NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD OTTOBRE 2015

ADHD Atten Deficit Hyperact Disord. 2015.

DEMOGRAPHIC, DEVELOPMENTAL AND PSYCHOSOCIAL PREDICTORS OF THE DEVELOPMENT OF ANXIETY IN ADULTS WITH ADHD.

Grogan K, Bramham J.

The purpose of this research was to investigate potential demographic, developmental and psychosocial predictors of anxiety in the context of ADHD. Participants included 267 adults with a diagnosis of ADHD (168 males:99 females) and an age range of 18ΓÇô70 years (M = 31 years; SD = 10.03 years). A background interview, parent questionnaire and rating scales were used to gather participant information. Correlations, independent t tests and one-way analysis of variances were used to identify variables associated with anxiety, and a stepwise multiple regression was used to identify potential predictors of anxiety. Variables associated with anxiety included childhood aggression, employment status, difficulties making friends, number of children and caffeine intake. Childhood aggression and caffeine intake were the potential predictors. Clinicians should be aware of these potential predictors of anxiety in the context of ADHD in order to minimise the likelihood of the development or maintenance of comorbid anxiety. Future research is needed in order to draw any conclusions on cause and effect

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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.

Am J Med Genet A. 2015 Feb;167A:379-84.

CHOLESTEROL LEVELS IN FRAGILE X SYNDROME.

Berry-Kravis E, Levin R, Shah H, et al.

Fragile X syndrome (FXS) is associated with intellectual disability and behavioral dysfunction, including anxiety, ADHD symptoms, and autistic features. Although individuals with FXS are largely considered healthy and lifespan is not thought to be reduced, very little is known about the long-term medical health of adults with FXS and no systematically collected information is available on standard laboratory measures from metabolic screens. During the course of follow up of a large cohort of patients with FXS we noted that many patients had low cholesterol and high density lipoprotein (HDL) values and thus initiated a systematic chart review of all cholesterol values present in charts from a clinic cohort of over 500 patients with FXS. Total cholesterol (TC), low density lipoprotein (LDL) and HDL were all significantly reduced in males from the FXS cohort relative to age-adjusted population normative data. This finding has relevance for health monitoring in individuals with FXS, for treatments with cholesterol-lowering agents that have been proposed to target the underlying CNS disorder in FXS based on work in animal models, and for potential biomarker development in FXS

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Am J Orthopsychiatry. 2015 Sep;85:504-13.

THE ASSOCIATION BETWEEN YOUTH VIOLENCE EXPOSURE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) SYMPTOMS IN A SAMPLE OF FIFTH-GRADERS.

Lewis T, Schwebel DC, Elliott MN, et al.

The purpose of the current study was to examine the association between violence exposures (no exposure, witness or victim only, and both witness and victim) and attention-deficit/hyperactivity disorder (ADHD) symptoms, as well as the potential moderating role of gender. Data from 4,745 5th graders and their primary caregivers were drawn from the Healthy Passages study of adolescent health. Parent respondents completed the DISC Predictive Scales for ADHD, and youth provided information about exposure to violence. Results indicated that youth who reported both witnessing and victimization had more parent-reported ADHD symptoms and were more likely to meet predictive criteria for ADHD. Among those with both exposures, girls exhibited a steeper increase in ADHD symptoms and higher probability of meeting predictive criteria than did boys. Findings indicate that being both victim-of and witness-to violence is significantly associated with ADHD symptoms particularly among girls.

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Ann Thorac Surg. 2015 Aug;100:663-70.

ASSOCIATION BETWEEN METHOD OF CEREBRAL PROTECTION DURING NEONATAL AORTIC ARCH SURGERY AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Sistino JJ, Atz AM, Ellis C, Jr., et al.

BACKGROUND: Neonates undergoing repair of the aortic arch are at risk for adverse neurodevelopmental outcomes, including attention deficit/hyperactivity disorder (ADHD). The purpose of this study was to compare the effect of deep hypothermic circulatory arrest versus regional cerebral perfusion on the long-term outcome of ADHD.

METHODS: This study is a cross-sectional observational study of ADHD in children who underwent neonatal aortic arch surgery. Attention Deficit/Hyperactivity Disorder-IV surveys were used to determine the prevalence of ADHD. Review of the medical records was performed to determine the primary method of cerebral protection and to extract related surgical variables.

RESULTS: Surveys were sent to parents of 134 children, with 57 surveys completed (43%). The percentage of children classified as having ADHD was 44%. Children with a diagnosis of interrupted aortic arch had the highest prevalence of ADHD (85%). Multivariate analysis demonstrated that interrupted aortic arch was associated with an increased ADHD inattention score ($p < 0.01$), and a decreased Child Health Questionnaire-50 psychosocial score ($p < 0.01$). Low Child Health Questionnaire-50 psychosocial summary scores are associated with increased behavioral problems and are lower in patients with ADHD.

CONCLUSIONS: Attention deficit/hyperactivity disorder is common after neonatal aortic arch surgery and may be primarily related to genetic predisposition. We found insufficient evidence to show that either deep hypothermic circulatory arrest or regional cerebral perfusion decreased the risk of ADHD

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Annu Rev Psychol. 2015 Jan;66:459-85.

CHILDHOOD ANTECEDENTS AND RISK FOR ADULT MENTAL DISORDERS.

Pine DS, Fox NA.

Progress in treating and preventing mental disorders may follow from research that integrates development, genetics, and neuroscience. This review first delineates how longitudinal research has identified three particular groups of disorders shown to differ on the basis of symptom trajectories and risk-factor profiles. In the next section, the review describes how research on genetic contributions to psychopathology has elucidated the nature of risk for two groups of disorders, the neurodevelopmental and psychotic disorders. In the third section, the review describes how research on environmental contributions to psychopathology has targeted early temperament, its associated perturbations in information-processing functions, and its relations to a third group of disorders, the emotional disorders. For all three groups of disorders, such integrative research has generated ideas about novel interventions. The hope is that over the coming decade such ideas will lead to novel treatments that alter the trajectory of risk in developmental psychopathology

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Aust N Z J Psychiatry. 2015 Feb;49:181-82.

OLD DRUG TIPEPIDINE AS NEW HOPE FOR CHILDREN WITH ADHD.

Hashimoto K, Sasaki T.

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Biological Trace Element Research. 2015.

WERE PLASMA TRACE ELEMENT LEVELS CHANGED IN THE CHILDREN WITH ADHD?

Viktorinova A, Ursinyova M, Trebaticka J, et al.

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BMC Psychiatry. 2015;15:45.

A COMPARISON OF CLINICAL CHARACTERISTICS BETWEEN ADOLESCENT MALES AND FEMALES WITH EATING DISORDERS.

Welch E, Ghaderi A, Swenne I.

BACKGROUND: Eating disorders (ED) are serious disorders that have a negative impact on both the psychological and the physiological well-being of the afflicted. Despite the fact that ED affect both genders, males are often underrepresented in research and when included the sample sizes are often too small for separate analyses. Consequently we have an unclear and sometimes contradictory picture of the clinical characteristics of males with ED. The aim of the present study was to improve our understanding of the clinical features of adolescent males with eating disorders.

METHODS: We compared age at presentation, weight at presentation, history of significantly different premorbid weight and psychiatric (Attention Deficit Hyperactivity Disorder (ADHD)) and somatic comorbidity (celiac disease and diabetes) of 58 males to 606 females seeking medical care for eating disorders at the Children's Hospital in Uppsala, Sweden during the years 1999-2012. As all boys were diagnosed with either AN or Other Specified Feeding or Eating Disorder (OSFED) atypical AN, the age and weight comparisons were limited to those girls fulfilling the diagnostic criteria for AN or OSFED atypical AN.

RESULTS: There was no significant difference in age at presentation. Differences in weight at presentation and premorbid weight history were mixed. A significantly higher percentage of males had a history of a BMI

greater than two standard deviations above the mean for their corresponding age group. As well, there was a higher prevalence of ADHD among the males whereas celiac disease and diabetes only was found among the females.
CONCLUSIONS: A better understanding of the clinical characteristics of males with ED at presentation should improve our ability to identify males with ED and thereby aid in tailoring the best treatment alternatives

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Bol Asoc Med P R. 2015 Apr;107:97-99.
ARE YOUNG ADULTS WITH ADHD UNDERTREATED?
Bonet-Pagan Y, Gonzalez-Alonso R, Castaing-Lespier P.

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Brain Imaging Behav. 2015.
ADHD AND CANNABIS USE IN YOUNG ADULTS EXAMINED USING FMRI OF A GO/NOGO TASK.
Rasmussen J, Casey BJ, van Erp TGM, et al.
Children diagnosed with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for substance abuse. Response inhibition is a hallmark of ADHD, yet the combined effects of ADHD and regular substance use on neural networks associated with response inhibition are unknown. Task-based functional Magnetic Resonance Imaging (fMRI) data from young adults with childhood ADHD with (n = 25) and without (n = 25) cannabis use ΓëÑ monthly in the past year were compared with a local normative comparison group (LNCG) with (n = 11) and without (n = 12) cannabis use. Go/NoGo behavioral and fMRI data were evaluated for main and interaction effects of ADHD diagnosis and cannabis use. ADHD participants made significantly more commission errors on NoGo trials than controls. ADHD participants also had less frontoparietal and frontostriatal activity, independent of cannabis use. No main effects of cannabis use on response inhibition or functional brain activation were observed. An interaction of ADHD diagnosis and cannabis use was found in the right hippocampus and cerebellar vermis, with increased recruitment of these regions in cannabis-using controls during correct response inhibition. ADHD participants had impaired response inhibition combined with less fronto-parietal/striatal activity, regardless of cannabis use history. Cannabis use did not impact behavioral response inhibition. Cannabis use was associated with hippocampal and cerebellar activation, areas rich in cannabinoid receptors, in LNCG but not ADHD participants. This may reflect recruitment of compensatory circuitry in cannabis using controls but not ADHD participants. Future studies targeting hippocampal and cerebellar-dependent function in these groups may provide further insight into how this circuitry is altered by ADHD and cannabis use

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Brain Injury. 2015.
DESCRIBING THE ATTENTION PROFILE OF CHILDREN AND ADOLESCENTS WITH ACQUIRED BRAIN INJURY USING THE VIRTUAL CLASSROOM.
Gilboa Y, Kerrouche B, Longaud-Vales A, et al.
Objectives: The objectives of the study were: (1) to describe the attention deficits profile of children with significant acquired brain injury (ABI) in comparison to matched controls, using the virtual classroom (VC); (2) to assess the utility of the VC in detecting attention deficits in children with ABI, as compared to classical neuropsychological tests and questionnaire-based assessment of attention; and (3) to determine how performance in the VC is affected by demographic and injury severity variables.
Methods: Forty-one children with ABI and 35 age- and gender-matched controls, aged 8–16, were assessed with the VC. The results of the VC were compared to sub-tests of the Test of Everyday Attention for Children (TEA-Ch), the Conners' Parent Rating Scales-Revised: Short (CPRS-R:S) questionnaire and analysed according to demographic and injury severity variables.

Results: Significant differences were found between the groups regarding the number of targets correctly identified in the VC. Significant inter-correlations were obtained between the VC variables. Significant correlations were found between the VC variables, the sub-tests of TEA-Ch and the CPRS-R:S and the demographic characteristics of the sample.
Conclusion: The VC appears to be a sensitive and ecologically valid assessment tool for use in the diagnosis of attention deficits among children with ABI.

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Child Care Health Dev. 2015 Jan;41:1-14.

BEYOND SYMPTOM CONTROL FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): WHAT CAN PARENTS DO TO IMPROVE OUTCOMES?

Tarver J, Daley D, Sayal K.

Attention-deficit hyperactivity disorder (ADHD) and its associated behavioural manifestations develop and progress as the result of complex gene-environment interactions. Parents exert a substantial influence and play a major role in their child's social environment. Despite this, recent evidence has suggested that adapting the child's environment via parenting interventions has minimal effects on child ADHD symptoms when analysing data from informants who are probably blind to treatment allocation. However, adverse parenting and family environments may act as a source of environmental risk for a number of child outcomes beyond ADHD symptoms. This is a narrative review that critically discusses whether parenting interventions are beneficial for alternative functioning outcomes in ADHD including neuropsychological, academic and social functioning and disruptive behaviour and how parenting and familial environments may be associated with these outcomes. In addition, the review explores how parental depression and parenting efficacy impact on capacity for optimal parenting and whether parenting interventions benefit parents too. A review of the evidence suggests that with modification, parenting interventions are beneficial for a number of outcomes other than ADHD symptom reduction. Improving the parent-child relationship may have indirect benefits for disruptive behaviour. Furthermore, parenting behaviours may directly benefit child neuropsychological, academic and social functioning. Parenting interventions can have therapeutic benefits for parents as well as children, which is important as parent and child well-being is likely to have a transactional relationship. Evaluation of the clinical success of parenting interventions should focus on a wider range of outcomes in order to aid understanding of the multifaceted benefits that they may be able to offer. Parenting interventions should not be seen as a redundant adjunct to medication in multi-modal treatment approaches for ADHD; they have the potential to target outcomes that, at present, medication seems less able to improve

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Child Care Health Dev. 2015 Jan;41:93-102.

OVERCOMING BARRIERS TO EFFECTIVE EARLY PARENTING INTERVENTIONS FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): PARENT AND PRACTITIONER VIEWS.

Smith E, Koerting J, Latter S, et al.

BACKGROUND: The importance of early intervention approaches for the treatment of attention-deficit hyperactivity disorder (ADHD) has been increasingly acknowledged. Parenting programmes (PPs) are recommended for use with preschool children with ADHD. However, low 'take-up' and high 'drop-out' rates compromise the effectiveness of such programmes within the community.
METHODS: This qualitative study examined the views of 25 parents and 18 practitioners regarding currently available PPs for preschool children with ADHD-type problems in the UK. Semi-structured interviews were undertaken to identify both barriers and facilitators associated with programme access, programme effectiveness, and continued engagement.
RESULTS AND CONCLUSIONS: Many of the themes mirrored previous accounts relating to generic PPs for disruptive behaviour problems. There were also a number of ADHD-specific themes. Enhancing parental motivation to change parenting practice and providing an intervention that addresses the parents' own needs (e.g. in relation to self-confidence, depression or parental ADHD), in addition to those of the child, were considered of particular importance. Comparisons between the views of parents and practitioners highlighted a need to increase awareness of parental psychological barriers among practitioners and for better

programme advertising generally. Clinical implications and specific recommendations drawn from these findings are discussed and presented

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Child Neuropsychol. 2015;21:465-80.

ENHANCING NEUROBEHAVIORAL GAINS WITH THE AID OF GAMES AND EXERCISE (ENGAGE): INITIAL OPEN TRIAL OF A NOVEL EARLY INTERVENTION FOSTERING THE DEVELOPMENT OF PRESCHOOLERS' SELF-REGULATION.

Healey DM, Halperin JM.

Poor self-regulation during the preschool years predicts a wide array of adverse adult outcomes and, as such, is an important treatment target. We assessed the efficacy of a novel early intervention aimed at fostering the development of preschoolers' self-regulation. Enhancing Neurobehavioral Gains with the Aid of Games and Exercise (ENGAGE) involves parents and children playing a wide range of games targeting self-regulation on a daily basis over a 5-week period. Twenty-five New Zealand families, in whom parents identified their children as difficult to manage, took part in this study. Parent hyperactivity, aggression, and attention problems ratings on the BASC-2 were used to assess improvements in behavioral self-regulation, and subtests of the Stanford Binet-5 and NEPSY-2 were used to assess improvements in cognitive control. Improvements in parent-rated hyperactivity, aggression, and attention problems were maintained throughout the 12-month follow-up. In addition, improvements were found in two neurocognitive areas associated with self-regulation. While more rigorous randomized controlled trials are necessary, ENGAGE shows promise as a novel intervention for developing self-regulation in at-risk preschoolers

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Child Neuropsychol. 2015;21:509-30.

WORKING MEMORY DEFICITS IN BOYS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD): AN EXAMINATION OF ORTHOGRAPHIC CODING AND EPISODIC BUFFER PROCESSES.

Alderson RM, Kasper LJ, Patros CH, et al.

The episodic buffer component of working memory was examined in children with attention deficit/hyperactivity disorder (ADHD) and typically developing peers (TD). Thirty-two children (ADHD = 16, TD = 16) completed three versions of a phonological working memory task that varied with regard to stimulus presentation modality (auditory, visual, or dual auditory and visual), as well as a visuospatial task. Children with ADHD experienced the largest magnitude working memory deficits when phonological stimuli were presented via a unimodal, auditory format. Their performance improved during visual and dual modality conditions but remained significantly below the performance of children in the TD group. In contrast, the TD group did not exhibit performance differences between the auditory- and visual-phonological conditions but recalled significantly more stimuli during the dual-phonological condition. Furthermore, relative to TD children, children with ADHD recalled disproportionately fewer phonological stimuli as set sizes increased, regardless of presentation modality. Finally, an examination of working memory components indicated that the largest magnitude between-group difference was associated with the central executive. Collectively, these findings suggest that ADHD-related working memory deficits reflect a combination of impaired central executive and phonological storage/rehearsal processes, as well as an impaired ability to benefit from bound multimodal information processed by the episodic buffer

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Child Neuropsychol. 2015.

RELATING LAB TO LIFE: DECREMENTS IN ATTENTION OVER TIME PREDICT MATH PRODUCTIVITY AMONG CHILDREN WITH ADHD.

Fosco WD, Hawk LW.

A child's ability to sustain attention over time (AOT) is critical in attention-deficit/hyperactivity disorder (ADHD), yet no prior work has examined the extent to which a child's decrement in AOT on laboratory tasks relates to clinically-relevant behavior. The goal of this study is to provide initial evidence for the criterion

validity of laboratory assessments of AOT. A total of 20 children with ADHD (7-12 years of age) who were enrolled in a summer treatment program completed two lab attention tasks (a continuous performance task and a self-paced choice discrimination task) and math seatwork. Analyses focused on relations between attention task parameters and math productivity. Individual differences in overall attention (OA) measures (averaged across time) accounted for 23% of the variance in math productivity, supporting the criterion validity of lab measures of attention. The criterion validity was enhanced by consideration of changes in AOT. Performance on all laboratory attention measures deteriorated as time-on-task increased, and individual differences in the decrement in AOT accounted for 40% of the variance in math productivity. The only variable to uniquely predict math productivity was from the self-paced choice discrimination task. This study suggests that attention tasks in the lab do predict a clinically-relevant target behavior in children with ADHD, supporting their use as a means to study attention processes in a controlled environment. Furthermore, this prediction is improved when attention is examined as a function of time-on-task and when the attentional demands are consistent between lab and life contexts.

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Child Psychiatry Hum Dev. 2015 Oct;46:736-48.

LONGITUDINAL ASSOCIATIONS BETWEEN INTERNALIZING AND EXTERNALIZING COMORBIDITIES AND FUNCTIONAL OUTCOMES FOR CHILDREN WITH ADHD.

