescent' actual performance on attention tests were found after mindfulness training. Moreover, fathers, but not mothers, reported reduced parenting stress. Mothers reported reduced overreactive parenting, whereas fathers reported an increase. No effect on mindful awareness of adolescents or parents was found. Effects of mindfulness training became stronger at 8-week follow-up, but waned at 16-week follow-up. Our study adds to the emerging body of evidence indicating that mindfulness training for adolescents with ADHD (and their parents) is an effective approach, but maintenance strategies need to be developed in order for this approach to be effective in the longer term.

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Journal of Child Psychology and Psychiatry. 2012 Nov;53:1139-48.

NEUROPSYCHOLOGICAL CORRELATES OF EMOTIONAL LABILITY IN CHILDREN WITH ADHD.

Banaschewski T, Jennen-Steinmetz C, Brandeis D, et al.

Background: Emotional lability (EL) is commonly seen in patients with attention-deficit/hyperactivity disorder (ADHD). The reasons for this association remain currently unknown. To address this question, we examined the relationship between ADHD and EL symptoms, and performance on a range of neuropsychological tasks to clarify whether EL symptoms are predicted by particular cognitive and/or motivational dysfunctions and whether these associations are mediated by the presence of ADHD symptoms.
Methods: A large multi-site sample of 424 carefully diagnosed ADHD cases and 564 unaffected siblings and controls aged 6-18 years performed a broad neuropsychological test battery, including a Go/No-Go Task, a warned four-choice Reaction Time task, the Maudsley Index of Childhood Delay Aversion and Digit span backwards. Neuropsychological variables were aggregated as indices of processing speed, response variability, executive functions, choice impulsivity and the influence of energetic and/or motivational factors. EL and ADHD symptoms were regressed on each neuropsychological variable in separate analyses controlling for age, gender and IQ, and, in subsequent regression analyses, for ADHD and EL symptoms respectively.

Results: Neuropsychological variables significantly predicted ADHD and EL symptoms with moderate-to-low regression coefficients. However, the association between neuropsychological parameters on EL disappeared entirely when the effect of ADHD symptoms was taken into account, revealing that the association between the neuropsychological performance measures and EL is completely mediated statistically by variations in ADHD symptoms. Conversely, neuropsychological effects on ADHD symptoms remained after EL symptom severity was taken into account.
Conclusions: The neuropsychological parameters examined, herein, predict ADHD more strongly than EL. They cannot explain EL symptoms beyond what is already accounted for by ADHD symptom severity. The association between EL and ADHD cannot be explained by these cognitive or motivational deficits. Alternative mechanisms, including overlapping genetic influences (pleiotropic effects) and/or alternative neuropsychological processes need to be considered.

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J Clin Psychiatry. 2012;73:1335-41.
DEVELOPMENTAL PATHWAYS FOR DIFFERENT SUBTYPES OF EARLY-ONSET BIPOLARITY IN YOUTHS.
Masi G, Mucci M, Pfanner C, et al.
Objective: Two main patterns of comorbidity have been described in bipolar disorder in children and adolescents: the first including preexisting attention-deficit/hyperactivity disorder (ADHD) and related disruptive behavior disorders and the second including anxiety disorders, namely, the association of co-occurring multiple anxiety disorders, usually predating the onset of bipolarity. This study was aimed at exploring whether ADHD and multiple anxiety disorders may exhibit different pathways to specific bipolar phenotypes.
Method: We compared 49 youths (7 to 18 years) with bipolar disorder + ADHD without anxiety, 76 youths with bipolar disorder + multiple anxiety disorders without ADHD, and 52 youths with bipolar disorder without ADHD or multiple anxiety disorders who were referred to a third-level hospital and diagnosed according to DSM-IV-TR in the period 2005-2011. Subjects were evaluated for current and lifetime Axis I psychiatric disorders by using a structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version) and followed up for at least 6 months.
Results: Compared to both patients with bipolar disorder + multiple anxiety disorders and patients with bipolar disorder without ADHD and multiple anxiety disorders, patients with bipolar disorder + ADHD without anxiety were more frequently male, were younger, had an earlier onset of bipolar disorder, had a prevalent chronic course and irritable mood, were more likely to present with a bipolar disorder not otherwise specified diagnosis, had a greater clinical severity and functional impairment, had a manic/mixed index episode, had a higher risk of conduct disorder, and were more resistant to treatments, according to the CGI-Improvement scores (P <.0001). Patients with bipolar disorder + multiple anxiety disorders were similar to those with bipolar disorder without ADHD or multiple anxiety disorders, except for a higher rate of diagnosis of bipolar II disorder, more use of antidepressants, and less use of atypical antipsychotics.
Conclusions: The presence of comorbid ADHD versus anxiety disorders is indicative of fundamental differences in the phenomenology of bipolar disorder in youth. While ADHD prior to bipolar disorder is associated with a specific bipolar phenotype, bipolar patients with multiple anxiety disorders are similar to "typical" bipolar patients.

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J Clin Psychiatry. 2012;73:1326-27.
MORE ON MOOD DISORDERS IN YOUTH.
Wagner KD.

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J Clin Psychopharmacol. 2012 Oct;32:637-44.

A RANDOMIZED, DOUBLE-BLIND STUDY OF 30 VERSUS 20 MG DEXMETHYLPHENIDATE EXTENDED-RELEASE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: LATE-DAY SYMPTOM CONTROL.

Brams M, Turnbow J, Pestreich L, et al.

The objective of this study was to evaluate the safety and efficacy of dexmethylphenidate extended-release (d-MPH-ER) 30 versus 20 mg in children with attention-deficit/hyperactivity disorder (ADHD) in a 12-hour laboratory classroom setting. In a randomized, doubleblind, 3-penod x 3-treatment, crossover study, children aged 6 to 12 years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-diagnosed ADHD previously stabilized on MPH (40-60 mg/d) or d-MPH (20-Combined score from predose to 10, 11, and 12 hours post-dose [Avg (10-4 47) compared with d-MPH-ER 20 mg (- 2 02; P = 0 002) Most common adverse events (= 3% in any group) were decreased appetite (6.1%, 4.9%, and 0%), headache (4.3%, 4 3%, and 1.9%), abdominal pain (3 7%, 3 1%, and 3.1%), and tachycardia (1.2%, 3.1%, and 0.6%) for [sub]D[/sub]-MPH-ER 30 mg, d-MPH-ER 20 mg, and placebo, respectively). Significantly greater improvement in ADHD symptoms was noted with [sub]D[/sub]-MPH-ER 30 mg compared with d-MPH-ER 20 mg at hours 10 through 12. Tolerability was comparable between doses. Dexmethylphenidate extended-release 30-mg dose may provide further benefit to patients who do not maintain optimal symptom control later in the day with d-MPH-ER 20 mg.

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J Commun Disord. 2012.

PERSONAL FM SYSTEMS FOR CHILDREN WITH AUTISM SPECTRUM DISORDERS (ASD) AND/OR ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): AN INITIAL INVESTIGATION.

Schafer EC, Mathews L, Mehta S, et al.

The goal of this initial investigation was to examine the potential benefit of a frequency modulation (FM) system for 11 children diagnosed with autism spectrum disorders (ASD), attention-deficit hyperactivity disorder (ADHD), or both disorders through measures of speech recognition performance in noise, observed classroom behavior, and teacher-rated educational risk and listening behaviors. Use of the FM system resulted in significant average improvements in speech recognition in noise for the children with ASD and ADHD as well as large effect sizes. When compared to typically functioning peers, children with ASD and ADHD had significantly poorer average speech recognition performance in noise without the FM system but comparable average performance when the FM system was used. Similarly, classroom observations yielded a significant increase in on-task behaviors and large effect sizes when the FM system was in use during two separate trial periods. Although teacher ratings on questionnaires showed no significant improvement in the average level of educational risk of participants, they did indicate significant improvement in average listening behaviors during two trial periods with the FM system. Given the significantly better speech recognition in noise, increased on-task behaviors, and improved teacher ratings of listening behaviors with the FM system, these devices may be a viable option for children who have ASD and ADHD in the classroom. However, an individual evaluation including audiological testing and a functional evaluation in the child's primary learning environment will be necessary to determine the benefit of an FM system for a particular student. Learning Outcomes: 1. The reader will be able to describe the potential benefit of FM systems for children with ASD and/or ADHD. 2. The reader will be able to identify on-task versus off-task listening behaviors in children with ASD and/or ADHD. 3. The reader will be able to explain the components of a successful pre-fit education program that may be necessary prior to fitting an FM system in children with ASD.

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J Indian Assoc Child Adolesc Ment Health. 2012;8:25-37.

STUDY OF LEVEL OF STRESS IN THE PARENTS OF CHILDREN WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Sethi S, Gandhi R, Anand V.

Background: Parents who have children with attention-deficit hyperactivity disorder (ADHD) often experience high level of stress related to caring for their children. But not much research has been conducted in this area in India. This study aimed to assess the stress of parenting children with ADHD.

Methods: This is a clinic based comparative study wherein the parents of fifty children with ADHD were compared with parents of 50 healthy children. DSM-IV diagnostic criteria for ADHD and Conner's Parent Rating Scale were administrated to diagnose and assess subtype of ADHD and the severity of ADHD respectively. Parental Stress scale (PSS) was used to examine subjective stress experienced by the parents.
Results: Parents in the case group were more stressed than in control group and the difference was statistically significant. Stress was associated with all 3 subtypes of ADHD but it was highest with combined type and least with inattentive type. Also the combined subtype was the most severe form of ADHD.
Conclusion: The results of the study highlight that the parents of children with ADHD experience immense stress. Combined subtype (CT) was the most severe form of ADHD while the inattentive subtype was the least severe one. Further CT was associated with the highest levels of stress in parents, probably because of its highest degree of severity.

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J Med Econ. 2012;15:1078-87.
IDENTIFYING PATIENT SUBGROUPS WHO BENEFIT MOST FROM A TREATMENT: USING ADMINISTRATIVE CLAIMS DATA TO UNCOVER TREATMENT HETEROGENEITY.
Erder MH, Signorovitch JE, Setyawan J, et al.
Objectives: To illustrate how claims data can be used to (1) develop outcome scores that predict response to a traditional treatment and (2) estimate the economic impact of individualized assignment to a newer treatment based on the outcome score. An example application is based on two treatments for attention deficit hyperactivity disorder (ADHD): osmotic-release oral system methylphenidate (OROS-MPH) and lisdexamfetamine dimesylate (LDX).
Methods: Adolescents with ADHD initiating OROS-MPH (n=6320) or LDX (n=6394) were selected from the MarketScan claims database. A model was developed for predicting risk of switching/augmentation with OROS-MPH using multiple baseline characteristics. The model was applied to an independent sample to stratify patients by their predicted risk and, within each stratum, risk of switching/augmentation and ADHDrelated total costs were compared between OROS-MPH and LDX patients using inverse probability of treatment weighting.
Results: The prediction model resulted in substantial stratification, showing risk of switching/augmentation with OROS-MPH ranging from 11.3-42.1%. In the two strata where OROS-MPH had highest risk of switching/ augmentation, LDX had significantly lower risk of switching/augmentation than OROS-MPH (by 7.0-8.2%) and lower ADHD-related annual total costs (by $264-$625 per patient).
Limitations: The current study has used the risk of switching/augmentation as a proxy measure for treatment efficacy to establish the prediction model. Future research using a clinical measure for ADHD symptoms is warranted to verify the findings.
Conclusions: Combining multiple patient characteristics into a predicted score for treatment outcomes with a traditional treatment can help identify subgroups of patients who benefit most from a new treatment. In this analysis, ADHD patients with a high predicted score for switching/augmentation with OROS-MPH had a lower rate of switching/augmentation with LDX. Assigning OROS-MPH and LDX treatments based on the predicted scores that are heterogeneous in a patient population may help improve clinical outcomes and the costeffectiveness of care.

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J Mental Health Policy Econ. 2012;15:119-25.
ADHD MEDICATION USE FOLLOWING FDA RISK WARNINGS.
Barry CL, Martin A, Busch SH.
Background: In 2006, the U.S. Food and Drug Administration (FDA) investigated cardiac and psychiatric risks associated with attention deficit/hyperactivity disorder (ADHD) medication use. Aims of the Study: To examine how disclosure of safety risks affected pediatric ADHD use, and to assess news media coverage of the issue to better understand trends in treatment patterns.

Methods: We used the AHRQ's Medical Expenditure Panel Survey (MEPS), a nationally representative household panel survey, to calculate unadjusted rates of pediatric ADHD use from 2002 to 2008 overall and by parents' education. We examined whether children (ages 0 to 20) filled a prescription for any ADHD medication during the calendar year. Next, we used content analysis methods to analyze news coverage of the issue in 10 highcirculation newspapers, the 3 major television networks and a major cable news network in the U.S. We examined 6 measures capturing information conveyed on risk and benefits of ADHD medication use.
Results: No declines in medication use following FDA safety warnings overall or by parental education level were observed. News media coverage was relatively balanced in its portrayal of the risks and benefits of ADHD medication use by children.
Discussion: ADHD risk warnings were not associated with large declines in medication use, and balanced news coverage may have contributed to the treatment patterns observed. Self-reported surveys like the MEPS rely on the recall of respondents and may be subject to reporting bias. However, the validity of these data is supported by their consistency with other data on drug use from other sources. Implications for Health Care Provision and Use: These findings are in direct contrast to the substantial declines in use observed after pediatric antidepressant risk warnings in the context of a news media environment that emphasized risks over benefits.

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J Neuropsychiatry Clin Neurosci. 2011;23:4-5.
POSSIBLE ADHD IN A CHILD WITH AGENESIS OF THE CORPUS CALLOSUM.
Bloom AB, Getz GE, Schofield H.
Background: Agenesis of the corpus callosum (ACC) is associated with a wide range of emotional, behavioral, and cognitive presentations. Studies have consistently demonstrated slowed processing speed, weaknesses in complex problemsolving, and typically depressed IQ scores in ACC. Furthermore, although a wide range of comorbid neuropathies occur in this population, there are limited studies examining psychiatric comorbidity beyond pervasive developmental disorders. The current clinical case presentation examines possible attantion- deficit hyperactivity disorder (ADHD) in a child with ACC. Case
History/Results: This right-handed 8-year-old girl with ACC presented to a psychiatric outpatient clinic for a neuropsychological evaluation. A clinical interview, review of available medical information, a 5-hour battery of neuropsychological tests, and behavioral rating scales completed by her mother were obtained, and data will be presented. Attention deficits were observed in this child consistent with previous studies of ACC. The patient demonstrated intact cognitive functioning in numerous areas, including academic achievement, despite overall borderline IQ. She also demonstrated impaired performance in areas of executive functioning, visual memory, visual-motor, and constructional abilities. She demonstrated limitation in terms of attention and hyperactivity/ impulsivity on objective measures, her mother's report on rating scales, and per behavioral observations.
Conclusions: Although it remains unclear whether her collection of symptoms could be completely accounted for by ACC, treatment for ADHD may be warranted. ADHD has been related to other structural changes in the brain, which pharmacological intervention has been thought to help normalize, indicating a possible place for pharmacological treatment in ACC children, as well.

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J Neuropsychiatry Clin Neurosci. 2011;23:29.
CORTICAL THICKNESS CORRELATES OF ATTENTION PROBLEMS IN A LARGE-SCALE, REPRESENTATIVE COHORT OF 4-TO 18-YEAR-OLD HEALTHY CHILDREN WITHOUT ADHD.
Ducharme S, Hudziak J, Botteron K, et al.
Background: Children with ADHD have delayed cortical maturation in the prefrontal cortex and anomalies in the right OFC.1,2 Most neuroimaging studies have compared ADHD with controls categorically. However, it remains unclear whether ADHD is a discrete disorder or on a continuum with normal attention.3
Objective: To identify cortical-thickness correlates of attention problems in healthy children.

Methods: A sample of 205 representative 4- to 18-year-old healthy children from the NIH MRI Study of Normal Brain Development database were analyzed.4 Cortical thickness was measured with automated pipelines.5-7 Attention was measured with the Attention Problems scale (AP) of the CBCL.8 AP scores were regressed against local cortical thickness (40,962 points/hemisphere), using first- and second-order linear models, while controlling for age, gender, and total brain volume. Random field-theory corrections were implemented.9
Results: In a second- order model, a negative association was found with the left dorsolateral prefrontal cortex (DLPFC). The nullage null APnull interaction analysis revealed an association with bilateral OFC, right inferior frontal gyrus (IFG), and left middle temporal gyrus. In children age 13 or less (n=127), the right OFC was negatively associated with AP, and there were negative trends with the left OFC, bilateral anterior cingulate cortex, and right IFG. In contrast, children of 13+ (n=78) had small areas of positive associations distributed in frontal, temporal, and parietal lobes.
Conclusion: Findings suggest that the left DLPFC gets proportionally thinner as AP get closer to pathological threshold. The nullage null APnull interaction is compatible with a delayed cortical maturation. Results support the conceptualization of ADHD on a continuum.

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J Neuropsychiatry Clin Neurosci. 2012;24:7.

FREQUENCY OF FAMILY HISTORY OF IDIOPATHIC DEMENTIA IN CHILDREN AND YOUNG ADULTS WITH TOURETTE SYNDROME, PERVASIVE DEVELOPMENTAL DISORDER, OR ATTENTION-DEFICIT DISORDER.

Johnson SC, Foss J, Di Vito BM, et al.

Background/Objective: A recent provocative hypothesis links Alzheimer 's disease with Fragile X and Autism (Sukol et al., Neurology 2011). This study investigates the frequency of family history by depth and serial inquiry for idiopathic dementia (ID) in a referred sample of child and young adult patients with DSM-IV confirmed Tourette Syndrome (TS), Pervasive Developmental Disorder (PDD), and Attention-Deficit Disorder (ADD), all similarly evaluated at the Institute for Developmental and Behavioral Neurology.
Method: Retrospective chart analysis of 36 TS (26 men), 92 PDD (62 men), 372 ADD (265 men) seen and diagnosed between ages 4 and 25 years.
Results: TS patients, n=7 (19%); PDD, n=24 (26%); ADD, n=82 (22%) had affected grandparent (GP) and/or greatgrandparent (GGP); in paternal line: n559; in maternal line: n=60; 6 patients had multiple affected family members (gender affected: 75 female, 44 male).
Conclusions: There is no statistically significant different frequency of affected GP or GGP in these three developmental disorders. However, in each group, the frequency exceeds the estimated 13% in persons >65 years of age (Alzheimer's Association: Alzheimer's & Dementia, 2011) and was highest in the PDD population. Whether developmental disorders are linked with dementia in affected children or their families requires further investigation.

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J Neurother. 2011;15:406-07.

LONG-TERM EFFECTIVENESS OF NEUROFEEDBACK COMBINED WITH METACOGNITIVE TRAINING FOR CHILDREN WITH ADHD: A PILOT STUDY.

Leung WS, Pei J.

Introduction Neurofeedback is an alternative treatment to alleviate the primary symptoms of Attention Deficit Hyperactivity Disorder (ADHD), including inattention, hyperactivity, and impulsivity. Several studies have shown that neurofeedback training is effective in improving behavioral functioning, but more research is still needed to help us understand how the neurofeedback training benefits students with ADHD, especially in Canadian populations. Typically, most ADHD interventions focus on managing the behaviors in students with ADHD and neglecting the intervention in optimizing the academic performance of these students. In this study, the intervention incorporated metacognitive training as a part of the neurofeedback training to address both academic and behavioral difficulties. This paper covers part of a pilot study. In this paper, a secondary data analysis approach is used to evaluate the short-term impact of a 40-session neurofeedback training program combined withmetacognitive strategies training. The goal of this paper is

to determine whether the number of ADHD traits rated by caregivers changed from pretraining to posttraining. Methods In this secondary data analysis, the existing questionnaire and computerized assessment data from the ADD Centre (Mississauga), at the pretreatment and the immediate posttreatment points was collected. The sample size was 318, and the inclusion criteria were (a) a diagnosis of ADHD/ADD, and (b) 6 to 17 years of age at the time of training, completion of 40 sessions of 1-hr neurofeedback training combined with metacognitive strategies training (typically twice a week). The training program focuses on decreasing the theta wave activity (typically 3-7Hz) and increasing the sensorimotor rhythm (typically 13-15Hz). Metacognitive training was taught for 5 to 10min during the session to learn strategies related to academic tasks. The questionnaire data, collected for all participants, were completed by caregivers and included the (a) Conner's Global Index-Parent Version, (b) Diagnostic and Statistical Manual of Mental Disorders symptom list, and (c) ADD-Q. For a subset of 110 participants, computerized assessment data was also collected: Test of Variables of Attention and IVA+Plus-Visual & Auditory Attention Testing. These computerized assessment data were then later correlated with the questionnaire data to determine the reliability of the questionnaire results. Results In this study, significant behavior improvements in both hyperactive traits, $F(4, 132)=969.200$, $p<.0001$, and inattentive traits, $F(3, 123)= 389.440$, $p<.0001$, were reported on the 3 questionnaires and 2 computerized assessments from pre- and post 40 sessions of training. Furthermore, there are 5 control variables in this study: gender, age at the time of training, IQ at the time of training, medication used at the time of training, and ADHD subtypes. No significant difference between gender (male, n=252, and female, n=66), age at the time of training (age 6-12, n=212, and age 13- 17, n=67), IQ at the time of training (below average, n=20; average, n=97; above average, n=42), medication intake at the time of training (have medication, n=69, and no medication, n=209), and ADHD subtypes (ADHD Combined Type, n=95; ADHD Inattentive Type, n=96; ADD, n=19; ADHD without a labeled subtype, n=69) were found. Conclusions The results of this study provide evidence supporting the use of neurofeedback combined with metacognitive training as an effective intervention for ADHD.

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J Neurother. 2011;15:416-17.

PLANNING FOR A COLLABORATIVE MULTISITE, DOUBLE-BLIND, SHAM-CONTROLLED RANDOMIZED CLINICAL TRIAL OF NEUROFEEDBACK FOR ADHD.

Lofthouse N, Arnold LE, Arns M, et al.

Medication and behavior modification, the established treatments for attention deficit hyperactivity disorder (ADHD), are not universally effective or acceptable to all and have not been shown to have sustained effects beyond 2 years. The 8-year outcome paper (Molina et al., 2009) for the NIMH Multimodal Treatment Study of ADHD (the MTA) pointed out the need for new treatments with lasting effects. Among complementary/alternative treatments for ADHD, neurofeedback (NF) is one of the most prominent, despite its expense and technical difficulties. However, despite a meta-analysis of 6 randomized control trials (RCTs) with a large effect size (ES) for inattention and medium ESs for hyperactivity and impulsivity (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009) and 16 RCTs with a mean medium ES for overall ADHD, inattentive, and hyperactive/impulsive symptoms, many of these studies are small and have not used adequate blinding. The results from the recent National Institute of Mental Health (NIMH)-funded Ohio State University feasibility pilot study indicated that a well-blinded large RCT of NF utilizing a sham control of equal intensity and duration is feasible and necessary, although questions have been raised about whether the sham placebo was truly inert. As with any treatment, it is difficult to determine how much of the apparent treatment effect is specific to the treatment, and how much is placebo effect. Two small studies (Perreau-Link, Lessard, Levesque, & Beauregard, 2010 [N=8]; and Lansbergen et al., 2011 [N=14]) published after the Arns meta-analysis had a blinded sham control and showed no advantage of NF over placebo, raising questions about the unblinded studies. These inconclusive scientific results pose a public health dilemma. The treatment involves considerable initial expense and lengthy commitment by the patients and families. However, if NF has lasting specific benefit, the initial cost and time may compare favorably with medication. Therefore, it is important to know whether NF has a specific effect beyond placebo response, whether the persistence of benefit can be replicated, and whether a biological endophenotype can be identified who will reliably benefit from it. Without resolution of the effectiveness

question, this potentially valuable adjunct to the ADHD treatment armamentarium will not be fully utilized and widely accessible. In November 2010, Drs. Gene Arnold, Roger deBeus, Larry Hirshberg, and Nick Lofthouse presented a symposium on "EEG Neurofeedback for ADHD: Review of the Science and New Findings" at the annual meeting of Children and Adults with Attention-Deficit/ Hyperactivity Disorder. Chaired by Drs. Russell Barkley and Ann Abramowitz, this symposium led to a discussion about the possibility of a large-scale, multisite, double-blind, shamcontrolled RCT of NF for pediatric ADHD. This discussion continued with weekly telephone conferences involving a group of NF experts (Drs. Joel Lubar, Vincent Monastra, Cynthia Kerson, Henry Harbin, Roger deBeus, Larry Hirshberg, & Mr. Martijn Arns) and mainstream ADHD scientists (Drs. Gene Arnold, Keith McBurnett, Keith Conners, Helena Kraemer, & Nick Lofthouse). In April 2011, these discussions led to an agreed-upon preapplication letter of intent to NIMH for multimillion dollar funding of this project. This proposed study is the first to involve planning and execution by both mainstream ADHD scientists (to ensure credible scientific rigor) and NF experts/advocates (to ensure credible and rigorous treatment). In such a study, it is essential that all stakeholders have input so that the results, whatever they are, will be credible to all. This proposal is significant and innovative at the scientific, clinical, and public health level. Scientifically, the lack of a large well-controlled, double-blinded examination of NF has been a critical barrier to progress in the field, with disagreement between NF and most mainstream ADHD investigators about interpretation of the available data. On a clinical and public health level, testing of this promising treatment in a way that is rigorous in both clinical method and research design is greatly needed to see whether NF is an effective alternative treatment option for the many youth who do not respond to or refuse current evidencebased treatments and to see if NF holds additional promise as a complimentary treatment option. This 60-min oral presentation will present the theoretical, scientific, clinical, and public health background for the proposed study and discuss the collaborative team's agreements, disagreements, and resolutions in developing the NIMH letter of intent. The study's main objectives, specific hypotheses, design, participants, instruments, and procedures will also be reviewed. Finally, we will report whether our efforts to obtain NIMH funding were successful, and the next step in our collaboration.

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J Obsessive-Compulsive Relat Disord. 2012;1:283-93.

UNIQUE SACCADIC ABILITIES ASSOCIATED WITH TOURETTE SYNDROME: PURE AND COMORBID GROUPS A CONTROLLED STUDY.

Tajik-Parvinchi DJ, Sandor P.

Tourette Syndrome (TS) is a childhood onset disorder characterized by motor and vocal tics. TS often co-occurs with Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD). Since neural networks associated with TS overlap with that of saccadic eye movements, saccadic performance may reflect psychopathology underlying TS+comorbidity. The aims of the present study were to determine whether heterogeneity in TS samples and use of various saccadic conditions are responsible for inconsistent findings. We examined: (1) saccadic behaviour in children groups: TS-only, TS+ADHD, TS+ADHD+OCD and healthy Controls; (2) the effect of different saccadic conditions. Participants (8-16 years) either looked towards (prosaccade) or in the opposite direction (antisaccade) of a peripheral visual stimulus in three conditions: fixation dot disappeared simultaneously (standard), 200. ms prior to (Gap200) and 800. ms following (Overlap800) stimulus onset. The findings demonstrated that sample heterogeneity and use of various saccadic conditions contribute to inconsistent findings. The TS+ADHD+OCD group displayed an enhanced saccadic ability substantiating the hypothesis of an enhanced adaptive cognitive control in certain groups of children with TS. The TS+ADHD group displayed significantly higher rates of antisaccade errors and unable to reduce their error rates. These findings lend further support to the nosological hypothesis.

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J Obsessive-Compulsive Relat Disord. 2012;1:228-33.

SOCIAL IMPAIRMENT IN CHILDREN WITH OBSESSIVE COMPULSIVE DISORDER: DO COMORBID PROBLEMS OF INATTENTION AND HYPERACTIVITY MATTER?

Kim KL, Reynolds KC, Alfano CA.

Available studies examining the social relationships of children with obsessive compulsive disorder (OCD) suggest the presence of significant social difficulties. A notable limitation of these studies, however, is a lack of consideration for the potential impact of comorbidity on social variables. Given the high rate of attention-deficit/hyperactivity disorder (ADHD) in youth with OCD, and extensive evidence for ADHD-specific social impairments, the current study examined the interpersonal functioning and peer relationships of youth, ages 6-15 years, with primary OCD (n=24) and a non-psychiatric control group (n=18) while accounting for comorbid problems of inattention/hyperactivity. Overall results based on parent and child reports revealed that children with OCD, regardless of ADHD symptomology, were less socially-competent, had fewer dyadic friendships, and greater difficulty making new friends compared to controls. Children with OCD were just as likely, however, to have a best friend. Findings are considered in terms of their potential implications for intervention.

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J Popul ther Clin Pharmacol. 2012;19:e416-e417.

PROFILE OF EXECUTIVE AND ATTENTION FUNCTIONS IN A SAMPLE OF 31 RUSSIAN ADOPTED ADHD CHILDREN COMPARED WITH 31 PROBABLE GENETIC ADHD CHILDREN.

Corredera A, Boix C, Colome R, et al.

Objective: In recent years there has been a significant increase in the rates of international adoption in our country. Children from the Russian Federation between 1997 and 2007 accounted for 60% of all adoptions (Callejon- Poo et al 2011). Several authors (Gray et al 2006, Miller et al 2009) have reported that ADHD is the cognitive-behavioural disorder diagnosed more frequently in this population. ADHD is a neurodevelopmental disorder that impairs executive function as a primary neuropsychological deficit. During the past decade the incidence of alcoholism among Russian childbearing age women has increased by 48% (Gonzalvo- Olivan 2004), so that these children represent a risk factor, along with the institutionalization time prior to adoption. Our goal is to compare the profile of executive and attention functions in a sample of children adopted from Russia with a diagnosis of ADHD, with probable genetic ADHD children.

Materials & Methods: Thirty one adopted children who consult the Learning Disabilities Unit (UTAE) of the Neurology's Department of Sant Joan de Deu's Hospital (Barcelona), diagnosed of ADHD according to DSM-IV, age ranged between 6 and 10 years, were compared with 31 probable genetic ADHD children who consult in the same unit. We analyze the Intelligence Quotient (IQ), the executive and attention functions and the results of Achenbach's questionnaires and ADHD's ratings scales both for parents and teachers.

Results: Preliminary data suggests that ADHD Russian adopted children have higher internalizing and externalizing problems (according to Achenbach's Questionnaire), lower IQ scores and higher difficulties in executive and attention functions than the sample of probable genetic ADHD children.

Conclusions: Russian adopted children tend to have more cognitive and behavioural problems compared to probable genetic ADHD children. This profile is the one described in the Fetal Alcohol Spectrum Disorders. Given the importance of cognitive and behavioural aspects within the family environment, school and sociability, we recommend a routine monitoring of Russian adopted children to implement therapeutic interventions as early as possible.

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J Psychiatry Neurosci. 2012;37:389-98.

COMPARISON OF BRAIN VOLUME ABNORMALITIES BETWEEN ADHD AND CONDUCT DISORDER IN ADOLESCENCE.

Stevens MC, Haney-Caron E.

Background: Previous studies of brain structure abnormalities in conduct disorder and attention-deficit/hyperactivity disorder (ADHD) samples have been limited owing to cross-comorbidity, preventing

clear understanding of which structural brain abnormalities might be specific to or shared by each disorder. To our knowledge, this study was the first direct comparison of grey and white matter volumes in diagnostically "pure" (i.e., no comorbidities) conduct disorder and ADHD samples.
Methods: Groups of adolescents with noncormobid conduct disorder and with noncomorbid, combined-subtype ADHD were compared with age- and sex-matched controls using DARTEL voxel-based analysis of T1,-weighted brain structure images. Analysis of variance with post hoc analyses compared whole brain grey and white matter volumes among the groups.
Results: We included 24 adolescents in each study group. There was an overall 13% reduction in grey matter volume in adolescents with conduct disorder, reflecting numerous frontal, temporal, parietal and subcortical deficits. The same grey matter regions typically were not abnormal in those with ADHD. Deficits in frontal lobe regions previously identified in studies of patients with ADHD either were not detected, or group differences from controls were not as strong as those between the conduct disorder and control groups. White matter volume measurements did not differentiate conduct disorder and ADHD.
Limitations: Our modest sample sizes prevented meaningful examination of individual features of ADHD or conduct disorder, such as aggression, callousness, or hyperactive versus inattentive symptom subtypes.
Conclusion: The evidence supports theories of frontotemporal abnormalities in adolescents with conduct disorder, but raises questions about the prominence of frontal lobe and striatal structural abnormalities in those with noncomorbid, combined-subtype ADHD. The latter point is clinically important, given the widely held belief that ADHD is associated with numerous frontal lobe structural deficits, a conclusion that is not strongly supported following direct comparison of diagnostically pure groups. The results are important for future etiological studies, particularly those seeking to identify how early expression of specific brain structure abnormalities could potentiate the risk for antisocial behaviour.

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J Sleep Res. 2012;21:25.

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

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

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a triad of symptoms involving hyperactivity, impulsivity and inattention. Several studies in children with attention deficit hyperactivity disorder (ADHD) showed a high prevalence of excessive daytime sleepiness. To our knowledge, no study has objectively assessed sleepiness in adults with ADHD. Moreover, it has been shown that adults with ADHD were at risk for driving accidents. The objectives of this study are to quantify objective sleepiness and its impact on driving performance in adult with ADHD.
Methods: Twenty-four subjects with ADHD (age (mean (plus or minus) SE) = 35.8 (plus or minus) 1.9) and 10 control subjects [age (mean (plus or minus) SE) = 32.6 (plus or minus) 1.4] were included. Nocturnal polysomnography was performed to identify potential sleep disorder. The next day patients were submitted to a Maintenance Wakefulness Test (MWT) at 10H, 12H, 14H, 16H to examine their level of daytime sleepiness. After a training of 15 min, a driving test of 1 h was carried out at 17H on a simulator (Oktal) to evaluate driving performance.
Results: They were divided into three groups according to their level of sleepiness at the MWT: the 'sleepy' group consisted of fourteen subjects (mean sleep latency (SL) = 23.1 (plus or minus) 1.4 min) and the 'alert' group included ten subjects (LE = 36.9 (plus or minus) 1.3 min). The two patients groups differ significantly at the MWT ($F(1, 22) = 66.1$, $P < 0.001$). The 'control' group exhibited less inappropriate line crossings (20.8 (plus or minus) 3.8) than the 'alert' group (48.2 (plus or minus) 8.7) and the 'sleepy' group (51.2 (plus or minus) 6.9) ($F(2, 40) = 5.16$, $P < 0.01$). Moreover, driving performance degrades over time for ADHD participants when it improves for control subjects ($F4,80 = 13.51$, $P = 0.0001$).
Conclusion: In our sample, half of the patients suffer of excessive daytime sleepiness, which deteriorates significantly their driving performance.

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J Sleep Res. 2012;21:237.

ANALYSIS OF EEG ASYMMETRY BEFORE AND AFTER SLEEP IN ATTENTION DEFICIT HYPERACTIVITY DISORDER BOYS.

Gingras MA, Chevrier E, Braun CMJ, et al.

Objectives: EEG activity before and after a night of sleep follows a normal trend of decreased power in attention deficit hyperactivity disorder (ADHD) boys (Gingras et al., ESRS 2010). ADHD adults are reported to show an atypical lateralization of Alpha and Beta wake EEG activity but this has not been evaluated in ADHD children yet. The aim of the present study was to evaluate wake EEG lateralization in ADHD boys.
Methods: Twelve boys diagnosed with ADHD but no comorbidity (age: 11.0 (plus or minus) 1.2) and 15 healthy boys (age: 10.7 (plus or minus) 1.6) were recorded in a sleep laboratory for two consecutive nights using a 20-electrode EEG montage. Wake EEG was recorded at 256 Hz for 5 min with eyes opened and 5 min with eyes closed, 10-15 min before lights out in the evening and after lights on in the morning. Spectral analysis of wake EEG was performed on 15 four-second artifact free epochs. Data from night 2 was submitted to Fast Fourier transform with a resolution of 0.25 Hz and cosine window smoothing. Four frequency bands were created: Delta (0.75-3.75 Hz), Theta (4.0-7.75 Hz), Alpha (8.0-12.75 Hz) and Beta (13.0-30 Hz) and Spectral data was log-transformed. A lateralization coefficient was calculated using [(Right - Left) per cent Right + Left) null 100]. EEG lateralization coefficients were compared using a 2 Groups (ADHD, Controls) null 2 Moments (evening, morning) null 4 Frequency Bands (Delta, Theta, Alpha, Beta) ANOVAs for 10 pairs of homologous electrodes, for Eyes Closed and Eyes Opened condition separately. Significant results were followed by LSD post hoc tests.
Results: Significant Moments (middle dot) Frequency Bands interaction: Beta activity showed a right lateralization in the prefrontal area in the evening and a left lateralization in the morning (Eyes Opened condition only). Significant Groups null Frequency Bands interactions: the right lateralization of Beta activity over prefrontal, frontal and temporo-parietal areas was stronger in ADHD boys than control, in both Eyes Closed and Eyes Opened conditions. Significant Groups null Moment null Frequency Bands interactions: ADHD boys showed a stronger morning right lateralization of Alpha activity over the parietal area than controls (Eyes Opened condition only).
Conclusion: The present results support previous observations of impaired interhemispheric functional connectivity in ADHD boys. These results are also compatible with a neurodevelopmental continuity of this phenomenon from childhood to adulthood.

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J Sleep Res. 2012;21:237.

IDENTIFYING ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN PAEDIATRIC RESTLESS LEGS SYNDROME.

Merino-Andreu M, Tapia-Canelas O, Ledezma-Soria J, et al.

Objectives: Restless Legs Syndrome (RLS) is a chronic neurological disorder characterized by an urge to move the legs, usually accompanied by uncomfortable and unpleasant leg sensations, symptoms worse in the evening or at night and they are partially relieved by movement and symptoms worse when lying or sitting. Other associated features commonly found in RLS include sleep disturbance and periodic limb movements (PLM). Paediatric RLS has a prevalence of 1.9% in school aged children and 2% in adolescents and much more frequent in children with Attention Deficit Hyperactivity Disorder (ADHD). ADHD is more likely to be diagnosed in RLS subjects and their symptoms are commonly confused. The aim of the study is to define early manifestations that can identify ADHD in RLS patients.
Methods: We have evaluated 32 subjects diagnosed of definitive RLS, divided in two groups: with or without ADHD criteria (RA+ and RA-). Various psychopathologies, severity of RLS symptoms, nocturnal polysomnography and serum ferritin levels were assessed. Diagnosis of RLS was made according to the International RLS Group rules and ADHD was identified using DSM-IV R criteria.
Results: ADHD was found in 17 (53%) subjects, with similar age distribution and male predominance in both groups. Growing pains, diurnal and nocturnal restless and RLS severity score (measured with RLS severity scale) were higher in RA+ subjects when compared with RA- subjects. In our study, polysomnographic findings were similar in both groups.

Conclusion: Our results show that, though they are commonly found as two comorbid conditions, there are clinical features that can distinguish ADHD in paediatric RLS population. We suggest that patients with RLS should be evaluated for ADHD and vice versa.

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J Sleep Res. 2012;21:305.

SLEEP-WAKE CYCLE DISTURBANCES IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER - PRELIMINARY RESULTS.

Adamowicz T, Anacleto T, Simoes L, et al.

Objectives: The objective of this study was to compare sleep-wake cycle patterns of boys with Attention Deficit/Hyperactivity Disorder (ADHD) to healthy controls.

Methods: Nine boys diagnosed with ADHD according to DSM-IV, mean age 8.78 years (0.67), were compared to 11 healthy boys, mean age 9 (0.63) years. All the children were students from public schools of Curitiba, Southern Brazil. For both groups, exclusion criteria were IQ < 70 and current usage of stimulant medication. During seven consecutive days, boys wore actigraphs and their parents filled sleep logs. Rest/activity parameters (L5, M10 and RA - relative amplitude) were also analyzed. L5 is the sequence of the five least active hours in the 24-h average activity profile; M10 is the sequence of the ten most active hours in the 24-h average activity profile; RA is a proportional measure, giving a ratio of activity during L5 to activity during M10. Data of both groups were compared by means Student's t-test. A P value <0.05 was considered statistically significant. Dependent variables were sleep onset, offset, duration and efficiency, L5, M10 and RA.

Results: Boys with ADHD showed shorter sleep duration [433.8 (65.6) null 513.4 (23.5); t(18) = 3.76; P = 0.001] and shorter sleep efficiency [86.1 (5.5) null 95.8 (2.7)%; t(18) = 5.2; P < 0.001] than controls. There was no difference when sleep onset [11:28 pm (53 min) null 10:33 pm (68 min) null t(18) = -1.94; P = 0.07; ADHD null controls] and offset [7:52 am (72 min) null 7:33 am (62 min); t(18) = -0.65; P = 0.52; ADHD null controls] were compared. On activity parameters analysis, it was detected higher L5 values on ADHD group [11.02 (2.13) null 7.85 (1.88); t(18) = -3.5; P = 0.002], indicating greater nocturnal activity. For the RA, the ADHD group had lower values than the control group [0.91 (0.03) null 0.93 (0.02); t(18) = 2.6; P = 0.018]. There was no difference between groups on M10 analysis [232.3 (43.77) null 236.1 (36.4); t(18) = 0.22; P = 0.83; ADHD null controls, respectively].

Conclusion: In our sample, ADHD boys showed sleep/wake cycle disturbances when compared to healthy boys, including a reduction of RA, which suggest a reduction of the strength of circadian rhythms in these patients.

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J Sleep Res. 2012;21:22-23.

SLEEP-WAKE PATTERNS AS REPORTED BY PARENTS IN CHILDREN WITH ADHD COMPARED TO MATCHED CONTROLS.

Allen Gomes A, Parchao C, Almeida A, et al.

Objective: This study aimed to compare sleep, as reported by parents, (i) in ADHD versus in community children, and (ii) in medicated versus non medicated ADHD children.

Methods: Parents filled out a previously validated questionnaire about sleep-wake patterns (adapt. from Clemente et al., 1997, published by Bos et al., 2009). Thirty children (83.3% male), 5- 13 years old, with a diagnosis of ADHD according to their pedopsychiatrists, took part of the study. This clinical sample was obtained at the Department of Children and Adolescents Mental Health, Magalhaes Lemos Hospital, Oporto Hospital Centre, Portugal. A group of 30 children matched for sex, age and school year, were selected from a large community sample.

Results: Several statistically significant differences (P < 0.05) emerged between the clinical sample and the community matched sample: ADHD children showed later bedtimes, stronger bedtime resistance, and longer sleep latency; they fell asleep into parents bed, and needed something special to fall asleep, more often; obtained shorter sleep on school nights (1 h less per night, in median); had more frequent symptoms of nightmares, sleep talking, fear from darkness, and, most notably, loud snoring, 26.7% (as defined by

Ferreira et al., 2000); and showed higher daytime somnolence. Comparing ADHD children taking metilphenidate (n = 13) versus not taking medication (n = 17), the former tended to present later bedtimes (P ~ 0.05) and higher bedtime resistance (P < 0.05), tended to show more nightmares (P < 0.10), but appeared to return to sleep autonomously more easily.
Conclusion: Our results are in line with previous findings in children with a diagnosis of ADHD, and indicate that these children may have more sleep problems than typical development children. Alternatively, these results may reflect misdiagnose situations, thus, special attention should be directed to the differential diagnosis between sleep disturbances and ADHD. These results have important implications for ADHD diagnose and therapeutics in children.

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J Sleep Res. 2012;21:45.
PHARMACOTHERAPY AND GROWTH IN ADHD.
Lecendreux M.
Studies providing longitudinal data suggest that treating children with ADHD with stimulant medication generally results in a reduction in both height and weight gain. On average, the reduction in height amounts to approximately 1 cm/year during the first 1-3 years of treatment and the reduction in weight gain about 3 kg less than predicted. Current data indicate that the initial effect of stimulants on growth appears to attenuate over time. It is possible that the effects of stimulants on growth are dose-dependent. Significant effects on weight and height may require average doses of methylphenidate exceeding 1.5 mg/kg/day which are given continuously. Preschool children may be particularly vulnerable to growth effects. The National Institute of Mental Health Preschool ADHD Treatment Study reported that children between 3 and 5 years of age treated with methylphenidate had annual growth rates 20.3% less than expected for height (1.38 cm/year) and 55.2% for weight (-1.32 kg/ year). Reduced caloric intake and suboptimal nutrition due to appetite suppression are likely causes of growth suppression. Hypothetically, dysregulation of receptors in the growth system could also be responsible. Adaptation of receptors could contribute to tolerance to growth inhibition over time and to catch-up growth after the medication has been discontinued. Acute effects on growth hormone and prolactin have been observed, but do not yet explain persisting growth deficits. A hypothesis that ADHD itself is associated with dysregulated growth, either decreased or increased has been put forward, but current evidence is contradictory. The hypothesis that ADHD was associated with growth dysregulation using an epidemiologic study of ADHD children in France. Our findings suggest that medication-naive ADHD was associated with being taller and heavier for young children. In contrast, for older children medication-naive ADHD was associated with being shorter and lighter. Further research is needed into the causal mechanisms and the long term implications of continuous treatment from childhood to adulthood for ultimate height. The role of stimulants on sleep shoud also be considered, knowing that GH release is closely linked to the sleep-wake cycle and feeding state. Understanding orexin/hypocretin physiology could open new therapeutic possibilities in the treatment of sleep and GH-related pathologies in children with ADHD children and/or neurodevelopmental disorders.

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J Sleep Res. 2012;21:238.
PARASOMNIAS IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Soria-Bretones C, Garcia-Bellon M, Garciajimenez MA.
Objectives: Our aim is to describe the prevalence of Restless Legs Syndrome (RLS) and other parasomnias in children diagnosed of Attention-Deficit Hyperactivity Disorder (ADHD) in our city, provided the high co-morbidity we find in our clinical practice.
Methods: Observational descriptive cross-sectional study in ADHD patients referred to our service for EEG since 2007 (n = 65).
Measures: Child's Sleep Habits Questionnaire and questionnaire based on Owen's test for RLS and Periodic Leg Movements (PLM), answered by parents by phone or live interviews. International RLS Study Group criteria for RLS (2002) were followed.

Results: Sample age: 4-17 years old (9.9 (plus or minus) 3.05). RLS prevalence: global 18.5%; criteria of probable RLS criteria: 10.8%; definitive RLS: 7.7%. Male predominance (91.7%). Compared to subjects without RLS, we find higher prevalence of bruxism (62.9%), fear of sleeping alone (62.8%) and nightmare arousals (57.1%). Sleep disorders: 24.1% have insomnia symptoms. Some parasomnia in 20.5% of subjects, which in order of prevalence are: somniloquy, nightmares, enuresis, bruxism and sleepwalking. Sleep habits: with increasing age, reduction of nocturnal sleep hours and increase of daytime tiredness, meaning insufficient sleep and a consequent sleep debt. 27.8% show excessive daytime sleepiness (EDS).
Conclusion: 1. RLS prevalence in ADHD turns out to be higher than expected. This is probably due to common symptoms in both disorders, which can be confused. 2. Other parasomnias and sleep disorders show similar prevalence in children with and without ADHD, in the same age range. 3. As a finding, we report progressively insufficient sleep hours in increasing ages.

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Journal of the American Academy of Child & Adolescent Psychiatry. 2012 Oct;51:990-1002.

ECONOMIC IMPACT OF CHILDHOOD AND ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE UNITED STATES.

Doshi JA, Hodgkins P, Kahle J, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent mental disorders in children in the United States and often persists into adulthood with associated symptomatology and impairments. This article comprehensively reviews studies reporting ADHD-related incremental (excess) costs for children/adolescents and adults and presents estimates of annual national incremental costs of ADHD.
Method: A systematic search for primary United States-based studies published from January 1, 1990 through June 30, 2011 on costs of children/adolescents and adults with ADHD and their family members was conducted. Only studies in which mean annual incremental costs per individual with ADHD above non-ADHD controls were reported or could be derived were included. Per-person incremental costs were adjusted to 2010 U.S. dollars and converted to annual national incremental costs of ADHD based on 2010 U.S. Census population estimates, ADHD prevalence rates, number of household members, and employment rates by age group.
Results: Nineteen studies met the inclusion criteria. Overall national annual incremental costs of ADHD ranged from $143 to $266 billion (B). Most of these costs were incurred by adults ($105B-$194B) compared with children/adolescents ($38B-$72B). For adults, the largest cost category was productivity and income losses ($87B-$138B). For children, the largest cost categories were health care ($21B-$44B) and education ($15B-$25B). Spillover costs borne by the family members of individuals with ADHD were also substantial ($33B-$43B).
Conclusion: Despite a wide range in the magnitude of the cost estimates, this study indicates that ADHD has a substantial economic impact in the United States. Implications of these findings and future directions for research are discussed.

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J Am Acad Child Adolesc Psychiatry. 2012;51:1160-72.

ARE AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DIFFERENT MANIFESTATIONS OF ONE OVERARCHING DISORDER? COGNITIVE AND SYMPTOM EVIDENCE FROM A CLINICAL AND POPULATION-BASED SAMPLE.

Van Der Meer JMJ, Oerlemans AM, Van Steijn DJ, et al.

Objective: Autism spectrum disorders (ASD) and attention-deficit/ hyperactivity disorder (ADHD) frequently co-occur. Given the heterogeneity of both disorders, several more homogeneous ASD-ADHD comorbidity subgroups may exist. The current study examined whether such subgroups exist, and whether their overlap or distinctiveness in associated comorbid symptoms and cognitive profiles gives support for a gradient overarching disorder hypothesis or a separate disorders hypothesis.
Method: Latent class analysis was performed on Social Communication Questionnaire (SCQ) and Conners' Parent Rating Scale (CPRS-R:L) data for 644 children and adolescents (5 through 17 years of

age). Classes were compared for comorbid symptoms and cognitive profiles of motor speed and variability, executive functioning, attention, emotion recognition, and detail-focused processing style.
Results: Latent class analysis revealed five classes: two without behavioral problems, one with only ADHD behavior, and two with both clinical symptom levels of ASD and ADHD but with one domain more prominent than the other (ADHD[+ASD] and ASD[+ADHD]). In accordance with the gradient overarching disorder hypothesis were the presence of an ADHD class without ASD symptoms and the absence of an ASD class without ADHD symptoms, as well as cognitive functioning of the simple ADHD class being less impaired than that of both comorbid classes. In conflict with this hypothesis was that there was some specificity of cognitive deficits across classes.
Conclusions: The overlapping cognitive deficits may be used to further unravel the shared etiological underpinnings of ASD and ADHD, and the nonoverlapping deficits may indicate why some children develop ADHD despite their enhanced risk for ASD. The two subtypes of children with both ASD and ADHD behavior will most likely benefit from different clinical approaches.

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J Am Acad Child Adolesc Psychiatry. 2012;51:1197-207.
ATYPICAL PULVINAR-CORTICAL PATHWAYS DURING SUSTAINED ATTENTION PERFORMANCE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Li X, Sroubek A, Kelly MS, et al.
Objective: The neurobiological basis of inattentiveness, a core feature of attention-deficit/hyperactivity disorder (ADHD), is not yet well understood. Structural abnormalities in thalamus, especially the pulvinar nuclei, have recently been reported in ADHD. Pulvinar nuclei maintain reciprocal connections with cortical/subcortical areas, and play a central coordinating role during visual attention processing. The objective of this study was to test the hypothesis that children and young adolescents with ADHD would show atypical pulvinar-cortical functional pathways during sustained attention performance, and that these functional abnormalities would be associated with the inattentive symptoms of the disorder.
Method: Visual attention task-based functional magnetic resonance imaging (fMRI) data from 22 children and young adolescents with ADHD and 22 demographically matched, normal control subjects were analyzed. Cortical activation maps and temporal correlations of activity patterns between pulvinar nuclei and the remainder of brain were constructed for each participant. Correlations between activation magnitude of pulvinar and diagnostic measures were calculated in subjects with ADHD.
Results: Compared to controls, subjects with ADHD showed significantly reduced pulvinar activations bilaterally, significantly decreased functional connectivity between bilateral pulvinar and right prefrontal regions, and significantly increased connectivity between the right pulvinar and bilateral occipital regions. In addition, the activation magnitude in the left pulvinar was negatively correlated with the DSM-IV inattentive index in ADHD group.
Conclusions: Allied with previous evidence of structural abnormalities in pulvinar, the current data suggest that inappropriate development of pulvinar may lead to disrupted functional circuits for visual attention processing, and that these disruptions contribute significantly to the pathophysiological mechanisms of the inattentiveness symptoms in ADHD.

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J Can Acad Child Adolesc Psychiatry. 2012;21:282-88.
EFFCACY OF METHYLPHENIDATE IN ADHD CHILDREN ACROSS THE NORMAL AND THE GIFTED INTELLECTUAL SPECTRUM.
Grizenko N, Zhang DDQ, Polotskaia A, et al.
Objective: This study evaluates whether attention-defcit/hyperactivity disorder (ADHD) children with a borderline intelligence quotient (IQ) (70(less-than or equal to)FSIQ<80), normal IQ (80(less-than or equal to)FSIQ<120) and high IQ (FSIQ(greater-than or equal to)120) respond differently to psychostimulant treatment.
Method: 502 children, aged 6 to 12 years, with an IQ range from 70 to 150 participated in a two-week, double-blind, placebo-controlled, crossover methylphenidate (MPH) trial.

Results: In addition to differences in socioeconomic background and parental education, higher IQ children were found to present with less severe symptoms. No signifcant differences were found with regards to treatment response.
Conclusion: ADHD children within the normal and high levels of intellectual functioning all respond equally to psychostimulant treatment, and that proper medication management is necessary for all children with the disorder.

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Med Sci Monit. 2012;18:CS94-CS104.
EVALUATION OF A NEUROTHERAPY PROGRAM FOR A CHILD WITH ADHD WITH BENIGN PARTIAL EPILEPSY WITH ROLANDIC SPIKES (BPERS) USING EVENT-RELATED POTENTIALS.
Pachalska M, Kropotov ID, Manko G, et al.
Background: We hypothesized that there would be a good response to relative beta training, applied to regulate the dynamics of brain function in a patient with benign partial epilepsy with Rolandic Spikes (BPERS), associated with neuropsychiatric deficits resembling the symptoms of attention deficithyperactivity disorder (ADHD).
Case Report: The patient, E.Z., age 9.3, was suffering from neuropsychiatric symptoms, cognitive dysfunction, especially attention deficits, and behavioral changes, rendering him unable to function independently in school and in many situations of everyday life. He was treated for epilepsy, but only slight progress was made. The patient took part in 20 sessions of relative beta training combined with behavioral training. We used standardized neuropsychological testing, as well as ERPs before the experiment and after the completion of the neurotherapy program. Neuropsychological testing at baseline showed multiple cognitive deficits. Over the course of neurotherapy, E.Z.'s verbal and non-verbal IQ increased significantly. His cognitive functions also improved, including immediate and delayed logical and visual recall on the WMS-III, maintaining attention on the WMS-III, and executive functions, but remained below norms. Physiologically, the patient showed substantial changes after neurotherapy, including fewer spikes and an increased P300 NOGO component.
Conclusions: The cognitive deficits characteristic for ADHD in a child with BPERS may be unresponsive to antiepileptic treatment, but are reversible after a carefully selected neurotherapy program, combined with antiepileptic treatment. Event Related Potentials (ERPs) in the GO/NOGO task can be used to assess functional brain changes induced by neurotherapeutical programs.

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Neuropsychology. 2012 Nov;26:684-94.
DECOMPOSING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)-RELATED EFFECTS IN RESPONSE SPEED AND VARIABILITY.
Karalunas SL, Huang-Pollock CL, Nigg JT.
Objective: Slow and variable reaction times (RTs) on fast tasks are such a prominent feature of attention-deficit/hyperactivity disorder (ADHD) that any theory must account for them. However, this has proven difficult because the cognitive mechanisms responsible for this effect remain unexplained. Although speed and variability are typically correlated, it is unclear whether single or multiple mechanisms are responsible for group differences in each. RTs are a result of several semi-independent processes, including stimulus encoding, rate of information processing, speed–accuracy trade-offs, and motor response, which have not been previously well characterized.
Method: A diffusion model was applied to RTs from a forced-choice RT paradigm in two large, independent case-control samples (N [sub]Cohort 1[sub] = 214 and N [sub]Cohort 2[sub] = 172). The decomposition measured three validated parameters that account for the full RT distribution and assessed reproducibility of ADHD effects.
Results: In both samples, group differences in traditional RT variables were explained by slow information processing speed, and unrelated to speed–accuracy trade-offs or nondecisional processes (e.g., encoding, motor response).

Conclusions: RT speed and variability in ADHD may be explained by a single information processing parameter, potentially simplifying explanations that assume different mechanisms are required to account for group differences in the mean and variability of RTs.

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New Engl J Med. 2012;367:2006-14.

MEDICATION FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER AND CRIMINALITY.

Lichtenstein P, Halldner L, Zetterqvist J, et al.

BACKGROUND: Attention deficit-hyperactivity disorder (ADHD) is a common disorder that has been associated with criminal behavior in some studies. Pharmacologic treatment is available for ADHD and may reduce the risk of criminality.

METHODS: Using Swedish national registers, we gathered information on 25,656 patients with a diagnosis of ADHD, their pharmacologic treatment, and subsequent criminal convictions in Sweden from 2006 through 2009. We used stratified Cox regression analyses to compare the rate of criminality while the patients were receiving ADHD medication, as compared with the rate for the same patients while not receiving medication.

RESULTS: As compared with nonmedication periods, among patients receiving ADHD medication, there was a significant reduction of 32% in the criminality rate for men (adjusted hazard ratio, 0.68; 95% confidence interval [CI], 0.63 to 0.73) and 41% for women (hazard ratio, 0.59; 95% CI, 0.50 to 0.70). The rate reduction remained between 17% and 46% in sensitivity analyses among men, with factors that included different types of drugs (e.g., stimulant vs. nonstimulant) and outcomes (e.g., type of crime).

CONCLUSIONS: Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication. These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD. (Funded by the Swedish Research Council and others.)

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Nord J Psychiatry. 2012 Oct;66:320-28.