Armstrong D, Lycett K, Hiscock H, et al.

This study examined functional outcomes for children with ADHD by comorbidity status. Children with ADHD (5–13 years) were recruited from 21 pediatric practices and followed up 12 months later (n = 199). Parent and teacher-reported baseline and 12 month surveys measured peer problems, daily functioning, quality of life (QoL), parent mental health, and family QoL. The Anxiety Disorders Interview Schedule for Children IV assessed mental health comorbidities at baseline. Linear regression models were conducted, adjusting for socio-demographics, ADHD severity, and baseline functioning (where possible). In adjusted analyses, children with ADHD and co-occurring internalizing and externalizing comorbidities had poorer QoL, greater peer problems, and poorer family QoL, compared to children with ADHD alone. The parents of children with ADHD and internalizing and externalizing comorbidities alone, also reported poorer family QoL, compared to children with ADHD alone. Children with ADHD and co-occurring internalizing and externalizing comorbidities appear particularly vulnerable to poorer functioning.

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Clin Drug Investig. 2015 Feb;35:133-40.

INTERPRETING THE RESULTS OF A RETROSPECTIVE COMPARISON OF TEST AND REFERENCE TREATMENTS IN A RANDOMIZED CLINICAL TRIAL SETTING.

Fridman M, Erder MH.

BACKGROUND AND OBJECTIVES: The retrospective comparison of test and reference treatment arms in a randomized prospective clinical trial is potentially useful in economic modeling seeking to assess the cost effectiveness of alternative therapies.

METHODS: To enhance the credibility of such retrospective comparisons, we propose the application of the following adjustments to significance levels obtained from standard statistical methodology: (1) a significance test for the lower bound of the 95 % confidence interval for the observed difference, (2) a conservative Bonferroni method of adjustment for multiple comparisons, (3) an adjusted p-value calculated using Scheffe's single-step method, and (4) Bayesian 95 % credibility intervals with a prior centered at zero.

RESULTS: These adjustments were applied to data from a randomized double-blind concurrent trial (SPD489-325) that established the efficacy and safety of lisdexamfetamine dimesylate (LDX) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Prospectively planned analyses demonstrated that the reduction in the symptoms of ADHD was significantly greater than placebo in patients treated with either LDX or the reference treatment, osmotic-release oral system methylphenidate (OROS-MPH). Retrospective analyses showed that the improvement in the symptoms of ADHD was greater in

patients treated with LDX than OROS-MPH. We now show that this observation remained significant after the application of the four statistical penalties.
CONCLUSIONS: By adjusting the significance level, it is possible to compare quantitatively such retrospective results with prospectively defined comparisons. However, the qualitative level of such retrospective evidence should remain secondary to that obtained from prospectively specified comparisons in a randomized clinical trial

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Clin EEG Neurosci. 2015 Apr;46:126-29.
A PROLONGED RHYTHMIC MIDTEMPORAL DISCHARGE IN A CHILD WITHOUT SEIZURES.
Fawaz A, Nasreddine W, Bustros S, et al.
Rhythmic midtemporal discharge (RMTD) is one of the benign epileptiform variants, typically consisting of runs of 4-Hz to 7-Hz activity, lasting up to 10 seconds and maximal over the midtemporal area. We report a child who, during an admission for diagnostic closed-circuit television (CCTV) and electroencephalographic (EEG) monitoring, was found to have prolonged rhythmic monomorphic discharges, alternating over both midtemporal areas, with one of the discharges lasting up to 82 minutes. An analysis of the dominant frequency, during the longest discharge, showed that it was monomorphic throughout. On the basis of various features of these discharges, we concluded that they represented RMTD of unusual duration

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Clin Neurophysiol. 2015 Jun;126:1159-70.
EVENT RELATED POTENTIALS STUDY OF ABERRATIONS IN VOICE CONTROL MECHANISMS IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Korzyukov O, Tapaskar N, Pflieger ME, et al.
OBJECTIVE: The present study was designed to test for neural signs of impulsivity related to voice motor control in young adults with ADHD using EEG recordings in a voice pitch perturbation paradigm.
METHODS: Two age-matched groups of young adults were presented with brief pitch shifts of auditory feedback during vocalization. Compensatory behavioral and corresponding bioelectrical brain responses were elicited by the pitch-shifted voice feedback.
RESULTS: The analysis of bioelectrical responses showed that the ADHD group had shorter peak latency and onset time of motor-related bioelectrical brain responses as compared to the controls.
CONCLUSIONS: These results were interpreted to suggest differences in executive functions between ADHD and control participants.
SIGNIFICANCE: We hypothesize that more rapid motor-related bioelectrical responses found in the present study may be a manifestation of impulsiveness in adults with ADHD at the involuntary level of voice control

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Clin Pediatr (Phila). 2015 Jan;54:98.
HYPERACTIVE CHILDREN: COULD THEY HAVE SLEEP DISORDERED BREATHING?
Cherlopalle S, Enja M, Kolikonda MK, et al.

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Clin Pediatr (Phila). 2015 Feb;54:138-44.
TOURETTE SYNDROME: A GENERAL PEDIATRICIAN'S 35-YEAR EXPERIENCE AT A SINGLE CENTER WITH FOLLOW-UP IN ADULTHOOD.
Byler DL, Chan L, Lehman E, et al.
A retrospective analysis of a 35-year single-center experience with pediatric tics and Tourette syndrome was conducted. 482 charts from 1972 to 2007 were reviewed. Follow-up surveys were mailed to last known

address and 83 patients responded (17%). Response rate was affected by long interval from last visit; contact information was often incorrect as it was the address of the patient as a child. Males constituted 84%. Mean tic onset was 6.6 years. At first visit, 83% had multiple motor tics and >50% had comorbidities. 44% required only 1 visit and 90% less than 12 visits. Follow-up showed positive clinical and social outcomes in 73/83 survey responses. Of those indicating a poor outcome, mean educational level was lower and attention deficit/hyperactivity disorder and learning disabilities were significantly higher. Access to knowledgeable caregivers was a problem for adult patients. A shortage of specialists may in part be addressed by interested general pediatricians

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Clin Psychol Rev. 2015 Mar;36:1-12.

DEVELOPMENTAL PATHWAYS TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DISRUPTIVE BEHAVIOR DISORDERS: INVESTIGATING THE IMPACT OF THE STRESS RESPONSE ON EXECUTIVE FUNCTIONING.

Johnson AC.

A current theory suggests multiple pathways to the onset of attention-deficit/hyperactivity disorder (ADHD) and comorbid oppositional defiant disorder or conduct disorder, proposing that heterogeneous factors lead to various patterns of behavior, cognitive impairments, and even physiological signs which are categorized as ADHD and comorbid disorders. This review focused on one proposed pathway to the onset of ADHD and ODD/CD in order to examine how low physiological arousal, as indicated by atypical hypothalamic-pituitary-adrenal axis and sympathetic adrenomedullary functioning, might be associated with cognitive impairment. First, the cognitive deficits associated with ADHD and disruptive behavior disorders were reviewed. In order to understand the atypical response, studies of the typical stress response and its relationship to cognition, particularly executive functioning, were then examined. Finally, this review summarized findings of an atypical stress response among children with ADHD and ODD/CD. Review of the literature led to the conclusion that the theorized pathway may be improved by taking into account the effects of stress on executive functioning given that an atypical stress response would likely be associated with impairment in this area. Future research directions needed to advance our understanding of the relationship between low arousal, ADHD, and ODD/CD were highlighted

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Clin EEG Neurosci. 2015;46:285-91.

HOW THE INDIVIDUAL ALPHA PEAK FREQUENCY HELPS UNRAVEL THE NEUROPHYSIOLOGIC UNDERPINNINGS OF BEHAVIORAL FUNCTIONING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

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

Attention-deficit/hyperactivity disorder (ADHD) has been associated with an elevated resting-state theta/beta power ratio and elevated theta power. However, the potential confounding effect of a low individual alpha peak frequency (IAPF) on the theta-power estimate has often been disregarded when studying the relationship between ADHD and the theta/beta power ratio or theta power alone. The aim of the present study was to assess whether the theta/beta power ratio and relative theta power are correlated with behavioral functioning in children with ADHD, as expected from previous studies. Subsequently, the influence of IAPF and the amount of supposed overlap between the individually determined alpha-band and the fixed theta-band were studied. For 38 children (aged 8-15 years), electroencephalographic (EEG) and investigator-scored ADHD Rating Scale IV data were available. Additional neurocognitive data were available for 32 children. As expected, the theta/beta power ratio and theta were positively related to the ADHD core symptoms. This relationship strengthened when controlling for IAPF, although correlations did not significantly differ from one another. Eight of 38 children (21%) showed a supposed overlap between their individually determined alpha band and the theta band. Neurocognitive performance did not show any relationship with the theta/beta power ratio or theta. The results of this study confirm that the theta/beta power ratio and theta power are indeed correlated with behavioral symptoms in children with ADHD and underscore the relevance of taking the IAPF into account

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Cochrane Database Syst Rev. 2015;5:CD010012.

L-ACETYLCARNITINE FOR TREATING FRAGILE X SYNDROME.

Rueda JR, Guillen V, Ballesteros J, et al.

BACKGROUND: People with fragile X syndrome (FXS) have an intellectual dysfunction that can range from very mild to severe. Symptoms can include speech and language delays and behavioural difficulties such as aggression or self injurious behaviours, emotional lability, and anxiety-related problems (for example obsessive-compulsive symptoms and perseverative behaviours). In some cases, affected people may have an additional diagnosis of attention deficit hyperactivity disorder or an autism spectrum disorder.

OBJECTIVES: To review the efficacy and safety of L-acetylcarnitine in improving the psychological, intellectual, and social performance of people with FXS.

SEARCH METHODS: In May 2015 we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, Web of Science, and two other databases. We also searched three trials registers, four theses databases, and the reference lists of relevant studies and reviews.

SELECTION CRITERIA: Randomised controlled trials (RCTs) that assessed the efficacy of L-acetylcarnitine, at any dose, in people of any age diagnosed with FXS compared with placebo.

DATA COLLECTION AND ANALYSIS: For each trial, two review authors independently extracted data on the children included and interventions compared, and assessed the risk of bias of the studies across the following domains: randomisation sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other potential sources of bias.

MAIN RESULTS: We found only two RCTs that compared oral L-acetylcarnitine (LAC) with oral placebo in children with FXS. The studies included a total of 83 participants, all of them male, who were treated and followed for one year. The age of participants at the start of treatment ranged from 6 to 13 years, with a mean age of 9 years. Neither study provided information on randomisation, allocation concealment procedures, or blinding of outcome assessment, and we received no responses from the authors we emailed for clarification. We therefore rated studies as being at unclear risk of bias on these domains. We judged both studies to be at low risk of bias for blinding of participants and personnel, incomplete outcome data, and selective reporting, but to be at high risk of other bias, as at least one study was funded by a drug company, and in both studies people working for the company were part of the research team.We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of the available evidence. Overall, the quality of the evidence was low due to the imprecision of results and high risk of other bias.Regarding the primary outcome of psychological and learning capabilities, both studies assessed the effect of interventions on children's verbal and non-verbal intellectual functioning using the Wechsler Intelligence Scale for Children - Revised. The authors did not provide detailed data on those results but said that they found no important differences between treatment and placebo.Both studies evaluated the impact of the treatment on hyperactive behaviour using the Conners' Abbreviated Parent-Teacher Questionnaire. In one study, teachers' assessments of the children found no clear evidence of a difference (mean difference (MD) 0.50, 95% confidence interval (CI) -5.08 to 6.08, n = 51; low-quality evidence). The other study stated that there were no differences between treated and untreated participants, but did not provide detailed data for inclusion in the meta-analysis.Parents' assessments favoured LAC in one study (MD -0.57, 95% CI -0.94 to -0.19, n = 17; low-quality evidence), but not in the other (MD -2.80, 95% CI -7.61 to 2.01, n = 51; low-quality evidence), though changes were not large enough to be considered clinically relevant.Regarding social skills, one study reported no clear evidence of a difference in Vineland Adaptive Behavior composite scores (MD 8.20, 95% CI -0.02 to 16.42, n = 51; low-quality evidence), yet results in the socialisation domain favoured LAC (MD 11.30, 95% CI 2.52 to 20.08, n = 51; low-quality evidence).Both studies assessed the safety of the active treatment and recorded no side effects. Neither of the included studies assessed the secondary outcome of caregiver burden. AUTHORS' CONCLUSIONS: Low-quality evidence from two small trials showed that when compared to placebo, LAC may not improve intellectual functioning or hyperactive behaviour in children with FXS

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Compr Psychiatry. 2015 Feb;57:85-96.

CO-OCCURRENCE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS WITH OTHER PSYCHOPATHOLOGY IN YOUNG ADULTS: PARENTING STYLE AS A MODERATOR.

Ni HC, Gau SS.

The extent to which parenting styles can influence secondary psychiatric symptoms among young adults with ADHD symptoms is unknown. This issue was investigated in a sample of 2284 incoming college students (male, 50.6%), who completed standardized questionnaires about adult ADHD symptoms, other DSM-IV symptoms, and their parents' parenting styles before their ages of 16. Among them, 2.8% and 22.8% were classified as having ADHD symptoms and sub-threshold ADHD symptoms, respectively. Logistic regression was used to compare the comorbid rates of psychiatric symptoms among the ADHD, sub-threshold ADHD and non-ADHD groups while multiple linear regressions were used to examine the moderating role of gender and parenting styles over the associations between ADHD and other psychiatric symptoms. Both ADHD groups were significantly more likely than other incoming students to have other DSM-IV symptoms. Parental care was negatively associated and parental overprotection/control positively associated with these psychiatric symptoms. Furthermore, significant interactions were found of parenting style with both threshold and sub-threshold ADHD in predicting wide-ranging comorbid symptoms. Specifically, the associations of ADHD with some externalizing symptoms were inversely related to level of paternal care, while associations of ADHD and sub-threshold ADHD with wide-ranging comorbid symptoms were positively related to level of maternal and paternal overprotection/control. These results suggest that parenting styles may modify the effects of ADHD on the risk of a wide range of temporally secondary DSM-IV symptoms among incoming college students, although other causal dynamics might be at work that need to be investigated in longitudinal studies

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Dev Cogn Neurosci. 2015 Feb;11:56-64.

WHO ARE THOSE "RISK-TAKING ADOLESCENTS"? INDIVIDUAL DIFFERENCES IN DEVELOPMENTAL NEUROIMAGING RESEARCH.

Bjork JM, Pardini DA .

Functional magnetic resonance imaging (fMRI) has illuminated the development of human brain function. Some of this work in typically-developing youth has ostensibly captured neural underpinnings of adolescent behavior which is characterized by risk-seeking propensity, according to psychometric questionnaires and a wealth of anecdote. Notably, cross-sectional comparisons have revealed age-dependent differences between adolescents and other age groups in regional brain responsiveness to prospective or experienced rewards (usually greater in adolescents) or penalties (usually diminished in adolescents). These differences have been interpreted as reflecting an imbalance between motivational drive and behavioral control mechanisms, especially in mid-adolescence, thus promoting greater risk-taking. While intriguing, we caution here that researchers should be more circumspect in attributing clinically significant adolescent risky behavior to age-group differences in task-elicited fMRI responses from neurotypical subjects. This is because actual mortality and morbidity from behavioral causes (e.g. substance abuse, violence) by mid-adolescence is heavily concentrated in individuals who are not neurotypical, who rather have shown a lifelong history of behavioral disinhibition that frequently meets criteria for a disruptive behavior disorder, such as conduct disorder, oppositional-defiant disorder, or attention-deficit hyperactivity disorder. These young people are at extreme risk of poor psychosocial outcomes, and should be a focus of future neurodevelopmental research

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Dev Cogn Neurosci. 2015 Apr;12:114-22.

SPONTANEOUS ACTIVITY IN THE WAITING BRAIN: A MARKER OF IMPULSIVE CHOICE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Hsu CF, Benikos N, Sonuga-Barke EJ.

BACKGROUND: Spontaneous very low frequency oscillations (VLFO), seen in the resting brain, are attenuated when individuals are working on attention demanding tasks or waiting for rewards (Hsu et al.,

2013). Individuals with attention-deficit/hyperactivity disorder (ADHD) display excess VLFO when working on attention tasks. They also have difficulty waiting for rewards. Here we examined the waiting brain signature in ADHD and its association with impulsive choice. METHODS: DC-EEG from 21 children with ADHD and 21 controls (9-15 years) were collected under four conditions: (i) resting; (ii) choosing to wait; (iii) being "forced" to wait; and (iv) working on a reaction time task. A questionnaire measured two components of impulsive choice. RESULTS: Significant VLFO reductions were observed in controls within anterior brain regions in both working and waiting conditions. Individuals with ADHD showed VLFO attenuation while working but to a reduced level and none at all when waiting. A closer inspection revealed an increase of VLFO activity in temporal regions during waiting. Excess VLFO activity during waiting was associated with parents' ratings of temporal discounting and delay aversion. CONCLUSIONS: The results highlight the potential role for waiting-related spontaneous neural activity in the pathophysiology of impulsive decision-making of ADHD

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Dev Med Child Neurol. 2015 Apr;57:385-92.

ATTENTION SKILLS AND EXECUTIVE FUNCTIONING IN CHILDREN WITH NOONAN SYNDROME AND THEIR UNAFFECTED SIBLINGS.

Pierpont EI, Tworog-Dube E, Roberts AE.

AIM: Emerging research indicates that gene mutations within the RAS-MAPK signaling cascade, which cause Noonan syndrome and related disorders, affect neurophysiologic activity in brain regions underlying attention and executive functions. The present study examined whether children with Noonan syndrome are at heightened risk for symptoms of attention-deficit-hyperactivity disorder (ADHD) and executive dysfunction relative to an unaffected sibling comparison group, and investigated three key aspects of behavioral attention: auditory attention, sustained attention, and response inhibition.

METHOD: Children and adolescents with Noonan syndrome (n=32, 17 males, 15 females, mean age 11y 3mo, SD 3y) and their unaffected siblings (n=16, eight males, eight females, mean age 11y, SD 3y 6mo) were administered standardized tests of intellectual functioning and clinic-based measures of behavioral attention. Parent ratings of ADHD symptoms, executive functioning, and behavior were also obtained.

RESULTS: Children with Noonan syndrome demonstrated higher rates of past ADHD diagnosis, as well as reduced performance compared with unaffected siblings on behavioral attention measures. Parent-rated functional impairments in attention, social skills, working memory, and self-monitoring were more prevalent in the Noonan syndrome group. The relationship between attention regulation skills (sustained attention and inhibitory control) and intellectual test performance was significantly stronger in the Noonan syndrome group than the comparison group.

INTERPRETATION: Clinical screening/evaluation for ADHD and executive dysfunction in Noonan syndrome is recommended to facilitate appropriate intervention and to address functional impact on daily life activities

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Dev Med Child Neurol. 2015 Sep;57:829-34.