SUICIDAL AND SELF-HARM BEHAVIOUR ASSOCIATED WITH ADOLESCENT ATTENTION DEFICIT HYPERACTIVITY DISORDER—A STUDY IN THE NORTHERN FINLAND BIRTH COHORT 1986.

Hurtig T, Taanila A, Moilanen I, et al.

Background: Suicidal behaviour, i.e. suicidal ideation and suicidal acts, as well as self-harm behaviour, are relatively common among adolescents. Depression and/or female gender seem to be risk factors for suicidal behaviour. However, the role of attention deficit hyperactivity disorder (ADHD) in these behaviours is still unclear.

Aim: To study the effect of ADHD on suicidal or self-harm behaviour in adolescents from a general population sample.

Methods: The sample was derived from a population-based Northern Finland Birth Cohort 1986 (n = 9432). Based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (Kiddie-SADS-PL) interview performed in a subpopulation (n = 457), the associations between suicidal behaviour and deliberate self-harm (DSH) and the diagnosis of ADHD were studied.

Results: Compared with adolescents without ADHD (n = 169), those with ADHD (n = 104) had more suicidal ideation (57% vs. 28%, P < 0.001) and DSH (69% vs. 32%, P < 0.001). In binary logistic models, the effect of ADHD on suicidal ideation remained strong (OR = 6.1) after controlling for several other predictors. Other contributing factors in suicidal behaviour included female gender, childhood emotional and behavioural problems, concurrent depression and anxiety, and, specifically in DSH, behavioural disorder, substance abuse and strains in family relations.

Discussion and clinical implications: ADHD is a risk factor for suicidal ideation and DSH. These findings in a general population sample speak for a need to target mental health interventions at children and adolescents with relevant symptoms of ADHD.

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Nord J Psychiatry. 2012;66:396-402.

A COMPARISON BETWEEN CHILD PSYCHIATRIC OUTPATIENTS WITH AD/HD AND ANXIETY/DEPRESSION.

Thaulow CM, Jozefiak T.

Background: Studies have shown that children with attention-deficit/ hyperactivity disorder (AD/HD) have a lower quality of life (QoL), and lower school and psychosocial functioning than healthy children.
Aims: This is the first study to compare these domains and child competence between children with AD/HD- and anxiety/depression-related problems and healthy children using data from multiple informants.
Method: Children were matched by age and sex, resulting in two clinical groups consisting of 62 children with AD/HD-related problems, 49 children with anxiety/depression-related problems and a reference group of 65 healthy schoolchildren. The Inventory of Life Quality for Children and Adolescents (parent and child report), the Child Behaviour Checklist (parent report), the Teacher's Report Form and the Children's Global Assessment Scale (therapist evaluation) were used. Differences between group means were analysed by t-tests and analysis of variance.
Results: The AD/HD group reported a significantly higher QoL than did the Anxiety/Depression group. However, no significant differences in QoL were found between the two clinical groups by parent proxy report. The AD/HD group reported a significantly higher QoL than shown by parent proxy evaluation. According to parent and teacher reports, both clinical groups showed significantly lower school functioning than the group of healthy children. Further, the AD/HD group showed significantly lower school functioning and total competence than the Anxiety/Depression group.
Conclusion: To obtain a full clinical picture of subgroups of patients with AD/HD- and anxiety/depression-related problems referred to child mental health outpatient treatment, clinicians should always use multiple informants to evaluate symptoms/problems, functioning and QoL.

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Pediatr Nephrol. 2012;27:2091-97.

NORTRIPTYLINE FOR TREATING ENURESIS IN ADHDA RANDOMIZED DOUBLE-BLIND CONTROLLED CLINICAL TRIAL.

Ghanizadeh A, Haghighat R.

Background: Treating enuresis in children with attention deficit hyperactivity disorder (ADHD) has not been previously reported. This study aims to investigate the efficacy, tolerability, and adverse effects of nortriptyline for treating enuresis in children with ADHD.
Methods: Forty-three children aged from 5 to 14 years old were randomized into two groups. The treatment group received methylphenidate plus nortriptyline, while the placebo group received methylphenidate plus placebo. Nortriptyline and placebo were administered for 30 days and methylphenidate was administered for 45 days. The major outcome measure was parent-reported frequency of enuresis for 2 weeks prior to the intervention, during the intervention, and for 2 weeks after stopping the adjuvant therapy. Adverse effects were also checked.
Results: While nortriptyline statistically decreased the incidence of nocturnal enuresis during the intervention, the number of enuresis events did not significantly change in the placebo group. In addition, enuresis was not different from the baseline frequency of enuresis after stopping nortriptyline or placebo administration. Both nortriptyline and placebo were tolerated well.
Conclusions: Administration of nortriptyline for treating enuresis in ADHD has not been investigated before. Nortriptyline is statistically superior to placebo. However, enuresis will relapse after stopping nortriptyline in children with ADHD who continue taking methylphenidate.

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Pediatrics. 2012;130:S91-S97.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS, ADAPTIVE FUNCTIONING, AND QUALITY OF LIFE IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Sikora DM, Vora P, Coury DL, et al.

OBJECTIVE: The purpose of the current study was to evaluate the frequency of co-occurring attention-deficit/hyperactivity disorder (ADHD) symptoms in a well-defined cohort of children with autism spectrum

disorders (ASDs) and to examine the relationship between ADHD symptoms and both adaptive functioning and health-related quality of life as reported by parents or other primary caregivers.
METHODS: T scores on 2 ADHD-related scales from the Child Behavior Checklist were used to indicate the presence of ADHD symptoms. Participants were divided into groups based on whether their parents/ caregivers rated them as having clinically significant T scores on the Attention Problem and Attention Deficit Hyperactivity Problem subscales. Standard scores from the Vineland Adaptive Behavior Scales, Second Edition and raw scores from the Pediatric Quality of Life Inventory were then compared between groups with the use of multivariate analyses.
RESULTS: Approximately 40% of participants had 1 elevated T score, and 19% had both ADHD-related T scores elevated on the Child Behavior Checklist. The ASD + ADHD group had lower scores on the Vineland Adaptive Behavior Scales, Second Edition and the Pediatric Quality of Life Inventory in comparison with the ASD alone group.
CONCLUSIONS: Results suggest greater impairment in adaptive functioning and a poorer health-related quality of life for children with ASDs and clinically significant ADHD symptoms in comparison with children with ASDs and fewer ADHD symptoms. Physicians are encouraged to evaluate for the presence of ADHD symptoms in their patients with ASDs and, if present, include symptom treatment in the overall care plan.

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Pediatrics. 2012;130:S125-S138.

CLINICAL PRACTICE PATHWAYS FOR EVALUATION AND MEDICATION CHOICE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN AUTISM SPECTRUM DISORDERS.

Mahajan R, Bernal MP, Panzer R, et al.

BACKGROUND AND OBJECTIVE: Hyperactivity, impulsivity, and inattention (referred to as "ADHD [attention-deficit/hyperactivity disorder] symptoms") occur in 41% to 78% of children with autism spectrum disorders (ASDs). These symptoms often affect quality of life, interfering with learning or interventions that target primary ASD symptoms. This practice pathway describes the guidelines for evaluation and treatment of children and adolescents with ASD and comorbid ADHD symptoms.
METHODS: Current research in this area is limited, and, therefore, these recommendations are based on a systematic literature review and expert consensus in the Autism Speaks Autism Treatment Network Psychopharmacology Committee.
RESULTS: The recommended practice pathway includes the Symptom Evaluation Pathway for systematic assessment of ADHD symptoms across settings; examination for comorbid sleep, medical, or psychiatric comorbidities that may contribute to symptoms; and evaluation of behavioral interventions that may ameliorate these symptoms. For children for whom medication is being considered to target the ADHD symptoms, the medication choice pathway provides guidance on the selection of the appropriate agent based on a review of available research, assessment of specific advantages and disadvantages of each agent, and dosing considerations.
CONCLUSIONS: These recommendations provide a framework for primary care providers treating children who have ASD and ADHD symptoms. Our systematic review of the current evidence indicates the need for more randomized controlled trials of the medications for ADHD symptoms in ASD. There will also be a need for studies of the effectiveness of these practice pathways in the future.

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Pharm Care Espana. 2012;14:183-92.

INVOLVEMENT OF COMMUNITY PHARMACISTS ON ATTENTION-DEFI CIT/HYPERACTIVITY DISORDER PATIENTS. A PILOT STUDY.

Palomino MD, Martin-Calero MJ, Marques G.

Purpose: Available pharmacological treatments of attention-defi cit/hyperactivity disorder (ADHD) are focus on reducing symptoms, however they have numerous side effects. Pharmacists are not included within the interdisciplinary team treating this disorder.
Objective: This study wants to contribute from community pharmacies to the assistential process of ADHD patients.

Method: A descriptive, transversal and observational study was carried out. The setting was community pharmacies from Andalusia, Spain. Subjects were patients, parents or guardians with prescriptions of methylphenidate and/or atomoxetine. During March-June 2009, the subjects fi lled in a questionnaire with information about the patient, medical diagnosis, prescribed medication, adverse drug reactions (ADR), alerts, the degree of knowledge of treatment and the role of the pharmacist.
Results: 59 community pharmacies were recruited, and 136 questionnaires were completed; 83% of the sample were male, mainly children between 8-14 years old. Extended release methylphenidate, was the most prescribed treatment (90.6%) against atomoxetine (9.4%). Loss of appetite (68.10%), diffi culty sleeping (31.03%), headache (28.44%), mood swings (23.27%) and tics (13.79%), were the most prevalent ADR. Except the tics, OROS methylphenidate induced these effects in higher percentage than immediate release forms. 2.2 ADR/patient was found using methylphenidate and 4.3 ADR/patient with atomoxetine. Treatments were dispensed in 98% of the cases, giving information about the drug (29%), health education (26%) and the patients were sent back to the doctor when necessary (12%).
Conclusion: The intervention of community pharmacists on ADHD patients could be an important contribution in order to improve the effectiveness and safety of treatments.

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PLoS ONE. 2012;7.
WORKING MEMORY-RELATED FUNCTIONAL BRAIN PATTERNS IN NEVER MEDICATED CHILDREN WITH ADHD.
Massat I, Slama H, Kavec M, et al.
Attention Deficit/Hyperactivity Disorder (ADHD) is a pervasive neurodevelopmental disorder characterized by 3 clusters of age-inappropriate cardinal symptoms: inattention, hyperactivity and impulsivity. These clinical/behavioural symptoms are assumed to result from disturbances within brain systems supporting executive functions including working memory (WM), which refers to the ability to transiently store and flexibly manipulate task-relevant information. Ongoing or past medications, co-morbidity and differences in task performance are potential, independent confounds in assessing the integrity of cerebral patterns in ADHD. In the present study, we recorded WM-related cerebral activity during a memory updating N-back task using functional Magnetic Resonance Imaging (fMRI) in control children and never medicated, prepubescent children with ADHD but without comorbid symptoms. Despite similar updating performance than controls, children with ADHD exhibited decreased, below baseline WM-related activation levels in a widespread cortico-subcortical network encompassing bilateral occipital and inferior parietal areas, caudate nucleus, cerebellum and functionally connected brainstem nuclei. Distinctive functional connectivity patterns were also found in the ADHD in these regions, with a tighter coupling in the updating than in the control condition with a distributed WM-related cerebral network. Especially, cerebellum showed tighter coupling with activity in an area compatible with the brainstem red nucleus. These results in children with clinical core symptoms of ADHD but without comorbid affections and never treated with medication yield evidence for a core functional neuroanatomical network subtending WM-related processes in ADHD, which may participate to the pathophysiology and expression of clinical symptoms.

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PLoS ONE. 2012;7.
ASSOCIATION OF SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER WITH PHYSICAL ACTIVITY, MEDIA TIME, AND FOOD INTAKE IN CHILDREN AND ADOLESCENTS.
Van Egmond-Frohlich AWA, Weghuber D, De Zwaan M.
Introduction: The aim of the study was to assess the association between attention deficit/hyperactivity disorder (ADHD) symptoms and potentially obesogenic behaviors.
Methods: Data of 11,676 German children and adolescents (6-17 years) were analyzed. Television/video exposure, physical activity, food frequency and portion size were assessed using questionnaires. A dietary quality index, energy density and volumes of consumed food, and total energy intake were calculated. The parent-rated hyperactivity/inattention subscale of the Strengths and Difficulties Questionnaire (SDQ-HI) was used as a continuous measure of ADHD symptoms. Associations were analyzed with general linear models adjusting for sex, age, socioeconomic status, migrant status, parental BMI, and parental smoking.

Results: SDQ-HI scores correlated positively with physical activity, average energy density of food, volume of beverages, total energy intake, and television exposure and negatively with the nutritional quality score (HuSKY) even after adjustment for parental variables (BMI, smoking, socioeconomic status, migrant status), age, sex, as well as the other SDQ subscales. The adjusted association of the SDQ-HI scores with the nutritional quality score was stronger in girls and the associations with food volume, food energy, and total energy intake was significant only in girls.
Conclusions: Poor nutritional quality, high energy intake and television exposure appear to be independently associated with ADHD symptoms. The relationship between food energy intake and ADHD symptoms was especially pronounced in girls and this may help to explain the reported association of ADHD symptoms with overweight in adolescent girls.

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PLoS ONE. 2012;7.

FTO AT RS9939609, FOOD RESPONSIVENESS, EMOTIONAL CONTROL AND SYMPTOMS OF ADHD IN PRESCHOOL CHILDREN.

Velders FP, de Wit JE, Jansen PW, et al.

The FTO minor allele at rs9939609 has been associated with body mass index (BMI: weight (kg)/height (m)2) in children from 5 years onwards, food intake, and eating behaviour. The high expression of FTO in the brain suggests that this gene may also be associated with behavioural phenotypes, such as impulsivity and control. We examined the effect of the FTO minor allele (A) at rs9939609 on eating behaviour, impulsivity and control in young children, thus before the BMI effect becomes apparent. This study was embedded in the Generation R Study, a population-based cohort from fetal life onwards. 1,718 children of European descent were genotyped for FTO at rs9939609. With logistic regression assuming an additive genetic model, we examined the association between the FTO minor allele and eating behaviour, impulsivity and control in preschool children. There was no relation between FTO at rs9939609 and child BMI at this age. The A allele at rs9939609 was associated with increased food responsiveness (OR 1.21, p = 0.03). Also, children with the A allele were less likely to have symptoms of ADHD (OR 0.74, p = 0.01) and showed more emotional control (OR 0.64, p = 0.01) compared to children without the A allele. Our findings suggest that before the association between FTO and BMI becomes apparent, the FTO minor allele at rs9939609 leads to increased food responsiveness, a decreased risk for symptoms of ADHD and better emotional control. Future studies are needed to investigate whether these findings represent one single mechanism or reflect pleiotropic effects of FTO.

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PLoS ONE. 2012;7.

A BRAIN-COMPUTER INTERFACE BASED ATTENTION TRAINING PROGRAM FOR TREATING ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lim CG, Lee TS, Guan C, et al.

Attention deficit hyperactivity disorder (ADHD) symptoms can be difficult to treat. We previously reported that a 20-session brain-computer interface (BCI) attention training programme improved ADHD symptoms. Here, we investigated a new more intensive BCI-based attention training game system on 20 unmedicated ADHD children (16 males, 4 females) with significant inattentive symptoms (combined and inattentive ADHD subtypes). This new system monitored attention through a head band with dry EEG sensors, which was used to drive a feed forward game. The system was calibrated for each user by measuring the EEG parameters during a Stroop task. Treatment consisted of an 8-week training comprising 24 sessions followed by 3 once-monthly booster training sessions. Following intervention, both parent-rated inattentive and hyperactive-impulsive symptoms on the ADHD Rating Scale showed significant improvement. At week 8, the mean improvement was -4.6 (5.9) and -4.7 (5.6) respectively for inattentive symptoms and hyperactive-impulsive symptoms (both $p<0.01$). Cohen's d effect size for inattentive symptoms was large at 0.78 at week 8 and 0.84 at week 24 (post-boosters). Further analysis showed that the change in the EEG based BCI ADHD severity measure correlated with the change ADHD Rating Scale scores. The BCI-based

attention training game system is a potential new treatment for ADHD. Trial Registration: ClinicalTrials.gov NCT01344044.

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PLoS ONE. 2012;7.

MONITORING CORTICAL EXCITABILITY DURING REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN CHILDREN WITH ADHD: A SINGLE-BLIND, SHAM-CONTROLLED TMS-EEG STUDY.

Helfrich C, Pierau SS, Freitag CM, et al.

Background: Repetitive transcranial magnetic stimulation (rTMS) allows non-invasive stimulation of the human brain. However, no suitable marker has yet been established to monitor the immediate rTMS effects on cortical areas in children.

Objective: TMS-evoked EEG potentials (TEPs) could present a well-suited marker for real-time monitoring. Monitoring is particularly important in children where only few data about rTMS effects and safety are currently available.

Methods: In a single-blind sham-controlled study, twenty-five school-aged children with ADHD received subthreshold 1 Hz-rTMS to the primary motor cortex. The TMS-evoked N100 was measured by 64-channel-EEG pre, during and post rTMS, and compared to sham stimulation as an intraindividual control condition.

Results: TMS-evoked N100 amplitude decreased during 1 Hz-rTMS and, at the group level, reached a stable plateau after approximately 500 pulses. N100 amplitude to supra-threshold single pulses post rTMS confirmed the amplitude reduction in comparison to the pre-rTMS level while sham stimulation had no influence. EEG source analysis indicated that the TMS-evoked N100 change reflected rTMS effects in the stimulated motor cortex. Amplitude changes in TMS-evoked N100 and MEPs (pre versus post 1 Hz-rTMS) correlated significantly, but this correlation was also found for pre versus post sham stimulation.

Conclusion: The TMS-evoked N100 represents a promising candidate marker to monitor rTMS effects on cortical excitability in children with ADHD. TMS-evoked N100 can be employed to monitor real-time effects of TMS for subthreshold intensities. Though TMS-evoked N100 was a more sensitive parameter for rTMS-specific changes than MEPs in our sample, further studies are necessary to demonstrate whether clinical rTMS effects can be predicted from rTMS-induced changes in TMS-evoked N100 amplitude and to clarify the relationship between rTMS-induced changes in TMS-evoked N100 and MEP amplitudes. The TMS-evoked N100 amplitude reduction after 1 Hz-rTMS could either reflect a globally decreased cortical response to the TMS pulse or a specific decrease in inhibition.

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PLoS ONE. 2012;7.

COMPREHENSIVE PHENOTYPE/GENOTYPE ANALYSES OF THE NOREPINEPHRINE TRANSPORTER GENE (SLC6A2) IN ADHD: RELATION TO MATERNAL SMOKING DURING PREGNANCY.

Thakur GA, Sengupta SM, Grizenko N, et al.

Objective: Despite strong pharmacological evidence implicating the norepinephrine transporter in ADHD, genetic studies have yielded largely insignificant results. We tested the association between 30 tag SNPs within the SLC6A2 gene and ADHD, with stratification based on maternal smoking during pregnancy, an environmental factor strongly associated with ADHD.

Methods: Children (6-12 years old) diagnosed with ADHD according to DSM-IV criteria were comprehensively evaluated with regard to several behavioral and cognitive dimensions of ADHD as well as response to a fixed dose of methylphenidate (MPH) using a double-blind placebo controlled crossover trial. Family-based association tests (FBAT), including categorical and quantitative trait analyses, were conducted in 377 nuclear families.

Results: A highly significant association was observed with rs36021 (and linked SNPs) in the group where mothers smoked during pregnancy. Association was noted with categorical DSM-IV ADHD diagnosis (Z = 3.74, P = 0.0002), behavioral assessments by parents (CBCL, P = 0.00008), as well as restless-impulsive subscale scores on Conners'-teachers (P = 0.006) and parents (P = 0.006). In this subgroup, significant association was also observed with cognitive deficits, more specifically sustained attention, spatial working

memory, planning, and response inhibition. The risk allele was associated with significant improvement of behavior as measured by research staff (Z = 3.28, P = 0.001), parents (Z = 2.62, P = 0.009), as well as evaluation in the simulated academic environment (Z = 3.58, P = 0.0003).
Conclusions: By using maternal smoking during pregnancy to index a putatively more homogeneous group of ADHD, highly significant associations were observed between tag SNPs within SLC6A2 and ADHD diagnosis, behavioral and cognitive measures relevant to ADHD and response to MPH. This comprehensive phenotype/genotype analysis may help to further understand this complex disorder and improve its treatment. Clinical trial registration information - Clinical and Pharmacogenetic Study of Attention Deficit with Hyperactivity Disorder (ADHD); www.clinicaltrials.gov; NCT00483106.

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PLoS ONE. 2012 Sep;7.
COMORBID EXTERNALISING BEHAVIOUR IN AD/HD: EVIDENCE FOR A DISTINCT PATHOLOGICAL ENTITY IN ADOLESCENCE.
Perera S, Crewther D, Croft R, et al.
While the profiling of subtypes of Attention Deficit Hyperactivity Disorder (AD/HD) have been the subject of considerable scrutiny, both psychometrically and psychophysiologically, little attention has been paid to the effect of diagnoses comorbid with AD/HD on such profiles. This is despite the greater than 80% prevalence of comorbidity under the DSM-IV-TR diagnostic definitions. Here we investigate the event related potential (ERP) and psychometric profiles of Controls, AD/HD, and comorbid AD/HD (particularly AD/HD+ODD/CD) groups on six neurocognitive tasks thought to probe the constructs of selective and sustained attention, response inhibition and executive function. Data from 29 parameters extracted from a child group (age range 6 to 12; 52 Controls and 64 AD/HD) and from an adolescent group (age range 13 to 17; 79 Controls and 88 AD/HD) were reduced via a Principal Components Analysis, the 6 significant eigenvectors then used as determinants of cluster membership via a Two-Step Cluster Analysis. Two clusters were found in the analysis of the adolescent age group—a cluster dominated by Control and AD/HD participants without comorbidity, while the second cluster was dominated by AD/HD participants with externalising comorbidity (largely oppositional defiant/conduct disorder ODD/CD). A similar segregation within the child age group was not found. Further analysis of these objectively determined clusters in terms of their clinical diagnoses indicates a significant effect of ODD/CD comorbidity on a concurrent AD/HD diagnosis. We conclude that comorbid externalising behaviour in AD/HD constitutes a distinct pathological entity in adolescence.

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2013;40:292-97.
ALLELE-SPECIFIC ASSOCIATIONS OF 5-HTTLPR/RS25531 WITH ADHD AND AUTISM SPECTRUM DISORDER.
Gadow KD, DeVincent CJ, Siegal VI, et al.
Background: The aims of the present study were to examine the association between a common serotonin transporter gene (SLC6A4) polymorphism 5-HTTLPR/rs25531 with severity of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) symptoms.
Methods: Mothers and teachers completed a validated DSM-IV-referenced rating scale for ADHD and ASD symptoms in 118 children with ASD.
Results: Analyses indicated that children with at least one copy of the S or LG allele obtained significantly more severe maternal ratings of hyperactivity (p=0.001; (eta)p2=0.097) and impulsivity (p=0.027; (eta)p2=0.044) but not inattention (p=0.061; (eta)p2=0.032), controlling for ASD severity, than children homozygous for the LA allele. Conversely, mothers' ratings indicated that children with LA/LA genotype had more severe ASD social deficits than S or LG allele carriers (p=0.003; (eta)p2=0.081), controlling for ADHD symptom severity. Teachers' ratings though consistent with mothers' ratings of hyperactivity and social deficits were marginally significant (p=0.07/p=0.09). There was some evidence that the magnitude of parent-teacher agreement regarding symptom severity varied as a function of the child's genotype.

Conclusion: The 5-HTTLPR/rs25531 polymorphism or its correlates may modulate severity of ADHD and ASD symptoms in children with ASD, but in different ways. These tentative, hypothesis-generating findings require replication with larger independent samples.

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Psychiatry Res. 2012;198:482-88.

THE QUANTITATIVE EEG THETA/BETA RATIO IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND NORMAL CONTROLS: SENSITIVITY, SPECIFICITY, AND BEHAVIORAL CORRELATES.

Ogrim G, Kropotov J, Hestad K.

The purpose of the present study was to determine if the theta/beta ratio, and theta and beta separately, correlate with behavioral parameters, and if these measures discriminate between children and adolescents with attention deficit/hyperactivity disorder (ADHD) and normal gender- and age-matched controls. Participants comprised 62 patients and 39 controls. A continuous performance test (CPT), a GO/NOGO test and two rating scales were used to measure behavior in the patient group. EEG spectra were analyzed in eyes-closed and eyes-opened conditions, and in a GO/NOGO task in both groups. Neither the theta/beta ratio at CZ, nor theta and beta separately, discriminated significantly between patients and controls. When each person was compared with the database, significant elevations of theta were found in 25.8% of the patients and in only one control subject (2.6%). In the ADHD group, theta at CZ was positively correlated with inattention and executive problems and negatively correlated with hyperactivity/impulsivity. Beta correlated with good attention level in the control group, but with ADHD symptoms in the patients. Omission errors in the GO/NOGO test discriminated between patients and controls with an accuracy of 85%. For theta at CZ, the accuracy was 62%. Significantly elevated theta characterized a subgroup of ADHD patients, and correlated with inattention and executive problems.

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Psychiatry Res. 2012;198:334-35.

FAMILY-BASED ASSOCIATION STUDY OF COCAINE- AND AMPHETAMINE-REGULATED TRANSCRIPT (CARTPT) AND PROTEIN INTERACTION WITH C-KINASE-1 (PICK1) GENES IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Hsu CD, Tzang RF, Loh EW, et al.

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Psychiatry Res Neuroimaging. 2012.

THALAMIC SHAPE AND CONNECTIVITY ABNORMALITIES IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Xia S, Li X, Kimball AE, et al.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by widespread structural and functional abnormalities in the cortico-striato-thalmo-cortical (CSTC) loops that subserve attention and executive functions. In this study, we analyzed thalamic shape and its white matter connections using structural MRI and diffusion tensor imaging (DTI) data acquired from children with ADHD (n=19) and controls (n=19). Shape morphology of the thalamus was assessed using shape-based analysis, while connectivity between the thalamus and other brain regions was determined using probabilistic diffusion tractography. Shape-based analysis indicated significant regional atrophy in the left thalamus in children with ADHD compared to controls. Group analyses of white matter connectivity measures showed significantly decreased mean fractional anisotropy (FA) and volume of the tracts between thalamus and striatum, hippocampus, and prefrontal lobe in children with ADHD compared to controls. The structural abnormalities within the thalamus and the reduced integrity of the white matter tracks between thalamus and other brain regions, as shown from the results of this study, may be the anatomical bases of the impaired cognitive performances in the attention and executive function domains in ADHD.

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Psychiatry Res Neuroimaging. 2012;204:32-39.

REDUCED INSULAR VOLUME IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lopez-Larson MP, King JB, Terry J, et al.

The aim of this study was to evaluate whether structural differences in the insula and anterior cingulate cortex (ACC), two critical areas of the "salience network," co-exist in adolescents with attention deficit hyperactivity disorder (ADHD) compared with healthy controls (HC). In addition we aimed to determine if structural changes within these regions correlate with attention and inhibitory function. Nineteen adolescents with ADHD and 25 HC received MRI scans on a 3. T magnet. Morphometric analysis was performed with FreeSurfer. Youths with ADHD were found to have a bilateral reduction in anterior insular (AIC) gray matter volumes compared to HC. Furthermore, the left AIC was found to positively correlate with oppositional symptoms, while the right AIC was found to associate with both attention problems and inhibition. To our knowledge this is the first report of a bilateral reduction in AIC volumes in ADHD. Our findings suggest a role for the insula in modulating attention and inhibitory capacity in ADHD.

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Psychol Med. 2012 Oct;42:2225-34.

ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN INVESTIGATION OF AGE-RELATED DIFFERENCES IN BEHAVIOURAL SYMPTOMS, NEUROPSYCHOLOGICAL FUNCTION AND CO-MORBIDITY.

Bramham J, Murphy DGM, Xenitidis K, et al.

Background: The outcomes of attention deficit hyperactivity disorder (ADHD) have been studied extensively in the first decades of life, but less is known about ADHD in adulthood. Hence we investigated cross-sectional age-related differences in behavioural symptoms, neuropsychological function and severity of co-morbid disorders within a clinically referred adult ADHD population.

Method: We subdivided 439 referrals of individuals with ADHD (aged 16–50 years) into four groups based on decade of life and matched for childhood ADHD severity. We compared the groups on measures of self- and informant-rated current behavioural ADHD symptoms, neuropsychological performance, and self-rated co-morbid mood and anxiety symptoms.

Results: There was a significant age-related reduction in the severity of all ADHD symptoms based on informant-ratings. In contrast, according to self-ratings, inattentive symptoms increased with age. Neuropsychological function improved across age groups on measures of selective attention and response inhibition. There was a mild correlation between the severity of depression symptoms and increasing age.

Conclusions: This observational study suggests that, in adulthood, ADHD symptoms as measured using informant-ratings and neuropsychological measures continue to improve with increasing age. However the subjective experience of people with ADHD is that their symptoms worsen. This dichotomy may be partially explained by the presence of co-morbid affective symptoms. The main limitation of the study is that it is cross-sectional rather than longitudinal, and the latter design would provide more conclusive evidence regarding age-related changes in an adult ADHD population.

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Res Autism Spectr Disord. 2013;7:1-8.

AN EVALUATION OF THE COMPONENTS OF A SOCIAL STORIES(TRADEMARK) INTERVENTION PACKAGE.

Iskander JM, Rosales R.

The present study examined the effectiveness of Social Stories(trademark), and Social Stories paired with a differential reinforcement procedure on disruptive behaviors of two elementary school children diagnosed with pervasive developmental disorder-not otherwise specified (PDD-NOS) and attention deficit hyperactivity disorder (ADHD). We implemented a multiple-baseline design across target behaviors, whereby the Social Story was implemented first, followed by the pairing of the story and a differential reinforcement of zero behavior (DRO) procedure. Results indicate that while the use of a Social Story was

effective in decreasing problem behavior when compared to baseline levels, the pairing of the story with a DRO procedure resulted in lower average levels of the target behaviors across both participants.

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Res Dev Disabil. 2012 Nov;33:2080-87.

MOTOR SKILLS OF CHILDREN NEWLY DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER PRIOR TO AND FOLLOWING TREATMENT WITH STIMULANT MEDICATION.

Brossard-Racine M, Shevell M, Snider L, et al.

Motor difficulties are common in children with Attention Deficit Hyperactivity Disorder (ADHD). Although preliminary evidence has suggested that methylphenidate can improve the motor skills in children with ADHD and Developmental Coordination Disorder (DCD), the effect of stimulant medication on motor performance in children newly diagnosed with ADHD with or without motor impairment remains unclear. A cohort study of 49 medication-naïve children (39 male; mean age 8.4 ± 1.3 years) with ADHD was conducted. Children were evaluated using the Movement Assessment Battery for Children and the developmental test of visual motor integration at diagnosis and again three months following daily treatment with a stimulant medication. Motor difficulties were highly present at baseline (73.5%) but resolved in a subset after treatment with stimulant medication, suggesting that their motor difficulties may be attributed in part to their attentional problems. Nevertheless, motor impairment persisted in 55.1% of the sample. The severity of the behavioural symptoms was significantly associated with balance skills in children without motor impairments ($r^2 = 0.30$, $p < 0.01$) and with visual motor integration skills in children with persisting motor difficulties ($r^2 = 0.27$, $p < 0.01$). Attentional difficulties negatively affect the motor skills of children with ADHD. Following the use of stimulant medication, an important subset continued to demonstrate motor difficulties. The improvement in behaviour was insufficient to resolve motor problems and these children should therefore be targeted for rehabilitation services.

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Res Dev Disabil. 2013;34:656-68.

PARENT-CHILD INTERACTION OF MOTHERS WITH DEPRESSION AND THEIR CHILDREN WITH ADHD.

Lee PC, Lin KC, Robson D, et al.

Attention deficit/hyperactivity disorder (ADHD) is a developmental disorder that may have a chronic and pervasive impact on the child's function and cause long-term stress to parents. A higher rate of depression is associated with mothers of children with ADHD. This observational study aimed to investigate the effect of maternal depression and the child's ADHD on the quality of the parent-child interaction in children with ADHD and their mothers with depression. The study participants comprised 39 mother-son dyads including children with ADHD and mothers with depression, children with ADHD and mothers without depression, and children without ADHD and mothers without depression. The Specific Affect Coding System, 20-code version was used to code interactional affect, including positive engagement, negative engagement, negative disengagement, and neural affect. There were no statistically significant group-by-context interaction effects or group effects on all affective variables between the group of children with ADHD and mothers without depression and the group of children without ADHD and mothers without depression. Stimulant medication may account for these nonsignificant findings. No significant difference of positive affect between neutral and conflict-solving contexts was observed in depressed mothers whose children were diagnosed as ADHD. Children with ADHD whose mothers were depressed were less positive in their parent-child interaction compared with children in the other groups. Maternal depression may play an important role in the affective presentation of dyads of children with ADHD and mothers with depression. Implications for clinical practice and future research are provided.

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Res Dev Disabil. 2013;34:640-49.

EARLY IDENTIFICATION OF ASPERGER SYNDROME IN YOUNG CHILDREN.

Hoffmann W, Konig U, Heinzel-Gutenbrunner M, et al.

This study was designed to identify items of the ADI-R that allow an early and sensitive identification of children with possible Asperger syndrome (AS). The aim was to obtain an economic short interview suitable for screening purposes. The study was based on data from a clinical sample of 5-18-year-old children and adolescents (mean age 10.9. years) with either Attention-Deficit Hyperactivity Disorder (ADHD; n= 43) or AS (n= 62). The introductory questions and 36 items, which contribute to the diagnostic algorithm of the ADI-R, were subjected to content analysis and stepwise discriminant function analysis. Eight meaningful items were found, which were shown to be good predictors of AS and to discriminate between the children with AS and those with ADHD. The short interview was especially useful for the assessment and screening of children up to 11. years in our sample, because in this subgroup, sensitivity was even higher (.92) and specificity was also excellent (.90). Eight items with high discriminatory power allowed sensitive and economic screening for young children with suspected AS.

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Res Dev Disabil. 2013;34:710-20.

ASSOCIATION BETWEEN EARLY ATTENTION-DEFICIT/HYPERACTIVITY SYMPTOMS AND CURRENT VERBAL AND VISUO-SPATIAL SHORT-TERM MEMORY.

Gau SSF, Chiang HL.

Deficits in short-term memory are common in adolescents with attention-deficit/hyperactivity disorder (ADHD), but their current ADHD symptoms cannot well predict their short-term performance. Taking a developmental perspective, we wanted to clarify the association between ADHD symptoms at early childhood and short-term memory in late childhood and adolescence. The participants included 401 patients with a clinical diagnosis of DSM-IV ADHD, 213 siblings, and 176 unaffected controls aged 8-17 years (mean age, 12.02 (plus or minus) 2.24). All participants and their mothers were interviewed using the Chinese Kiddie Epidemiologic version of the Schedule for Affective Disorders and Schizophrenia to obtain information about ADHD symptoms and other psychiatric disorders retrospectively, at an earlier age first, then currently. The participants were assessed with the Wechsler Intelligence Scale for Children - 3rd edition, including Digit Span, and the Spatial working memory task of the Cambridge Neuropsychological Test Automated Battery. Multi-level regression models were used for data analysis. Although crude analyses revealed that inattention, hyperactivity, and impulsivity symptoms significantly predicted deficits in short-term memory, only inattention symptoms had significant effects (all $p < 0.001$) in a model that included all three ADHD symptoms. After further controlling for comorbidity, age of assessment, treatment with methylphenidate, and Full-scale IQ, the severity of childhood inattention symptoms was still significantly associated with worse verbal ($p = 0.008$) and spatial (p ranging from 0.017 to 0.002) short-term memory at the current assessment. Therefore, our findings suggest that earlier inattention symptoms are associated with impaired verbal and visuo-spatial short-term memory at a later development stage. Impaired short-term memory in adolescence can be detected earlier by screening for the severity of inattention in childhood.

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Res Dev Disabil. 2013;34:562-72.

PREDICTORS OF DIAGNOSIS OF CHILD PSYCHIATRIC DISORDER IN ADULT-INFANT SOCIAL-COMMUNICATIVE INTERACTION AT 12 MONTHS.

Marwick H, Doolin O, Allely CS, et al.

To establish which social interactive behaviours predict later psychiatric diagnosis, we examined 180 videos of a parent-infant interaction when children were aged one year, from within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. Sixty of the videos involved infants who were later diagnosed with a psychiatric disorder at seven years, and 120 were a randomly selected sex-matched control group. Interactive behaviours for both the caregiver and the one year old infant were coded from the videos according to eight holistic categories of interpersonal engagement: Well-being, Contingent

Responsiveness, Cooperativeness, Involvement, Activity, Playfulness, Fussiness, and Speech. Lower levels of adult activity and speech in interaction at one year significantly predicted overall diagnosis of child psychiatric disorder.

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Ther Adv Psychopharmacol. 2011;1:71-75.

DOSE OF METHYLPHENIDATE DURING SERVICE TRANSITION FOR ADULTS WITH ADHD.

Adamou M, Bowers S.

Objectives: We wanted to investigate how one element of the transitional process of adolescents to an adult ADHD service, namely the use of medication, fared when compared to the recommendations of national guidelines.

Methods: We did a chart review of the dose of stimulants in a cohort of transitional patients after they were transferred to an adult ADHD service, whilst investigating if other variables such as severity of ADHD, age, gender and comorbidity played any role in determining the dose of stimulants at transition.

Results: The dose of stimulants when calculated in mg/kg was almost half the recommended whist the patients were also severely symptomatic. Reported comorbidity with Autistic Spectrum Disorders was also very high.

Conclusions: A handover approach of adolescents with ADHD to an adult service, may hide gaps at least as far as prescribing is concerned. This gap may need considerable resources to address successfully. We suggest that establishing transitional processes may help minimise this problem.

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Value Health. 2012;15:A334.

SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF TREATMENTS USED FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

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

OBJECTIVES: Although many treatments for ADHD are used off-label, in the UK, only atomoxetine (ATX), dexamphetamine (DEX), and methylphenidate (MPH) are licensed for use in children and adolescents. The objective of this review was to systematically review and synthesise the existing clinical evidence, by indirectly comparing the licensed treatments and a drug in development, lisdexamfetamine (LDX).

METHODS: A systematic review of randomised controlled clinical trials, dated 1960 or later, in children and adolescents with ADHD that included at least one of LDX, MPH, DEX, or ATX was performed. Network meta-analysis methods for dichotomous outcomes were employed to evaluate treatment efficacy (response defined by either the ADHD Rating Scale [ADHD-RS] or Clinical Global Impression- Improvement scale [CGI-I]) and safety outcomes (all cause withdrawals [WDW] and withdrawal due to adverse events [AEWDW]).

RESULTS: The systematic review included 32 trials, dated 2000 or later, including data on LDX, ATX, and MPH (extended release [MPH-ER], intermediate release [MPH-intR] and immediate release [MPH-IR]). No trials for DEX meeting the inclusion criteria were found. Sufficient data were identified for each of the outcomes: ADHD-RS, 16 trials; CGI-I, 20 trials; WDW, 28 trials; and AEWDW, 27 trials. The efficacy relative risks (95% confidence intervals [CI]) for LDX versus ATX were ADHD-RS, 1.41 (1.24, 1.61); CGI-I, 1.55 (1.28, 1.87); and for LDX versus MPH-ER (the most commonly used MPH formulation) were ADHD-RS, 1.22 (1.08, 1.38); and CGI-I, 1.23 (1.04, 1.45). The safety relative risks (95% confidence intervals [CI]) for LDX versus ATX were WDW, 0.75 (0.49, 1.17); AEWDW, 1.72 (0.46, 6.37); and for LDX versus MPH-ER were WDW: 1.15 (0.74, 1.78), and AEWDW: 2.70 (0.75, 9.71).

CONCLUSIONS: The evidence synthesis of efficacy favours LDX over ATX and MPH-ER for the treatment of ADHD. The analysis of safety data proved inconclusive due to small event rates.

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Value Health. 2012;15:A335.

COSTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) BEING COMPLIANT OR NON-COMPLIANT TO PHARMACOLOGICAL TREATMENT: RESULTS FROM A DUTCH OBSERVATIONAL STUDY.

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

OBJECTIVES: The discussion on compliance versus non-compliance exercises many minds in ADHD. Given the potential economic impact, we investigated societal costs among compliant and non-compliant children with ADHD.

METHODS: A cross-sectional retrospective survey among parents of a child aged 6-18 (members of the Dutch patient organization) with ADHD was conducted in September 2010. The TiC-P questionnaire was used to collect data on medical and non-medical resource use. Reference prices (2010) from the Netherlands were taken as unit costs. Differences were analysed using Students' t-tests. Compliance status was based on parent evaluation and based on pre-defined definitions supported by expert opinion.

RESULTS: This first analysis was based on 473 and 219 children who were compliant or non-compliant to pharmacological treatment, respectively. Mean age was 11.2 years, 82.8% were boys. Compliance had a significant influence on total treatment costs, with total mean monthly costs being (euro)543 (SD (euro) 1141) and (euro)879 (SD (euro)1368) for compliant and non-compliant children, respectively (p=0.001). The most important cost items were medical consultations (23.4% vs. 26.3%), coaching and extra support lessons at school (24.0% vs. 18.5%), skills trainings (18.2% vs. 19.0%), and child day care (13.8% vs. 11.0%). Medication constituted 4.8% and 2.7% of total costs. Next to compliance, regression analysis showed that comorbidity also had a significant influence on total treatment costs (p=0.000). In a regression model in which compliance and comorbidity were independent variables, both were significant (p=0.003 and p=0.000, respectively). Mean costs were (euro)253 and (euro)659 (compliant vs. non-compliant) for children without comorbidity and (euro)669 and (euro)950 for children with comorbidity. Adding a dummy for comorbiditynullcompliance did not show a significant interaction between the two.

CONCLUSIONS: Children compliant to ADHD medication have significant lower monthly costs compared to non-compliant children. So, effective methods to improve compliance medication in this patient population may be cost-effective.

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Value Health. 2012;15:A340.

SYSTEMATIC REVIEW OF HEALTH STATE UTILITIES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Zimovetz E, Setyawan J, Beard S, et al.

OBJECTIVES: To systematically identify and review published evidence on healthstate utility weights in paediatric and adolescent ADHD.

METHODS: Utility weights were identified as part of a wider systematic review, which was performed to identify input parameter values for an economic model in ADHD. PubMed, EMBASE, Cochrane National Health Service's Economic Evaluation Database, EconLit, and Health Economic Evaluations Database were searched from 1960 to May 2011. The review focused on articles reporting utility weights in ADHD by level of treatment response.

RESULTS: A total of 1,648 unique titles and abstracts were retrieved; 1,630 records were excluded upon title (or abstract) review and 12 upon full-text review. The review included 6 studies reporting utilities by level of response, 2 of which further stratified utilities by treatment type. One study reported utilities for 4 health states ('normal', 'borderline to mildly ill', 'moderately to markedly ill', and 'severely ill'). One study used the EQ-5D instrument completed by parents; 2 assessed parents' preferences using standard gamble; 1 used statistical mapping (for responder and nonresponder states) and time trade-off (TTO) interviews and visual analogue scales (for 4 disease-severity health states); 1 calculated scores from other utility studies; and 1 did not report methods explicitly. Utilities for responders ranged between 0.98 and 0.80; utilities for non-responders ranged between 0.93 and 0.70. TTO-derived utilities for the 4 health states were rated by members of the general public and ranged from 0.839 ('normal') to 0.444 ('severely ill'). The review assessed the methodological compliance of each included study with NICE Reference Case.

CONCLUSIONS: Our review identified utility estimates potentially suitable for use in ADHD economic evaluations. Appropriateness of these for inclusion in a particular analysis needs to be assessed in terms of the modelled heath states and the clinical outcomes used to define these.

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Research report

Visual attentional engagement deficits in children with Specific Language Impairment and their role in real-time language processing

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ABSTRACT

In order to become a proficient user of language, infants must detect temporal cues embedded within the noisy acoustic spectra of ongoing speech by efficient attentional engagement. According to the neuro-constructivist approach, a multi-sensory dysfunction of attentional engagement – hampering the temporal sampling of stimuli – might be responsible for language deficits typically shown in children with Specific Language Impairment (SLI). In the present study, the efficiency of visual attentional engagement was investigated in 22 children with SLI and 22 typically developing (TD) children by measuring attentional masking (AM). AM refers to impaired identification of the first of two sequentially presented masked objects (O1 and O2) in which the O1–O2 interval was manipulated. Lexical and grammatical comprehension abilities were also tested in both groups. Children with SLI showed a sluggish engagement of temporal attention, and individual differences in AM accounted for a significant percentage of unique variance in grammatical performance. Our results suggest that an attentional engagement deficit – probably linked to a dysfunction of the right fronto-parietal attentional network – might be a contributing factor in these children's language impairments.

1. Introduction

Children with Specific Language Impairment (SLI) show significant deficits in language abilities, without accompanying problems such as hearing impairment, neurological damage, or a deficit in nonverbal intelligence. These children show performance Intelligence Quotients (IQ) that fall within the normal range for their age, pass screening

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tests for hearing acuity, present no signs of neurological impairment, and do not display the typical symptoms of autism spectrum disorders (Leonard, 1998). Epidemiological studies suggest that the prevalence of SLI may be as high as 7% among 5-year-olds (Tomblin et al., 1997). In clinically referred studies, males outnumber females, by approximately 3 to 1 (Leonard, 1998). Children with SLI are two or three times more likely than typically developing (TD) children to have siblings with language problems or parents with a history of language problems.

The language impairment is not uniform in children with SLI; different areas within language tend to be more adversely affected than other areas. For many children, grammar is most seriously impaired, with somewhat milder limitations seen in vocabulary and phonology (Leonard, 1998). These children's comprehension of language is often more advanced than their language production abilities.

A central research question is whether this impairment is language-specific (e.g., Eyer and Leonard, 1995; Rice et al., 1995) or whether it derives from a more general deficit. According to general processing limitation approaches (e.g., Kail, 1994; Leonard, 1998; Leonard et al., 2007), children with SLI show difficulties in information processing as exhibited by restricted or inefficient working memory (WM) (Dollaghan and Campbell, 1998; Ellis Weismer et al., 1999; Gathercole and Baddeley, 1990; Marton and Schwartz, 2003; Montgomery, 2000), and sluggish speed of processing (Kail, 1994; Leonard et al., 2007; Miller et al., 2001). This deficit is viewed as general in nature because it is present in non-linguistic as well as linguistic tasks. Furthermore, deficits are seen in visual as well as auditory tasks.

Deficits in visual processing have been documented at least since the work of Tallal et al. (1981). These investigators found that children with SLI had difficulty relative to same-age peers in discriminating letter-like visual forms made visible through 75-msec light flashes. As part of evaluating Kail's (1994) generalized slowing hypothesis – that children with SLI are slower in all aspects of processing – several research teams have revealed slower response times (RTs) to visual stimuli of a non-linguistic nature on the part of children with SLI (Miller et al., 2001, 2006; Windsor et al., 2001, 2008). In some studies, the slowing has not been observed in all tasks. However, slower RTs have been seen for visual processing at least as often as for auditory processing. For example, Kohnert and Windsor (2004) found that children with SLI were slower than same-age peers on simple and choice visual detection tasks, but not simple auditory detection tasks.

Recent research has begun to focus on the role of attention during non-linguistic processing, in part because of the assumed importance of attention when performing timed tasks such as those used in speed of processing studies. For example, Schul et al. (2004) found that children with SLI were slower on a visual attention task than a group of TD children matched for age. Finneran et al. (2009) found that children with SLI were less accurate than age controls on a visual task of sustained attention (see Ebert and Kohnert, 2011 for a recent review).

Weaknesses in visual processing are also reflected in tasks of visual WM. Several studies have found deficits in children with SLI in this area of functioning (e.g., Bavin et al., 2005; Hoffman and Gillam, 2004). However, the findings for visual WM may not be independent of those seen for visual attention. Models of WM include attention as an essential process, as seen for example, in the model of Cowan (1999). It appears that brain mechanisms that control selective attention might also be those that refresh representations in WM (Gazzaley and Nobre, 2012; Jonides et al., 2005). In a study employing fMRI, Eliis Weismer et al. (2005) found that children with SLI differed from TD peers in fronto-parietal regions associated with both attention and WM.

One hypothesis, not yet fully explored in SLI, is related to the possibility that the impairment in language might also reflect a multi-sensory limitation associated with temporal engagement of attention, which refers to the ability to process an (auditory or visual) stimulus immediately followed by a second stimulus (see Hari and Renvall, 2001 for a review). In particular, a brief object that is clearly perceptible alone can be rendered invisible by the subsequent presentation of a second object nearby in time: i.e., object substitution masking (see Enns and Di Lollo, 2000 for a review). Despite the great amount of information flooding the scenes, we are able to engage our attentional resources on one object. Thus, attentional engagement can be thought of as a multi-sensory mechanism designed to enhance perception of a complex sensory world, by selecting a specific object to process further. Temporal engagement of attention is crucially involved in object substitution masking (Potter et al., 2002), and it could be specifically impaired not only in children with developmental dyslexia (DD; e.g., Facoetti et al., 2008; Ruffino et al., 2010) but also with SLI, as proposed by the "Sluggish Attentional Shifting" hypothesis of Hari et al. (2001; see Vidyasagar and Pammer, 2010 for a recent review).

According to the neuro-constructivist framework, in which development itself is the key to understanding developmental disorders (Karmiloff-Smith, 1998), a multi-sensory dysfunction of attentional engagement – hampering the temporal sampling of the relevant objects – might be responsible for the typical language deficits shown in children with SLI. Indeed, in order to become a proficient user of language, infants must detect temporal cues embedded within the noisy acoustic spectra of ongoing speech by rapid auditory processing (e.g., Benasich and Tallal, 2002; Goswami, 2011; Tallal, 1980, 2004; Tallal et al., 1993; Wright et al., 1997). A multi-sensory sluggish attentional engagement can mimic a primary rapid signal processing deficit because the inefficient attentional window will expose object perception to major interference from near temporal noisy distracters.

The engagement of temporal attention can be studied by measuring the identification of the first object (O1) when the second object (O2) is presented. O1 accuracy is usually unimpaired at short O1–O2 intervals, (e.g., 180 msec) even when it is measured in elderly normal individuals (Kavcic and Daffy, 2003). If attentional engagement toward O1 is not successfully completed by the time that O2 is presented, then O1 accuracy could be impaired (e.g., Facoetti et al., 2008; Kavcic and Daffy, 2003; Potter et al., 2002; Ruffino et al., 2010). It is known that when two visual stimuli are successively presented, they compete for processing resources (see Keysers and Perrett, 2002 for a review). When the O1–O2 interval is short, O2 is often the first to be identified, but as the O1–O2

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interval increases, O1 is increasingly likely to be the first to be identified (Potter et al., 2002). Thus, an object attracts attentional processing resources rapidly, but in the first perceptual stage attentional engagement is labile, so detection of O2 draws resources away from O1 (Potter et al., 2002; Hommel and Akyürek, 2005). This O1 accuracy changes as a function of the O1–O2 interval and has been termed attentional masking (AM) (e.g., Facoetti et al., 2008; Kavcic and Daffy, 2003; Ruffino et al., 2010).

Attentional engagement deficit is probably a multi-sensory dysfunction present in auditory as well as visual domains. Regarding auditory tasks, primary school-age children with SLI and DD often exhibit an impairment in the processing of rapid sound sequences (e.g., Helenius et al., 1999; Merzenich et al., 1996; Montgomery et al., 2005; Tallal, 1980, 2004; Tallal et al., 1993, 2004; Wright et al., 1997; Vandermosten et al., 2011; but see Studdert-Kennedy, 2002). As proposed by Hari and Renvall (2001), the deficit in processing sound sequences could be due to a prolonged auditory engagement of temporal attention (e.g., Facoetti et al., 2005, 2010; Petkov et al., 2005). Indeed, children with SLI and DD have shown substantial speech-sound perception deficits caused by very serious problems with auditory noise exclusion, which can have tragic consequences for normal linguistic development (Geiger et al., 2008; Ziegler et al., 2005, 2009). Moreover, children with DD have also exhibited deficits in the visual noise exclusion process (Geiger et al., 2008; Sperling et al., 2005, 2006). Visual attentional deficits have been also described in DD with poor phonological decoding skills (e.g., Cestnick and Coltheart, 1999; Facoetti et al., 2006; Facoetti et al., 2010; Ruffino et al., 2010). To our knowledge, no study has investigated visual attentional engagement in children with SLI.

Given the temporal nature of language processing over multiple time scales such as phonemic, syllabic and prosodic (e.g., Goswami, 2011; Hari and Renvall, 2001; Zion Golumbic et al., 2012), it is reasonable to ask what role the time-course of attentional engagement might play in ongoing language processing in children with SLI. For example, in the case of the lexicon, children might identify and predict word initial segments and selectively engage attention to those points in time to aid in processing. Similar processes may enable listeners to engage attention where inflectional morphemes or pronouns might appear in the sentences (see Stevens and Bavelier, 2012, for a recent review).

Our hypothesis is that if individuals with SLI require more time to engage attention, then it is less likely they will be able to accurately process a rapid sequence of linguistic stimuli (see Hari and Renvall, 2001). To date, no studies have investigated the relationship between the time-course required to engage visual attention and the fine-tuned ability of processing linguistic information in children with SLI. A relationship between the visual and linguistic domains could suggest that children with SLI have a multi-sensory limitation in information processing.

In summary, two main research questions were investigated in the present study: (i) Is the time-course of visual attentional engagement sluggish in children with SLI? (ii) Is there any relationship between a deficit in visual attentional engagement and the deficit in language ability in children with SLI?

2. Methods

2.1. Participants

Forty-four Italian children were recruited, aged 4;7 to 7;8 (years;months). Twenty-two of the children were diagnosed with SLI; the remaining 22 children exhibited typical development (TD) and were matched with the children with SLI according to chronological age (within 2 months) and performance IQ (within 10 points). The performance IQ was evaluated using the Italian version of the Wechsler Preschool and Primary Scale of Intelligence–III (WPPSI, Fancello and Gianchetti, 2008) for the SLI group, whereas the Italian version of the Raven's Coloured Progressive Matrices (CPM) (Belacchi et al., 2008) was used for the TD group. Several studies have found high correlations, ranging from .67 (e.g., Nehring and Court, 1992; Raven et al., 1998) to .87 (James, 1984), between the CPM and the WPPSI. No differences were found in either mean age or performance IQ between the groups: age [SLI: $M = 6;3$; $SD = 1;0$; range = 4;9–7;8; TD: $M = 6;2$; $SD = 0;11$; range = 4;7–7;8; $t(42) = .206$ $p = .838$]; performance IQ [SLI: $M = 99$; $SD = 13$; range = 85–128; TD: $M = 102$; $SD = 12$; range = 90–130; $t(42) = .977$ $p = .334$].

Children with SLI were recruited through a Health Service in Padua (Centro Medico di Foniatria) and were diagnosed by psychologists and speech therapists employed by this agency. Following Leonard's (1998) criteria, children were included in the SLI group only if they did not present with other conditions that could potentially cause or contribute to their language impairment. Thus, children with SLI showed: typical cognitive abilities on a psychological assessment (WPPSI); normal hearing; and the absence of both neurological and psychiatric disorders. Six standardized language tests were used by therapists to identify below age-level receptive and expressive language skills in the areas of vocabulary and grammar. The test data for each participant with SLI can be seen in Table 1. The tests for receptive vocabulary were: the Italian version of the PPVT-R (Stella et al., 2000) or Test di Valutazione del Linguaggio (Cianchetti and Fancello, 2003). For receptive morphosyntax, the tests were Test di Comprensione Grammaticale per Bambini (Chilosi and Cipriani, 1995) or the Italian version of the TROG-2 (Suraniti et al., 2009). The tests for expressive vocabulary were: Test di Valutazione del Linguaggio (Cianchetti and Fancello, 2003) or the Italian version of the Boston Naming Test (Riva et al., 2000). Regarding expressive morphosyntax, this skill was evaluated by therapists through a spontaneous language sample. All participants had qualified for enrollment in speech–language therapy in the National Health Service, but no child had yet begun therapy at the time of the experiment.

TD children were recruited from preschools and primary schools in Padua. According to parent and teacher report, children had: normal language; typical cognitive developmental; normal or corrected-to-normal vision; and the absence of both neurological and psychiatric disorders. Normal hearing was tested by pure-tone hearing screening bilaterally (20 dB HL) at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz (American Speech-Language-Hearing Association, 1997). Finally, a standardized nonword repetition task was administered to children with TD (VAUMeLF, Bertelli and Bilancia, 2006), revealing age-

Table 1 – Expressive and receptive language of participants with SLI: summary scores.