FEATURES OF DEVELOPMENTAL COORDINATION DISORDER IN ACTIVE CHILDHOOD EPILEPSY: A POPULATION-BASED STUDY.

Reilly C, Atkinson P, Das KB, et al.

AIMS: To provide data on parent-reported features of developmental coordination disorder (DCD) and describe neurobehavioural comorbidity in children with epilepsy and DCD.

METHOD: Eighty-five (74% of those eligible) children (44 males, 41 females; age range 5-15y) with active childhood epilepsy (an epileptic seizure in the last year and/or currently taking antiepileptic drugs) in a population-based cohort underwent comprehensive multidisciplinary assessment. The DCD Questionnaire (DCD-Q) was completed by parents (n=69) of children with an IQ>34, of whom 56 did not have cerebral palsy (CP), and were considered for a diagnosis of DCD.

RESULTS: Of those considered for a DCD diagnosis, 16 (29%) met DSM-IV-TR criteria whereas 34 (61%) scored in the at-risk range on the DCD-Q. The sensitivity of the DCD-Q was 100% (95% CI 76-100) and

specificity was 55% (95% CI 39-70). Significant predictors of higher scores on the DCD-Q included the presence of autism spectrum disorder, CP, and early seizure onset. Increasing age and IQ were independently associated with higher DCD-Q scores. Intellectual disability, attention-deficit-hyperactivity disorder, academic underachievement, and specific memory problems were the most common neurobehavioural difficulties in those with both DCD and epilepsy.
INTERPRETATION: Parent-reported symptoms of DCD are very common in childhood epilepsy. The DCD-Q has good sensitivity but lower specificity in this population

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Dusunen Adam. 2015;28:204-12.

ASSOCIATION OF INTERNET ADDICTION IN HIGH SCHOOL STUDENTS WITH ADHD AND TOBACCO/ALCOHOL USE.

Metin O, Saracli O, Atasoy N, et al.

Objective: Our study aims at assessing the association between internet addiction (IA) and attention deficit hyperactivity disorder (ADHD) and tobacco and alcohol use/experimentation in high school students living in the province of Zonguldak.
Method: The study included 771 students enrolled in three high schools. They were assessed with a sociodemographic data form prepared by the researchers, the Chen Internet Addiction Scale (CIAS), and the Adult Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder (ADD/ADHD) Diagnostic and Assessment Inventory based on the DSM-IV.
Results: In 61 cases (7.9%), IA was established, in 90 cases (11.7%) ADHD. Of the cases with IA, 40 (65.6%) were male, 21 (34.4%) female. Internet access from home ($p<0.001$) and tobacco ($p<0.001$) or alcohol ($p<0.001$) use/experimentation history were found to be associated with higher CIAS scores. The rate of ADHD was found to be higher among those with IA (36.1%) than those without IA (9.6%). There was a significant correlation between ADHD scale scores and CIAS scores ($r=0.38$, $p<0.001$).
Conclusion: According to our results, IA is associated with ADHD and alcohol/tobacco use. There is a need for follow-up studies to assess the causality of the association between ADHD, tobacco or alcohol use, and IA

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Epidemiology. 2015;26:458-65.

VITAMIN D IN PREGNANCY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER-LIKE SYMPTOMS IN CHILDHOOD.

Morales E, Julvez J, Torrent M, et al.

Background: Vitamin D status during prenatal brain development may influence risk of attention deficit and hyperactivity disorder (ADHD) symptoms in childhood. However, there are no prospective studies addressing this hypothesis. We aimed to examine whether maternal vitamin D status in pregnancy is associated with risk of ADHD-like symptoms in offspring.
Methods: We conducted a prospective study analyzing data from 1,650 mother-child pairs from five birth cohorts embedded in the INMA Project (Spain, 1997-2008). Maternal vitamin D status in pregnancy was estimated by measuring plasma concentration of 25-hydroxyvitamin D3 [25(OH)D3] at 13 weeks of gestation. Children were assessed by teachers for ADHD-like symptoms at ages 4-5 years using the Diagnostic and Statistical Manual of Mental Disorders ADHD form list.
Results: After adjustment, the number of total ADHD-like symptoms in children decreased by 11% per 10 ng/ml increment of maternal 25(OH)D3 concentration (incidence rate ratio [IRR] = 0.89; 95% confidence interval [CI] = 0.80, 0.98). Similarly, the number of symptoms in the ADHD subscales decreased in relation to higher maternal 25(OH)D3 concentration (IRR per 10 ng/ml increment = 0.89; 95% CI = 0.79, 0.99 for the inattention scale; and IRR = 0.88; 95% CI = 0.78, 0.99 for the hyperactivity-impulsivity scale). Using diagnostic criteria, we found an association of increasing maternal 25(OH)D3 with a lower risk of ADHD DSM-IV (relative risk ratio per 10 ng/ml increment = 0.87; 95% CI = 0.72, 1.06) and ICD-10 hyperkinetic disorder (relative risk ratio = 0.72; 95% CI = 0.49, 1.04) in children.

Conclusion: Higher maternal circulating levels of 25(OH)D3 in pregnancy are associated with lower risk of developing ADHD-like symptoms in childhood

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Eur Neuropsychopharmacol. 2015 Jan;25:17-25.

EFFECTS OF METHYLPHENIDATE AND MDMA ON APPRAISAL OF EROTIC STIMULI AND INTIMATE RELATIONSHIPS.

Schmid Y, Hysek CM, Preller KH, et al.

Methylphenidate mainly enhances dopamine neurotransmission whereas 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") mainly enhances serotonin neurotransmission. However, both drugs also induce a weaker increase of cerebral noradrenaline exerting sympathomimetic properties. Dopaminergic psychostimulants are reported to increase sexual drive, while serotonergic drugs typically impair sexual arousal and functions. Additionally, serotonin has also been shown to modulate cognitive perception of romantic relationships. Whether methylphenidate or MDMA alter sexual arousal or cognitive appraisal of intimate relationships is not known. Thus, we evaluated effects of methylphenidate (40 mg) and MDMA (75 mg) on subjective sexual arousal by viewing erotic pictures and on perception of romantic relationships of unknown couples in a double-blind, randomized, placebo-controlled, crossover study in 30 healthy adults. Methylphenidate, but not MDMA, increased ratings of sexual arousal for explicit sexual stimuli. The participants also sought to increase the presentation time of implicit sexual stimuli by button press after methylphenidate treatment compared with placebo. Plasma levels of testosterone, estrogen, and progesterone were not associated with sexual arousal ratings. Neither MDMA nor methylphenidate altered appraisal of romantic relationships of others. The findings indicate that pharmacological stimulation of dopaminergic but not of serotonergic neurotransmission enhances sexual drive. Whether sexual perception is altered in subjects misusing methylphenidate e.g., for cognitive enhancement or as treatment for attention deficit hyperactivity disorder is of high interest and warrants further investigation

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Eur Child Adolesc Psychiatry. 2015.

ONE-YEAR FOLLOW-UP OF TWO NOVEL CBTS FOR ADOLESCENTS WITH ADHD.

Boyer BE, Geurts HM, Prins PJM, et al.

Long-term effects of two CBTs for adolescents with ADHD are explored: One aimed at improving planning skills (Plan My Life; PML), the other a solution-focused therapy (SFT) without focusing on planning skills. In a RCT, adolescents with ADHD (n = 159) were assigned to PML or SFT and improved significantly between pre- and posttest with large effect sizes Boyer et al (Eur Child Adolesc Psychiatry. doi:10.1007/s00787-014-0661-5), with marginal differences in favor of PML. One-year follow-up data were gathered. Initial improvements remained stable or continued to improve from posttest to 1-year follow-up. 25.9 % of adolescents showed normalized functioning. However, no treatment differences were found. These results are consistent with the finding that treatment of ADHD improves long-term outcomes, but not to the point of normalization. Earlier found differences at 3-month follow-up in favor of PML disappeared, indicating that focusing treatment on planning skills is not necessary for improvement or that a more prolonged planning-focused treatment is needed

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Eur Child Adolesc Psychiatry. 2015.

TOWARDS AN ICF CORE SET FOR ADHD: A WORLDWIDE EXPERT SURVEY ON ABILITY AND DISABILITY.

de SE, Mahdi S, Coghill D, et al.

This is the second in a series of four empirical studies designed to develop International Classification of Functioning, Disability and Health (ICF and Children and Youth version, ICF-CY) core sets for attention deficit hyperactivity disorder (ADHD). The objective of this stage was to gather the opinions from international experts on which ability and disability concepts were considered relevant to functioning in ADHD. An email-based survey was carried out amongst international experts in ADHD. Relevant functional ability and

disability concepts were extracted from their responses and linked to the ICF/-CY categories by two independent researchers using a standardised linking procedure. 174 experts from 11 different disciplines and 45 different countries completed the survey. Meaningful concepts identified in their responses were linked to 185 ICF/-CY categories. Of these, 83 categories were identified by at least 5 % of the experts and considered the most relevant to ADHD: 30 of these were related to Body functions (most identified: attention functions, 85 %), 30 to Activities and Participation (most identified: school education, 52 %), 20 to Environmental factors (most identified: support from immediate family, 61 %), and 3 to Body structures (most identified: structure of brain, 83 %). Experts also provided their views on particular abilities related to ADHD, naming characteristics such as high-energy levels, flexibility and resiliency. Gender differences in the expression of ADHD identified by experts pertained mainly to females showing more internalising (e.g. anxiety, low self-esteem) and less externalising behaviours (e.g. hyperactivity), leading to a risk of late- and under-diagnosis in females. Results indicate that the impact of ADHD extends beyond the core symptom domains, into all areas of life and across the lifespan. The current study in combination with three additional preparatory studies (comprehensive scoping review, focus groups, clinical study) will provide the scientific basis to define the ADHD ICF/-CY core sets for multi-purpose use in basic and applied research and every day clinical practice

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Eur J Integr Med. 2015;7:312-17.

CASE REPORT OF A 16 YEAR OLD YOUTH WITH DIAGNOSES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD), ASPERGER'S SYNDROME AND DYSLEXIA RECEIVING HOMOEOPATHIC AND TAUTOPATHIC TREATMENT.

Fibert P.

Introduction: ADHD is a common and growing problem which manifests and is diagnosed via a cluster of behaviours such as inability to regulate emotions or manage motivational delay and problems with executive functioning. It frequently accompanies autism spectrum disorders and dyslexia. Homoeopathy is a system of therapeutics based on the Law of Similars where 'like cures like'. Conditions are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the condition to be treated. The aim of this case report is to describe the homoeopathic treatment and progress of one 16 year old youth with diagnoses of ADHD, Asperger's syndrome and dyslexia subjected to in-utero cannabis exposure.
Methods: The youth received individualised homoeopathic medicines and additional ultra-molecular dilutions of cannabis. Outcome was measured using the parent completed Conner's Parent Rating Scale-Revised-Long version (CPRS:R-L) every 4 months, with DSMIV total score selected for analysis; and Measure Your Own Medical Outcome Measure (MYMOP) every 6 weeks, completed by parent and patient.
Results: At start of treatment the patient's DSMIV total T score was 90+ (highest possible); after 18 months it was 59 (within normal range). MYMOP score at start of treatment was 4.5 and 1.75 after 18 months.
Conclusion: Treatment by a homoeopath over 1 1/2 years was associated with improvements in ADHD status and patient generated outcomes. Ultra molecular dilutions of a recreational drug the patient was subjected to in-utero appear to have contributed to improvements. Systematic research with larger numbers would be required to confirm or refute this single case observation

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Eur Neuropsychopharmacol. 2015;25:1611-21.

DIFFERENCES IN MAINTENANCE OF RESPONSE UPON DISCONTINUATION ACROSS MEDICATION TREATMENTS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Buitelaar J, Asherson P, Soutullo C, et al.

The attention-deficit/hyperactivity disorder (ADHD) treatment literature has been focused on onset-of-effect and short-term effect size, with little exploration of ADHD symptoms upon medication discontinuation. The objective of this narrative review and analysis was to better understand the relapse of ADHD symptoms upon discontinuation of medication treatment in children, adolescents, and adults with ADHD who have responded to medication treatment and to explore differences among different medications in maintaining treatment response. Randomized withdrawal studies of dexmethylphenidate hydrochloride (d-MPH), methylphenidate

modified-release (MPH-LA), lisdexamphetamine dimesylate (LDX), guanfacine extended-release (GXR), and atomoxetine (ATX) in both children/adolescents and adults with ADHD were reviewed. The percentage of relapse was significantly higher and the time-to-relapse significantly shorter with placebo compared to active treatment in patients who were previously stable on 5 weeks to 1 year of active treatment, suggesting clinically significant benefit with continued long-term pharmacotherapy. However, percentage of relapse at each time point studied after discontinuing stimulants and GXR appears substantially higher than observed when discontinuing ATX, suggesting longer maintenance of response after discontinuing ATX than after stimulants and GXR. Additionally, slope of relapse percentages over time appears to be more rapid with stimulants or GXR than with ATX. These differences in maintenance of response among ATX, GXR, and stimulants may reflect differences in mechanisms of action and persistence of the medication effect. Alternatively, they may be due to methodological differences, including study design and response/relapse definitions. Continued investigation is needed regarding factors that affect risk of symptom relapse upon discontinuation of pharmacotherapy

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Eur Psychiatry 2015;30:932-942

MENTAL DISORDERS AND TRANSITION TO ADULT MENTAL HEALTH SERVICES:A SCOPING REVIEW.

Reale L, Bonati M.

Background: Data are progressively accumulating regarding the transition to adult services.
Methods: A comprehensive search using the MEDLINE, Embase, PsycINFO, and Cochrane databases up until 16 March 2015 was conducted in order to summarize recent evidence on the transition from child to adult mental health services for patients with mental disorders. Authors extracted data and assessed study quality independently.
Results: The main findings of the 33 included studies were discussed taking into consideration four aspects: experiences of patients, carers, and clinicians, accounts of transition, current services models and protocols, and outcomes of transition. Of the 33 studies, 17 focused on a specific mental disorder: seven on attention deficit hyperactivity disorder, four on intellectual disability, three on eating disorders, two on serious emotional disorders and one on autism spectrum disorder. An attempt was also made to integrate the studies' conclusions in order to improve transitional care.
Conclusions: The review reveals an evident need for longitudinal, controlled, health services research to identify and evaluate optimal service models with systematic and seamless transition protocols for patients with mental disorders requiring continuity of care into adult mental services.

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Expert Rev Neurother. 2015.

ATOMOXETINE MONOTHERAPY COMPARED WITH COMBINATION THERAPY FOR THE TREATMENT OF ADHD: A RETROSPECTIVE CHART REVIEW STUDY.

Clemow DB, Mason OW, Sarkis EH, et al.

OBJECTIVE: To analyze Clinical Global Impression-Severity (CGI-S) in ADHD patients treated with atomoxetine (ATX) monotherapy versus ATX combination therapy with another ADHD-indicated medication.
METHODS: This was a 2-site retrospective observational chart review study of child and adult ADHD patients, not necessarily treatment naïve, but treated ≥50 days post baseline with an endpoint assessment. To adjust for measured confounders, monotherapy (n = 77) versus combination (n = 108) cohort comparisons were performed using propensity score stratification and adjusted ANCOVA.
RESULTS: There were no significant baseline cohort differences after propensity stratification. CGI-S scores after a mean 264 days of treatment were not statistically significantly different between cohorts, with no cohort differences observed in any assessed symptom subcategory. The cohorts were similar in discontinuation due to any reason, adverse event, and lack of efficacy.
CONCLUSION: ATX combination therapy showed no evidence of additional benefit over ATX monotherapy in the treatment of ADHD in a community-based setting.

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Int J Psychiatry Med. 2015;50:60-72.

TEACHING CHILD PSYCHIATRIC ASSESSMENT SKILLS: USING PEDIATRIC MENTAL HEALTH SCREENING TOOLS.

Hargrave TM, Arthur ME.

This article describes the workshop "Teaching Child Psychiatric Assessment Skills: Using Mental Health Screening Instruments," presented at the 35th Forum for Behavioral Sciences in Family Medicine on 20 September 2014. The goals of the presentation were (1) to teach family medicine behavioral health educators to use both general and problem-specific mental health screening tools (MHSTs) in their work with trainees to help satisfy the Accreditation Council for Graduate Medical Education (ACGME) mandate for behavioral and mental health experience during family medicine residency, (2) to reflect on how MHSTs might be integrated into the flow of family medicine teaching practices, and (3) to exemplify how evidence-based methods of adult education might be used in teaching such content. One general MHST, the Pediatric Symptom Checklist-17 and one problem-specific MHST for each of the four commonest pediatric mental health issues: for attention-deficit hyperactivity disorder, the Vanderbilt; for Anxiety, the Screen for Childhood Anxiety-Related Emotional Disorders; for Depression, the Patient Health Questionnaire-9 for teens; and for Aggression, the Retrospective-Modified Overt Aggression Scale, were practiced at least twice in the context of a clinical vignette. All of the selected MHSTs are free in the public domain and available for download from the website: www.CAPPCNY.org. Participants were asked to reflect on their own office practice characteristics and consider how MHSTs might be integrated into their systems of care. This workshop could be replicated by others wishing to teach the use of MHSTs in primary care settings or teaching programs

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Int J Environ Res Public Health. 2015;12:11893-909.

CHILDHOOD ADHD SYMPTOMS: ASSOCIATION WITH PARENTAL SOCIAL NETWORKS AND MENTAL HEALTH SERVICE USE DURING ADOLESCENCE.

Bussing R, Meyer J, Zima BT, et al.

OBJECTIVE: This study examines the associations of childhood attention-deficit/hyperactivity disorder (ADHD) risk status with subsequent parental social network characteristics and caregiver strain in adolescence; and examines predictors of adolescent mental health service use.

METHODS: Baseline ADHD screening identified children at high risk (n = 207) and low risk (n = 167) for ADHD. At eight-year follow-up, parents reported their social network characteristics, caregiver strain, adolescents' psychopathology and mental health service utilization, whereas adolescents self-reported their emotional status and ADHD stigma perceptions. Analyses were conducted using ANOVAs and nested logistic regression modeling.

RESULTS: Parents of youth with childhood ADHD reported support networks consisting of fewer spouses but more healthcare professionals, and lower levels of support than control parents. Caregiver strain increased with adolescent age and psychopathology. Increased parental network support, youth ADHD symptoms, and caregiver strain, but lower youth stigma perceptions were independently associated with increased service use.

CONCLUSIONS: Raising children with ADHD appears to significantly impact parental social network experiences. Reduced spousal support and overall lower network support levels may contribute to high caregiver strain commonly reported among parents of ADHD youth. Parental social network experiences influence adolescent ADHD service use. With advances in social networking technology, further research is needed to elucidate ways to enhance caregiver support during ADHD care.

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International Journal of Medical Informatics. 2015;84:974-81.

EVALUATION OF AN EDUCATIONAL WEBSITE FOR PARENTS OF CHILDREN WITH ADHD.

Ryan GS, Haroon M, Melvin G.

Introduction: ADHD is a relatively common neuro-developmental condition characterized by hyperactivity, impulsivity and inattention. The provision of timely and accurate information about the condition and about strategies to manage it is vital especially because of widespread misconceptions about it.

Aim: To see the effect of an educational website on (i) parental perceptions (ii) knowledge levels, and to obtain feedback to optimise user-experience.
Method: Parents whose children had ADHD (or were close to diagnosis) were recruited. Following a 30-item baseline knowledge test parents/carers were directed to an educational website on ADHD. After this they were re-contacted for follow up testing and feedback.
Results: n= 172, 14 were lost to follow up. Ninety-one (59.4 %) participants were known to have accessed the website at follow up. The majority of carers accessed the website just once or twice (32.7%). Of those who did not access the website 65% cited a lack of time as the reason while 29% cited they were unable to access the internet at the time. The majority (74%) of those accessing the site were just browsing for general information. Parents showed increased knowledge post website use p= 0.000. Of those accessing the website the majority (85.5%) felt it was relevant to them and would use it again (90.8%). Content analysis of open-ended feedback identified eight core themes including website appearance, content, functionality, perceptions, target audience, usability, usage patterns with areas for improvement noted in four areas.
Conclusion: Websites can be used as an adjunct to information given at clinic. Although a majority of parents will access them, there are still barriers to access e.g. time. Websites do seem to improve parent/carer knowledge levels

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Iran J Psychiatry. 2015;10:165-74.
COMPARISON OF SENSORIMOTOR RHYTHM (SMR) AND BETA TRAINING ON SELECTIVE ATTENTION AND SYMPTOMS IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD): A TREND REPORT.
Mohammadi MR, Malmir N, Khaleghi A.
Objective: The aim of this study was to assess and compare the effect of two neurofeedback protocols (SMR/theta and beta/theta) on ADHD symptoms, selective attention and EEG (electroencephalogram) parameters in children with ADHD.
Method: The sample consisted of 16 children (9-15 year old: 13 boys; 3 girls) with ADHD-combined type (ADHD-C). All of children used methylphenidate (MPH) during the study. The neurofeedback training consisted of two phases of 15 sessions, each lasting 45 minutes. In the first phase, participants were trained to enhance sensorimotor rhythm (12-15 Hz) and reduce theta activity (4-8 Hz) at C4 and in the second phase; they had to increase beta (15-18 Hz) and reduce theta activity at C3. Assessments consisted of d2 attention endurance test, ADHD rating scale (parent form) at three time periods: before, middle and the end of the training. EEG signals were recorded just before and after the training.
Result: Based on parents' reports, inattention after beta/theta training, and hyperactivity/impulsivity were improved after the end of the training. All subscales of d2 test were improved except for the difference between maximum and minimum responses. However, EEG analysis showed no significant differences .
Conclusion: Neurofeedback in conjunction with Methylphenidate may cause further improvement in ADHD symptoms reported by parents and selective attention without long-term impact on EEG patterns. However, determining the exact relationship between EEG parameters, neurofeedback protocols and ADHD symptoms remain unclear

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Isr Med Assoc J. 2015 Aug;17:481-85.
LONG-TERM FUNCTIONAL OUTCOMES IN ISRAELI ADULTS DIAGNOSED IN CHILDHOOD WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Jaber L, Kirsh D, Diamond G, et al.
BACKGROUND: Childhood attention deficit hyperactivity disorder (ADHD) is a chronic health problem with significant risk for long-term morbidity in adulthood.
OBJECTIVES: We examined long-term outcomes of ADHD in a population-based sample of childhood ADHD cases prospectively assessed as adults.
METHODS: Long-term outcomes for 70 adults who were diagnosed with ADHD during childhood were examined and compared with data on the general population.

RESULTS: Most subjects admitted to persistence of ADHD-related symptoms in adulthood, despite discontinuation of regular medical treatment and follow-up. Areas most severely affected by past and ongoing symptoms included driving performance and incidence of motor vehicle accidents, and rates of marriage stability over time. Relatively unaffected were occupational and academic achievements and military service.
CONCLUSIONS: There is a need for outreach and better services for adults who were previously diagnosed with ADHD. This condition remains a marker of a certain degree of risk regarding marital stability, interpersonal relations and driving habits

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J Abnorm Child Psychol. 2015 Feb;43:391-400.

TREATMENT PATTERNS OF YOUTH WITH BIPOLAR DISORDER: RESULTS FROM THE NATIONAL COMORBIDITY SURVEY-ADOLESCENT SUPPLEMENT (NCS-A).

Khazanov GK, Cui L, Merikangas KR, et al.

Despite growing evidence that bipolar disorder often emerges in adolescence, there are limited data regarding treatment patterns of youth with bipolar disorder in community samples. Our objective was to present the prevalence and clinical correlates of treatment utilization for a nationally representative sample of US adolescents with bipolar disorder. Analyses are based on data from the National Comorbidity Survey-Adolescent Supplement, a face-to-face survey of 10,123 adolescents (ages 13-18) identified in household and school settings. We found that of adolescents meeting DSM-IV criteria for bipolar I or II disorder (N = 250), 49 % were treated for depression or mania, 13 % were treated for conditions other than depression or mania, and 38 % did not report receiving treatment. Treatment for depression or mania was associated with increased rates of suicide attempts, as well as greater role disability and more comorbid alcohol use relative to those who had not received treatment. Treated adolescents had triple the rate of ADHD and double the rates of behavior disorders than those without treatment. Our findings demonstrate that a substantial proportion of youth with bipolar disorder do not receive treatment, and of those who do, many receive treatment for comorbid conditions rather than for their mood-related symptoms. Treatment was more common among youth with severe manifestations and consequences of bipolar disorder and those with behavior problems. These trends highlight the need to identify barriers to treatment for adolescents with bipolar disorder and demonstrate that those in treatment are not representative of youth with bipolar disorder in the general population

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J Affect Disord. 2015 Mar;174:378-89.

COMORBIDITY IN PEDIATRIC BIPOLAR DISORDER: PREVALENCE, CLINICAL IMPACT, ETIOLOGY AND TREATMENT.

Frias A, Palma C, Farriols N .

BACKGROUND: Research on pediatric bipolar disorder (PBD) is providing a plethora of empirical findings regarding its comorbidity. We addressed this question through a systematic review concerning the prevalence, clinical impact, etiology and treatment of main comorbid disorders involved.
METHOD: A comprehensive database search was performed from 1990 to August 2014. Overall, 167 studies fulfilled the inclusion criteria.
RESULTS: Bipolar youth tend to suffer from comorbid disorders, with highest weighted mean prevalence rate arising from anxiety disorders (54%), followed by attention deficit hyperactivity disorder (ADHD) (48%), disruptive behavior disorders (31%), and substance use disorders (SUD) (31%). Furthermore, evidence indicates that ADHD and anxiety disorders negatively affect the symptomatology, neurocognitive profile, clinical course and the global functioning of PBD. Likewise, several theories have been posited to explain comorbidity rates in PBD, specifically common risk factors, one disorder being a risk factor for the other and nosological artefacts. Lastly, randomized controlled trials highlight a stronger therapeutic response to stimulants and atomoxetine (vs. placebo) as adjunctive interventions for comorbid ADHD symptoms. In addition, research focused on the treatment of other comorbid disorders postulates some benefits from mood stabilizers and/or SGA.

LIMITATIONS: Epidemiologic follow-up studies are needed to avoid the risk of nosological artefacts. Likewise, more research is needed on pervasive developmental disorders and anxiety disorders, especially regarding their etiology and treatment.
CONCLUSIONS: Psychiatric comorbidity is highly prevalent and is associated with a deleterious clinical effect on pediatric bipolarity. Different etiological pathways may explain the presence of these comorbid disorders among bipolar youth. Standardized treatments are providing ongoing data regarding their effectiveness for these comorbidities among bipolar youth

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J Atten Disord. 2015 Apr;19:301-12.

CHILDHOOD ADHD SYMPTOMS ARE ASSOCIATED WITH LIFETIME AND CURRENT ILLICIT SUBSTANCE-USE DISORDERS AND IN-SITE HEALTH RISK BEHAVIORS IN A REPRESENTATIVE SAMPLE OF LATINO PRISON INMATES.

Gonzalez RA, Velez-Pastrana MC, Ruiz Varcarcel JJ, et al.

OBJECTIVE: This study aimed to explore retrospective childhood ADHD symptomatology, psychiatric comorbidity, rates of substance-use disorders (SUD), as well as their association with high-risk health behaviors in prison and adverse health outcomes.
METHOD: A randomly selected representative sample of inmates in the Puerto Rico correctional system (N = 1,179) was assessed with the Spanish-language Wender Utah Rating Scale (WURS); the Composite International Diagnostic Interview (CIDI) modules for lifetime/current major depression disorder (MDD), generalized anxiety disorder (GAD), and SUD; the Davidson Trauma Scale (DTS; posttraumatic stress disorder [PTSD]); and self-reports of in-site high-risk behaviors.
RESULTS: Wald chi(2) tests revealed significant associations of ADHD with MDD and PTSD, as well as increased risk for overdosing and intravenous drug use in prison. A logistic regression model adjusted for mood and anxiety comorbidity predicted lifetime SUD diagnosis (odds ratio = 2.38; 95% confidence interval = [1.15, 4.94]).
CONCLUSION: Our results provide further evidence on the association of drug dependence and ADHD symptoms, and their overrepresentation among prison inmates

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J Atten Disord. 2015 Mar;19:179-90.

ADHD SYMPTOMATOLOGY AND RISKY HEALTH, DRIVING, AND FINANCIAL BEHAVIORS IN COLLEGE: THE MEDIATING ROLE OF SENSATION SEEKING AND EFFORTFUL CONTROL.

Graziano PA, Reid A, Slavec J, et al.

OBJECTIVE: To examine the extent to which effortful control (EC) and sensation seeking (SS) tendencies explain the association between the severity of ADHD symptoms and risky behaviors.
METHOD: Participants included 555 college students (66% females) who completed self-report measures assessing their ADHD symptoms, EC abilities, SS tendencies, and risky health (e.g., substance use) and driving/financial behaviors (e.g., misuse of credit cards).
RESULTS: Severity of college students' ADHD symptoms, EC abilities, and SS tendencies were related to all risky behaviors. Multiple mediational analyses further indicated that students' SS tendencies significantly mediated the association between ADHD symptoms and the risky health factor but not the risky driving/financial factor. EC, however, significantly mediated the association between ADHD symptoms and both the risky health and driving/financial factors.
CONCLUSION: The current study provides initial data showing potentially different mechanisms that explain the link between college students' severity of ADHD symptoms and risky behaviors

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J Atten Disord. 2015 Mar;19:211-21.

ADHD SYMPTOMATOLOGY, FEAR OF INTIMACY, AND SEXUAL ANXIETY AND BEHAVIOR AMONG COLLEGE STUDENTS IN CHINA AND THE UNITED STATES.

Marsh LE, Norvilitis JM, Ingersoll TS, et al.

OBJECTIVE: ADHD is marked by an apparent contradiction in social relationships: Those with the disorder have more difficulty establishing close relationships but report increased rates of risky sexual behavior. Two studies examined the relationship between ADHD symptomatology and fear of intimacy, sexual anxiety, and sexual behavior in college students.

METHOD: In the first study, college students in China (n = 300) and the United States (n = 233) completed a series of questionnaires. In the second, 192 American college students completed a follow-up series of measures.

RESULTS: In the first study, those with more ADHD symptoms did not report lower levels of sexual anxiety but did report greater fear of intimacy. In the second, students partially replicated the results of the first study, reporting greater fear of intimacy in those with more symptoms of ADHD. Those with more symptoms also reported lower expectations for the intimacy in their relationships and lower levels of relationship self-competence on one of four domains.

DISCUSSION: ADHD symptomatology, particularly inattention, was related to multiple aspects of risky sexual behavior

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J Atten Disord. 2015 May;19:355-67.

A META-ANALYSIS OF DECISION-MAKING AND ATTENTION IN ADULTS WITH ADHD.

Mowinckel AM, Pedersen ML, Eilertsen E, et al.

OBJECTIVE: Deficient reward processing has gained attention as an important aspect of ADHD, but little is known about reward-based decision-making (DM) in adults with ADHD. This article summarizes research on DM in adult ADHD and contextualizes DM deficits by comparing them to attention deficits.

METHOD: Meta-analytic methods were used to calculate average effect sizes for different DM domains and continuous performance task (CPT) measures.

RESULTS: None of the 59 included studies (DM: 12 studies; CPT: 43; both: 4) had indications of publication bias. DM and CPT measures showed robust, small to medium effects. Large effect sizes were found for a drift diffusion model analysis of the CPT.

CONCLUSION: The results support the existence of DM deficits in adults with ADHD, which are of similar magnitude as attention deficits. These findings warrant further examination of DM in adults with ADHD to improve the understanding of underlying neurocognitive mechanisms

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J Atten Disord. 2015 Apr;19:335-42.

SENSATION SEEKING AND COCAINE DEPENDENCE IN ADULTS WITH REPORTED CHILDHOOD ADHD.

Ballon N, Brunault P, Cortese S.

OBJECTIVE: To compare measures of sensation seeking in a clinical group of cocaine-dependent (CD) patients with and without a history of probable childhood ADHD and in non-cocaine-dependent (NCD) healthy volunteers.

METHOD: Patients (n = 75; 42 with and 33 without probable childhood ADHD) and comparisons (n = 84) were assessed with the Diagnostic Interview for Genetic Studies, the Wender Utah Rating Scale for childhood ADHD, and the Zuckerman Seeking Sensation Scale.

RESULTS: We found significantly higher prevalence rates of probable childhood ADHD in CD versus NCD ($p < .001$). The mean total scores of sensation seeking were significantly higher in CD versus NCD participants ($p < .001$) as well as in CD patients with versus those without a probable history of childhood ADHD ($p < .001$).

CONCLUSION: Our study sets the basis for longitudinal investigation assessing whether the persistence of high level of sensation seeking in adults with childhood ADHD contributes to the transition to cocaine dependence

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J Atten Disord. 2015 Mar;19:222-30.

ANXIETY IN COLLEGE STUDENTS WITH ADHD: RELATIONSHIP TO COGNITIVE FUNCTIONING.

Prevatt F, Dehili V, Taylor N, et al.

OBJECTIVE: This study sought to explore how anxiety impacts college students with ADHD, especially with regard to cognitive functioning.

METHOD: 473 college students with ADHD and a control group of 200 college students without ADHD completed self-report measures of anxiety, ADHD symptomatology and tests of cognitive functioning.

RESULTS: Students with ADHD reported significantly more anxiety than students without ADHD. Within the ADHD group, the relationship between anxiety and inattention was similar to the relationship between anxiety and hyperactivity/impulsivity. Students with ADHD reported more anxiety with regard to academics compared to life-in-general. There were no gender differences for anxiety; however, freshman indicated more anxiety than upper-classmen. Anxiety and inattention were found to interact such that students with low levels of inattention but high levels of anxiety performed better on tasks of cognitive ability.

CONCLUSION: Anxiety in college students with ADHD can take many forms, and interventions require a multi-focused approach. There may be some positive aspects to anxiety

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J Atten Disord. 2015 Jun;19:476-88.

BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTIONING-PRESCHOOL (BRIEF-P) APPLIED TO TEACHERS: PSYCHOMETRIC PROPERTIES AND USEFULNESS FOR DISRUPTIVE DISORDERS IN 3-YEAR-OLD PRESCHOOLERS.

Ezpeleta L, Granero R, Penelo E, et al.

OBJECTIVE: We provide validation data on the Behavior Rating Inventory of Executive Functioning-Preschool version (BRIEF-P) in preschool children.

METHOD: Teachers of a community sample of six hundred and twenty 3-year-olds, who were followed up at age 4, responded to the BRIEF-P, and parents and children answered different psychological measures.

RESULTS: Confirmatory factor analysis achieved adequate fit of the original structure (five-first-order-factor plus three-second-order-factor model) after excluding four items. The derived dimensions obtained satisfactory internal consistency, moderate convergent validity with psychopathology and temperament, and good ability to discriminate between children with ADHD. BRIEF-P scales were not associated with a performance-based measure of attention. The teacher's BRIEF-P adds significant clinical information for the diagnosis of ADHD (DeltaR(2) from 5.3 to 15.3) when used with other instruments for the assessment of psychopathology, functional impairment, or performance-based attention.

CONCLUSION: The BRIEF-P may be useful in the identification of preschool children, specifically those with ADHD, who might have a dysfunction in executive functioning

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J Atten Disord. 2015 Mar;19:200-10.

EVALUATING THE CONSTRUCT VALIDITY OF ADULT ADHD AND SCT AMONG COLLEGE STUDENTS: A MULTITRAIT-MULTIMETHOD ANALYSIS OF CONVERGENT AND DISCRIMINANT VALIDITY.

Leopold DR, Bryan AD, Pennington BF, et al.

OBJECTIVE: To advance our understanding of adult ADHD and sluggish cognitive tempo (SCT), the present study investigates their construct validity by exploring the nature of trait- and method-related variance in self- and parent-ratings of ADHD and SCT.

METHOD: Using a multitrait-multimethod (MTMM) design, response variance in college undergraduates' (n = 3,925) and a subset of their parents' (n = 2,242) ratings was decomposed into method, trait, and error-specific variance.
RESULTS: Global evidence for convergent and discriminant validity was supported, but parameter-level comparisons suggest that method effects, situational specificity, and ADHD's core feature--inattention--are prominent.
CONCLUSION: This investigation offers two important conclusions: (a) SCT appears to be a related but separate factor from ADHD; and (b) self- and parent-ratings of emerging adult ADHD exhibit low to moderate correlations and support the situational specificity hypothesis, suggesting that multiple raters should be consulted when assessing adult ADHD. Implications of these findings and recommendations for the continued study of SCT are discussed

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J Atten Disord. 2015 Jun;19:455-67.
AN INTEGRATED MODEL OF EXECUTIVE FUNCTIONING IS HELPFUL FOR UNDERSTANDING ADHD AND ASSOCIATED DISORDERS.
Crippa A, Marzocchi GM, Piroddi C, et al.
OBJECTIVE: The aim of this study is to test the discriminative capacity of executive function (EF) tasks to better define the cognitive functioning of children with ADHD and comorbidities.
METHOD: One hundred four children were presented with a battery of new EF tasks and a rating scale filled out by parents.
RESULTS: Preliminary analysis of the neuropsychological tasks revealed the presence of five factors: Speed of Processing, Inhibition, Planning, Execution, and Retrospective Memory. All children with ADHD were impaired in Execution (a measure describing the capacity to achieve a goal). ADHD-only children were specifically impaired in Planning, while ADHD + reading disorder (RD) children were impaired in Speed of Processing and Retrospective Memory. Children with ADHD + oppositional defiant disorder (ODD) did not show impairment in any other EF domains. The five EF processes correlated with the EF Questionnaire.
CONCLUSION: The present study describes different cognitive profiles in children with ADHD with or without comorbid disorders using neuropsychological EF measures

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J Atten Disord. 2015 Mar;19:251-59.
ADHD SYMPTOMS AND ACADEMIC ADJUSTMENT TO COLLEGE: THE ROLE OF PARENTING STYLE .
Jones HA, Rabinovitch AE, Hubbard RR.
OBJECTIVE: The primary aim of this study was to examine relationships among parenting style, symptoms of ADHD, and academic adjustment in college students. Specifically, we investigated whether parenting style may act as a buffer in the negative relationship between ADHD symptoms and academic adjustment.
METHOD: Participants were 200 undergraduate students attending a large public university. Questionnaires measuring their ADHD symptoms, parent's parenting style, and academic adjustment were completed.
RESULTS: Results indicated small but significant moderation effects for authoritarian parenting and authoritative parenting on the relationship between ADHD symptoms and academic adjustment.
CONCLUSION: Although research has revealed that different parenting styles may relate to different outcomes in children with ADHD, for young adults, the effects of parenting on academic adjustment may be diluted. Future research should investigate variables that may be more salient predictors of functional outcomes for this population, such as organizational skills

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J Atten Disord. 2015 Apr;19:328-34.