Child[a]	Age[b]	P-IQ[c]	Expressive language			Receptive language			
			Lexicon		Grammar	Lexicon		Grammar	
			TVL[d]	BNT[e]	EM[f]	PPVT[g]	TVL[h]	TCGB[i]	TROG-2[j]
1 *	4; 9	109	1°		H	78		<50°	
2	4; 11	94	1°		L		15°	<25°	
3	5; 0	128	5°		H		55°	<50°	
4	5; 2	85	1°		H		1°	<10°	
5 *	5; 2	90	1°		L	71		<25°	
6 *	5; 4	87	1°		H		1°	<10°	
7 *	5; 5	85	45°		H		55°	<10°	
8	5; 8	95	1°		H	73		<25°	
9 *	5; 8	85	35°		H	84			14°
10	6; 0	106	1°		L	67			34°
11 *	6; 2	104	1°		H		35°	<10°	
12	6; 6	97	5°		H	81		<50°	
13 *	6; 6	97	1°		H		5°	<10°	
14 *	6; 8	85		−1.07 SD	H	89		<25°	
15	6; 9	117	1°		H		5°	<25°	
16 *	6; 10	104		−1.27 SD	H	65		<10°	
17	7; 5	85		−.99 SD	L	93		<10°	
18	7; 5	96		−1.72 SD	H	86		<10°	
19	7; 6	85		−1.72 SD	L	103			16°
20	7; 7	118	5°		H	75		<10°	
21	7; 7	111		−1.28 SD	H	86		<10°	
22 *	7; 8	106		−3.28 SD	L	77			10°

a Child: Children indicated with an asterisk were excluded from analysis of the pronoun comprehension task data.
b Age is expressed in years; months.
c P-IQ (Performance IQ, WPPSI-III) has a mean of 100 and a SD of 15 (Fancello and Gianchetti, 2008).
d TVL (Test di Valutazione del Linguaggio): Expressive vocabulary is expressed in 11 centile points (1°, 5°, 15°, 25°, 35°, 45°, 55°, 65°, 75°, 85°, 95°) (Cianchetti and Fancello, 2003).
e BNT (Italian version of the Boston Naming Test): Six-years of age: mean for correct responses is 26.59 (SD 7; 9) for males and 25.36 (SD 5.02) for females. Seven-years of age: mean for correct responses is 34.81 (SD 6; 85) for males and 33.88 (SD 4.22) for females (Riva et al., 2000).
f EM: Expressive Morphosyntax was evaluated by clinicians through spontaneous language samples as adequate (A), lightly inadequate (L) or highly inadequate (H).
g PPVT has mean of 100 and a SD of 15 (Stella et al., 2000).
h TVL (Test di Valutazione del Linguaggio): Receptive vocabulary is expressed in 11 centile points (1°, 5°, 15°, 25°, 35°, 45°, 55°, 65°, 75°, 85°, 95°) (Cianchetti and Fancello, 2003).
i TCGB (Test di Comprensione Grammaticale per Bambini): results are expressed in 5 centile points (<10°, <25°, <50°, <75°, <95°) (Chilosi and Cipriani, 1995).
j TROG-2: results are expressed in centile points.

appropriate performance. In Italian, nonword repetition tasks are an accurate means of identifying children as language impaired or free of language impairment (Bortolini et al., 2006).

Experimental procedures were conducted according to guidelines for the protection of human participants of the University of Padua; parental consent was obtained for each child before inclusion in the study.

2.2. *Material and procedure*

Three tasks were administered to all participants – an AM task, and two language comprehension tasks. The tasks were administered separately over two or three sessions in random order (one session per day), each lasting 30 min. The children were tested individually in a quiet room, with only the examiner present.

All tasks were presented on a Toshiba Satellite Pro laptop computer. To perform the tasks we used E-Prime software (Schneider et al., 2002).

2.2.1. *Attentional masking task*

The experiment was conducted in a dimly lit (luminance of 1.5 cd/m^2) and quiet room. Participants were seated in front of a monitor; viewing distance was 40 cm. The fixation mark was a cross presented in the center of the screen (.3° of visual angle). The mask was a 'white noise' mask. Stimuli were nonverbal objects, obtained by removing three line segments from an eight-like figure (1.6 × 2.7°), comprising seven line segments; four objects were used (see Fig. 1). Participants viewed the sequence of stimuli binocularly. All visual stimuli were black (.6 cd/m^2), whereas the background was white (119 cd/m^2). Each trial began with the onset of the fixation mark (duration 1000 msec). Participants were instructed to keep their eyes on the fixation mark throughout the entire duration of the trial.

Three conditions were planned and training was provided at the beginning of the experimental session (see Fig. 1 for a schematic representation of the stimulus sequence for the AM task). The three conditions were the following:

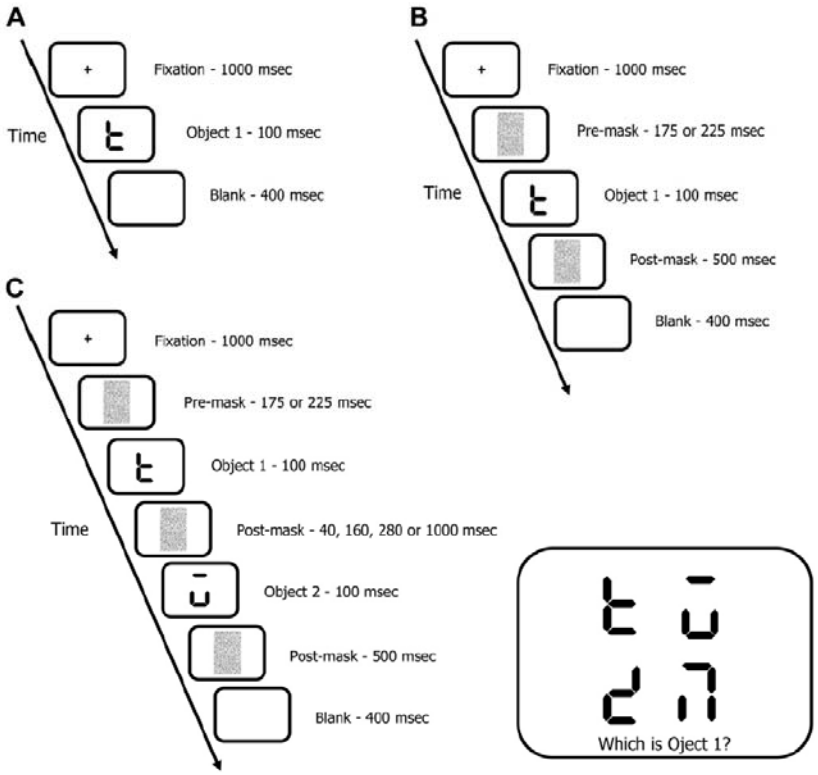

Fig. 1 – A schematic representation of the stimulus sequence used in the AM task: A – UC; B – MC; C – AMC.

1. Unmasked Condition (UC; see Fig. 1A). In order to control for visual-perceptual abilities, a single object (O) was displayed (duration 100 msec) and followed by a blank (duration 400 msec). The participants had to identify the object, choosing between the four possible object stimuli displayed on the screen until their responses were given. The participants responded by pointing, and the experimenter entered the response by pressing the corresponding key on the computer keyboard. No feedback was provided. The session consisted of eight trials.
2. Masked Condition (MC; see Fig. 1B). In this condition, a mask was presented for a variable and randomized time interval (175 and 225 msec) to maintain the subject's alertness. The mask was followed by the target (duration 100 msec), followed, in turn, by the post-mask (duration 500 msec). The participants had to identify the object by choosing among the four possible object stimuli displayed on the screen. Again, pointing responses were required, and the experimenter entered the response by pressing the corresponding key on the computer keyboard. No feedback was provided. The session consisted of eight trials.
3. Attentional Masking Condition (AMC; see Fig. 1C). In order to measure the time-course of temporal attention, the children's accuracy in identifying the first object of two sequentially masked objects was recorded. After 1000 msec, the mask was presented for a variable and randomized time interval (175 and 225 msec). The O1 was then presented for a duration of 100 msec at the central location and replaced by the post-mask. The O2 was then displayed for 100 msec after a variable time interval (i.e., 40, 160, 280 and 1000 msec) and immediately replaced by the mask which, in turn, was displayed for 500 msec. The O1–O2 interval between the two objects was 140, 260, 380 and 1100 msec. The O1 and O2 were selected at random (with replacement) among the four possible symbols. At the end of the trial, participants were required to identify the target (O1) by choosing among the four possible object stimuli displayed on the screen. These four objects came onto the screen immediately following the blank (duration 400 msec). Each participant was instructed to use all the time needed to identify the target as accurately as possible. The pointing responses of the children were recorded by the experimenter without providing feedback to the children. The experimental session consisted of 32 trials (8 trials × 4 O1–O2 intervals).

2.2.2. *Language comprehension tasks*

We evaluated two kinds of linguistic abilities in the comprehension domain: the first was a simple lexical comprehension task, whereas the second was a more complex clitic pronoun comprehension task. For all children, the two tasks were administered separately over two sessions in random order

(one session per day). In each task, two different colored objects were displayed simultaneously on a computer screen, one on the left side and one on the right side. The two pictures remained visible on the computer screen for the entire duration of the trial. The examiner described the two objects to be sure that the children recognized the objects. The child was seated in front of the screen and listened to a recorded target sentence. Only one of the two objects displayed on the screen matched the sentence target. The auditory stimuli were presented binaurally by computer over Sony headphones (at 60 dB).

The following procedure was used to prepare the stimuli. A female speaker with a neutral dialect read the stimuli using a high-quality microphone connected to a computer in an isolated acoustic room. Targets were read at a normal rate and with a normal prosodic variation. Then, each record was edited in a waveform using an Auditacy software package to identify the acoustic onset and offset of each target.

The tasks required the child to judge which of the two objects on the computer screen matched the target. The children were instructed to respond by striking the specific key on the keyboard that matched the appropriate picture (/a/, marked with a pink dot, coincided with the picture on the left side of the screen, whereas /l/, marked with a green dot, coincided with the picture on the right side of the screen). The children were instructed to rest their forefingers on the two keys. Moreover, the children were instructed to always respond as quickly and accurately as possible. A set of practice trials preceded each task. The examiner repeated the practice trials as many times as necessary to ensure that the child understood the task. The dependent variables were accuracy and response time (RT).

2.2.2.1. Lexical comprehension task. The lexical task aimed to measure the children's ability to access words, including their phonological and semantic features. In particular, the children had to judge which of two pictures displayed on the screen was the target word based on hearing the (single) word (e.g., 'luna' [moon]). Each word pair was presented twice. For example, for the pair 'moon/dog' the target was 'moon' on one trial and 'dog' on another trial. The order of the pictures on the screen (left/right) was random. This design feature was intended to avoid any effects of a child's preference for one of the two pictures, or for one side of the screen over the other. All words were appropriate for 5-year-olds' comprehension and production abilities. In each word pair, the two words were matched for syllable length (2 or 3 syllables); moreover, each word in a pair differed in terms of segment onset, semantic features (e.g., animacy), and rhyme [e.g., /lu na/vs./ca ne/ (moon vs. dog) or /pe ko ra/vs./ta vo lo/ (sheep vs. table)] (see Appendix A).

The experimental session consisted of 32 trials (16 word pairs in 2 blocks). For each trial, RTs were measured beginning immediately with the first phoneme of the word (e.g., timing began with /l/ in the two-syllable word /luna/ 'moon')/. In this way, children who were sensitive to the phonological difference between the two words could respond immediately after the onset of the target. Pressing of the response key stopped the clock. Responses occurring prior to the first phoneme of the word were scored as false alarms (negative RT). Responses in which children were not focused on the trial were considered as unscorable.

2.2.2.2. Pronoun comprehension task. The third person of the direct object clitic pronoun in Italian marks person (third), number (singular or plural), and grammatical gender (masculine or feminine). In particular, clitic pronouns assume two singular forms (masculine 'lo' and feminine 'la') and two plural forms (masculine 'li' and feminine 'le'). Importantly, the number and gender of the clitic pronoun is based on the number and gender to which it refers. That is, nouns are always inflected by the final vowel, which marks gender (masculine or feminine) and number (singular or plural). For example, for feminine 'cake' vs. 'cakes' the corresponding singular vs. plural forms are 'torta' and 'torte', respectively; for masculine 'tomato' vs. 'tomatoes' the singular vs. plural forms are 'pomodoro' and 'pomodori', respectively. Gender and number information in nouns is mastered at approximately 3 years of age by TD Italian children (e.g., Caselli et al., 1994).

Given a sentence such as 'il bambino la mangia' (the boy eats it) listeners can understand which kind of food the boy is eating (e.g., cake or tomato) only by processing the clitic pronoun. In this example, the clitic pronoun 'la' denotes a feminine noun. As can be seen, then, the pronoun comprehension task was designed to measure the children's ability to access the grammatical features of number (singular vs. plural) and gender (masculine vs. feminine) of the clitic pronoun and apply this information to determine the appropriate referent on the computer screen.

In this task, the children had to processes separately the gender and number of the pronouns. When an item required a distinction in number, the singular referent was depicted by a single object (e.g., one cake) and the plural referent was depicted by two objects (e.g., two bananas) of the same type. When an item required a distinction in gender, the masculine and feminine referents were either one object each (e.g., one apple and one ice-cream cone) or two objects each (e.g., two candies and two melons).

For all items in the pronoun comprehension task, the children listened to target sentences of the same syntactic structure [il bambino + clitic pronoun + mangia, 'the boy (clitic pronoun) eats']. Thus, responses were based solely on the number and gender of the clitic pronoun.

The task consisted of 32 trials (4 word pairs × 4 clitic pronouns × 2 blocks) (see Appendix B). The order of item presentation was random. Across the 32 trials, the location of the target picture appeared equally often at the left and right side of the screen. For each trial, RTs were measured immediately after the pronoun. For example, for the sentence 'il bambino le mangia', timing began immediately after the clitic le. Responses occurring prior to the end of the pronoun were scored as false alarms (negative RT), and those responses in which children were not focused on the trial were considered as unscorable.

3. Results

3.1. *AM task*

The mean percentages of O1 accuracy identification, and the corresponding standard deviations for the three conditions (Unmasked, Masked and Attentional masking) are shown in Table 2.

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Table 2 – Mean accuracy (and standard deviation) as a function of group (children with SLI and TD) and condition (Unmasked, Masked and Attentional masking).

Group	Condition					
	Unmasked	Masked	Attentional masking			
			140 msec	260 msec	380 msec	1100 msec
SLI	.89 (.14)	.93 (.13)	.39 (.28)	.61 (.29)	.72 (.30)	.82 (.25)
TD	.94 (.12)	.90 (.17)	.58 (.28)	.73 (.26)	.76 (.26)	.85 (.19)
Total	.92 (13)	.92 (.15)	.49 (.29)	.67 (.28)	.74 (.28)	.83 (.22)

In order to ensure that group differences were not due simply to problems with perceptual masking, a mixed 2 × 2 ANOVA was calculated, with mean accuracy in the UC and MC as a within-subjects factor and participant group (SLI and TD) as a between-subjects factor. The results showed no difference between groups ($F < 1$), or between conditions, $F < 1$. Moreover, no significant interaction was found, $F(1,42) = 3.47$, $p = .069$, $\eta^2 = .07$.

The interference caused by O2 on O1 [Attentional Masking Condition (AMC)] was then analyzed with a mixed 4 × 2 ANOVA that had O1–O2 interval (140, 260, 380 and 1100 msec) as a within-subjects factor and Group (SLI and TD) as a between-subjects factor. Since the O1–O2 interval factor was not linear, a logarithmic transformation was applied to the data. The results showed that the O1–O2 interval main effect was significant $F(3,126) = 36.62$, $p < .001$, $\eta^2 = .49$, whereas the Group main effect was not significant, $F(1,42) = 1.41$, $p = .173$, $\eta^2 = .05$. Importantly, the Group × O1–O2 interval interaction was significant, $F(3,126) = 3.72$, $p = .013$, $\eta^2 = .08$ (see Fig. 2), indicating that the time-course of the attentional engagement differed between the two groups.

To verify the crucial Group × O1–O2 interaction, we compared the slope of the time-course of attentional engagement between SLI and TD children using the mean percentages of accurate responses. To meet this aim, for each participant a linear regression with the raw scores expressed as a function of the O1–O2 interval was computed. A t-test on the regression coefficients (standard β) showed that AM was steeper for the children with SLI (mean = .44, SD = .28) than for the TD children (mean = .28, SD = .22), $t(42) = 2.08$, $p = .04$, $d = .57$.

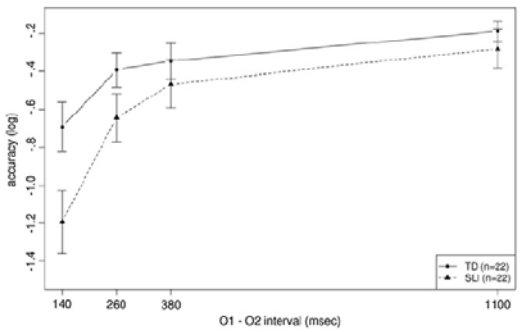

Fig. 2 – Mean O1 accuracy and standard error (after logarithmic transformation) as a function of group (children with SLI and TD) and O1–O2 intervals.

To obtain a general index of the attentional engagement deficit, the mean between the accuracy at 140 msec and at 1100 msec of the O1–O2 interval was calculated (AM effect). The accuracy at 140 msec is an index of the maximum degree of interference caused by O2 on O1, whereas the accuracy at 1100 msec is an index of the duration of attentional engagement. To control for any effects attributable to perceptual masking, the masked effect was removed by subtracting the AM effect from accuracy scores in the MC.

The AM effect could be an informative measure of the interference caused by O2 on O1 due to sluggish attentional engagement: the larger the AM effect, the slower the engagement of temporal attention. Pairwise comparisons showed a significant difference between the SLI and TD groups in the AM effect (SLI = .33, SD = .21; TD = .19, SD = .17), $t(42) = 2.45$, $p = .02$. $d = .66$.

The pattern of substitutions was also of our interest for the interference caused by O2 on O1: if the AM effect was related to sluggish attentional engagement on O1 then children should identify O2 more frequently than chance level (i.e., with three possible substitutes, chance was assumed to be .33). The children with SLI show a specific bias to O2 with a percentage (.58) significantly greater than chance, $t(21) = 5.03$, $p < .0001$, 95% confidence interval .48–.68. On the contrary, in children with typical development, the relative percentage of O2 (.39) was not significant, $t(21) = .88$, $p = .39$, 95% confidence interval .25–.54.

3.2. *Language comprehension task*

Prior to analysis of the children's RTs, two type of responses were excluded. The first type came from trials in which the response was incorrect. The second type of response involved RTs less than 10 msec and were considered to be too short to be genuine responses to the stimuli (Leonard et al., 2007). The mean of the remaining RTs for each participant was then calculated and then outliers removed (Kail, 1994). Outliers were defined as any RTs greater than 2 SD above or below the mean. This procedure was repeated until no outlier was present. Using this outlier procedure all RTs below 300 msec were removed from the pronoun task data. For the lexical task data, since shorter RTs are common in such tasks both in children with SLI and in TD group, the lower limit was 250 msec.

3.2.1. *Lexical comprehension*

The accuracy of the children with SLI (mean = .96, SD = .05) on the lexical comprehension task was similar than that of the

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TD children (mean = .98, SD = .02), $t(42) = -1.95$ $p = .058$, with an effect size of $d = -.45$. Because RT is not meaningful if children's accuracy is at chance levels, we included only those children performing above the level of chance (i.e., above .65; binomial test, $\alpha = .10$, one tailed). For the lexical comprehension task, all participants were included. The RTs were normally distributed for both groups (Kolmogorov–Smirnov test, all $ps > .05$). For this task, the children with SLI showed significantly slower RTs than the TD children (SLI: mean = 1180 msec, SD = 308, median = 1050 msec; TD: mean = 972 msec, SD = 220, median = 931 msec): $t(42) = 2.57$, $p = .014$, $d = -.67$.

A significant negative correlation was found ($r = -.331$, $p = .028$) between accuracy and RTs, indicating that children who were slower were also less accurate. We then calculated for each participant the inverse efficiency (IE; e.g., Kennett et al., 2001; Townsend and Ashby, 1983), obtained by dividing the mean RT by the proportion of correct responses. The measure of IE can be considered as a measure of how much time the children needed to correctly respond; thus both speed and accuracy were taken into account with this measure. Children with SLI (mean IE = 1236, SD = 359) showed less efficient access to lexical representations than the TD group (mean IE = 989, SD = 225), $t(42) = 2.73$, $p = .008$, $d = -1.10$.

3.2.2. *Pronoun comprehension*

On the pronoun comprehension task, the children with SLI were less accurate (mean = .65, SD = .15) than the TD children (mean = .91, SD = .11), $t(42) = -6.43$, $p < .001$, $d = -1.68$. Given our requirement for above-chance accuracy for inclusion in the analysis of RTs, only 12 children with SLI were included in RT analyses. In contrast, all TD children scored above chance levels and were therefore included. The RTs were normally distributed for both groups (Kolmogorov–Smirnov test, all $ps > .05$). The children with SLI appeared to be somewhat slower than the TD children, but this difference was not significant (SLI: mean = 1760 msec, SD = 595, median = 1855 msec; TD: mean = 1461 msec, SD = 574, median = 1242 msec), $t(32) = 1.43$, $p = .163$, $d = .50$).

A significant negative correlation was found between accuracy and RTs ($n = 34$, $r = -.429$, $p = .036$), indicating that children who were slower were also less accurate. Analysis based on the IE revealed that the children with SLI ($n = 12$) were significantly less efficient than the TD children ($n = 22$) (SLI: mean = 2341, SD = 926; TD: mean = 1667, SD = 831), $t(32) = 2.17$, $p = .037$, $d = -.81$).

3.3. *The relationship between AM and language comprehension*

3.3.1. *AM and lexical comprehension*

All 44 children could be included in the examination of the relationship between AM and lexical comprehension, as all children performed above the level of chance on the lexical task. Correlation coefficients between the AM effect, age, performance IQ, and IE of the lexical comprehension task in 22 children with SLI and 22 TD children were performed (see Table 3). For the children with SLI, the results showed a highly significant correlation between the AM effect and all other variables. Moreover, as expected, a significant correlation between age and IE was found. For the TD children, age and IE were correlated with the AM effect. A correlation between age and IE was also found.

Table 3 – Correlation coefficients between AM, age, performance IQ, and IE on the lexical comprehension task in 22 children with SLI (shaded) and 22 TD children (unshaded).

TD ($n = 22$)	SLI ($n = 22$)			
	AM	Age	P-IQ	IE
AM	–	−.472*	−461*	.452*
Age	−.423*	–	.114	−.751**
P-IQ	−.208	.227	–	.007
IE	.423*	−.665**	−321	–

Note: *$p < .05$; **$p < .01$.

On the basis of the results reported in Table 3, we planned a series of regression analyses to explore in a more stringent way the relationship between the AM effect and lexical comprehension. Given that our children ranged in age from 4; 7 to 7; 8, and that age was highly correlated with IE, we wanted to explore the contribution of the AM effect to lexical processing, controlling for the effect of age. For this reason, one fixed-order entry multiple regression analysis was performed for each group (see Table 4). For each regression, the outcome variable was the IE of lexical comprehension, the first predictor was age, and the second predictor was the AM effect.

For the children with SLI, age accounted for a significant 56% of the variance, whereas the AM effect did not explain any additional variance. For the TD children, age accounted for a significant 44% of the variance; the AM effect failed to account for any additional variance.

3.3.2. *AM and pronoun comprehension*

Recall that only 12 children with SLI (and all 22 TD children) performed above the level of chance on the pronoun comprehension task and could therefore be included in the examination of the relationship between the AM effect and pronoun comprehension. Correlation coefficients between the AM effect, age, performance IQ and IE of the lexical comprehension task were performed, separately for the SLI and TD groups (see Table 5). For the children with SLI, the results showed that age and IE were correlated with the AM effect. For the TD children, age and IE were correlated with the AM effect; a relation between IE and age was also found.

To explore the relationship between the AM effect and pronoun comprehension while controlling for the effect of age, we conducted the same set of fixed-order entry multiple

Table 4 – Multiple regression analysis on inverse efficiency in lexical comprehension.

	Lexical comprehension					
	SLI ($n = 22$)			TD ($n = 22$)		
	R^2 change	β	p	R^2 change	β	p
Step 1: Age	.564	−.751	<.001	.442	−.665	.001
Step 2: AM	.012	.125	.471	.024	.172	.363

Table 5 – Correlation coefficients between AM, age, performance IQ and IE on the pronoun comprehension task in 12 children with SLI (shaded) and in 22 TD children (unshaded).

TD ($n = 22$)	SLI ($n = 12$)			
	AM	Age	P-IQ	IE
AM	_	−.567*	−.404	.831**
Age	−.423*	_	−.043	−.454
P-IQ	−.208	.227	_	−.135
IE	−.366	−.428*	254	_

Note: *$p < .05$; **$p < .01$.

regression analysis used above (see Table 6). For children with SLI the AM effect significantly accounted for 48% of the variance beyond that explained by age. For the TD children, age accounted for a significant 18% of the variance. The AM effect failed to account for any additional variance.

4. Discussion

4.1. *Is the time-course of visual attentional engagement sluggish in children with SLI?*

The main aim of the present study was to investigate the attentional engagement efficiency in children with SLI by measuring their identification of the first of two rapidly masked objects. An object attracts attentional processing resources rapidly, but in the first perceptual stage, the attentional engagement is labile. Thus the O1 identification is reduced because the detection of O2 draws resources away from O1 (i.e., object competition or interference).

Our results showed that children with SLI had a deeper AM than TD at the shortest O1–O2 interval (140 msec), suggesting that attentional engagement could be weak and/or less resistant to a rapidly following competitive object. Moreover, the different slopes of the time-course of attentional engagement between SLI and TD children appear to confirm this interpretation. These results suggest that in children with SLI, the temporal window in which the object is engaged appears to be abnormally sluggish, hampering the efficient sampling of the perceptual object necessary to understand ongoing information flow. This result is compatible with two previous studies exploring AM in children with DD (Facoetti et al., 2008; Ruffino et al., 2010). According to these studies, dyslexia arises, not only from deficits in systems that are exclusively linguistic in nature, but also from a visual attentional impairment, which, in turn, can lead to a language disorder (Boden and Giaschi, 2007; Facoetti et al., 2000; Roach and Hogben, 2007).

Table 6 – Multiple regression analysis on inverse efficiency in pronouns comprehension.

	Pronoun comprehension					
	SLI ($n = 12$)			TD ($n = 22$)		
	R^2 change	β	p	R^2 change	β	p
Step 1: Age	.206	−.454	.138	.183	−.428	.047
Step 2: AM	.484	.845	.005	.042	.225	.326

The AM effect observed in the present study cannot be attributed to group differences in pure visual-perceptual abilities. The SLI group, like the TD group, showed a clear ability to perceive O1 in the UC and at longest O1–O2 interval.

Moreover, these results also appear to rule out a visual persistence deficit (e.g., Di Lollo et al., 1983) because in the MC and at longest O1–O2 interval the O1 identification was similar in the children with and without SLI. This result also allows us to exclude a simple backward masking deficit (e.g., Montgomery et al., 2005; Wright et al., 1997) or a general perceptual noise-exclusion deficit (e.g., Geiger et al., 2008; Ziegler et al., 2005, 2009). Although it has long been maintained that backward masking reflects a perceptual phenomenon, it is now clear that target and mask stimuli compete for processing resources (i.e., the "object substitution" theory; for a review see Enns and Di Lollo, 2000). Thus, deployment of multi-sensory temporal attention could be crucially involved in allowing perceptual identification of an object (target) immediately followed by a second object (mask). Importantly, multi-sensory backward masking is also strongly modulated by spatial as well as temporal attention (e.g., Enns, 2004; Zhang and Formby, 2007).

Finally, these results cannot be explained in term of restricted or inefficient WM (e.g., Dollaghan and Campbell, 1998; Gathercole and Baddeley, 1990; Marton and Schwartz, 2003; Montgomery, 2000), because O1 perception was different between the two groups only when O2 was displayed at the shortest O1–O2 interval, but not at longer intervals. Indeed, it would be expected that a WM deficit would impair the O1 identification when a longer, rather than shorter time separated it from O2 presentation. Moreover, recent models (Cowan et al., 2005; Gazzaley and Nobre, 2012) have indicated that individual differences in WM are associated with variation in selective attentional abilities and that factors that limit attentional capacity can impair performance on WM tasks. For these reasons, a pure WM disorder does not appear to be an accurate explanation of the AM deficits described here.

In summary, as our O2 substitution finding suggested, the results are consistent with a sluggish engagement of temporal attention in the children with SLI rather than with a basic perceptual or WM deficit in these children. It appears that the temporal window during which the engagement of attention toward a visual stimulus is labile appears to be longer in children with SLI than in TD children.

The ventral regions of the right fronto-parietal circuit are the cortical regions controlling multi-sensory attentional engagement in humans (e.g., Battelli et al., 2007; Corbetta and Shulman, 2002, 2011; Downar et al., 2000). Functional magnetic resonance imaging (fMRI) studies have demonstrated predominantly right fronto-parietal activations associated with engagement of temporal attention (e.g., Giesbrecht and Kingstone, 2004; Marois et al., 2000). In addition, attentional disengagement may be prolonged even four-fold in patients with left-side neglect due to damage of the right parietal lobe (Husain et al., 1997). Interestingly, patients with right inferior parietal damage show a severe loss in the

perception of apparent motion also in their "good" right visual field (Battelli et al., 2003). These deficits are probably due to a bilateral impairment in temporal attention to the transient events that drive the apparent motion percept. It is interesting that this motion perception deficit is similar to that shown by children with SLI and DD (e.g., Cestnick and Coltheart, 1999; Sperling et al., 2006). The multi-sensory order of events, whether two events are seen as simultaneous or successive, is also crucial for language development. Judgment of temporal order, simultaneity and high-level motion are all compromised following right parietal lesions and degraded after transcranial magnetic stimulation over the right parietal but not elsewhere (see for a review Battelli et al., 2007). The right parietal lobe could serve as part of a "when pathway" for both visual and auditory attention.

A sluggish deployment of temporal attention in children with SLI could be compatible with a mild dysfunction of the right inferior parietal cortex. In agreement with the present results, showing a clear prolongation of engagement of attention in children with SLI, psychophysical and behavioral results (i.e., temporal order judgment between visual hemifields, perception of a line motion illusion and spatial cueing tasks) suggest that dyslexic adults and children suffer from a left-side "mineneglect" (e.g., Facoetti et al., 2001; Hari et al., 2001).