ADULT ADHD SCREENING IN ALCOHOL-DEPENDENT PATIENTS USING THE WENDER-UTAH RATING SCALE AND THE ADULT ADHD SELF-REPORT SCALE.

Daigre C, Roncero C, Rodriguez-Cintas L, et al.

OBJECTIVE: The aim was to analyze the psychometric properties of two screening instruments, Wender-Utah Rating Scale (WURS) that evaluates childhood ADHD and Adult ADHD Self-Report Scales (ASRS) that assesses symptoms in adulthood, in alcohol-dependent patients.
METHOD: A total of 355 outpatients were included. Conners' adult ADHD diagnostic interview results were used as a gold standard in childhood and adulthood ADHD.
RESULTS: The WURS with a 41 cutoff had a sensitivity of 79.6% and a specificity of 60.3%. The ASRS with a 14 cutoff had a sensitivity of 86.7% and specificity of 66.1%. Analyzing both rating scales in combination, it was observed that patients with positive ASRS and WURS presented a sensitivity of 92.3%. Patients with positive ASRS, but negative WURS, presented a specificity of 73.6%.
CONCLUSION: WURS and ASRS are useful tools in the diagnosis of adult ADHD in alcohol-dependent patients; with the use of both instruments, the psychometric properties are substantially improved

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J Atten Disord. 2015 Mar;19:240-50.

RISKY SEXUAL BEHAVIOR AMONG COLLEGE STUDENTS WITH ADHD: IS THE MOTHER-CHILD RELATIONSHIP PROTECTIVE?

Huggins SP, Rooney ME, Chronis-Tuscano A.

OBJECTIVE: This study examined the extent to which ADHD was associated with risky sexual behaviors (RSBs) in a sample of 92 undergraduates with (n = 44) and without (n = 48) ADHD. Mother-child relationship quality was examined as a potential moderator.
METHOD: We conducted comprehensive assessments for ADHD and comorbid conditions and collected measures of RSB and mother-child relationship quality.
RESULTS: Female students with ADHD were least likely to use condoms than males overall and females without ADHD. An interaction between ADHD and mother-child relationship quality accounted for significant variance in the number of past-year sexual partners, such that a high-quality relationship was protective only for students with ADHD. No other significant associations were found between ADHD and RSB.
CONCLUSION: Results suggest that female college students with ADHD are at risk for unprotected sex. Moreover, a positive mother-child relationship may be protective for college students with ADHD in relation to RSB

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J Autism Dev Disord. 2015 Mar;45:645-57.

SIMPLEX AND MULTIPLEX STRATIFICATION IN ASD AND ADHD FAMILIES: A PROMISING APPROACH FOR IDENTIFYING OVERLAPPING AND UNIQUE UNDERPINNINGS OF ASD AND ADHD?

Oerlemans AM, Hartman CA, de Bruijn YG, et al.

Autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD) are highly heterogeneous neuropsychiatric disorders, that frequently co-occur. This study examined whether stratification into single-incidence (SPX) and multi-incidence (MPX) is helpful in (a) parsing heterogeneity and (b) detecting overlapping and unique underpinnings of the disorders. ASD and ADHD traits were measured in 56 ASD/31 ADHD SPX families, 59 ASD/171 ADHD MPX families and 203 control families. In ASD but not ADHD, behavioral traits were less elevated in SPX than MPX unaffected relatives, suggesting that SPX-MPX stratification may thus help parse ASD, but not ADHD heterogeneity. Particularly unaffected relatives from MPX ASD/ADHD families displayed elevated trait levels of both disorders, indicating shared (multifactorial) underpinnings underlying ASD and ADHD in these families. Cross-disorder traits were highest in MPX ASD unaffected siblings

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J Behav Ther Exp Psychiatry. 2015 Mar;46:158-63.

ATTENTION BIAS TO EMOTIONAL INFORMATION IN CHILDREN AS A FUNCTION OF MATERNAL EMOTIONAL DISORDERS AND MATERNAL ATTENTION BIASES.

Waters AM, Forrest K, Peters RM, et al.

BACKGROUND AND OBJECTIVES: Children of parents with emotional disorders have an increased risk for developing anxiety and depressive disorders. Yet the mechanisms that contribute to this increased risk are poorly understood. The present study aimed to examine attention biases in children as a function of maternal lifetime emotional disorders and maternal attention biases.

METHODS: There were 134 participants, including 38 high-risk children, and their mothers who had lifetime emotional disorders; and 29 low-risk children, and their mothers without lifetime emotional disorders. Mothers and children completed a visual probe task with emotional face pairs presented for 500 ms.

RESULTS: Attention bias in children did not significantly differ solely as a function of whether or not their mothers had lifetime emotional disorders. However, attention bias in high-risk children was significantly related to their mothers' attention bias. Specifically, children of mothers with lifetime emotional disorders showed a greater negative attention bias if their mothers had a greater tendency to direct attention away from positive information.

LIMITATIONS: This study was cross-sectional in nature, and therefore unable to assess long-term predictive effects. Also, just one exposure duration of 500 ms was utilised.

CONCLUSION: Attention bias for negative information is greater in offspring of mothers who have lifetime emotional disorders and a reduced positive bias, which could be a risk marker for the development of emotional disorders in children

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J Child Neurol. 2015 Mar;30:320-25.

GENETIC PREDISPOSITION INCREASES THE TIC SEVERITY, RATE OF COMORBIDITIES, AND PSYCHOSOCIAL AND EDUCATIONAL DIFFICULTIES IN CHILDREN WITH TOURETTE SYNDROME.

Eysturoy AN, Skov L, Debes NM.

This study aimed to examine whether there are differences in tic severity, comorbidities, and psychosocial and educational consequences in children with Tourette syndrome and genetic predisposition to Tourette syndrome compared with children with Tourette syndrome without genetic predisposition to Tourette syndrome. A total of 314 children diagnosed with Tourette syndrome participated in this study. Validated diagnostic tools were used to assess tic severity, comorbidities, and cognitive performance. A structured interview was used to evaluate psychosocial and educational consequences related to Tourette syndrome. The children with Tourette syndrome and genetic predisposition present with statistically significant differences in terms of severity of tics, comorbidities, and a range of psychosocial and educational factors compared with the children with Tourette syndrome without genetic predisposition. Professionals need to be aware of genetic predisposition to Tourette syndrome, as children with Tourette syndrome and genetic predisposition have more severe symptoms than those children with Tourette syndrome who are without genetic predisposition

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J Child Psychol Psychiatry. 2015 Feb;56:105-07.

A DOUBLE-EDGED SWORD: ADVANTAGES AND DISADVANTAGES TO THE CURRENT EMPHASIS ON BIOGENETIC CAUSES OF CHILD PSYCHOPATHOLOGY.

Burt SA.

Research on child psychopathology is a largely biogenetic endeavor these days, at least according to current funding priorities at the National Institutes of Health in the US. This heavy focus on genetic contributions to child psychopathology has some real advantages. Available research has conclusively indicated that child and adolescent mental health problems are partially genetic in origin and, moreover, are related to neural structure and function (as an example, see Plomin et al.). Moreover, these genetic effects may be responsible for some previously reported 'environmental' effects, such that, what appear to be direct environmental risk

factors may in fact reflect genetic/familial risks. As one example, Sengupta et al. (this issue) found that maternal smoking during pregnancy was in fact a marker of maternal and paternal psychopathology. Put another way, the association between ADHD and maternal smoking during pregnancy may index a genetic/familial risk for a more severe form of ADHD, rather than a direct effect of uterine exposure to cigarettes. A final, more subtle reason for the current trend towards biogenetic research is that it has the rarely-discussed but all-too-important 'allure of the unknown'. We have only just recently been able to directly explore the biological underpinnings of psychopathology; and as technology advances, so too will the insights gained (presumably). This offers both funding agencies and individual scientists the very real possibility of making a major new discovery - a siren's call for most of us. In sharp contrast, decades of research have explored putatively environmental contributions to child and adolescent psychopathology. New paradigm-shifting discoveries are thus likely to be fewer in number and farther between (if we continue using traditional study designs that omit joint consideration of biology, that is). In short, biogenetic research just feels more cutting edge at the moment. The clear merits of such work notwithstanding, there are a number of critical disadvantages to the current emphasis on genetics. These issues are presented below, not necessarily in order of importance

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J Child Psychol Psychiatry. 2015 Feb;56:155-61.

HYPOSPADIAS AND INCREASED RISK FOR NEURODEVELOPMENTAL DISORDERS.

Butwicka A, Lichtenstein P, Landen M, et al.

BACKGROUND: Hypospadias (aberrant opening of the urethra on the underside of the penis) occurs in 1 per 300 newborn boys. It has been previously unknown whether this common malformation is associated with increased psychiatric morbidity later in life. Studies of individuals with hypospadias also provide an opportunity to examine whether difference in androgen signaling is related to neurodevelopmental disorders. To elucidate the mechanisms behind a possible association, we also studied psychiatric outcomes among brothers of the hypospadias patients.

METHODS: Registry study within a national cohort of all 9,262 males with hypospadias and their 4,936 healthy brothers born in Sweden between 1973 and 2009. Patients with hypospadias and their brothers were matched with controls by year of birth and county. The following outcomes were evaluated (1) any psychiatric (2) psychotic, (3) mood, (4) anxiety, (5) eating, and (6) personality disorders, (7) substance misuse, (8) attention-deficit hyperactivity disorder (ADHD), (9) autism spectrum disorders (ASD), (10) intellectual disability, and (11) other behavioral/emotional disorders with onset in childhood.

RESULTS: Patients with hypospadias were more likely to be diagnosed with intellectual disability (OR 3.2; 95% CI 2.8-3.8), ASD (1.4; 1.2-1.7), ADHD (1.5; 1.3-1.9), and behavioral/emotional disorders (1.4; 1.2-1.6) compared with the controls. Brothers of patients with hypospadias had an increased risk of ASD (1.6; 1.3-2.1) and other behavioral/emotional disorders with onset in childhood (1.2; 0.9-1.5) in comparison to siblings of healthy individuals. A slightly higher, although not statistically significant, risk was found for intellectual disability (1.3; 1.0-1.9). No relation between other psychiatric diagnosis and hypospadias was found.

CONCLUSIONS: This is the first study to identify an increased risk for neurodevelopmental disorders in patients with hypospadias, as well as an increased risk for ASD in their brothers, suggesting a common familial (genetic and/or environmental) liability

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J Child Psychol Psychiatry. 2015 Jan;56:58-66.

THE POSSIBLE INVOLVEMENT OF GENETIC VARIANTS OF NET1 IN THE ETIOLOGY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMORBID WITH OPPOSITIONAL DEFIANT DISORDER.

Liu L, Cheng J, Li H, et al.

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) often coexist and shared some genetic influences. Evidence from the existing literature indicated that comorbid with ODD may increase the heterogeneity of ADHD genetics. Our present study sought to investigate the role of norepinephrine transporter gene (NET1) for ADHD comorbid with ODD.

METHODS: Six single nucleotide polymorphisms (SNPs) of NET1 were genotyped for a total of 1,815 ADHD cases, including 587 subjects (32.3%) with ODD. Chi-square tests were conducted for pseudo case-control study comparing allelic and genotypic distributions between ADHD with and without ODD. Among them, there were 1,249 probands together with their parents composing trios for family-based association studies using transmission disequilibrium tests (TDTs). In addition, 1,337 ADHD probands have detailed information of ODD symptoms and were included for quantitative analyses with genotypes using analyses of covariance (ANCOVA). To consider the overlap and correlation of other comorbidities with ODD and eliminate their potential confounding effect, we further repeated above analyses for 'pure ADHD+ODD' versus 'ADHD-only' after excluding other comorbidities except for ODD.
RESULTS: The pseudo case-control study showed different allelic and genotypic distributions of SNP rs3785143 between ADHD with ODD and those without ODD. Family-based association tests indicated overtransmission of the T allele of rs3785143 in ADHD with ODD trios, but no biased transmission in those without ODD. ANCOVA showed association between genotypes of rs3785143 with ODD symptoms in ADHD probands, especially with 'Argumentative/Defiant Behavior (ADB)' dimension after controlling gender, age, clinical subtypes and intelligence. Above association still existed after removing the samples with other comorbidities.
CONCLUSION: NET1 was associated with comorbidity of ODD and ODD symptoms in ADHD probands. Our findings emphasize the importance of considering the comorbidity of ODD in ADHD genetic studies, especially ADHD with ADB. However, further replication in independent sample or different populations is still needed

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J Child Psychol Psychiatry. 2015 Feb;56:193-202.
OCULOMOTOR EXECUTIVE FUNCTION ABNORMALITIES WITH INCREASED TIC SEVERITY IN TOURETTE SYNDROME.
Jeter CB, Patel SS, Morris JS, et al.
BACKGROUND: Reports conflict as to whether Tourette syndrome (TS) confers deficits in executive function. This study's aim was to evaluate executive function in youths with TS using oculomotor tasks while controlling for confounds of tic severity, age, medication, and severity of comorbid disorders.
METHOD: Four saccade tasks requiring the executive functions of response generation, response inhibition, and working memory (prosaccade, antisaccade, 0-back, and 1-back) were administered. Twenty youths with TS and low tic severity (TS-low), nineteen with TS and moderate tic severity (TS-moderate), and 29 typically developing control subjects (Controls) completed the oculomotor tasks.
RESULTS: There were small differences across groups in the prosaccade task. Controlling for any small sensorimotor differences, TS-moderate subjects had significantly higher error rates than Controls and TS-low subjects in the 0-back and 1-back tasks. In the 1-back task, these patients also took longer to respond than Controls or TS-low subjects.
CONCLUSIONS: In a highly controlled design, the findings demonstrate for the first time that increased tic severity in TS is associated with impaired response inhibition and impaired working memory and that these executive function deficits cannot be accounted for by differences in age, medication or comorbid symptom severity

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J Clin Psychiatry. 2015 Jul;76:e870-e876.
NEUROPSYCHIATRIC SYMPTOMS AND EXPENDITURE ON COMPLEMENTARY AND ALTERNATIVE MEDICINE.
Purohit MP, Zafonte RD, Sherman LM, et al.
OBJECTIVE: Neuropsychiatric symptoms affect 37% of US adults. These symptoms are often refractory to standard therapies, and patients may consequently opt for complementary and alternative medicine therapies (CAM). We sought to determine the demand for CAM by those with neuropsychiatric symptoms compared to those without neuropsychiatric symptoms as measured by out-of-pocket expenditure.
METHOD: We compared CAM expenditure between US adults with and without neuropsychiatric symptoms (n = 23,393) using the 2007 National Health Interview Survey. Symptoms included depression, anxiety,

insomnia, attention deficits, headaches, excessive sleepiness, and memory loss. CAM was defined per guidelines from the National Institutes of Health as mind-body therapies, biological therapies, manipulation therapies, or alternative medical systems. Expenditure on CAM by those without neuropsychiatric symptoms was compared to those with neuropsychiatric symptoms.
RESULTS: Of the adults surveyed, 37% had >/= 1 neuropsychiatric symptom and spent $14.8 billion out-of-pocket on CAM. Those with >/= 1 neuropsychiatric symptom were more likely than those without neuropsychiatric symptoms to spend on CAM (27.4% vs 20.3%, P < .001). Likelihood to spend on CAM increased with number of symptoms (27.2% with >/= 3 symptoms, P < .001). After adjustment was made for confounders using logistic regression, those with >/= 1 neuropsychiatric symptom remained more likely to spend on CAM (odds ratio [OR] = 1.34; 95% CI, 1.22-1.48), and the likelihood increased to 1.55 (95% CI, 1.34-1.79) for >/= 3 symptoms. Anxiety (OR = 1.40 [95% CI, 1.22-1.60]) and excessive sleepiness (OR = 1.36 [95% CI, 1.21-1.54]) were the most closely associated with CAM expenditure.
CONCLUSIONS: Those with >/= 1 neuropsychiatric symptom had disproportionately higher demand for CAM than those without symptoms. Research regarding safety, efficacy, and cost-effectiveness of CAM is limited; therefore, future research should evaluate these issues given the tremendous demand for these treatments

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J Intellect Disabil Res. 2015 Mar;59:248-56.
CLUMSINESS IN FINE MOTOR TASKS: EVIDENCE FROM THE QUANTITATIVE DRAWING EVALUATION OF CHILDREN WITH DOWN SYNDROME.
Vimercati SL, Galli M, Stella G, et al.
INTRODUCTION: Drawing tests are commonly used for the clinical evaluation of cognitive capabilities in children with learning disabilities. We analysed quantitatively the drawings of children with Down Syndrome (DS) and of healthy, mental age-matched controls to characterise the features of fine motor skills in DS during a drawing task, with particular attention to clumsiness, a well-known feature of DS gross movements.
METHODS: Twenty-three children with DS and 13 controls hand-copied the figures of a circle, a cross and a square on a sheet. An optoelectronic system allowed the acquisition of the three-dimensional track of the drawing. The participants' posture and upper limb movements were analysed as well.
RESULTS: Results showed that the participants with DS tended to draw faster but with less accuracy than controls.
DISCUSSION: While clumsiness in gross movements manifests mainly as slow, less efficient movements, it manifests as high velocity and inaccurate movements in fine motor tasks such as drawing

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J Interpers Violence. 2015 Mar;30:782-95.
MENTAL HEALTH AND BULLYING IN THE UNITED STATES AMONG CHILDREN AGED 6 TO 17 YEARS.
Benedict FT, Vivier PM, Gjelsvik A.
This article examines the association between mental health disorders and being identified as a bully among children between the ages of 6 and 17 years. Data from the 2007 National Survey of Children's Health were examined. A total of 63,997 children had data for both parental reported mental health and bullying status. Bivariate analysis and logistic regression was performed to assess the association between mental health status and being identified as a bully with an age-stratified analysis and sub-analysis by type of mental health disorder. In 2007, 15.2% of U.S. children ages 6 to 17 years were identified as bullies by their parent or guardian. Children with a diagnosis of depression, anxiety, or depression had a threefold increased odds of being a bully. The diagnosis of depression is associated with a 3.31 increased odds (95% CI = [2.7, 4.07]) of being identified as a bully. Children with anxiety and attention deficit and hyperactivity disorder (ADHD) had similar odds. The diagnosis of a mental health disorder is strongly associated with being identified as a bully. In particular, depression, anxiety, and ADHD are strongly associated with being identified as a bully. These findings emphasize the importance of providing psychological support to not only victims of bullying but

bullies as well. Understanding the risk profile of childhood bullies is essential in gaining a better grasp of this public health problem and in creating useful and appropriate resources and interventions to decrease bullying

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J Prim Prev. 2015 Feb;36:33-40.

ONE-YEAR FOLLOW-UP OF GUIDED SELF-HELP FOR PARENTS OF PRESCHOOL CHILDREN WITH EXTERNALIZING BEHAVIOR.

Ise E, Kierfeld F, Dopfner M .

Self-help programs are an effective intervention for parents of children with externalizing behavior. A number of studies have shown that self-administered parent training has positive short-term effects on a child's behavior, but there is little research done on long-term outcomes. This paper reports results from a 1-year follow-up of a randomized controlled prevention trial of self-administered parent training with minimal therapist contact. In the initial prevention trial, we randomly assigned 48 preschool children with elevated levels of externalizing behavior to either a treatment group (TG) or a waitlist control group (WLC). The intervention consisted of written material and brief weekly telephone consultations. Thirty-six families (25 TG families, 11 WLC families) completed the self-help program. Twenty-five of these participated in a follow-up assessment 1 year after the intervention. There were no significant changes from post-test to follow-up on measures of child behavior (e.g., Attention-Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder symptom rating scales) and parental mental health, indicating that gains achieved post-intervention were maintained for at least 1 year. Moreover, the percentage of children with substantial behavior problems was reduced from pre-intervention to follow-up. These findings provide evidence that telephone-assisted self-help programs can be effective in the prevention of disruptive behavior problems

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J Psychopharmacol. 2015 Jan;29:3-14.

SAFETY AND TOLERABILITY OF ATOMOXETINE IN TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADULT PATIENTS: AN INTEGRATED ANALYSIS OF 15 CLINICAL TRIALS.

Camporeale A, Porsdal V, De BK, et al.

The safety profile of atomoxetine in the treatment of attention deficit hyperactivity disorder has been studied in many clinical trials. We performed an integrated safety analysis of 15 clinical trials in adults with attention deficit hyperactivity disorder. The analysis pooled patient data into three groups: acute placebo-controlled trials; long-term placebo-controlled trials; all trials. In total, 4829 adults (18-77 years, median: 36 years) were exposed to atomoxetine. Statistically significantly more atomoxetine-treated than placebo-treated patients experienced treatment-emergent adverse events (81.3% vs. 68.3% acute; 90.6% vs. 76.8% long term) and discontinued due to adverse events (8.9% vs. 4.0% acute; 17.9% vs. 6.3% long term). No statistically significant differences were observed in the proportion of patients experiencing serious adverse events. No previously unknown adverse events were identified. The most common adverse events included nausea, dry mouth, decreased appetite, insomnia and erectile dysfunction. Mean increases in heart rate (+5.2 beats per min) and blood pressure (systolic +2 mmHg, diastolic +1.9 mmHg) were modest. The proportion of patients experiencing clinically significant increases in blood pressure and heart rate at any time was statistically significantly higher with atomoxetine (systolic blood pressure 13-17%, diastolic blood pressure 37-40%, heart rate 42-43%) compared to placebo (systolic blood pressure 8-13%, diastolic blood pressure 29-34%, heart rate 21-26%). There was no increased risk of suicidal ideation or behaviour. Our findings confirm atomoxetine's known safety profile. From a safety perspective, atomoxetine is a useful treatment option for adults with attention deficit hyperactivity disorder

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J Youth Adolesc. 2015 Feb;44:239-70.

ADVANCING A BIOPSYCHOSOCIAL AND CONTEXTUAL MODEL OF SLEEP IN ADOLESCENCE: A REVIEW AND INTRODUCTION TO THE SPECIAL ISSUE.

Becker SP, Langberg JM, Byars KC.

Sleep problems in adolescence have been identified as an international public health issue. Over the past few decades, notable advances have been made in our understanding of the patterns and consequences of sleep in adolescence. Despite these important gains, there is much about the role of sleep in adolescence that remains to be understood. This Special Issue brings together studies that examine sleep as it specifically pertains to adolescent development and adjustment. In this introductory article, we argue for the importance of grounding the study of sleep and adolescence in developmental science and a developmental psychopathology framework. First, a review of the literature is used to outline a biopsychosocial and contextual model of sleep in adolescence. Second, attention-deficit/hyperactivity disorder (ADHD) is used as an exemplar of the proposed model given the pervasiveness of sleep problems among youth with ADHD and the likelihood that sleep problems and ADHD symptoms are interconnected in complex ways. Finally, a brief introduction to the empirical articles included in the Special Issue is provided, with particular attention given to how these articles fit within the proposed biopsychosocial and contextual model. Along with the framework proposed in this article, the studies included in this Special Issue advance the current literature and point to critical directions for future research

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J Abnorm Child Psychol. 2015 Oct;43:1219-32.

HYPERACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): IMPAIRING DEFICIT OR COMPENSATORY BEHAVIOR?

Sarver DE, Rapport MD, Kofler MJ, et al.

Excess gross motor activity (hyperactivity) is considered a core diagnostic feature of childhood ADHD that impedes learning. This view has been challenged, however, by recent models that conceptualize excess motor activity as a compensatory mechanism that facilitates neurocognitive functioning in children with ADHD. The current study investigated competing model predictions regarding activity level's relation with working memory (WM) performance and attention in boys aged 8–12 years (M = 9.64, SD = 1.26) with ADHD (n = 29) and typically developing children (TD; n = 23). Children's phonological WM and attentive behavior were objectively assessed during four counterbalanced WM tasks administered across four separate sessions. These data were then sequenced hierarchically based on behavioral observations of each child's gross motor activity during each task. Analysis of the relations among intra-individual changes in observed activity level, attention, and performance revealed that higher rates of activity level predicted significantly better, but not normalized WM performance for children with ADHD. Conversely, higher rates of activity level predicted somewhat lower WM performance for TD children. Variations in movement did not predict changes in attention for either group. At the individual level, children with ADHD and TD children were more likely to be classified as reliably Improved and Deteriorated, respectively, when comparing their WM performance at their highest versus lowest observed activity level. These findings appear most consistent with models ascribing a functional role to hyperactivity in ADHD, with implications for selecting behavioral treatment targets to avoid overcorrecting gross motor activity during academic tasks that rely on phonological WM.

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J Abnorm Child Psychol. 2015 Oct;43:1257-69.

MATERNAL DEPRESSION HISTORY MODERATES PARENTING RESPONSES TO COMPLIANT AND NONCOMPLIANT BEHAVIORS OF CHILDREN WITH ADHD.

Thomas SR, O'Brien KA, Clarke TL, et al.

Maternal depression and parenting are robust predictors of developmental outcomes for children with attention-deficit/hyperactivity disorder (ADHD). However, methods commonly used to examine parent–child interactions in these families do not account for temporal associations between child and parent behavior that have been theorized to maintain negative child behavior. Moreover, studies examining associations

between maternal depression and parenting in families of children with ADHD have not compared mothers who were currently depressed, remitted, and never clinically depressed. This study utilized sequential analysis to examine how maternal reinforcement of compliant and noncompliant child behavior differs as a function of maternal depression history. Within the 82 participating mother-child dyads, 21 mothers were currently depressed, 29 mothers had a lifetime history of depression but were in remission for at least 1 month, and 32 mothers had never been clinically depressed. 24 girls (29.6 %) and 57 boys (70.4 %) between the ages of 6–12 years old (M = 8.7, SD = 2.0) and were diagnosed with ADHD. Results indicated that all mothers were less likely to respond optimally than non-optimally to child compliant and noncompliant behaviors during observed parent–child interactions; however, currently depressed mothers were least likely to reinforce child compliance and responded most coercively to child noncompliance relative to the other groups. Remitted mothers in this sample were more coercive than never clinically depressed mothers, but were more likely to follow through with commands than never clinically depressed mothers. Implications for behavioral parent training programs aimed at skill development for depressed mothers of children with ADHD are discussed

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J Abnorm Child Psychol. 2015 Oct;43:1233-42.

FEEDBACK MAY HARM: ROLE OF FEEDBACK IN PROBABILISTIC DECISION MAKING OF ADOLESCENTS WITH ADHD.

Pollak Y, Shoham R.

Inept probabilistic decision making is commonly associated with ADHD. In experimental designs aimed to model probabilistic decision making in ADHD, feedback following each choice was, in the majority of studies, part of the paradigm. This study examined whether feedback processing plays a role in the maladaptive choice behavior of subjects with ADHD by comparing feedback and no-feedback conditions. Sixty adolescents (49 males), ages 13–18, with and without ADHD, performed a descriptive probabilistic choice task in which outcomes and probabilities were explicitly provided. Subjects performed the task either with or without feedback. Under the no-feedback condition, adolescents with ADHD and controls performed similarly, whereas under the feedback condition, subjects with ADHD chose the unfavorable outcomes more frequently and risked smaller sums than controls. These finding demonstrate the crucial role of feedback in the decision making of adolescents with ADHD

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J Adolesc. 2015 Oct;44:48-56.

MENTAL HEALTH PROBLEMS AND RESILIENCE IN INTERNATIONAL ADOPTEES: RESULTS FROM A POPULATION-BASED STUDY OF NORWEGIAN ADOLESCENTS AGED 16–19 YEARS.

Askeland KG, Hysing M, Aarø LE, et al.

The aim of the study was to investigate mental health and resilience in adolescents who have been internationally adopted and their non-adopted peers and examine the potential interaction between adoption status and resilience on mental health problems. Data from the population based youth@hordaland-survey, conducted in Hordaland County, Norway, in 2012 was used. In all, 10 257 adolescents aged 16–19 years provided self-reported data on several mental health instruments. Of these, 45 adolescents were identified as internationally adopted. Adoptees reported more symptoms of depression, attention-deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and perfectionism than non-adopted adolescents, but there were no differences regarding resilience. Adolescents with higher resilience scores reported fewer symptoms of mental health problems, however, no interaction effects were found for adoption status and total resilience score on measures of mental health problems. Our findings indicate that knowledge of resilience factors can form the basis for preventive interventions

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J Affective Disord. 2016;189:110-17.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER, ITS TREATMENT WITH MEDICATION AND THE PROBABILITY OF DEVELOPING A DEPRESSIVE DISORDER: A NATIONWIDE POPULATION-BASED STUDY IN TAIWAN.

Lee M-J, Yang K-C, Shyu Y-C, et al.

Objective The purpose of this study is to determine the risk of developing depressive disorders by evaluating children with attention-deficit/hyperactivity disorder (ADHD) in comparison to controls that do not have ADHD, as well as to analyze whether the medications used to treat ADHD, methylphenidate (MPH) and atomoxetine (ATX), influence the risk of depression.

Methods A group of patients newly diagnosed with ADHD (n=71,080) and age- and gender-matching controls (n=71,080) were chosen from Taiwan's National Health Insurance database during the period of January 2000 to December 2011. Both the patients and controls were monitored through December 31, 2011. We also explore the potential influence of the length of MPH and ATX treatment on developing depressive disorders.

Results The ADHD patients showed a significantly increased probability of developing a depressive disorder when compared to the control group (ADHD: 5.3% vs. controls: 0.7%; aHR, 7.16, 99% CI: 6.28-8.16). Regarding treatment with MPH, a longer MPH use demonstrates significant protective effects against developing a depressive disorder (aOR, 0.91, 99%CI: 0.88-0.94). However, the duration of ATX treatment could not be significantly correlated with the probability of developing a depressive disorder. Limitations The database employed in this study lacks of comprehensive clinical information for the patients with ADHD. Potential moderating factors between ADHD and depression were not considered in-depth in this study.

Conclusions The results of this study reveal that youths diagnosed with ADHD have a greater risk of developing depressive disorders. Long-term treatment with MPH correlated to the reduced probability of developing a depressive disorder among youths with ADHD

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J Autism Dev Disord. 2015.

OBSTETRICAL MODE OF DELIVERY AND CHILDHOOD BEHAVIOR AND PSYCHOLOGICAL DEVELOPMENT IN A BRITISH COHORT.

Curran EA, Cryan JF, Kenny LC, et al.

The association between mode of delivery [specifically birth by Cesarean section (CS)] and induction of labor (IOL) psychological development at age 7 was assessed [including autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD) and behavioral difficulties]. The Millennium cohort study, a nationally representative UK cohort of children (including 13,141 children), was used. There was no association between planned CS and ASD [aOR 0.58; (95 % CI 0.19ΓÇô1.79)] or ADHD [aOR 0.54; (95 % CI 0.18ΓÇô1.64)] analyses. Induced vaginal delivery was significantly associated with behavioral difficulties in unadjusted [OR 1.26; (95 % CI 1.03ΓÇô1.54)], but not adjusted analysis [OR 1.15; (95 % CI 0.82ΓÇô1.60)]. There was no association between mode of delivery and ASD or ADHD in this cohort. Further research is needed to understand the relationship between mode of delivery and IOL and psychological development

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Journal of Cardiovascular Electrophysiology. 2015;26:1039-44.

LONG-QT SYNDROME AND THERAPY FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Zhang C, Kutyifa V, Moss AJ, et al.

ADHD Therapy in LQTS Introduction Stimulants are the mainstay therapy for attention deficit/hyperactivity disorder (ADHD) and are associated with adrenergic side effects. There are limited data on the clinical course of patients treated for ADHD who have long-QT syndrome (LQTS), for which +¦-blockade is the goal of therapy. Methods LQTS patients from the Rochester-based LQTS Registry (open-enrollment between 1979 and 2003; follow-up from 1979 to present) treated with stimulant or nonstimulant ADHD medications (n = 48) were compared to a 2:1 age-, gender-, and QTc-duration matched LQTS control group not exposed to ADHD medications (n = 96). Kaplan-Meier and Cox proportional hazards regression analyses were used to evaluate risk of cardiac events (syncope, aborted cardiac arrest, and sudden cardiac death) in LQTS patients treated

with ADHD medications. Results During a mean follow-up of 7.9 -¦ 5.4 years after initiation of ADHD medication at a mean age 10.7 -¦7.3 years, there was a 62% cumulative probability of cardiac events in the ADHD treatment group compared to 28% in the matched LQTS control group (P < 0.001). Time-dependent use of ADHD medication was associated with an increased risk for cardiac events (HR = 3.07; P = 0.03) in the multivariate Cox model adjusted for time-dependent +¦-blocker use and prior cardiac events. Subgroup gender analyses showed that time-dependent ADHD medication was associated with an increased risk in male LQTS patients (HR = 6.80, P = 0.04). Conclusions LQTS patients treated with ADHD medications have increased risk for cardiac events, particularly syncope, and this risk is augmented in males. The findings highlight the importance of heightened surveillance for LQTS patients on ADHD medications

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J Child Adolesc Ment Health. 2015.

ENCOUNTERING A CARTWHEELING PRINCESS: RELATIONAL PSYCHOANALYTIC THERAPY OF A CHILD WITH ATTACHMENT DIFFICULTIES AND ADHD.

Laidlaw C, Howcroft G.

Objective: This study was conducted to demonstrate the use and process of contemporary relational psychoanalytic child therapy to address the interpersonal implications of attention deficit hyperactivity disorder and interlinked insecure attachment processes.

Method: This therapy case study explicates the seven-month therapeutic process of a seven-year-old girl child highlighting the need for the child therapist to balance interventions aimed at both the internal and external world of the child. In essence, this account traces therapeutic scenarios of both painful and joyful material by means of paying close attention to the entwined transference and countertransference dynamics as well as creatively and authentically engaging with the child's way of making sense of self-states, others and even medication.

Results: Key features of this account include the foundational role of assessment and the compelling mediating role of a puppet as a co-therapist within the analytic space between psychotherapist and patient.

Conclusion: Uniquely, as an inclusive psychoanalytic therapy, relational psychoanalytic child therapy reconfigures internal object relations of the child while simultaneously ushering changes into their familial and school context by utilising the mutuality established between the child and therapist as a central pivot

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J Child Neurol. 2015 Oct;30:1496-506.

PROCEDURAL LEARNING IN CHILDREN WITH DEVELOPMENTAL COORDINATION, READING, AND ATTENTION DISORDERS.

Magallón S, Crespo-Eguílaz N, Narbona J.

The aim is to assess repetition-based learning of procedures in children with developmental coordination disorder (DCD), reading disorder (RD) and attention-deficit hyperactivity disorder (ADHD). Participants included 187 children, studied in 4 groups: (a) DCD comorbid with RD and ADHD (DCD+RD+ADHD) (n = 30); (b) RD comorbid with ADHD (RD+ADHD) (n = 48); (c) ADHD (n = 19); and typically developing children (control group) (n = 90). Two procedural learning tasks were used: Assembly learning and Mirror drawing. Children were tested on 4 occasions for each task: 3 trials were consecutive and the fourth trial was performed after an interference task. Task performance by DCD+RD+ADHD children improved with training (P < .05); however, the improvement was significantly lower than that achieved by the other groups (RD+ADHD, ADHD and controls) (P < .05). In conclusion, children with DCD+RD+ADHD improve in their use of cognitive-motor procedures over a short training period. Aims of intervention in DCD+RD+ADHD should be based on individual learning abilities.

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J Child Neurol. 2015;30:1785-93.

WHEN IS EEG INDICATED IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Zaimo-çlu S, T++rkdo-çan D, Mazlum B, et al.

The authors investigated the parameters for predicting epileptiform abnormalities in a group of children diagnosed with attention-deficit/hyperactivity disorder (ADHD). The sample consisted of 148 subjects aged between 6 and 13 (8.76 -¦ 1.26; 25.7% female) years. Subtypes of ADHD and comorbid psychiatric disorders were defined according to DSM-IV criteria. The Wechsler Intelligence Scale for Children-Revised was applied to all patients. Most of the subjects (89.2%) had wakefulness and sleep electroencephalography examinations lasting about one hour. The authors found out that the coexistence of speech sound disorder (odds ratio [OR] 3.90, 95% confidence interval [CI]: 1.61-9.48) and higher Digit Span test performance (OR 1.24, 95% CI: 1.06-1.44) predicted the presence of accompanying epileptiform abnormalities. The prevalence of epileptiform abnormalities was 26.4%, and they were frequently localized in the frontal (41%) and centrotemporal (28.2%) regions. Higher percentage of speech sound disorder co-occurrence (64%) in subjects with rolandic spikes suggests that epileptiform abnormalities associated with ADHD can be determined genetically at least in some cases. Pathophysiology of epileptiform abnormalities in ADHD might have complex genetic and maturational background

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J Child Neurol. 2015 Oct;30:1520-25.