Thus, our data are compatible with a right inferior parietal dysfunction in SLI that could impair the temporal selection mechanism of multi-sensory attention crucially involved in the development of an efficient sampling of syllabic-objects perception (see Goswami, 2011 for a recent review).

4.2. *Is there any relationship between a deficit in attentional engagement and the deficit in language ability in children with SLI?*

Before discussing the relationship between AM and language processing, it is important to note that the results of the lexical and pronoun comprehension tasks replicated previous findings for Italian-speaking children with SLI. Earlier studies have shown that children with SLI are more likely to err on clitic pronouns than younger TD children whose mean lengths of utterance are similar to those of the children with SLI (Bortolini et al., 1997; Leonard and Bortolini, 1998). Furthermore, difficulty with this feature has proven to be an especially accurate index of identifying language impairment in Italian; measures of clitic pronoun use have shown very good sensitivity and specificity (Bortolini et al., 2002, 2006). In contrast, as is well known, lexical ability does not constitute as much of a problem as grammatical ability in children with SLI (e.g., Leonard, 1998). In the present study, the children with SLI and the TD children showed 96% and 98% accuracy, respectively, on the lexical comprehension task (medium effect size *d* of −.45), whereas the two groups showed 65% and 91% accuracy on the clitic pronoun comprehension task (very large effect size *d* of −1.68). The fact that the lexical task did not reveal group differences, notwithstanding the fact that some children with SLI in our sample showed vocabulary weaknesses (see Table 1), could be due to the fact that our lexical comprehension task was not sufficiently sensitive to capture such differences.

The RT findings for lexical comprehension and pronoun comprehension were also in line with previous research. Several studies have shown slower RTs by children with SLI on picture naming tasks (e.g., Leonard et al., 1983), sentence-embedded word recognition tasks (Montgomery, 2006, 2008) and on receptive lexical tasks as well (Miller et al., 2001). We are not aware of studies that have specifically examined RTs for clitic pronouns. However, slower RTs for other types of grammatical items are readily seen in the literature (e.g., Leonard et al., 2009; Miller et al., 2001; Montgomery and Leonard, 2006; Wulfeck and Bates, 1995). In the present study, the lack of RT differences between groups in the pronoun task should be not surprising in light of the small number of children with SLI participating in the task ($n = 12$) relative to the much larger numbers of participants in previous RT studies (e.g., Kail, 1994; Miller et al., 2001; Leonard et al., 2007).

Collectively, these findings indicate that the SLI and TD participants in the present study were representative, giving us confidence that relating the children's language processing performance to the AM results is quite appropriate.

Regarding the link between AM and language processing, we showed that the time-course that children needed to engage their attention had a relationship with the time needed to correctly process linguistic information. This result suggests that temporal attention limitations may have an adverse effect on higher level linguistic processing. As Miller et al. (2001) proposed, the operations central to language learning, such as the parsing and extraction of special linguistically relevant details in the speech stream, are strongly time-dependent. In fact, in order to become a proficient user of language, infants must detect temporal cues embedded within the noisy acoustic spectra of ongoing speech by efficient auditory processing (e.g., Benasich and Tallal, 2002; Tallal, 1980, 2004; Tallal et al., 1993; Wright et al., 1997). Given the temporal nature of language, a sluggishness in engagement of temporal attention could have a detrimental impact when time-depended information must be processed. In Italian, this may be the case for clitic pronouns; one important physical property of these morphemes is their short duration. According to findings from several different laboratories (Bortolini and Leonard, 1996; Gerken, 1991, 1994; Gerken et al., 1990; Leonard and Bortolini, 1998), children with SLI have greater difficulty in processing unstressed syllables when these elements immediately follow another weak syllable. This is precisely the context in which clitic pronouns often appear, as seen in the weak syllable – weak syllable sequence *no la* in *Il bambino la mangia*. Considering the sluggish attentional engagement in children with SLI, the brief duration of the pronoun could be a crucial factor because brief morphemes must be perceived and processed quickly given that there is a little time before new material will appear. If individuals require more time to engage attention, then it is unlikely they will be able to accurately complete tasks involving the rapid presentation of stimuli, which is typically the case for clitic pronouns.

In the case of the lexicon, the relationship between AM and lexical comprehension was not found. This might be because the lexicon might not be as highly time dependent. In fact, as Miller et al. (2001) have shown, RTs for picture naming and

picture matching tasks are not as slow as RTs for grammatical tasks. However, it is important to stress that this result could be altered by the ceiling effect found in lexical accuracy.

Finally, regarding children with typical language development, the regression analyses showed that age was the only significant predictor of performance on both the lexical and pronoun tasks. This result was expected given the age range studied here (5–7 years), a period when children are still developing language and not yet at mastery levels (e.g., Fenson et al., 1994; Tomasello, 2003).

5. Conclusion

In the present study, a sluggish engagement of visual temporal attention was observed in children with SLI relative to TD children with similar chronological ages and nonverbal IQ scores. In addition, individual differences in temporal engagement of attention predicted the grammatical performance across participants with SLI. Given this relationship, it seems that this slower engagement might be a contributing factor in the inefficient processing of rapid sequences of linguistic objects in the input. Among the processes that are necessary for syllabic and phonemic object perception, speech-sound segmentation may be linked to the selection mechanism of general temporal attention.

Attention is considered to be a system that is deeply involved in language processing (Conner et al., 2000); for this reason, it is not surprising if a language-learning impairment seem to be associated with an attentional dysfunction. In fact, recently, several researchers (Finneran et al., 2009; Im-Bolter et al., 2006; Montgomery, 2006, 2008; Rose et al., 2001; Spaulding et al., 2008) have begun to specifically relate attention (in particular the focus of attention and the ability to sustain attention) to language impairments in both the visual and auditory modalities.

Finally, we hypothesize that the neural basis of temporal engagement deficits in children with SLI could be a mild right fronto-parietal dysfunction.

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Appendix A. Lexical comprehension task

1. /'lu na/vs./'ka ne/ [moon – dog]
2. /'le :to/vs./'to po/ [bed – mouse]
3. /'fjo re/vs./'por ta/ [flower – door]
4. /'tre no/vs./'li bro/ [train – book]
5. /'ste :la/vs./'bor sa/ [star – bag]
6. /'pe ko ra/vs./'ta vo lo/ [sheep – table]
7. /lu 'ma ka/vs./ka ':pe :lo/ [snail – hat]
8. /'so le/vs./'mu :ka/ [sun – cow]
9. /'ga :to/vs./'mo to/ [cat – motorcycle]
10. /'lu po/vs./'go :na/ [wolf – skirt]
11. /'ti gre/ vs. /'bar ka/ [tiger – boat]
12. /ma 'ti ta/ vs. /ko 'ni ʎo/ [pencil – rabbit]
13. /di 'va no/vs./ma 'ja le/ [sofa – pig]
14. /ka 'va :lo/vs./pe ':ne :lo/ [horse – brush]
15. /ga ':li na/ vs. /o ':kja li/ [chicken – glassess]
16. /'pa pe ra/vs./ki 'ta :ra/ [gosling – guitar]

Appendix B. Pronoun comprehension task

1. mela vs. gelato [apple – ice-cream] (GENDER: "il bambino la mangia" vs. "il bambino lo mangia")
2. panino vs. pesca [sandwich – peach] (GENDER: "il bambino lo mangia" vs. "il bambino la mangia")
3. zucchina vs. cipolle [courgette – onions] (NUMBER: "il bambino la mangia" vs. "il bambino le mangia")
4. finocchi vs. cavolo [fennels – cabbage] (NUMBER: "il bambino li mangia" vs. "il bambino lo mangia")
5. pizza vs. pomodoro [pizza – tomato] (GENDER: "il bambino la mangia" vs. "il bambino lo mangia")
6. biscotto vs. carota [cookie – carrot] (GENDER: "il bambino lo mangia" vs. "il bambino la mangia")
7. pesci vs. salsicce [fishs – sausages] (GENDER: "il bambino li mangia" vs. "il bambino le mangia")
8. salami vs. frittate [salamis – omelettes] (GENDER: "il bambino li mangia" vs. "il bambino le mangia")
9. torta vs. banane [cake – bananas] (NUMBER: "il bambino la mangia" vs. "il bambino le mangia")
10. pollo vs. peperoni [chicken – paprikas] (NUMBER: "il bambino lo mangia" vs. "il bambino li mangia")
11. patate vs. funghi [potatos – mushrooms] (GENDER: "il bambino le mangia" vs. "il bambino li mangia")
12. fragole vs. bistecca [strawberries – steak] (NUMBER: "il bambino le mangia" vs. "il bambino la mangia")
13. caramelle vs. meloni [candies – melons] (GENDER: "il bambino le mangia" vs. "il bambino li mangia")
14. carciofi vs. formaggino [artichokes – cheese](NUMBER: "il bambino li mangia" vs. "il bambino lo mangia")
15. arance vs. cioccolata [oranges – choccolate] (NUMBER: "il bambino le mangia" vs. "il bambino la mangia")
16. jogurt vs. limoni [jogurt – lemons] (NUMBER: "il bambino lo mangia" vs. "il bambino li mangia")

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Zion Golumbic E, Poeppel D, and Schroeder CE. Temporal context in speech processing and attentional stream selection: A behavioral and neural perspective. *Brain and Language*, 122(3): 151–161, 2012.

P.7.a.014 **Methylphenidate effects on social functioning in children with ADHD**

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Background: Although their interest in social relations, ADHD children show problems to attune their behavior to other people and to the environment, apparently presenting a deficit of comprehension of the consequences of their behaviors to other. These features may show some overlap with Autism Spectrum Disorders (ASD) symptoms, such as lack of reciprocity. Recent literature suggests that Methylphenidate (MPH) can improve joint attention initiations, self-regulation, and regulated affective state, consequently having positive effects on social behaviors.

Objectives: The main aim of the study was to explore, by using the Italian Version of the Social Responsiveness Scale (SRS [1]), the social functioning of a sample of ADHD children and to compare it to ASD patients and healthy controls and preliminarily investigate the effects of MPH on social impairment in the ADHD group.

Methods: SRS was administered to 234 drug-naive children aged 4–13 and IQ >70. According to DSM-IV criteria, 93 children

were ADHD, 32 ASD, and 109 matched Children with Typical Development (CTD). Conner's Parent Rating Scale (CPRS), C-GAS and CGI were also administered. SRS Constantino's Symptom domains [1], and the four Grzadzinski's categories (Reciprocal Social Interaction (S), Communication (C), Restricted, Repetitive and Stereotyped Patterns of Behaviour/Interests (R) and Non-SCR [2]), were used to investigate the relation between social responsiveness and Conner's ADHD indices and dimensions. 38 ADHD patients were then treated with methylphenidate, (0.3 to 0.5 mg/kg/dose, bid or tid): SRS and CPRS administered again after 9–12 months of therapy.

Results: ADHD patients significantly differed from ASD in global impairment assessed by C-GAS (49.1±5.7 vs 45.6±5.4, $p = 0.008$) and in rate of comorbid diagnosis with ODD ($p < 0.001$). SRS Total T score in ADHD and in ASD were comparable and significantly higher than CTD ($p < 0.001$). 81.7% of ADHD showed a total SRS score >60 (ADHD+) and 18.2% <60 (ADHD–). SRS total and subscales scores in ADHD– were comparable to CTD and significantly different from ASD except for Social Awareness.

ADHD+ and ASD mean scores at each SRS subscale were similar. ADHD+ Total SRS scores significantly correlated to all Conners subscales except for Psychosomatic; SRS Social Motivation did not correlate with CPRS Oppositional and Hyperactivity. ADHD+ significantly differed from CTD in all CPRS subscale, while ADHD– revealed CPRS mean scores comparable to CTD on subscales Anxious/shy, Perfectionism and Social Problems.

MPH treatment for 9–12 months in the ADHD sample induced a significant improvement in total SRS score and each subscale apart from social cognition. A significant improvement was also shown in all SRS categories [2] apart from R category.

Discussion: This study highlights a significant impairment in social responsive behavior in ADHD children and adolescents. A subgroup of ADHD patients shows a SRS profile similar to ASD: in these patients methylphenidate appears affective not only on CPRS-measured ADHD symptoms but also on SRS-measured social impairment. This confirm the opportunity of considering a ADHD as a complex disorder, with the deficit in social responsiveness as a specific targets for a comprehensive therapeutic intervention.

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P.7.c.008 Clinical efficacy of lisdexamfetamine dimesylate in children and adolescents with ADHD: a post-hoc analysis

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Purpose: Lisdexamfetamine dimesylate (LDX), a long-acting prodrug stimulant, was shown to be an effective, once-daily treatment for children and adolescents diagnosed with at least moderately symptomatic attention-deficit/hyperactivity disorder (ADHD) in a phase 3 trial in Europe (SPD489–325) [1]. Patients treated with LDX showed significantly greater improvement in ADHD core symptoms than placebo, as indicated by a decrease in ADHD Rating Scale version IV (ADHD-RS-IV) score. This post-hoc analysis assessed the proportion of patients showing a clinical response at each study visit.

Methods: In this 7-week, multicentre, double-blind, parallel-group, dose-optimized study, children and adolescents (6–17 years) with ADHD were randomized (1:1:1) to a once-daily dose of LDX (30, 50, or 70 mg), osmotic-release oral-system methylphenidate (OROS-MPH, 18, 36, or 54 mg; reference arm) or placebo. ADHD-RS-IV total score was assessed at weekly, on-site visits with reference to baseline. Endpoint was the last on-treatment, post-randomization visit at which a valid ADHD-RS-IV total score was observed. In this post-hoc analysis, clinical response was predefined as ⩾25% or ⩾30% reduction from baseline in ADHD-RS-IV total score. P values were based on a Cochran–Mantel–Haenszel test controlling for country and age group. Number needed to treat (NNT) to achieve one responder was calculated as the inverse of the difference in proportions between the active treatment and placebo.

Results: Of 336 patients randomized, 196 completed the study. At baseline, mean (SD) ADHD-RS-IV total scores were similar across treatment groups [LDX, 40.7 (7.3); placebo, 41.0 (7.1); OROS-MPH, 40.5 (6.7)]. At endpoint, differences between LDX and placebo in the percentages of patients (95% CI) with ⩾ 25% or ⩾ 30% reduction in ADHD-RS-IV total score from baseline were 62.0 (51.6, 72.4; $p < 0.001$; NNT, 2) and 65.7 (55.5, 75.9; $p < 0.001$; NNT, 2), respectively. Differences between LDX and placebo in the proportions of patients (95% CI) with ⩾25% or ⩾30% reduction in ADHD-RS-IV total score from baseline were significant by the first on-treatment visit [⩾25% reduction, 30.0 (17.7, 42.2), $p < 0.001$, NNT, 4; ⩾30% reduction, 26.9 (15.0, 38.9), $p < 0.001$, NNT, 4] and every visit thereafter. At endpoint, differences between OROS-MPH and placebo in the percentages of patients (95% CI) with ⩾25% or ⩾30% reduction in ADHD-RS-IV total score from baseline were 44.9 (32.8, 57.1; $p < 0.001$; NNT, 3) and 47.8 (35.9, 59.7; $p < 0.001$; NNT, 3), respectively. Differences between OROS-MPH and placebo in the proportions of patients (95% CI) with ⩾25% or ⩾30% reduction in ADHD-RS-IV total score from baseline were significant by the first on-treatment visit [⩾25% reduction, 13.0 (1.4, 24.7), $p < 0.05$, NNT, 8; ⩾30% reduction, 13.1 (1.9, 24.2), $p < 0.05$, NNT, 8) and every visit thereafter.

Conclusions: LDX was more effective than placebo in improving core symptoms in children and adolescents with ADHD, as assessed by the proportions of patients with ⩾25% or ⩾30% reductions in ADHD-RS-IV total score from baseline at each study visit. Improvements in ADHD core symptoms were also observed for OROS-MPH.

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ADHD diagnosis from multiple data sources with batch effects

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The Attention Deficit Hyperactivity Disorder (ADHD) affects the school-age population and has large social costs. The scientific community is still lacking a pathophysiological model of the disorder and there are no objective biomarkers to support the diagnosis. In 2011 the ADHD-200 Consortium provided a rich, heterogeneous neuroimaging dataset aimed at studying neural correlates of ADHD and to promote the development of systems for automated diagnosis. Concurrently a competition was set up with the goal of addressing the wide range of different types of data for the accurate prediction of the presence of ADHD. Phenotypic information, structural magnetic resonance imaging (MRI) scans and resting state fMRI recordings were provided for nearly 1000 typical and non-typical young individuals. Data were collected by eight different research centers in the consortium. This work is not concerned with the main task of the contest, i.e., achieving a high prediction accuracy on the competition dataset, but we rather address the proper handling of such a heterogeneous dataset when performing classification-based analysis. Our interest lies in the clustered structure of the data causing the so-called *batch effects* which have strong impact when assessing the performance of classifiers built on the ADHD-200 dataset. We propose a method to eliminate the biases introduced by such batch effects. Its application on the ADHD-200 dataset generates such a significant drop in prediction accuracy that most of the conclusions from a standard analysis had to be revised. In addition we propose to adopt the dissimilarity representation to set up effective representation spaces for the heterogeneous ADHD-200 dataset. Moreover we propose to evaluate the quality of predictions through a recently proposed test of independence in order to cope with the unbalancedness of the dataset.

Keywords: ADHD, batch effect, dissimilarity space, Bayesian hypothesis testing, multivariate pattern classification

1. INTRODUCTION

The advance of computational methods for data analysis is opening new perspectives for exploiting of structural and functional magnetic resonance imaging (fMRI) data in the field of neuroscience. The statistical learning framework (Hastie et al., 2009), and specifically multivariate pattern analysis, is a prominent example of these methods. In this framework the approaches are data-driven, i.e., they do not require the complete and explicit modeling of the underlying physiology of the brain. For this reason these methods are referred to as *model free* or non-parametric.

The most intuitive application of multivariate pattern analysis to the domain of clinical studies is diagnosis. In diagnosis a sample of brain images is collected both from a population of typically developing subjects (controls) and from non-typically developing subjects (patients). A classification algorithm is trained on the data to produce a classifier that discriminates between patients and controls. The challenge is to achieve accurate prediction on future subjects. Since this approach is data-driven, a successful detection of the disease does not always correspond to a deeper understanding of the pathology. The classifier acts as an information extractor and the basic inference that is derived from an accurate classifier is that the data actually carry information about the condition of interest.

The adoption of this kind of approach for diagnosis has some drawbacks. Model free approaches are sensitive to the size of the training sample. The collection of a large amount of data, i.e., of a large number of controls and patients, is often a premise for a successful study based on multivariate pattern analysis.

In 2011 the ADHD-200 Initiative [1] promoted the collection of a very large dataset about the Attention Defict Hyperactivity Disorder (ADHD) in the young population. Concurrently a related competition, called ADHD-200 Global Competition, was set up to foster the creation of automatic systems to diagnose ADHD. The motivation of the ADHD-200 Initiative was that, despite a large literature of empirical studies, the scientific community had not reached a comprehensive model of the disorder and the clinical community lacked objective biomarkers to support the diagnosis.

[1] http://fcon_1000.projects.nitrc.org/indi/adhd200

The main aspect of the ADHD-200 dataset is its size. It represents one of the major efforts in the area of publicly available neuroimaging datasets concerned with a specific aim. The large size of the dataset is structured along two lines: the number of subjects and the types of data available for each subject. The dataset includes nearly 1000 subjects divided among typically developing controls and patients with different levels of ADHD, i.e., *inattentive*, *hyperactive*, and *combined*. Each subject is described by a heterogeneous set of data such as structural MRI, resting state fMRI and phenotypical information.

Analyzing the heterogeneous ADHD-200 dataset for the goal of the competition generates many difficulties. First of all the different types of data have to be transformed into a homogeneous vectorial representation space because this is a requirement for the majority of the most popular classification algorithms (Hastie et al., 2009). Secondly, the aggregation of datasets recorded from different institutions generates a clustered structure within the data. One example is that the data from each institution create a cluster. The effect of this clustered structure is usually problematic during the analysis phase and goes under the name of *batch effect*. The presence of batch effects conflicts with one of the basic assumptions of the statistical learning theory, i.e., that the data are independent and identically distributed (*iid*). Non-iid data may lead to sub-optimal training. More importantly, non-iid data within the test set lead to biased estimates of the performance of the classifier. Last but not least, if the data of the test set are not independent from those of the training set then the estimated performance of the classifier becomes optimistically biased. Nevertheless the presence of a specific structure in the data can also be exploited to get a more accurate classification (Dundar et al., 2007). The third kind of difficulty in analyzing the ADHD-200 dataset is its unbalanced distribution of the subjects in the diagnostic groups. **Table 1** reports that in the ADHD-200 dataset there are 575 typically developing subjects, 144 inattentive, 9 hyperactive, and 204 combined. In section 3 we will show that in unbalanced cases the standard statistic of prediction accuracy can be misleading to understand the actual performance of the classifier and that new methods should be adopted.

Table 1 | Subjects distribution of the ADHD-200 dataset with respect to the sites.

Site	0	1	2	3	All
PKGU	146	67	2	30	245
BHBU	21	5	0	0	26
KKI	48	23	0	23	94
NIMP	26	8	0	14	48
NYU	132	72	2	47	253
OHSU	73	17	1	20	111
UPIT	89	2	0	6	97
WUSL	40	10	4	4	58
	575	204	9	144	932

The columns indicate the diagnostic group: 0 typically developing control, 1 ADHD combined, 2 ADHD hyperactive, and 3 ADHD inattentive. The acronyms of sites are as follows: PKGU, Peking University; BHBU, Bradley Hospital Brown University; KKI, Kennedy Krieger Institute; NIMP, Neuroimage Multi-Center Project; NYU, New York University; OHSU, Oregon Hospital Science University; UPIT, University of Pittsburgh; and WUSL, Washington University Saint Louis.

In this work we propose solutions for the three issues just described. We propose the use of the dissimilarity representation (Pekalska et al., 2002; Balcan et al., 2008; Chen et al., 2009) as a mean to construct a common representation space for all the heterogeneous types of data available in the ADHD-200 dataset. In the dissimilarity space representation the data from a given source, e.g., the structural MRI scan of a subject, are projected into a vector just by providing a source-specific distance function. Once the data of all sources of a subject are transformed into vectors, they can be concatenated into a larger vector that represents a homogeneous description of the subject over multiple data sources.

We propose to address the issue of the batch effect by following some of the ideas presented in Dundar et al. (2007). The structure of the ADHD-200 dataset presents the same two levels of batch effect modeled in Dundar et al. (2007), i.e., a site-level and a subject-level. The site-level is due to the site specificities in the data collection process. The subject-level is due to the availability of multiple fMRI recordings for some subjects. Besides implementing the solution presented in Dundar et al. (2007), which is tailored to the improvement of the classification accuracy, we propose to conduct three different estimation processes of the classification performance in order to avoid the potential biases explained above.

The third issue, i.e., assessing the performance of the classifier on the unbalanced ADHD-200 dataset, is addressed by testing the statistical dependence between the predictions and the actual diagnostic group of each subject. We draw from the statistics literature and adopt a recent Bayesian test of independence for contingency tables (Casella and Moreno, 2009; Olivetti et al., 2012a).

The structure of this paper is the following. In section 2 we describe the ADHD-200 dataset and part of the publicly available pre-processing pipelines from which we started our analysis. In section 3 we describe the three main ingredients of our work, i.e., the dissimilarity representation, the model of the batch effects and the test of independence to assess whether and how the proposed classification system was able to discriminate ADHD subjects from healthy subjects. In section 4 we illustrate the experiments we conducted with all the necessary details to implement the proposed methods. To conclude, in section 5 we discuss the results of our experiments and we show that the postulated batch effects are the major contribution in the apparently positive classification results.

2. MATERIALS

Our study refers to the ADHD-200 initiative and dataset. The initiative is dedicated to support the scientific community in studying and understanding the neural basis of ADHD. The eight member institutions collected imaging datasets from almost 1000 young subjects (age 7–26) with and without ADHD, see **Table 1** for details.

The diagnosis of ADHD was segmented in four different levels: typically developing, hyperactive, inattentive, and combined

subjects. For each subject multiple types of data were collected: phenotypic data, structural (T1) MRI data, and fMRI resting-state data. For many subjects multiple fMRI resting state recordings were available. Accompanying phenotypic information included: age, gender, handedness, and IQ measure [2]. The ADHD-200 dataset is publicly available and freely distributed with the support of the International Neuroimaging Data-sharing Initiative[3].

In 2011 the ADHD-200 initiative set up a global competition to develop diagnostic classification systems for ADHD diagnosis based on structural and fMRI data of the brain. Even though the ADHD-200 dataset comprised three different levels of the ADHD disorder and the healthy subjects, the competition was designed to discriminate only among three categories: typically developing, ADHD combined, and ADHD inattentive [4]. In this work we restrict our analysis to discriminating two diagnostic categories, i.e., controls and ADHD patients, by aggregating ADHD combined and inattentive patients into one class. This choice is motivated by the inherent difficulty of discriminating even just the two main categories. Moreover the aim of this work is eminently methodological and our claims are appropriately addressed even with such a simplifying restriction.

In 2011 the ADHD-200 dataset was delivered in two stages the first part to be considered as the train set for the construction of classifiers and the second part as test set for performance evaluation. In this work we consider only the aggregation of the two parts as a single dataset. We will discuss how we split it into train set and test set only in section 4 after the introduction of the batch effect model and the related performance estimation processes.

In the following we refer to the whole dataset comprising the data of 923 subjects where the diagnostic classes are distributed as follows: 62% typically developing control, 38% ADHD combined or inattentive. For a few subjects the structural (T1) magnetic resonance imaging or the resting state fMRI recording were not available or corrupted. These subjects were excluded from our study.

Some sites provided multiple recordings of resting state fMRI for many of their subjects. In our analysis we considered all the recordings in order to improve the training process without discarding or aggregating part of them. **Table 2** shows the range of multiple resting state fMRI recordings with respect to the different sites. Different acquisition protocols were adopted by distinct sites. For example, in some sites the subjects were asked to keep their eyes closed while in other sites eyes were kept open. In this last case some sites proposed a fixation cross while others did not.

For the initial preprocessing of neuroimaging data we refer to the Neuro Bureau initiative[5] that provides high-quality and publicly available preprocessed versions of the ADHD-200 dataset in order to facilitate the development of algorithms for data analysis. Among the different pipelines supported by the Neuro Bureau initiative we focused on the data computed by the Burner and the Athena pipelines [6]. The Burner pipeline was managed by Carlton Chu using the Dartel toolbox from SPM8. The Athena pipeline was managed by Cameron Craddock using AFNI and FSL running on the Athena computer cluster at Virginia Tech's ARC.

Table 2 | Details on resting state fMRI recordings in the ADHD-200 dataset with respect to the sites.

Site	PKGU	BHBU	KKI	NIMP	NYU	OHSU	UPIT	WUSL
fMRI	1	1	1	1	1–2	1–4	1	1–6
Eyes	O	O	C	C	O	O	O	O
Screen	N	F	-	-	F	F	N	F

The first row shows the range of multiple recording sessions. The second row refers to the eye condition: O, open; C, closed. The third row shows the screen setup: F, fixation; N, no fixation.

The Burner pipeline created normalized gray matter maps. Structural images were segmented into gray matter and white matter probability maps. Then inter-subject registration was implemented through voxel-based morphometry (Ashburner and Friston, 2000) to the group average. The description of the pipeline reports this note which supports our investigation on batch effects: *"there are systematic biases in the segmented gray matters across different centers"*[7].

The Athena pipeline is primarily focused on resting state fMRI data processing. The pre-processing of fMRI data included the registration into MNI space at $4 \times 4 \times 4$ mm voxel resolution, slice time correction, a band pass filter between 0.009 and 0.08 Hz, and the removal of nuisance variance. For the analysis in the present study we focused on two alternative computational methods for encoding the information in fMRI signal: the former based on the notion of region of homogeneity (REHO), the latter based on spatial multiple regression for functional connectivity (SMR). Both of them are part of the Athena pipeline.

REHO (Zang et al., 2004) is a computational method that measures the similarity of the time series of a given voxel to those of its nearest neighbors. The Kendall's coefficient concordance is proposed as a measure of similarity. The output is a volume per subject where the value of each voxel is an estimate of the homogeneity of the BOLD signal during the resting state fMRI recording. We refer to these 10 volumes, which we denote as SMR0-9, when building the related representation space described in section 4.

The functional connectivity maps for the resting state network (SMR) were constructed using a modified approach based on dual regression proposed in Smith et al. (2009). A multiple regression was computed to extract the time courses of voxels corresponding to spatial templates of resting state network. The computation considered 10 distinct spatial templates. For each template the output is a volume where the value of a voxel is the correlation measure between the original and the extracted time courses. We

[2]We did not consider other available phenotypic information because of the too many missing values.

[3]http://fcon_1000.projects.nitrc.org/indi/adhd200

[4]The *hyperactive* categories included only a few subjects.