SLEEP STRUCTURE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Akinci G, Oztura I, Hiz S, et al.

The authors evaluated basic sleep architecture and non–rapid eye movement (NREM) sleep alterations in drug-nai¨ve attentiondeficit/ hyperactivity disorder (ADHD) children without psychiatric or other comorbidities. This cross-sectional case-control study included 28 drug-nai¨ve children with ADHD and 15 healthy controls. This subjective studies revealed that children with ADHD had a worse sleep quality and increased daytime sleepiness. Polysomnography data showed that the sleep macrostructure was not significantly different in children with ADHD. Sleep microstructure was altered in ADHD children by means of reduced total cyclic alternating pattern rate and duration of cyclic alternating pattern sequences. This reduction was associated with a selective decrease of A1 index during stage 2 NREM. SpO2 in total sleep was slightly decreased; however, the incidence of sleep disordered breathing showed no significant difference. The authors suggest that cyclic alternating pattern scoring would provide a further insight to obtain a better understanding of the sleep structure in children with ADHD.

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Journal of Child Psychology and Psychiatry. 2015 Oct;56:1074-82.

PHENOTYPIC AND GENETIC ASSOCIATIONS BETWEEN READING COMPREHENSION, DECODING SKILLS, AND ADHD DIMENSIONS: EVIDENCE FROM TWO POPULATION-BASED STUDIES.

Plourde V, Boivin M, Forget-Dubois N, et al.

Background: The phenotypic and genetic associations between decoding skills and ADHD dimensions have been documented but less is known about the association with reading comprehension. The aim of the study is to document the phenotypic and genetic associations between reading comprehension and ADHD dimensions of inattention and hyperactivity/impulsivity in early schooling and compare them to those with decoding skills.

Methods: Data were collected in two population-based samples of twins (Quebec Newborn Twin Study—QNTS) and singletons (Quebec Longitudinal Study of Child Development—QLSCD) totaling ˜ 2300 children. Reading was assessed with normed measures in second or third grade. Teachers assessed ADHD dimensions in kindergarten and first grade.

Results: Both decoding and reading comprehension were correlated with ADHD dimensions in a similar way: associations with inattention remained after controlling for the other ADHD dimension, behavior disorder symptoms and nonverbal abilities, whereas associations with hyperactivity/impulsivity did not. Genetic

modeling showed that decoding and comprehension largely shared the same genetic etiology at this age and that their associations with inattention were mostly explained by shared genetic influences.
Conclusion: Both reading comprehension and decoding are uniquely associated with inattention through a shared genetic etiology.

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J Dev Behav Pediatr. 2015 Sep;36:549-51.

INATTENTIVE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, STIMULANT MEDICATION, AND WEIGHT LOSS IN A 15-YEAR-OLD GIRL: ARE WE ENABLING THE DEVELOPMENT OF AN EATING DISORDER?

Iyer S, Kumar M, Reiff MI, et al.

Case: Nicole is a 15-year-old girl presenting to the Developmental Behavioral Pediatrics Clinic with symptoms of the inattentive type of Attention-Deficit/Hyperactivity Disorder (ADHD) and declining school performance over the last year. She expressed frustration over her inability to concentrate on schoolwork. Assuming that her poor grades were secondary to lack of effort, her parents withdrew privileges. Nicole became increasingly depressed. She stopped participating in activities, she previously enjoyed, and her parents reported that she stopped singing in the shower. After talking to a cousin with ADHD, Nicole concluded that she had ADHD as well. She asked her parents to arrange for an evaluation. Nicole met DSM-5 criteria for the diagnosis of inattentive ADHD and was started on a stimulant medication (mixed amphetamine salts). She had symptoms of a coexisting depression, although she did not meet criteria for diagnosis of a depressive disorder. At a 3-week follow-up visit, she showed improvement in targeted ADHD symptoms; homework was now easier and her grades improved. At a 2-month follow-up, Nicole's weight dropped from 53 kg (47th percentile) prestimulant treatment to 49 kg (31st percentile). She reported appetite suppression after taking the stimulant but did not feel that her eating habits had changed significantly. Her father reported that she had a preference for junk food and snacks. Nicole did not enjoy exercising and did not participate in extracurricular sports. She weighed herself several times a day, as she was worried about losing too much weight. Nicole's mood continued to be low, despite the fact that her grades improved, and her parents were more understanding of her challenges. She was otherwise healthy and reported regular menstrual cycles. Nicole requested an increase in the dose of stimulant medication for greater improvement in concentration during homework and in school. Her pediatric clinician was concerned about the possibility of an eating disorder in addition to depression. She asked herself, "Are we treating inattentive ADHD effectively or are we enabling an eating disorder?"

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J Dev Behav Pediatr. 2015 Oct;36:553-61.

GROUP VISITS TO IMPROVE PEDIATRIC ATTENTION-DEFICIT HYPERACTIVITY DISORDER CHRONIC CARE MANAGEMENT.

Bauer NS, Szczepaniak D, Sullivan PD, et al.

Objective: Children with attention-deficit hyperactivity disorder (ADHD) may experience continued impairment at home and school even after medication initiation. Group visits offer a way for pediatricians to provide more time to address ongoing needs. A pilot study was undertaken to examine whether a group visit model improved ADHD management in the pediatric medical home.
Methods: Parents and children aged 6 to 18 years with ADHD were recruited and randomized to group visits or a usual care control. Data included attendance at ADHD follow-up visits, parent-rated ADHD symptoms, adaptive functioning, and quality of life. Longitudinal linear mixed models (continuous variables) and generalized linear mixed models (binary outcomes) were used to compare groups. In our statistical models, child and family were random effects; study assignment was a fixed effect.
Results: Twenty families representing 29 children participated (intervention: 9 parents/13 children and control: 11 parents/16 children). Aside from race, baseline characteristics of participants were similar. None of the intervention families missed the expected 5 ADHD follow-up visits over 1 year; control families missed 1 or more visits over the same period. Intervention families reported an improved level of adaptive functioning at 12 months compared with control (mean severity score: 3.7 vs 4.4, $p = .003$). All families reported greater limitations and poorer quality of life compared with national norms.

Conclusion: Group visits in the pediatric medical home can improve adherence, and preliminary results show a variety of improvements for the family.

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Journal of Head Trauma Rehabilitation. 2015;30:311-23.

AWARENESS DEFICITS IN CHILDREN AND ADOLESCENTS AFTER TRAUMATIC BRAIN INJURY: A SYSTEMATIC REVIEW.

Caplan B, Brenner L, Bogner J, et al.

Objectives: To systematically review empirical research on awareness deficits in children and adolescents following traumatic brain injury (TBI).

Methods: PsycINFO, MEDLINE, Cochrane Library, CINAHL (Cumulative Index to Nursing and Allied Health Literature), ERIC (Education Resources Information Centre), PsycBITE, and Web of Science were searched from inception to August 8, 2013, using key terms relating to awareness of deficits and brain injury in childhood/adolescence. Studies of children or adolescents with traumatic brain injury (TBI), systematic measurement of awareness of deficits, and reporting of quantitative data were included. Details of participants, methodology, and findings were summarized for each study, and methodological quality was rated.

Results: Review of 12 eligible studies yielded mixed evidence concerning the presence of awareness deficits after childhood TBI. Awareness deficits were most evident both for memory and executive function impairments and for children and adolescents with severe TBI. Methodological variability, including sampling characteristics, objects of awareness, measurement issues, and approach to statistical analysis, contributed to the mixed findings.

Conclusions: Further research focusing on factors contributing to awareness deficits following pediatric TBI, the course of recovery, and relation to functional outcomes is warranted

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J Neural Transm. 2015.

BLINK RATE AND BLINK TIMING IN CHILDREN WITH ADHD AND THE INFLUENCE OF STIMULANT MEDICATION.

Groen Y, B+Ârger NA, Koerts J, et al.

Spontaneous eye blink rate is modulated by task demands and internal state, and is demonstrated to reflect central dopamine activity. Also, spontaneous eye blinks are strategically timed around salient stimuli. This study investigates whether children with attention deficit hyperactivity disorder (ADHD) show reduced blink rates, blink modulation and blink timing, and whether this is influenced by stimulant medication. The electrooculogram was measured in 18 typically developing children, 16 children with ADHD off methylphenidate (Mph), and 16 children with ADHD on Mph during a rest period and during performance of a 60-min visual selective attention task. Blink rate and timing was extracted from the electrooculogram. No evidence was found for aberrant blink rate or blink modulation in children with ADHD off Mph. All groups increased blink rates from rest to task, and no group differences were found in blink rate during rest and task, or in the modulation of blink rate from rest to task. Time-on task resulted in a similar increase in blink rates in all three groups. Stimulant medication appeared not to influence blink rate and blink modulation, except that in the ADHD off Mph group the blink rate was enhanced only under conditions with performance feedback. All groups inhibited blinks before stimulus presentation and strategically timed their blinks after the stimulus. Children with ADHD off Mph showed reduced blink inhibition before the stimulus; however, given the low incidence (<1 % of the trials) and long latency this is not likely to impair their visual intake

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J Neurodevelopmental Disord. 2015;7.

CEREBRAL VOLUMETRIC ABNORMALITIES IN NEUROFIBROMATOSIS TYPE 1: ASSOCIATIONS WITH PARENT RATINGS OF SOCIAL AND ATTENTION PROBLEMS, EXECUTIVE DYSFUNCTION, AND AUTISTIC MANNERISMS.

Huijbregts SCJ, Loitfelder M, Rombouts SA, et al.

Background: Neurofibromatosis type 1 (NF1) is a single-gene neurodevelopmental disorder, in which social and cognitive problems are highly prevalent. Several commonly observed central nervous system (CNS) abnormalities in NF1 might underlie these social and cognitive problems. Cerebral volumetric abnormalities are among the most consistently observed CNS abnormalities in NF1. This study investigated whether differences were present between NF1 patients and healthy controls (HC) in volumetric measures of cortical and subcortical brain regions and whether differential associations existed for NF1 patients and HC between the volumetric measures and parent ratings of social skills, attention problems, social problems, autistic mannerisms, and executive dysfunction.
Methods: Fifteen NF1 patients (mean age 12.9 years, SD 2.6) and 18 healthy controls (HC, mean age 13.8 years, SD 3.6) underwent 3 T MRI scanning. Segmentation of cortical gray and white matter, as well as volumetry of subcortical nuclei, was carried out. Voxel-based morphometry was performed to assess cortical gray matter density. Correlations were calculated, for NF1-patients and HC separately, between MRI parameters and scores on selected dimensions of the following behavior rating scales: the Social Skills Rating System, the Child Behavior Checklist, the Social Responsiveness Scale, the Behavior Rating Inventory of Executive Functioning, and the Dysexecutive Questionnaire.
Results: After correction for age, sex, and intracranial volume, larger volumes of all subcortical regions were found in NF1 patients compared to controls. Patients further showed decreased gray matter density in midline regions of the frontal and parietal lobes and larger total white matter volume. Significantly more social and attention problems, more autistic mannerisms, and poorer executive functioning were reported for NF1 patients compared to HC. In NF1 patients, larger left putamen volume and larger total white matter volume were associated with more social problems and poorer executive functioning, larger right amygdala volume with poorer executive functioning and autistic mannerisms, and smaller precentral gyrus gray matter density was associated with more social problems. In controls, only significant negative correlations were observed: larger volumes (and greater gray matter density) were associated with better outcomes.
Conclusions: Widespread volumetric differences between patients and controls were found in cortical and subcortical brain regions. In NF1 patients but not HC, larger volumes were associated with poorer behavior ratings

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Journal of Pediatric Orthopaedics. 2015.

PRELIMINARY EVIDENCE OF AN ASSOCIATION BETWEEN ADHD MEDICATIONS AND DIMINISHED BONE HEALTH IN CHILDREN AND ADOLESCENTS.

Howard JT, Walick KS, Rivera JC.

BACKGROUND: The US Centers for Disease Control and Prevention estimate that 3.5 million children use psychotropic drugs for attention-deficit hyperactivity disorder (ADHD). With an increase in use of these types of drugs, thorough understanding of their potential side effects on the growing skeleton is needed. The purpose of this study was to determine whether there is an association between use of ADHD medication and diminished bone health.
METHODS: Three waves of the National Health and Nutrition Examination Survey public-use data set, collected from 2005 through 2010, were compiled for this study (N=5315). Bone health was measured using dual-energy x-ray absorptiometry scans, which were performed for participants aged 8 to 17 years to determine bone mineral density (BMD) for 3 regions: (1) total femur; (2) femoral neck; and (3) lumbar. Use of ADHD medications was determined by self-reported responses to questions regarding prescription drug use, which were answered by either the respondent or the respondent's parent or guardian. Multiple statistical techniques were used to produce estimates of association between ADHD medication use and z score age and sex standardized BMD measures, including survey adjusted univariate, survey adjusted multiple linear regression, and generalized estimating equations with a propensity-matched subsample (N=1967). Multivariate models adjusted for covariates including time period, age, sex, race/ethnicity, family income to poverty ratio, and total number of prescription medications.
RESULTS: Conservative estimates of the difference in standardized BMD measures between the ADHD medication group and the nonmedicated group range from -0.4855 (±0.27; P<0.001) for total femoral, -0.4671 (±0.27; P<0.001) for femoral neck, and -0.3947 (±0.29; P<0.01) for lumbar. Significantly more children on

ADHD medications versus match subjects on no medication had BMDs with in osteopenic range (38.3% vs. 21.6%, P<0.01).
DISCUSSION: The findings suggest that there are real and nontrivial differences in BMD for children and adolescents taking ADHD medications, as compared with similar children not taking any prescription medications. Prescribing physicians and parents should be aware of potential bone health risks associated with these medications.
LEVEL OF EVIDENCE: Level III-case-control study.

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J Psychopathol Behav Assess. 2015.
PARENT MANAGEMENT OF ORGANIZATION, TIME MANAGEMENT, AND PLANNING DEFICITS AMONG ADOLESCENTS WITH ADHD.
Sibley MH, Campez M, Perez A, et al.
Organization, Time Management, and Planning (OTP) problems are a key mechanism of academic failure for adolescents with ADHD. Parents may be well positioned to promote remediation of these deficits; yet, almost nothing is known about OTP management behaviors among parents of middle and high school students with ADHD. In a sample of 299 well-diagnosed adolescents with ADHD, a measure of parental OTP management was psychometrically validated. Latent Class Analysis was conducted to detect distinct patterns of parental OTP management and yielded four unique classes: Parental Control (18.7 %), Parent-Teen Collaboration (20.4 %), Homework Assistance (20.4 %), and Uninvolved (40.5 %). Logistic Regression analyses indicated that maladaptive parental OTP strategies were related to higher levels of parent and adolescent psychopathology. Parental OTP management did not relate to current adolescent OTP skills or GPA, indicating that parents did not select OTP management strategies in immediate response to adolescent functioning. Implications for parent-directed intervention are discussed

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J Psychopathol Behav Assess. 2015.
ERRATUM TO: PARENT MANAGEMENT OF ORGANIZATION, TIME MANAGEMENT, AND PLANNING DEFICITS AMONG ADOLESCENTS WITH ADHD.
Sibley MH, Campez M, Perez A, et al.

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Medicine. 2015;94.
UNINTENTIONAL INJURIES IN PRESCHOOL AGE CHILDREN: IS THERE A CORRELATION WITH PARENTING STYLE AND PARENTAL ATTENTION DEFICIT AND HYPERACTIVITY SYMPTOMS.
Acar E, Dursun OB, Esin IS, et al.
Unintentional injuries are the leading cause of death among children. Previous research has shown that most of the injuries occur in and around the home. Therefore, parents have a key role in the occurrence and prevention of injuries. In this study, we examined the relationship among home injuries to children and parental attention deficit hyperactivity disorder (ADHD) symptoms, parental attitudes, and children's behavioral problems. Forty children who were admitted to the emergency department because of home injuries constitute the study group. The control group also consisted of 40 children, who were admitted for mild throat infections. The parents filled out questionnaires assessing parental ADHD, child behavioral problems, and parenting attitudes. Scores were significantly higher for both internalizing disorders and externalizing disorders in study groups. We also found that ADHD symptoms were significantly higher among fathers of injured children compared with fathers of control groups. Democratic parenting was also found to correlate with higher numbers of injuries. Parenting style, as well as the psychopathology of both the parents and children, is important factors in children's injuries. A child psychiatrist visit following an emergency procedure may help to prevent further unintentional injuries to the child

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MMW Fortschr Med. 2015 May;157:22.
"THE DECISIVE FACTOR IS THE MOTIVATION OF THE CHILDREN".
Anon.

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NeuroImage. 2016;124:75-84.
WHITE MATTER ABNORMALITIES AND IMPAIRED ATTENTION ABILITIES IN CHILDREN BORN VERY PRETERM.
Murray AL, Thompson DK, Pascoe L, et al.
While attention impairments are commonly observed in very preterm (<. 32. weeks' gestational age) children, neuroanatomical correlates of these difficulties are unclear. We aimed to determine whether the microstructural organization of key white matter tracts thought to be involved in attention (cingulum bundle, superior longitudinal fasciculi, reticular activating system, and corpus callosum) were altered in very preterm children compared with term-born controls. We also aimed to determine whether alterations in microstructural organization of these tracts were associated with attention functioning in very preterm children. One hundred and forty-nine very preterm children and 36 term-born controls underwent neuroimaging and assessment of their attention abilities at 7. years. Constrained spherical deconvolution and probabilistic tractography was used to identify the key white matter tracts. Altered microstructural organization and reduced tract volume within reticular activating system and corpus callosum were found in the very preterm group compared with the control group. Diffusion and volume changes in the cingulum bundle, superior longitudinal fasciculi, reticular activating system, and corpus callosum were related to variations in attention functioning in the very preterm children. These findings emphasize that white matter tract integrity is associated with later attentional abilities in very preterm children

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NeuroImage Clin. 2015;7:222-29.
DISTINCT FRONTAL LOBE MORPHOLOGY IN GIRLS AND BOYS WITH ADHD.
Dirlikov B, Shiels RK, Crocetti D, et al.
OBJECTIVE: This study investigated whether frontal lobe cortical morphology differs for boys and girls with ADHD (ages 8-12 years) in comparison to typically developing (TD) peers.
METHOD: Participants included 226 children between the ages of 8-12 including 93 children with ADHD (29 girls) and 133 TD children (42 girls) for which 3T MPRAGE MRI scans were obtained. A fully automated frontal lobe atlas was used to generate functionally distinct frontal subdivisions, with surface area (SA) and cortical thickness (CT) assessed in each region. Analyses focused on overall diagnostic differences as well as examinations of the effect of diagnosis within boys and girls.
RESULTS: Girls, but not boys, with ADHD showed overall reductions in total prefrontal cortex (PFC) SA. Localization revealed that girls showed widely distributed reductions in the bilateral dorsolateral PFC, left inferior lateral PFC, right medial PFC, right orbitofrontal cortex, and left anterior cingulate; and boys showed reduced SA only in the right anterior cingulate and left medial PFC. In contrast, boys, but not girls, with ADHD showed overall reductions in total premotor cortex (PMC) SA. Further localization revealed that in boys, premotor reductions were observed in bilateral lateral PMC regions; and in girls reductions were observed in bilateral supplementary motor complex. In line with diagnostic group differences, PMC and PFC SAs were inversely correlated with symptom severity in both girls and boys with ADHD.
CONCLUSIONS: These results elucidate sex-based differences in cortical morphology of functional subdivisions of the frontal lobe and provide additional evidence of associations among SA and symptom severity in children with ADHD

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Neuropsychopharmacology. 2015 Jan;40:43-49.