[5]http://neurobureau.projects.nitrc.org/ADHD200/Introduction.html

[6]http://neurobureau.projects.nitrc.org/ADHD200/Data.html

[7]http://www.nitrc.org/plugins/mwiki/index.php?title=neurobureau:BurnerPipeline

refer to these volumes when building the representation spaces described in section 4.

In addition to all data reported above we considered also the information on head motion during the fMRI scan sessions. For each fMRI recording we referred to the motion parameters estimated during the computation of the head movement correction.

3. METHODS

The proposed method consists of four main components: the construction of homogeneous representation spaces for all data sources, the batch effect model, a classification algorithm meant to extract information from the data and a statistical test to make inferences about the classification process. In this section we describe three of the four components while the actual classification algorithm and all the details necessary for implementation will be described in section 4. In the following we describe the dissimilarity representation technique together with the explicit model of the batch effects that we considered for building the representation spaces of all data sources. Then we introduce recently proposed a Bayesian test of independence between the predicted and the true class labels to assess whether the classifier built from the data is able to discriminate the two diagnostic groups.

3.1. THE DISSIMILARITY REPRESENTATION

The dissimilarity representation (Pekalska and Duin, 2005) is a Euclidean embedding technique, i.e., a method to represent general objects, e.g., structural (T1) MRI scans, as vectors. It is defined by first selecting a set of those objects, called *prototypes*, from their native space, e.g., a set of MRI scans from the available dataset. Then each new object, e.g., any new structural MRI scan, is mapped into the vector of distances from the prototypes. This representation (Pekalska et al., 2002; Balcan et al., 2008; Chen et al., 2009) is usually presented in the context of classification and clustering problems and was proven to keep the separation between classes when present in their original space (Balcan et al., 2006).

The dissimilarity representation is a *lossy* transformation in the sense that some information is lost when projecting the data into the dissimilarity space. In Pekalska et al. (2006) the approximation was studied to decide among competing prototype selection policies only for classification tasks. In Olivetti et al. (2012b) the approximation was characterized in the unsupervised setting and a scalable prototype selection policy was described.

Let $\mathcal{X}$ be the space of the objects of interest, e.g., structural (T1) MRI scans, and let $X \in \mathcal{X}$. Let $d : \mathcal{X} \times \mathcal{X} \mapsto \mathbb{R}^+$ be a distance function between objects in $\mathcal{X}$, e.g., the correlation distance. Note that d is not assumed to be necessarily metric. Let $\Pi = \{\tilde{X}_1, \ldots, \tilde{X}_p\}$, where $\forall i\ \tilde{X}_i \in \mathcal{X}$ and p is finite. Each $\tilde{X}_i$ is called *prototype* or *landmark*. The *dissimilarity representation* or *projection*, is defined as $\phi^d_\Pi(X) : \mathcal{X} \mapsto \mathbb{R}^p$ s.t.

$$\phi^d_\Pi(X) = [d(X, \tilde{X}_1), \ldots, d(X, \tilde{X}_p)] \quad (1)$$

and maps an object X from its original space $\mathcal{X}$ to a vector of $\mathbb{R}^p$.

3.1.1. Number and selection of the prototypes

The degree of approximation of the dissimilarity representation depends on the choice of the prototypes. In order to achieve a compact but accurate representation we need to define both the number of the prototypes and their selection process. First we illustrate a procedure to measure how accurate a given representation is. Then we describe the adopted procedure to select the prototypes. By using these two ingredients, in section 4 we will show how we selected the desired number of prototypes.

Following Olivetti et al. (2012b), we define the distance between projected objects as the Euclidean distance between them: $\Delta^d_\Pi(X, X') = ||\phi^d_\Pi(X) - \phi^d_\Pi(X')||_2$, i.e., $\Delta^d_\Pi : \mathcal{X} \times \mathcal{X} \mapsto \mathbb{R}^+$. Other distances may be considered but we note that many learning algorithms rely on the Euclidean distance (Hastie et al., 2009) and for this reason we adopt it. It is intuitive that, in order to have an accurate dissimilarity representation, Δ^d_Π and d must be strongly related. As a measure of the quality of approximation of the dissimilarity representation we adopt the Pearson correlation coefficient r between the two distances over all possible pairs of objects in the dataset. An accurate approximation of the relative distances between objects in $\mathcal{X}$ results in values of ρ far from zero and close to 1.

The definition of the set of prototypes with the goal of minimizing the loss of the dissimilarity projection is an open issue in the dissimilarity space representation literature. Following Pekalska et al. (2006) and Olivetti et al. (2012b), we adopt the *farthest first traversal* (FFT) selection algorithm, also known as k-center algorithm. This algorithm selects the prototypes sequentially: the first prototype is drawn at random from the dataset. Then any further prototype is defined as the point in the dataset maximizing the sum of the distances from the previously selected prototypes. This algorithm is both accurate and effective (Pekalska et al., 2006; Olivetti et al., 2012b).

3.2. MODELLING THE BATCH EFFECTS

The ADHD-200 dataset is the aggregation of datasets collected by multiple institutions. Moreover in the ADHD-200 dataset multiple fMRI resting state recordings are available for many of the subjects involved in the study. These facts motivate why at least two levels of batch effects should be expected. First each site is expected to have its own specificity about the collected MRI data and the specific sample of subjects selected for the study. MRI hardware specifications of each site, the actual MRI sequences used, the local ADHD and healthy population addressed and the local best practices at each step of the collection process are examples of the site specificity. A second-level of batch effect arises because in this work we consider each available run of fMRI recordings as a new example to be used for improving the classification step. This choice *virtually* increases the number of subjects from 923 to 1339. The availability of multiple recordings for some of the subjects creates a second-level of batch effect because the variability within subject is expected to be much lower than the variability across different subjects, even within the same site.

In data analysis the identification, modeling and removal of batch effects is mainly addressed by the literature in statistics and in the applied fields of epidemiology and genomics. To the

best of our knowledge there is no neuroimaging literature on the issue of batch effects within data. In statistics and epidemiology the issue is also referred to as *correlated samples*, meaning that samples from the same batch share a certain degree of correlation not related to the phenomenon of interest of the study. Well known models to deal with correlated samples are the *random effect model* (Ishwaran, 2000) and the *generalized linear mixed effect model* (GLMM) (McCulloch et al., 2008). In genomics the batch effect literature was recently reviewed in Chen et al. (2011) where six algorithms for batch effect removal were compared. In this field the identification of batch effects is usually done by means of the principal variation component analysis (PVCA) algorithm (Boedigheimer et al., 2008). It is our understanding that the algorithms in the field of genomics are mainly devoted to removing the batch effects, while in the statistics literature there is more emphasis into modeling their effects. Moreover the techniques of the genomics literature are tightly related to the specificity of the genomic data, e.g., high variance in gene expression microarray data is usually related to a high degree of information, and not all the assumptions of that field of application might be transferred to the fields of neuroimaging and of disorder diagnosis in a straightforward way. In addition, the present work is concerned with statistical classification and we note that the issue of exploiting the batch effect structure within a dataset in classification problems has almost been neglected in the machine learning literature. To the best of our knowledge only in Dundar et al. (2007) a method was proposed to account for the two-level batch effect mentioned above, i.e., the site-level and the subject-level. The algorithm proposed in Dundar et al. (2007) is related to the GLMM algorithm, but while the GLMM is meant for explanatory data analysis, the algorithm we adopted is meant for predictive modeling, which is the aim of this paper.

The method of Dundar et al. (2007) is based on the simple idea of creating new binary variables, one for each site, where each variable indicates whether the given resting state run belongs to that site or not. Moreover even the second-level of the batch effect is modeled by additional binary variables, one for each subject, indicating to which subject the resting state run belongs to. The whole set of binary variables defines a binary vector where only two values at a time are set to 1 and all the other values are set to 0. This vector describes the two-level batch effect information for each available recording.

We notice that considering and modeling the batch effect structure has two potential effects on the analysis. First, we provide explicit information about natural structures present within the data. This may improve the classification performance when predictions are made from data belonging to the same batch. Second, we reduce the optimistic bias in the estimate of the performance of prediction if we account for these dependency structure when building the test set. It is straightforward to notice that if examples in the test set are not drawn independently from those of the train set, then the estimated performance of the classifier is optimistically biased. Moreover if the samples in the test set are not drawn independently *from each other*, then the estimated performance of the classifier is biased, even though not necessarily in an optimistic way.

3.3. EVALUATION OF THE CLASSIFICATION RESULTS

We used the dissimilarity representation to create a vectorial description of each subject of the ADHD-200 dataset for each available data source. A classification algorithm was then trained to assess the ADHD-related information in each data source. In a further group of experiments the vectors from multiple data sources of each subject were concatenated into a higher dimensional vector to extract information about the joint effect of multiple data sources. In all cases the evaluation of the classifier for discriminating among the classes of interest, i.e., controls and ADHD patients, was assessed through a statistical test.

As noted in Olivetti et al. (2012a), when the dataset is unbalanced with respect to the class-label distribution, the accuracy (or the error rate) of a classifier can be a misleading statistic to assess whether the classifier actually discriminated the classes. For example, given a test set of 100 instances where 90 are of class 0 and 10 of class 1, a classifier that incurs in 10 misclassification errors, i.e., the estimated error rate is $\hat{\epsilon} = 10/100 = 0.1$, could be either highly accurate in discriminating the two classes or completely inaccurate. These two extreme cases are illustrated in **Figure 1** by means of their confusion matrices. A confusion matrix reports the joint results of the predictions and the true class-labels. The table on the left shows a classifier that always predicts the most frequent class, i.e., class **0**, thus providing no evidence of learning the discrimination problem. Conversely, the table on the right shows evidence that the classifier correctly discriminates between the two classes and incurs in 10 errors over 90 examples but just for the frequent class. A solution to the issue of evaluating classifiers through the estimated accuracy in unbalanced cases is testing the full confusion matrix, as described in the next section.

3.3.1. *The bayesian test of independence*

The literature answering the question "did the classifier learn to discriminate the classes?" was recently reviewed in Olivetti et al. (2012a) and a novel approach based on the analysis of the statistical independence between predicted and true class labels was proposed based on the work of Casella and Moreno (2009). In this work we adopt this latest approach that we summarize here. The intuitive idea is that, following the definition of statistical independence between random variables, in the case of a classifier predicting at random the predicted class labels are statistically independent from the true class labels. Conversely, the more the predictions match the true class labels, the stronger is the statistical dependence between them. The Bayesian test of independence between categorical variables first proposed in Casella and

	0	**1**
0	90	0
1	10	0

	0	**1**
0	80	10
1	0	10

FIGURE 1 | Two examples of confusion matrices with true class labels on the rows and predicted class labels on the columns. Both confusion matrices have the same estimated prediction accuracy, i.e., $\hat{PA} = \frac{90+0}{100} = \frac{80+10}{100} = 0.1$. Nevertheless in the first case there is no evidence that the classifier is able to discriminate **0** from **1**, while in the second one there is.

Moreno (2009) computes the ratio of the posterior distribution of the following two hypotheses:

- H_0: the predictions are statistically *independent* from the true class labels.
- H_1: the predictions are statistically *dependent* from the true class labels.

According to the Bayesian hypothesis testing framework (Kass and Raftery, 1995) that ratio can be rewritten as

$$\frac{P(H_1|\text{data})}{P(H_0|\text{data})} = \frac{P(H_1)}{P(H_0)} \frac{P(\text{data}|H_1)}{P(\text{data}|H_0)} = \frac{P(H_1)}{P(H_0)} B_{10} \tag{2}$$

Where B_{10} is called *Bayes factor* and measures the evidence of the data in favor of H_1 with respect to H_0. When $B_{10} \ggg 1$ the evidence in favor of H_1 against H_0 is strong. More detailed guidelines for the interpretation of these values are reported in Kass and Raftery (1995).

In order to compute B_{10} for the hypotheses of interest of this work it is necessary to define a sampling model for the confusion matrix under each hypothesis. Following Olivetti et al. (2012a) and Casella and Moreno (2009), we adopt the multinomial sampling model. A matter of debate of the computation of B_{10} is the definition of the prior distribution of the parameters under each hypothesis, namely $p(\theta_0|H_0)$ in $p(\text{data}|\theta_0, H_0)$ and $p(\theta_1|H_1)$ in $p(\text{data}|\theta_1, H_1)$. For this reason Casella and Moreno (2009) proposed the use of the *intrinsic prior* class (Berger and Pericchi, 1996) which concentrates the mass of $p(\theta_1|H_1)$ around $p(\theta_0|H_0)$ and creates multiple priors according to the observed data. Here we provide the approximate formula for B_{10} as derived in Casella and Moreno (2009)[8]:

$$B_{10}(\boldsymbol{y}, t) = \frac{(t + \mathbf{c}^2 - 1)!}{(t + m + \mathbf{c}^2 - 1)!} \left[\frac{\Gamma(m + \mathbf{c})\Gamma(m + \mathbf{c})}{\Gamma(t + \mathbf{c})\Gamma(t + \mathbf{c})} \right] \frac{1}{M} \sum_{k=1}^{M} \frac{(\prod r_i(\mathbf{x}_k)!)(\prod c_j(\mathbf{x}_k)!)}{(\prod r_i(\mathbf{y})!)(\prod c_j(\mathbf{y})!)} \times \frac{\prod (x_{k_{ij}} + y_{ij})!}{\prod x_{k_{ij}}!} \frac{1}{\prod_{ij} \hat{\theta}_{ij}^{x_{k_{ij}}}} \tag{3}$$

where $\boldsymbol{y}$ is the confusion matrix, $m = \sum_{ij} y_{ij}$ is the size of the test set, $\mathbf{c}$ is the number of classes ($\mathbf{c} = 2$ in our case), $\hat{\theta}_{ij} = \frac{y_{ij} + 1}{m + \mathbf{c}^2}$ and $\mathbf{x} = (x_{ij}) \sim \text{Multinomial}(t, \theta_{11}, \ldots, \theta_{ab})$, M is the number of iterations of the sampling approximation, $r_i()$ and $c_j()$ are operators that return the i-th row and j-th column of a matrix and t is an integer parameter. Note that we define $B_{10}(\boldsymbol{y}) = \min_{t \in \{0 \ldots m\}} B_{10}(\boldsymbol{y}, t)$.

4. EXPERIMENTS

In this section we describe the detailed implementation of the methods illustrated in section 3 on the ADHD-200 dataset for the goal of discriminating typical from non-typical subjects. We first describe the pre-processing steps to create preliminary representations of the initial measurements, i.e., T1 structural MRI, REHO, and SMR volumes from resting state fMRI recordings, motion and phenotypic information, as described in section 2. Then we describe the distance function for each data source that was used to create the dissimilarity representation along with the selection of the number of prototypes. After the construction of the representation space we mention the classification algorithm that we used in this work and we describe the three train/testing processes that we designed to assess the importance of each data source for the prediction of the clinical group and the importance of the batch effects.

4.1. PREPROCESSING

Each structural (T1) MRI volume was first smoothed using a Gaussian filter with 3 voxels diameter and then downscaled such that each dimension was reduced by half. Then the transformed volume was flattened into a vector after removing the voxels outside the brain. A common brain mask was defined as the set of voxels for which at least 5% of the subjects had a non-zero value. Each resulting vector consisted in approximately 1.5×10^3 values.

Each volume coming from the analysis of fMRI data through the Athena pipeline, i.e., REHO and SMR, was flattened into a vector after removing the voxels presenting no activity across 95% of the subjects. Each vector consisted in approximately 2.5×10^3 values.

Following Dundar et al. (2007) and section 3, the batch effect information was encoded at two levels leading to a vector of binary variables. The first 10 binary variables corresponded to the 10 sites involved in the ADHD0-200 data collection process. The remaining 923 binary variables were one for each subject. For each measurement available in the dataset, e.g., MRI scan, resting state run, this binary random vector indicated the site and subject to which it belonged to by setting the corresponding site-variable and subject-variable to 1 and keeping all the remaining values at 0.

Phenotypic and motion data were z-scored.

4.2. DISSIMILARITY REPRESENTATION: SOURCE-SPECIFIC DISTANCES AND PROTOTYPES

For each data source we created the dissimilarity representation in order to have a compact representation. The distances adopted were:

- Distance among volumes (T1 MRI, REHO, and SMR): correlation distance, $d(a, b) = 1 - r(a, b)$, where r is the Pearson correlation coefficient, of the related preprocessed vectors. This distance is the most common one in the neuroscience literature, see for example Kriegeskorte et al. (2008).
- Distance among vectors (phenotypic, motion, and batch effect): Euclidean distance.

The selection of the prototypes was done through the FFT algorithm described in section 3.1.1. We defined the number of prototypes by inspecting the correlation between the distances in the original space and the distances in the projected space. We observed high correlation, always $\boldsymbol{r} > 0.85$, with $p = 40$ prototypes for all data sources. In all cases correlation reached the maximum value with such a number of prototypes or less. For

[8]Here we take into account the corrections described in Olivetti et al. (2012a).

this reason we selected that number of prototypes for all data sources.

4.3. CLASSIFICATION ALGORITHM AND TESTING SCHEMA

In this work we adopted an ensemble learning method based on model averaging and decision trees known as *extremely randomized trees* (Geurts et al., 2006). This classification algorithm is a variation of the popular random forest algorithm (Breiman, 2001). Extremely randomized trees aim at reducing the variance of the resulting model. This class of algorithms is not influenced by different scaling in the data and it is known to fit both linear and non-linear aspects of the data.

In the following subsections we illustrate the classification experiments we conducted on the datasets resulting from the dissimilarity projection described above. The experiments aim at discriminating typical from non-typical developing subjects by estimating the classification performance. We conducted three groups of experiments with different cross-validation schemes to evaluate the importance of the batch effects. We describe the three groups of experiments and illustrate the classification results according to the common metric of the estimated classification accuracy, to the Bayesian test of independence introduced in section 3.3.1 and to the actual values of the confusion matrices.

All experiments were implemented in Python language on top of the numerical libraries NumPy and SciPy[9], the machine learning library Scikit-Learn (Pedregosa et al., 2011)[10] and the NiBabel library[11] to access neuroimaging data formats.

4.3.1. Information extraction from single source

In the first group of experiments a standard 10-fold stratified cross-validation scheme was used on each of the source-specific datasets. In this set of experiments subjects from the same site could appear in both the train and test sets of each cross-validation step. As mentioned in section 3.2 this fact should introduce optimistic bias if the batch effect at the site-level is strong. Moreover some subjects appeared multiple time in the dataset because multiple recordings were available for them. In this first group of experiments the same subject could appear both in the train set and the test set of each cross-validation step, causing the second-level of batch effect and the potential bias described in section 3.2. **Table 3** presents the classification results for this first group of experiments, describing each data source in terms of log of the Bayes factor of H_1 over H_0, estimated accuracy, and the four values of the aggregated confusion matrix. The confusion matrix was computed by summing up the confusion matrices of each fold of the cross-validation.

In the second group of experiments the 10-fold stratified cross-validation scheme was modified such that the train/test sets split was done on the subjects. The aim was to remove part of the potential batch effect due to the presence of multiple recordings for some of the subjects. In each fold 1/10 of the subjects were drawn uniformly at random for the test set and the remaining 9/10 for the train set. In this way each subject would appear either in the train set or in the test set but not in both. Moreover we constrained the test set to have no more than one fMRI recording per subject by choosing one of them uniformly at random when necessary. Following this procedure we eliminated the possible bias due to non-independent examples within the test set. The results of classification for each data source are reported in **Table 4**. As expected the values of $\log(B_{10})$ were significantly reduced with respect to the values in **Table 3**, confirming the presence of the batch effect. We note that the accuracy values change marginally while the $\log(B_{10})$ values decrease significantly.

Table 3 | Single source standard *k*-fold cross-validation.

Data	$\log(B_{10})$	PA	TP	TN	FP	FN
PHEN	10.17	0.61	178	651	170	340
STRU	31.19	0.66	112	776	45	406
MOT	−1.73	0.60	71	733	88	447
REHO	28.10	0.66	158	729	92	360
SMR0	3.95	0.61	90	737	84	428
SMR1	−0.66	0.60	78	731	90	440
SMR2	2.98	0.61	77	750	71	441
SMR3	1.72	0.61	80	741	80	438
SMR4	7.40	0.62	86	753	68	432
SMR5	0.46	0.60	77	739	82	441
SMR6	1.94	0.61	89	730	91	429
SMR7	4.50	0.61	110	713	108	408
SMR8	1.68	0.60	94	722	99	424
SMR9	3.95	0.61	90	737	84	428
BAEF	12.21	0.63	134	713	108	384

The table presents the results of the diagnosis from classifiers built upon a single type of data. The columns report the log of the Bayes factor for the hypothesis of dependence vs. independence [$\log(B_{10})$], the prediction accuracy (PA), the number of true positive ADHD diagnosis (TP), the number of true negative ADHD diagnosis (TN), the number of false positive ADHD diagnosis (FP), and the number of false negative ADHD diagnosis (FN). The data considered in the analysis are: phenotypic data (PHEN), the structural MRI data (STRU), the motion parameters (MOT), the region of homogeneity of fMRI resting state (REHO), the spatial multiple regression of fMRI resting state (SMR0-9), and the batch effect (BAEF). Note that TP + TN + FP + FN = 1339 because multiple recordings are available for many subjects virtually increasing the total number of subjects.

The third group of experiments was meant to remove both levels of the postulated batch effect. We implemented leave-one-site-out cross-validation so that subjects from each site were either in the train or in the test set but not in both. Moreover this avoided the possibility of having recordings of the same subjects both in the train and test set. Additionally, as in the second group of experiments, we constrained the test set to have no more than one fMRI recording per subject by choosing one of them uniformly at random when necessary. **Table 5** illustrates the single source results for this group of experiments. As expected most of the $\log(B_{10})$ values were significantly lower than those in **Table 4** and **Table 3** confirming the presence of the site batch effect.

4.3.2. Information extraction from multiple sources

In order to collect additional evidence of the presence of the batch effects within the data we conducted a further set of experiments

[9]http://www.scipy.org
[10]http://scikit-learn.org
[11]http://nipy.sourceforge.net/nibabel/

Table 4 | Single source 10-fold cross-validation on subjects.

Data	log(B_{10})	PA	TP	TN	FP	FN
PHEN	−2.37	0.56	101	415	149	255
STRU	−0.97	0.61	42	520	44	314
MOT	−2.32	0.60	43	509	55	313
REHO	17.05	0.65	101	504	60	255
SMR0	1.64	0.61	68	497	67	288
SMR1	0.12	0.60	65	494	70	291
SMR2	−0.02	0.61	55	507	57	301
SMR3	−1.75	0.60	49	505	59	307
SMR4	−0.58	0.60	50	511	53	306
SMR5	−0.65	0.60	49	512	52	307
SMR6	−0.63	0.60	57	501	63	299
SMR7	−2.32	0.59	57	487	77	299
SMR8	5.21	0.62	73	503	61	283
SMR9	1.64	0.61	68	497	67	288
BAEF	10.37	0.64	99	489	75	257

The table reports the results of diagnosis for the classifiers built upon each single type of data. The columns report the log of the Bayes factor for the hypothesis of dependence vs. independence [log(B_{10})], the prediction accuracy (PA), the number of true positive ADHD diagnosis (TP), the number of true negative ADHD diagnosis (TN), the number of false positive ADHD diagnosis (FP), and the number of false negative ADHD diagnosis (FN). The data considered in the analysis are: phenotypic data (PHEN), the structural MRI data (STRU), the motion parameters (MOT), the region of homogeneity of fMRI resting state (REHO), the spatial multiple regression of fMRI resting state (SMR0-9), and the batch effect (BAEF).

Table 5 | Single source leave-one-site-out cross-validation.

Data	log(B_{10})	PA	TP	TN	FP	FN
PHEN	−1.37	0.53	77	416	148	279
STRU	−0.87	0.56	29	494	70	327
MOT	1.41	0.55	29	482	82	327
REHO	−1.45	0.56	41	477	87	315
SMR0	−1.97	0.56	42	480	84	314
SMR1	−0.56	0.56	28	494	70	328
SMR2	−2.88	0.58	42	495	69	314
SMR3	−2.22	0.57	32	499	65	324
SMR4	−1.86	0.57	36	489	75	320
SMR5	−2.63	0.58	33	502	62	323
SMR6	−2.60	0.57	42	488	76	314
SMR7	−2.80	0.57	48	484	80	308
SMR8	−2.42	0.57	46	479	85	310
SMR9	−2.18	0.56	44	479	85	312
BAEF	3.10	0.50	82	376	188	274

The table shows the results of diagnosis from classifiers built upon each single type of data. The columns report the log of the Bayes factor for the hypothesis of dependence vs. independence [log(B_{10})], the prediction accuracy (PA), the number of true positive ADHD diagnosis (TP), the number of true negative ADHD diagnosis (TN), the number of false positive ADHD diagnosis (FP), and the number of false negative ADHD diagnosis (FN). The data considered in the analysis are: phenotypic data (PHEN), the structural MRI data (STRU), the motion parameters (MOT), the region of homogeneity of fMRI resting state (REHO), the spatial multiple regression of fMRI resting state (SMR0-9), and the batch effect (BAEF).

Table 6 | Multi source analysis.

	Data	log(B_{10})	PA	TP	TN	FP	FN
10-fold CV	TOP4	147.78	0.80	351	719	102	167
	ALL	72.04	0.72	245	722	99	273
10-fold CV on subjects	TOP4	24.53	0.67	174	442	122	182
	ALL	22.57	0.67	140	476	88	216
Leave-one-site-out	TOP4	0.04	0.50	94	375	189	262
	ALL	−1.75	0.57	97	432	132	259

The table reports the results of diagnosis from classifiers built upon multiple sources of data. The table shows three different kind of analysis: standard 10-fold CV, 10-fold CV on subjects, and leave-one-site-out. The columns report log of the Bayes factor for the hypothesis of dependence vs. independence [log(B_{10})], the prediction accuracy (PA), the number of true positive ADHD diagnosis (TP), the number of true negative ADHD diagnosis (TN), the number of false positive ADHD diagnosis (FP), and the number of false negative ADHD diagnosis (FN). The data considered in the multi sources analysis are: all the available sources of data (ALL) and the four most predictive in single source analysis (TOP4), respectively phenotypic data, the structural MRI data, and the region of homogeneity of fMRI resting state and the batch effect.

combining multiple data sources. We set up the three experiments analogous to those described above for the single source case. This time we used two new datasets: one combining all data sources and one combining the four most informative data sources according to **Table 3**, i.e., phenotypic, structural, REHO, and batch effect. **Table 6** confirms the importance of the batch effects showing the drastic decrease in the log(B_{10}) and accuracy-level when the batch effects are gradually removed. The apparent positive results [80% accuracy and log(B_{10}) > 100] of the first group of experiments, i.e., of basic 10-fold cross-validation, becomes null [50% accuracy and log(B_{10}) ≈ 0] in the third group of results where the two-level batch effect is removed.

5. DISCUSSION

Table 3 reports the results of the investigation on single sources to recognize what kind of data is more informative and effective for the diagnosis of ADHD with the proposed classification method. The analysis of **Table 3** does not consider the batch effects and the violation of the iid assumption. The estimate of prediction accuracy is computed by standard 10-fold cross-validation but only the Bayes factor clearly shows for which data source the classifier is learning the discrimination problem, i.e., phenotypic data (PHEN), structural data (STRU), regional homogeneity of fMRI resting state (REHO), and the batch effect data (BAEF). For these sources the log(B_{10}) is above 10, which is considered (see Kass and Raftery, 1995) very strong evidence in support of H_1 with respect to H_0. The value of the prediction accuracy is instead less informative. For example, the prediction accuracy of 61% for phenotypic data is close to that of many other sources that are not significant, like SMR0, SMR2, SMR3, SMR6, SMR7, and SMR9.

The results presented in **Table 4** show the effects of removing part of the postulated batch effects through the proposed method. The independence between train set and test set is kept at the subject-level by avoiding data from the same subject to appear in both of them. Moreover the presence of multiple records

belonging to the same subject is avoided in the test set to eliminate the related bias. Both the prediction accuracy and the $\log(B_{10})$ drop with respect to the values of **Table 3**. While the change in accuracy is marginal (0–5%), the reduction of $\log(B_{10})$ is very strong[12], which is evidence for the sensitivity of this parameter. These changes are clear evidence of the presence of the subject-level batch effect within the data.

In **Table 5** all the postulated batch effects are removed by using the leave-one-site-out cross-validation scheme together with the constraint of one record per subject in the test set. The results show a drop in the values of prediction accuracy and $\log(B_{10})$ with respect to **Table 4**. Again the decrease in accuracy is marginal (0–5%) while the reduction of $\log(B_{10})$ is very strong. This fact is clear evidence in support of the presence of the batch effect at site-level, in addition to the one at subject-level. Moreover we observe that, for the single source analysis, no single data source is sufficient to support the hypothesis of discriminating controls from ADHD patients.

The joint analysis of multiple data sources is addressed in **Table 6**. The results show the impact of removing the batch effects in analogy to what was done for the single source analyses. In a broad sense the results in **Table 6** also address the ADHD-200 Global Competition by using all available data sources for ADHD diagnosis. The analysis is conducted both for the whole set of data sources jointly and for the set of the four most informative data sources according to **Table 3**. The results show a significant drop in prediction accuracy and $\log(B_{10})$ when considering the batch effects in the estimation process. The prediction accuracy reaches an extreme value of 80% when the batch effects are not taken into account, which drops to 50% when all the batch effects are removed. The Bayes factor values show the same trend decreasing from $\log(B_{10}) > 100$ to $\log(B_{10}) \leq 0$[13].

6. CONCLUSIONS

Our results show that taking the batch effects into account and adopting a non-standard measure of the performance of the classifier, like the Bayesian test of independence, can prevent misleading conclusions in the analysis of large multi-site datasets. Nevertheless our results do not prove the absence of ADHD-related information within neuroimaging data. Our results are specific to the proposed representation spaces, i.e., of the dissimilarity representation, and of the proposed classification algorithm, i.e., extremely randomized trees. Different choices of the representation space and of the classification algorithm might lead to different results. What this work provides is a methodology to investigate the classification results in more detail.

In conclusion we argue that the assumptions on which the statistical learning framework relies may be violated by the presence of the batch effect and the consequence of these violations may lead to significant drawbacks during the analysis and may produce wrong inferences. In our study the estimated prediction accuracy decreased from 80% to chance level by taking two levels of batch effect into account. Moreover the value of $\log(B_{10})$ for the batch effect encoded data can be used as an effective tool to detect when the batch effect structure may affect the inference. The very high values in the "BAEF" entry of **Table 3** and of **Table 4** are evidence of this.

We claim that the major challenges of having large datasets in the neuroscience domain, like the ADHD-200 dataset, are not just related to the inherent difficulties of data collection but they also involve the analysis and the interpretation of the results. This work provides some of the essential tools for moving toward the successful analysis of such datasets.

We speculate that the topic of batch effects in neuroimaging data analysis is not confined to site and subject levels but can extend to many other aspects of the neuroimaging data production cycle. Moreover many other approaches, different from the proposed one, should be attempted in order to deal with them. To the best of our knowledge this topic is lacking literature and we welcome future work in this direction.

[12] Notice that this quantity is even in the log scale.

[13] According to Kass and Raftery (1995) when $\log(B_{10}) \leq 0$ the evidence supports H_0.

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FOCUS ON CHILDHOOD AND ADOLESCENT MENTAL HEALTH

Developmental Pathways for Different Subtypes of Early-Onset Bipolarity in Youths

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ABSTRACT

Objective: Two main patterns of comorbidity have been described in bipolar disorder in children and adolescents: the first including preexisting attention-deficit/hyperactivity disorder (ADHD) and related disruptive behavior disorders and the second including anxiety disorders, namely, the association of co-occurring multiple anxiety disorders, usually predating the onset of bipolarity. This study was aimed at exploring whether ADHD and multiple anxiety disorders may exhibit different pathways to specific bipolar phenotypes.

Method: We compared 49 youths (7 to 18 years) with bipolar disorder + ADHD without anxiety, 76 youths with bipolar disorder + multiple anxiety disorders without ADHD, and 52 youths with bipolar disorder without ADHD or multiple anxiety disorders who were referred to a third-level hospital and diagnosed according to *DSM-IV-TR* in the period 2005–2011. Subjects were evaluated for current and lifetime Axis I psychiatric disorders by using a structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version) and followed up for at least 6 months.

Results: Compared to both patients with bipolar disorder + multiple anxiety disorders and patients with bipolar disorder without ADHD and multiple anxiety disorders, patients with bipolar disorder + ADHD without anxiety were more frequently male, were younger, had an earlier onset of bipolar disorder, had a prevalent chronic course and irritable mood, were more likely to present with a bipolar disorder not otherwise specified diagnosis, had a greater clinical severity and functional impairment, had a manic/mixed index episode, had a higher risk of conduct disorder, and were more resistant to treatments, according to the CGI-Improvement scores ($P < .0001$). Patients with bipolar disorder + multiple anxiety disorders were similar to those with bipolar disorder without ADHD or multiple anxiety disorders, except for a higher rate of diagnosis of bipolar II disorder, more use of antidepressants, and less use of atypical antipsychotics.

Conclusions: The presence of comorbid ADHD versus anxiety disorders is indicative of fundamental differences in the phenomenology of bipolar disorder in youth. While ADHD prior to bipolar disorder is associated with a specific bipolar phenotype, bipolar patients with multiple anxiety disorders are similar to "typical" bipolar patients.

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Whether juvenile- and adult-onset bipolar disorders are the same or different disorders is still an open question. Clinical phenotypes and boundaries of bipolar disorder in youths are still debated,[1] given the possible developmentally different presentation of the early-onset form compared to adult "standards"[2–8] as well as the high rate of comorbidity.[9–12] The exploration of clinical presentations led to the definition of different phenotypes of bipolarity, not only according to *DSM-IV-TR* categorization (bipolar I and II disorder and bipolar disorder not otherwise specified [NOS]) but also in terms of course (episodic or chronic) and prevalent mood (euphoric or dysphoric-irritable).[7,8] A differentiation between a "narrow" and a "broad" phenotype, according to the full *DSM-IV* criteria has been proposed[13] and recently refined.[1,5,14,15] Within this context, the concepts of severe mood dysregulation and temper dysregulation disorder with dysphoria have been temporarily conceptualized in order to define these "nosological orphans."[1,15]

Regarding comorbidity, 2 broad patterns have been described. The first pattern includes preexisting attention-deficit/hyperactivity disorder (ADHD),[11,16–18] with rates ranging from 30% to 90%. The second pattern of comorbidity includes anxiety disorders.[9,12,19,20] According to Sala et al,[12] 44% of a series of 446 bipolar youths met criteria for at least an anxiety disorder. Multiple anxiety disorders have been more closely related to bipolarity.[19,21–23] This relationship may also explain the early finding that the offspring of adult bipolar probands often initially receive anxiety disorder diagnoses.[24,25] These findings are consistent with more recent studies addressing psychopathology in offspring of bipolar parents, who present high rates of ADHD, separation anxiety disorder, generalized anxiety disorder, and social phobia in early or middle childhood and obsessive-compulsive disorder, panic disorder, and bipolar disorder in adolescence.[25]

The aim of the present study was to explore whether early-onset comorbidity is related to specific clinical bipolar phenotypes in terms of age at onset, *DSM-IV* categorization, course, prevalent mood, pattern of comorbidity, and response to treatments. From a large sample of children and adolescents with a diagnosis of bipolar disorder, consecutively referred in the last 7 years, we selected 2 groups of patients according to the presence of ADHD or multiple anxiety disorders prior to bipolar disorder, defined as the current comorbidity with at least 2 anxiety disorders among the following: separation anxiety disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and specific phobias. We hypothesized that these 2 comorbidities may represent different pathways to bipolarity, leading to different clinical bipolar phenotypes. In order to explore this hypothesis,

Clinical Points

- The presence of comorbid attention-deficit/hyperactivity disorder (ADHD) versus anxiety disorders should be actively explored, as it is indicative of fundamental differences in the phenomenology of bipolar disorder in youths.
- ADHD plus bipolar disorder might represent a distinct early-onset phenotype within the bipolar spectrum.

we compared youths with bipolar disorder + ADHD, bipolar disorder + multiple anxiety disorders, and bipolar disorder without ADHD or multiple anxiety disorders.

METHOD

Patients

Our naturalistic study is based on a clinical database of 282 youths, aged 7 to 18 years (mean ± SD age = 13.3 ± 2.7 years), who were referred to our third-level hospital with a nationwide catchment area in the period 2005–2011 and who met *DSM-IV-TR* criteria for bipolar I or II disorder or bipolar disorder NOS. Part of this sample (54 patients) was included in previous studies. Subjects were evaluated for current and lifetime Axis I psychiatric disorders at intake by using historical information, a diagnostic interview, the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version (K-SADS-PL),[26] and prolonged observations of interactions with peers, parents, and/or examiners. Behavioral and social-emotional skills were observed directly by trained psychiatrists during interactive activities throughout the diagnostic phase. Inclusion criteria included number of symptoms, duration, and degree of impairment, according to Clinical Global Impressions-Severity of illness scale (CGI-S)[27] score ≥ 4 and Children's Global Assessment Scale (C-GAS)[28] score ≤ 60. All patients with mental retardation, pervasive developmental disorders, and schizophrenia were excluded. Details on the diagnostic procedure can be found elsewhere.[8] Thirty-five patients were randomly selected to establish the interrater reliability. A good interrater reliability for diagnosis of bipolar disorder (including the categorization in bipolar I disorder, bipolar II disorder, and bipolar disorder NOS) and other comorbid disorders with K-SADS-PL was found in this study: ie, κ coefficients of agreement higher than 0.75 (mean κ = 0.85, κ value for bipolar disorder = 0.82).[7]

On the basis of this diagnostic procedure, 49 bipolar patients presented a bipolar disorder + ADHD without current or lifetime comorbidity with anxiety disorders (bipolar disorder + ADHD group), 76 bipolar patients presented a comorbidity with at least 2 anxiety disorders (multiple anxiety disorder) without current or lifetime ADHD (bipolar disorder + multiple anxiety disorders group), and 52 bipolar patients did not present current or lifetime ADHD and anxiety disorders (bipolar disorder group).

Among the total sample of 282 bipolar patients, 96 (34.0%) presented a current comorbidity with ADHD, 181 (64.2%) presented a current comorbidity with at least 1 anxiety disorder, and 52 (18.4%) did not present current or lifetime ADHD and anxiety disorders. In order to remove the overlap between the first 2 groups, the 47 patients (16.7%) with co-occurring current or lifetime ADHD and anxiety disorder were excluded. On the basis of this procedure, 134 patients presented a comorbidity with at least 1 anxiety disorder without current or lifetime ADHD, 76 patients presented a current comorbidity with at least 2 anxiety disorders without current or lifetime ADHD, and 49 patients presented a bipolar disorder + ADHD without current or lifetime comorbidity with anxiety disorders. Thus, 76 patients were included in the group bipolar disorder + multiple anxiety (without ADHD), 49 in the group bipolar disorder + ADHD (without anxiety), and 52 in the group bipolar disorder (without ADHD or anxiety disorders).

All patients were categorized into groups according to course (episodic or chronic) and the prevalent mood. According to the prevalent mood, 2 groups have been described. The first includes patients with elated mood and/or euphoria and/or inflated self-esteem/grandiosity irrespective of the presence or absence of irritable mood (euphoric group); the second includes patients with irritable mood but not elated mood and/or euphoria and/or inflated self-esteem/grandiosity (irritable mood). The episodic/chronic and euphoric/irritable distinctions were made by the first author (G.M.) and each of the psychiatrists who administered the clinical interview and directly participated in the diagnostic process. A good interrater reliability was found, with κ coefficients of agreement higher than 0.80.[7]

Because the symptom criteria for ADHD and mania/hypomania overlap, in order to disentangle the 2 disorders, we considered an indicator of mood disorder to be the presence of clear euphoria/grandiosity/elated mood; very rapid alternations between manic and depressive symptoms, even when they did not meet duration criteria for manic or depressive symptoms; or an abnormal mood (sadness, anger, episodic irritability) and hyperarousal associated with a minimum of 3 manic symptoms (1 less symptom than required by the *DSM-IV* B criterion).[8]

The severity of the illness was recorded at baseline by CGI-S score. Functional impairment was assessed during the same visits by using the C-GAS on a scale from 0 (severe impairment) to 100 (superior functioning). Patients were followed up for at least 6 months with monthly visits. During the period of observation, all patients were naturalistically treated with valproic acid and/or lithium and/or atypical antipsychotics. Antidepressants were used only in association with mood stabilizers when depressive symptoms did not improve after mood stabilization (at least 8 weeks) or when anxiety disorders were particularly impairing. Patients were considered responders when they presented, after a

Table 1. Demographic and Clinical Features of Children and Adolescents With Bipolar Disorder With ADHD, With Bipolar Disorder With Multiple Anxiety Disorders, and With Bipolar Disorder Without ADHD or Multiple Anxiety Disorders

	Bipolar Disorder					
Feature	With ADHD (n = 49)	With Multiple Anxiety Disorders (n = 76)	Without ADHD or Multiple Anxiety Disorders (n = 52)	F/χ^2	*df*	*P*
Male sex, n (%)	40 (81.6)	34 (44.7)	33 (63.5)	17.2	2	.0001***
Age, mean (SD), y	12.5 (2.9)	14.5 (2.6)	14.6 (2.6)	10.2	176	<.0001***[a]
Age at onset, mean (SD), y	8.4 (2.4)	11.1 (3.0)	11.3 (3.0)	17.0	176	<.0001***[a]
Prebubertal onset (<12 ys), n (%)	45 (91.8)	43 (56.6)	32 (61.5)	18.3	2	<.0001***
Follow-up, mean (SD), mo	11.3 (1.8)	11.0 (2.0)	11.7 (1.6)	2.2	176	.109
CGI-S baseline score, mean (SD)	5.7 (0.7)	5.1 (1.0)	5.3 (0.7)	7.6	176	<.0001***[a]
CGI-I score, mean (SD)	2.8 (0.8)	2.1 (0.8)	2.4 (0.8)	11.4	176	.001***[a]
C-GAS baseline score, mean (SD)	38.2 (4.7)	41.8 (6.3)	41.5 (5.1)	10.6	173	<.0001***[a]
Responders, n (%)	18 (36.7)	57 (75.0)	29 (55.8)	18.3	2	<.0001***
Bipolar I disorder, n (%)	16 (32.7)	23 (30.3)	26 (50.0)	5.7	2	.059
Bipolar II disorder, n (%)	10 (20.4)	47 (61.8)	19 (36.5)	22.1	2	<.0001***
Bipolar disorder NOS, n (%)	23 (46.9)	6 (7.9)	7 (13.5)	30.2	2	<.0001***
Chronic course, n (%)	33 (67.3)	19 (25.0)	17 (32.7)	23.7	2	<.0001***
Irritable mood, n (%)	32 (65.3)	22 (28.9)	22 (42.3)	16.1	2	<.0001***
Psychotic symptoms, n (%)	10 (20.4)	14 (18.4)	20 (38.5)	7.4	2	.025*
Index episode manic/mixed, n (%)	39 (79.6)	35 (46.1)	29 (55.8)	14.0	2	<.0001***

[a]Bipolar disorder + ADHD versus bipolar disorder + anxiety and bipolar disorder + ADHD versus bipolar disorder (Tukey test).
*P < .05, ***P < .002 (Bonferroni correction).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, C-GAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of illness scale, NOS = not otherwise specified.

6-month follow-up, a CGI-Improvement score of 1 or 2 (very much improved or much improved), a CGI-S score ≤ 3, and a C-GAS score > 60 for at least 3 further consecutive monthly visits.

All the patients and their families participated voluntarily in the study after written informed consent was obtained for assessment and treatment procedures. The study was approved by the ethical committee of our hospital.

Statistical Analyses

Subjects were compared by using χ^2 analysis on categorical variables, analysis of variance on continuous variables, and Tukey post hoc comparisons on continuous variables. However, owing to the multiple comparisons and the number of patients, our results are prone to both type I and type II errors. Therefore, we used Bonferroni correction for multiple comparisons, setting significance at .002 level, 2-tailed.

RESULTS

As reported in Table 1, patients with bipolar disorder + ADHD were more frequently male (81.6% vs 44.7% in bipolar disorder + multiple anxiety disorders and 63.5% in bipolar disorder patients without ADHD or multiple anxiety disorders, P < .0001), were significantly younger (12.5 ± 2.9 years vs 14.5 ± 2.6 and 14.6 ± 2.6 in the other 2 groups, P < .0001), and presented an earlier onset of the disorder (8.4 ± 2.4 years vs 11.1 ± 3.0 and 11.3 ± 3.0 in the other groups, P < .0001), with a prepubertal onset in 91.8% of patients compared to the 56.6% in the group with bipolar disorder + multiple anxiety disorders and 61.5% in the bipolar disorder patients without ADHD or multiple anxiety disorders (P < .0001). Patients with bipolar disorder + ADHD had higher levels of clinical severity (CGI-S scores) (5.7 ± 0.7 vs 5.1 ± 1.0 in bipolar disorder + multiple anxiety disorders and 5.3 ± 0.7 in bipolar disorder patients without ADHD or multiple anxiety disorders, P < .0001) and functional impairment (C-GAS) (38.2 ± 4.7 vs 41.8 ± 6.3 and 41.5 ± 5.1 in the other groups, P < .0001). Response to treatment was poorer in the bipolar disorder + ADHD group, in terms of both CGI-I score (2.8 ± 0.8 vs 2.1 ± 0.8 and 2.4 ± 0.8 in the other 2 groups, P = .001) and rate of responders (36.7% vs 75.0% and 55.8% in the other 2 groups, P < .0001). Of note, Tukey post hoc comparisons on continuous variables showed that patients with bipolar disorder + ADHD significantly differed from those with bipolar disorder + multiple anxiety disorders and those with bipolar disorder without ADHD or multiple anxiety disorders, while the last 2 groups did not differ according to the selected parameters.

While rate of bipolar I disorder was similar in the 3 groups, patients with bipolar disorder + ADHD more frequently had a bipolar disorder NOS diagnosis (46.9% vs 7.9% and 13.5% in the other groups, P < .0001), while bipolar II disorder was less frequent in bipolar disorder + ADHD and more frequent in bipolar disorder + multiple anxiety disorders (20.4% in bipolar disorder + ADHD, 61.8% in bipolar disorder + multiple anxiety disorders, 36.5% in bipolar disorder without ADHD or multiple anxiety disorders, P < .0001).

Patients with bipolar disorder + ADHD presented the highest frequency of chronic course (67.3% vs 32.7% episodic) (P < .0001) and irritable mood (65.3% vs 34.7%

Table 2. Current and Lifetime Comorbidities in Children and Adolescents With Bipolar Disorder With ADHD, With Bipolar Disorder With Multiple Anxiety Disorders, and With Bipolar Disorder Without ADHD or Multiple Anxiety Disorders

	Bipolar Disorder				
Comorbidity, n (%)	With ADHD (n = 49)	With Multiple Anxiety Disorders (n = 76)	Without ADHD or Multiple Anxiety Disorders (n = 52)	χ^2_2	*P*
Generalized anxiety disorder	0 (0.0)	55 (72.4)	0 (0.0)		
Separation anxiety disorder	0 (0.0)	39 (51.3)	0 (0.0)		
Panic disorder	0 (0.0)	43 (56.6)	0 (0.0)		
Social phobia	0 (0.0)	43 (56.6)	0 (0.0)		
Simple phobia	0 (0.0)	22 (28.9)	0 (0.0)		
Obsessive-compulsive disorder	12 (24.5)	37 (48.7)	18 (34.6)	7.7	.021*
ADHD	49 (100)	0 (0.0)	0 (0.0)		
Oppositional defiant disorder	18 (36.7)	10 (13.2)	10 (19.2)	10.0	.007*
Conduct disorder	23 (46.9)	2 (2.6)	11 (21.2)	36.1	<.0001***

*$P < .05$, ***$P < .002$ (Bonferroni correction).
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 3. Treatment Comparisons in Children and Adolescents With Bipolar Disorder With ADHD, With Bipolar Disorder With Multiple Anxiety Disorders, and With Bipolar Disorder Without ADHD or Multiple Anxiety Disorders

	Bipolar Disorder				
Treatment, n (%)	With ADHD (n = 49)	With Multiple Anxiety Disorders (n = 76)	Without ADHD or Multiple Anxiety Disorders (n = 52)	χ^2_2	*P*
Antidepressants	11 (22.4)	40 (52.6)	16 (30.8)	13.1	.001***
Valproic acid	38 (77.6)	54 (71.1)	25 (48.1)	11.2	.004*
Lithium	24 (49.0)	22 (28.9)	27 (51.9)	8.4	.015*
Valproic acid + lithium	11 (22.4)	5 (6.6)	7 (13.5)	6.7	.036*
Atypical antipsychotics	25 (51.0)	16 (21.1)	23 (44.2)	13.7	.001***
Methylphenidate	16 (32.7)	0 (0.0)	0 (0.0)		
Psychotherapy	23 (46.9)	36 (47.4)	20 (38.5)	1.1	.566

*$P < .05$, ***$P < .002$ (Bonferroni correction).

elated) ($P < .0001$). Interestingly, in 79.6% of patients with bipolar disorder + ADHD compared to 46.1% and 55.8% in the other groups, the index episode was manic/mixed ($P < .0001$). The rate of psychotic symptoms did not differ significantly among the 3 groups.

Pattern of comorbidity significantly differentiated the 3 groups (Table 2). Subjects with bipolar disorder + ADHD presented the highest rate of disruptive behavior disorder comorbidity, namely, conduct disorder (46.9% vs 2.6% and 21.2% in the other groups, $P < .0001$).

Regarding treatments (Table 3), patients with bipolar disorder + multiple anxiety disorders more frequently used antidepressants (52.6% vs 22.4% in bipolar disorder + ADHD and 30.8% in bipolar disorder without ADHD or multiple anxiety disorders, $P = .001$) and less frequently used atypical antipsychotics (21.1% vs 51.0% in bipolar disorder + ADHD and 44.2% in bipolar disorder without ADHD and multiple anxiety disorders). Of course, stimulants were used only in the patients with bipolar disorder + ADHD. The rate of psychotherapy was similar among groups.

DISCUSSION

Comorbid conditions prior to bipolar disorder may be an additional important differential feature of bipolar disorder.[29–31] Pattern of comorbidity in early-onset bipolar disorders are related to 2 broad categories: ADHD and other disruptive behavior disorders on the 1 side and multiple anxiety disorders on the other. And both of these comorbidities usually predate the onset of bipolarity.[16,17,23]

Our results indicate that these different precursors to bipolarity are associated with well-distinct phenotypes. Patients with ADHD prior to bipolar disorder are more frequently male (probably as a consequence of the uneven gender distribution in ADHD patients), have an earlier onset of bipolar symptoms, have a prevalent chronic course and an irritable/dysphoric mood, are more likely to have bipolar disorder NOS, and usually have an index episode that is manic/mixed. A frequent complication is with other disruptive behavior disorders, namely, the most troublesome conduct disorder. Patients with these disorders present a poorer response to treatments, consistent with previous meta-analyses.[32] They fit diagnostic criteria for bipolar disorder, although with some atypical features (ie, very rapid alternations between manic and depressive symptoms, or sadness and anger associated to hyperarousal and manic symptoms). Their symptomatology may be hardly attributed to the ADHD or oppositional defiant disorder domains, even at the highest degree of severity.

On the opposite side, patients with an internalizing phase centered on multiple anxiety disorders prior to bipolar disorder have a later onset of the disorder, with prevalent

episodic course and elated mood, and their index episode can be either manic/mixed or depressive. Consistent with other findings,[12] they more frequently have bipolar II disorder. Data indicate also that they may be more responsive to pharmacologic treatments, according to the lower CGI-I score. These patients are more typical in terms of (episodic) course and (elated) mood compared to the bipolar disorder + ADHD group and similar to bipolar youths without ADHD or multiple anxiety disorders. Furthermore, they present a more frequent use of antidepressants and a less frequent use of atypical antipsychotics (probably due to a lesser severity). The frequent use of antidepressants is not surprising, given that patients with bipolar II disorder spent significantly more time with syndromal or subsyndromal depressive symptoms[10] and have frequent anxiety comorbidities. The risk of mood destabilization or (hypo)manic switches under antidepressant treatment in bipolar II disorder is still debated in adult patients,[33,34] while data in children and adolescents are still scarce.[35] A close monitoring of possible worsening after antidepressant monotherapy, such as irritability, behavioral dyscontrol, substance abuse, erratic life, and suicide risk, is warranted.

It may be debated whether these 2 comorbidities really represent "different pathways" to early-onset bipolarity. In our patients, as well as in other reports, both ADHD and multiple anxiety disorders preceded the onset of the bipolar symptoms, and they may be considered at least precursors or risk factors for subsequent bipolarity or, not alternatively, markers for different mood disorders within the bipolar spectrum. However, other early comorbidities may be relevant in affecting occurrence and features of bipolar disorder, such as the autism spectrum disorders, associated with a higher risk of bipolar disorder with psychotic symptoms.[36]

The underlying issue is whether these subtypes represent different disorders. Our data suggest that, while the bipolar disorder + multiple anxiety disorders group is similar to all the other bipolar patients without anxiety or ADHD comorbidity, bipolar disorder + ADHD is associated with a specific phenotype in terms of course and clinical presentation. This specificity has been recently supported by a magnetic resonance imaging study comparing striatal volumes (caudate, putamen, and globus pallidus) of youths from 4 groups: bipolar disorder with comorbid ADHD, bipolar disorder without comorbid ADHD, ADHD alone, and healthy control subjects.[37] The presence or absence of comorbid ADHD in patients with bipolar disorder was associated with distinct alterations in caudate volumes, suggesting that these groups have different, but related, mechanisms of neuropathology.

Further support for the specificity of ADHD + bipolar disorder comes from longitudinal studies. Adult bipolar patients with a history of childhood ADHD compared with bipolar patients without a history of ADHD have an earlier onset of their first affective episode, more frequent affective episodes, and more interpersonal violence, regardless of whether the ADHD symptoms remained in adulthood or not.[38] Consistently, Bernardi and coworkers[11] showed that adult patients with bipolar disorder plus ADHD, both persistent in adulthood or remitted, reported a significantly earlier onset of mood disorder, higher number of previous mood episodes, and significantly higher impulsivity than bipolar disorder patients without ADHD. Both these studies suggest that ADHD + bipolar disorder might represent a distinct early-onset phenotype of bipolar disorder.

Long-term naturalistic prospective studies might represent an important source of information, and the present findings are therefore of particular relevance to clinical practice in child and adolescent bipolar disorder. Prospective follow-up studies may clarify whether these children with different phenotypes may crystallize their symptomatology into a more classic (affective and episodic) presentation as they grow up or if they retain their "atypical" presentation or follow different pathways, mainly toward disruptive behavior disorders or depressive disorders.[14] The recent debate regarding the nosologic status of bipolar disorder NOS and the differentiation of putative clinical conditions, such as severe mood dysregulation and temper dysregulation disorder with dysphoria, may help to study more homogeneous populations and to explore possible biological, neuropsychological, and environmental features underlying these clinical pictures.[15]

Our naturalistic study presents several methodological limitations. First, only subjects referred to our third-level hospital who usually needed pharmacologic treatment were included, and this selection bias may limit the generalization of the conclusions, because our sample may represent a subgroup of more severely impaired subjects in terms of clinical presentation, pattern of comorbidity, and response to treatments. The subgrouping was based on clinical grounds. Only a selected number of features were considered as relevant, and the diagnostic exploration did not include other potentially important elements. Age at onset of bipolar disorder was assessed retrospectively and was based on historical information and previous clinical reports. In patients with ADHD prior to bipolar disorder and frequent comorbid oppositional defiant disorder or conduct disorder, it may be particularly difficult to define the precise onset of the mood disorder. Furthermore, the severity of the behavioral symptoms may have anticipated the referral, and this factor may have further affected the reconstruction of the exact onset of bipolar disorder. Keeping these issues in mind, we were particularly careful in defining the onset of bipolar disorder and comorbid disorders.

Another limitation is that we have used the outcome measure CGI, which is not a specific measure of bipolar disorder severity and improvement. Considering the high level of comorbidity in bipolar disorder, it may be difficult to disentangle the specific contribution of the co-occurring disorders (particularly ADHD and oppositional defiant disorder or conduct disorder) to the severity of symptomatology, as well as the specific effect of pharmacotherapy on manic/mixed symptoms. However, there is evidence that global ratings can be more sensitive to change during acute treatment

than scores on itemized symptom rating scales.[39,40] Furthermore, the CGI-I criterion corresponds to what clinicians use to determine whether to continue or interrupt a medication trial. In a naturalistic setting with unselected patients, characterized by high co-occurrence and changeability, an apparent improvement of 1 symptom, considered alone, may be consequent to a worsening of another symptom. For this reason, the course of the clinical picture as a whole is more reliably captured by a more global measure.

A better knowledge of the pathways leading to early mood disorders may increase our capacities for a possible prevention or at least a timely recognition in youths with internalizing or externalizing symptoms, with positive implications on both prognosis and treatment.[3] Given that the occurrence of comorbid ADHD has an impact on the long-term course of bipolar disorder,[11,37] further longitudinal studies may explore whether a timely treatment of ADHD may affect the outcome of some key features of bipolar disorder, such as frequency of episodes, and occurrence of impulsivity, violence, and hostility.

Drug names: lithium (Lithobid and others), methylphenidate (Daytrana, Ritalin, and others), valproic acid (Stavzor, Depakene, and others).
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Potential conflicts of interest: **Dr Masi** has served on advisory boards for Eli Lilly, Shire and Novartis; has received research grants from Eli Lilly and Shire; and has been speaker for Eli Lilly, Shire, Sanofi-Aventis, and Novartis. **Dr Pfanner** has received research grants from and has been speaker for Eli Lilly. **Dr Perugi** has served on advisory boards for Sanofi-Aventis, AstraZeneca, Janssen-Cilag, Lundbeck, BMS Otsuka and Eli Lilly; and has received grants from AstraZeneca, Eli Lilly, and Lundbeck. **Drs Mucci**, **Berloffa**, and **Magazù** do not have conflicts of interest to declare.
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