CHILD PSYCHIATRY BRANCH OF THE NATIONAL INSTITUTE OF MENTAL HEALTH LONGITUDINAL STRUCTURAL MAGNETIC RESONANCE IMAGING STUDY OF HUMAN BRAIN DEVELOPMENT.

Giedd JN, Raznahan A, Alexander-Bloch A, et al.

The advent of magnetic resonance imaging, which safely allows in vivo quantification of anatomical and physiological features of the brain, has revolutionized pediatric neuroscience. Longitudinal studies are useful for the characterization of developmental trajectories (ie, changes in imaging measures by age). Developmental trajectories (as opposed to static measures) have proven to have greater power in discriminating healthy from clinical groups and in predicting cognitive/behavioral measures, such as IQ. Here we summarize results from an ongoing longitudinal pediatric neuroimaging study that has been conducted at the Child Psychiatry Branch of the National Institute of Mental Health since 1989. Developmental trajectories of structural MRI brain measures from healthy youth are compared and contrasted with trajectories in attention-deficit/hyperactivity disorder (ADHD) and childhood-onset schizophrenia. Across ages 5-25 years, in both healthy and clinical populations, white matter volumes increase and gray matter volumes follow an inverted U trajectory, with peak size occurring at different times in different regions. At a group level, differences related to psychopathology are seen for gray and white matter volumes, rates of change, and for interconnectedness among disparate brain regions

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No To Hattatsu. 2015;47:349-53.

EVALUATION OF QUALITY OF LIFE IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER CHILDREN WITHOUT COMORBIDITY.

Sano F, Kanemura H, Aoyagi K, et al.

Object: Improving quality of life (QOL) is one of the most important therapeutic goals for children with attention-deficit hyperactivity disorder (AD/HD). The aim of this study was to measure QOL in AD/HD children without comorbidity and to examine associations between QOL and clinical symptoms of AD/HD for targeting early intervention.

Methods: Twenty-two enrolled patients and their parents completed the Questionnaire for Measuring Health-Related Quality of Life in Children (KINDL-R). Patients and teachers completed AD/HD rating scale-IV. Associations between QOL and clinical symptoms were assessed using t tests and correlations.

Results: Mean total score of the self-reported KINDL-R was 70.8. No difference in total QOL score was seen between AD/HD children and controls; however, the self-esteem subscale rated by AD/HD children was significantly higher than that of controls ($p<0.001$). Total KINDL-R score correlated negatively with AD/HD rating scale-IV rated by teachers ($p<0.05$). A difference was observed between AD/HD children in a lower QOL group and their parents in a subscale regarding QOL at school.

Conclusions: These findings suggest that evaluation of QOL in AD/HD children without comorbidity is useful for identifying AD/HD children who might benefit from early intervention

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Nurs Child Young People. 2015 Mar;27:10-11.

QB TEST IMPROVES DIAGNOSIS OF ATTENTION DEFICIT DISORDER.

Cole E.

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Pediatr Nephrol. 2015;30:1607.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH EARLY STAGES OF CHRONIC KIDNEY DISEASE.

Yousefichaijan P, Salehi B, Sharafkhah M, et al.

Introduction: The aimof this study was to investigate ADHD in children with early stages of chronic kidney disease (CKD) and to compare it with healthy children.

Material and methods: Seventy five 5-16-year-old children with early stages of CKD (stage 1, 2 and 3) and 75 healthy children without CKD were included in this case - control study as case and control groups, respectively. The participants were selected fromthose children who were referred to the pediatric clinic of Amir Kabir Hospital of Arak (Iran) in the form of simple probability and based on inclusion and exclusion criteria. ADHD was diagnosed using Conners Parent Rating Scale - 48 (CPRS-48) and DSM-IV criteria and was confirmed by a psychologist consultant.
Results: ADHD inattentive type was observed in 8 cases (10.6%) with CKD and 2 controls (2.6%) (p= 0.109).Moreover, in the case and control groups, 7 (9.3%) and 6 (8%) children were affected by ADHD hyperactiveimpulsive type (p= 0.997), and 9 (12%) and 12 (16%) children were affected by ADHD mixed type (p= 0.664), respectively.
Conclusions: No differences were found between the prevalence of ADHD in the children with early stages of CKD and the control group. However, due to the importance of the relationships between different types of psychiatric disorders and CKD and lack of enough evidence concerning the relationship between ADHD and different stages of CKD in children, conducting further studies in this field is recommended

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Pediatr Nephrol. 2015;30:1587-88.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH PRIMARY MONOSYMPTOMATIC NOCTURNAL ENURESIS: A CASE-CONTROL STUDY.

Yousefichaijan P, Sharafkhah M, Rafeie M, et al.

Introduction: The aimof this study was to investigate ADHD in children with primary monosymptomatic nocturnal enuresis (PMNE) and compare it with healthy children.
Material and methods: 100, 5-16-year-old children with PMNE and 100 healthy children without NE were included in this case - control study as case and control groups, respectively. Subjects were selected from children who were referred to the pediatric clinic of Amir Kabir Hospital of Arak, Iran, in the form of simple probability and based on inclusion and exclusion criteria. ADHD was diagnosed by Conners Parent Rating Scale - 48 (CPRS-48) and DSM-IV-TR criteria and was confirmed by psychologist consult.
Results: ADHD inattentive type was observed in 16 cases (16%) with PMNE and 5 controls (5%) (P=0.01). Despite this significant differences, in the case and control groups, 25 (25%) and 16 (16%) children were affected by ADHD hyperactive-impulsive type (p = 0.08), and 15 (15%) and 16 (16%) children were affected by ADHD mixed type (p = 0.84), respectively.
Conclusions: ADHD inattentive type in children with PMNE is significantly more common than healthy children. The observed correlation between ADHD inattentive type and PMNE makes psychological counseling mandatory in children with PMNE

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Pediatr Nephrol. 2015;30:1654-55.

PREVALENCE OF HYPERTENSION AMONG CHILDREN WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER (ADHD).

Yue M, Hamiwka L, Samuel S, et al.

Introduction: Attention deficit/hyperactivity disorder (ADHD) is an increasingly common neurobehavioral childhood disorder that frequently continues into adulthood. Most affected children are treated with psycho-stimulant agents which are known to be associated with a modest but significant increase in blood pressure and heart rate, however the clinical significance of this adverse effect is considered negligible. Our objective was to define the prevalence of hypertension detectable at single office visits, combined with 24h ambulatory blood pressure monitoring (ABPM), in a sample of otherwise healthy children with ADHD, treated by community pediatricians with any medication indicated for ADHD. Material and methods: Three collaborating community pediatricians in Calgary, provided lists of all children in their care, with documented histories of ADHD. Candidate subjects from the compiled list were randomly contacted; children aged 5 - 18 years receiving ongoing treatment with any type of medication indicated for ADHD were eligible for inclusion. Consenting participants had a full medical history and physical examination, anthropomorphic measurements and initiation of 24h ABPM. The Sleep Disturbance Scale for Children (SDSC) questionnaire was also

applied. Results: One hundred and forty five of 240 potential candidates were contacted; 55 children completed the study (47 males), average age 11.6 (-¦ 2.5) years, average BMI z-score -0.37 (-¦1.22). Most children, (82%) were treated with various formulations of short or long acting stimulant agents. Office blood pressure was greater than the 95th percentile in 3 (5.5%) children and in an additional 4 (7.3%) - greater than the 90th percentile. All 7 children who had elevated office BPs, had entirely normal ABPM results suggesting white coat hypertension however 15 (27.3%) children were found to be non-dippers on ABPM tests;91% of all participants had SDSC scores suggestive of disturbed sleep. Conclusions: Prevalence of white coat hypertension may be higher among children with ADHD medicated for their condition, however true hypertension and prehypertension, based on current definitions, does not appear to be frequent in this population. Highly prevalent non-dipping on ABPMmay be related to common sleep disturbances in children treated with stimulant medications for ADHD

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Pediatrics. 2015;136:e830-e837.

TIMING OF THE DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER.

Miodovnik A, Harstad E, Sideridis G, et al.

BACKGROUND AND OBJECTIVE: Symptoms of inattention, hyperactivity, and impulsivity are core features of attention-deficit/hyperactivity disorder (ADHD). However, children with autism spectrum disorder (ASD) often present with similar symptoms and may receive a diagnosis of ADHD first. We investigated the relationship between the timing of ADHD diagnosis in children with ASD and the age at ASD diagnosis.

METHODS: Data were drawn from the 2011-C2012 National Survey of Children's Health, which asked parents to provide the age(s) at which their child received a diagnosis of ADHD and/or ASD. Using weighted prevalence estimates, we examined the association between a previous diagnosis of ADHD and the age at ASD diagnosis, while controlling for factors known to influence the timing of ASD diagnosis.

RESULTS: Our study consisted of 1496 children with a current diagnosis of ASD as reported by parents of children ages 2 to 17 years. Approximately 20% of these children had initially been diagnosed with ADHD. Children diagnosed with ADHD before ASD were diagnosed with ASD 3 years (95% confidence interval 2.3-C3.5) after children in whom ADHD was diagnosed at the same time or after ASD. The children with ADHD diagnosed first were nearly 30 times more likely to receive their ASD diagnosis after age 6 (95% confidence interval 11.2-C77.8). The delay in ASD diagnosis was consistent across childhood and independent of ASD severity.

CONCLUSION: To avoid potential delays in ASD diagnosis, clinicians should consider ASD in young children presenting with ADHD symptoms

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Pediatrics. 2015 Aug;136:351-59.

PEDIATRIC PSYCHOPHARMACOLOGY FOR TREATMENT OF ADHD, DEPRESSION, AND ANXIETY.

Southammakosane C, Schmitz K.

The pediatric practitioner is often the first point-of-contact for children and adolescents suffering from mental illness. Part of the treatment planning for psychiatric diagnoses includes consideration of medication. Attention-deficit/hyperactivity disorder, one of the most common diagnoses, is very responsive to stimulant medications; for children who are unable to tolerate stimulants or who do not achieve satisfactory symptom management, central alpha-agonists and atomoxetine are effective and generally well-tolerated alternative or augmentative agents. Depression and anxiety disorders are also frequently encountered in the pediatric office setting. The use of selective serotonin reuptake inhibitors is considered first-line psychopharmacology for depression and anxiety symptoms. Despite concerns for suicidal ideation related to this medication class, the benefits typically outweigh the risks. This review provides basic clinical pharmacology of stimulant and nonstimulant attention-deficit/hyperactivity disorder medications and selective serotonin reuptake inhibitors intended to serve as a primer for the general pediatrician

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Phys Occup Ther Pediatr. 2015 Feb;35:1-12.

ASSESSING SENSORY PROCESSING PROBLEMS IN CHILDREN WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Pfeiffer B, Daly BP, Nicholls EG, et al.

AIMS: This exploratory study investigated whether children with attention-deficit/hyperactivity disorder (ADHD) are at greater risk than children without ADHD for problems with sensory processing and if certain sensory systems are more closely associated with the core symptoms of ADHD, specifically inattention and hyperactivity/impulsivity.

METHODS: The sample included 20 children with ADHD and 27 children without ADHD, ages 5 to 10 years. Assessments included the Sensory Processing Measure-Home Form and the Conners 3rd edition-Parent Short Form.

RESULTS: After controlling for age, children with ADHD exhibited more sensory processing problems on all scales of the Sensory Processing Measure with small to medium effect sizes observed (eta(2) = .27 to .61). For children with ADHD, the Social Participation (r = .50) and Planning and Ideas (r = .73) subtests of the Sensory Processing Measure were significantly associated with hyperactivity/impulsivity, but not with inattention on the subtests of the Conners Parent Short Form.

CONCLUSION: The results suggest the importance of assessing sensory processing issues in children with ADHD to guide in the intervention process

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PLoS ONE. 2015 Sep;10.

A NEW APPROACH TO INVESTIGATE THE ASSOCIATION BETWEEN BRAIN FUNCTIONAL CONNECTIVITY AND DISEASE CHARACTERISTICS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: TOPOLOGICAL NEUROIMAGING DATA ANALYSIS.

Kyeong S, Park S, Cheon KA, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is currently diagnosed by a diagnostic interview, mainly based on subjective reports from parents or teachers. It is necessary to develop methods that rely on objectively measureable neurobiological data to assess brain-behavior relationship in patients with ADHD. We investigated the application of a topological data analysis tool, Mapper, to analyze the brain functional connectivity data from ADHD patients. Methods: To quantify the disease severity using the neuroimaging data, the decomposition of individual functional networks into normal and disease components by the healthy state model (HSM) was performed, and the magnitude of the disease component (MDC) was computed. Topological data analysis using Mapper was performed to distinguish children with ADHD (n = 196) from typically developing controls (TDC) (n = 214). Results: In the topological data analysis, the partial clustering results of patients with ADHD and normal subjects were shown in a chain-like graph. In the correlation analysis, the MDC showed a significant increase with lower intelligence scores in TDC. We also found that the rates of comorbidity in ADHD significantly increased when the deviation of the functional connectivity from HSM was large. In addition, a significant correlation between ADHD symptom severity and MDC was found in part of the dataset. Conclusions: The application of HSM and topological data analysis methods in assessing the brain functional connectivity seem to be promising tools to quantify ADHD symptom severity and to reveal the hidden relationship between clinical phenotypic variables and brain connectivity.

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Psychiatr Serv. 2015;66:1074-82.

STATE VARIATION IN INCREASED ADHD PREVALENCE: LINKS TO NCLB SCHOOL ACCOUNTABILITY AND STATE MEDICATION LAWS.

Fulton BD, Scheffler RM, Hinshaw SP.

Objective: The study's objective was to investigate whether attention-deficit hyperactivity disorder (ADHD) diagnoses from 2003 to 2011 were associated with either public school consequential accountability reforms initiated by the No Child Left Behind (NCLB) Act, particularly for low-income children, or with state psychotropic medication laws that prohibit public schools from recommending or requiring medication use.

Methods: Logistic regression difference-in-differences models were estimated with repeated U.S. and state-representative cross-sections of responses to the 2003, 2007, and 2011 National Survey of Children's Health. Each wave included approximately 35,000 public school children between ages six and 13.
Results: From 2003 to 2007, the change in adjusted diagnostic prevalence was 2.8 percentage points higher for children ages six to 13 in households with incomes #185% of the federal poverty level residing in states first exposed to consequential accountability through NCLB (from 8.5% to 13.2%), compared with demographically similar children residing in other states (from 10.2% to 12.1%). From 2003 to 2011, the change in adjusted diagnostic prevalence was 2.2 percentage points lower for children ages six to 13 residing in states with a psychotropic medication law (from 8.1% to 7.8%), compared with children residing in other states (from 8.1% to 10.1%).
Conclusions: NCLB-initiated consequential accountability reforms were associated with more ADHD diagnoses among low-income children, consistent with increased academic pressures from NCLB for this subgroup. In contrast, psychotropic medication laws were associated with fewer ADHD diagnoses, because they may indirectly reduce diagnoses via restrictions on recommending or requiring medication use. Future research should investigate whether children most affected by these policies are receiving appropriate diagnoses

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Psychiatry Clin Neurosci. 2015;69:658-59.
EFFECTIVENESS OF ORAL TIPEPIDINE ADMINISTRATION FOR CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A 4-WEEK, OPEN-LABEL CLINICAL STUDY.
Tomoda A, Takiguchi S, Fujisawa TX, et al.

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Psychiatry Res. 2015 Jan;225:191-96.
CHILD BEHAVIOUR CHECKLIST EMOTIONAL DYSREGULATION PROFILES IN YOUTH WITH DISRUPTIVE BEHAVIOUR DISORDERS: CLINICAL CORRELATES AND TREATMENT IMPLICATIONS.
Masi G, Muratori P, Manfredi A, et al.
Two Child Behaviour Checklist (CBCL) profiles were correlated to poor self-regulation, Deficient Emotional Self-Regulation (DESR) (elevation between 1 and 2 Standard Deviations (SD) in Anxiety/Depression, Aggression, Attention subscales), and Dysregulation Profile (DP) (elevation of 2 Standard Deviations or more). We explored youths with Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) whether these profiles are associated with specific clinical features. The sample included 57 patients with DESR profile and 41 with DP profile, ages 9 to 15 years, all assigned to a non-pharmacological Multimodal Treatment Program. No differences resulted between groups in demographic features, diagnosis ratio, and comorbidities with Attention Deficit Hyperactivity Disorder (ADHD), Bipolar Disorder (BD), and Anxiety Disorder. The DP group was associated with higher scores in Withdrawn, Social Problem, Thought, Rule Breaking, and Somatic CBCL subscales, and higher scores in Narcissism and Impulsivity (but not Callous-Unemotional (CU)), according to the Antisocial Process Screening Device (APSD). After treatment, patients with DESR improved their personality traits (Narcissistic and Callous-Unemotional, but not Impulsivity), while changes in CBCL scales were modest. Patients with DP improved scales of Attention, Aggression, Anxiety-Depression, Rule Breaking, Withdrawal, Social Problem and Thought, while personality features did not change. These results suggest diagnostic implications of CBCL profiles, and indications for targeted treatment strategies

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Psychiatry Res. 2015 Jan;231:77-86.

DECREASED AMYGDALA-INSULA RESTING STATE CONNECTIVITY IN BEHAVIORALLY AND EMOTIONALLY DYSREGULATED YOUTH.

Bebko G, Bertocci M, Chase H, et al.

The Research Domain Criteria (RDoC) adopts a dimensional approach for examining pathophysiological processes underlying categorically defined psychiatric diagnoses. We used this framework to examine relationships among symptom dimensions, diagnostic categories, and resting state connectivity in behaviorally and emotionally dysregulated youth selected from the Longitudinal Assessment of Manic Symptoms study (n=42) and healthy control youth (n=18). Region of interest analyses examined relationships among resting state connectivity, symptom dimensions (behavioral and emotional dysregulation measured with the Parent General Behavior Inventory-10 Item Mania Scale [PGBI-10M]; dimensional severity measures of mania, depression, anxiety), and diagnostic categories (Bipolar Spectrum Disorders, Attention Deficit Hyperactivity Disorder, Anxiety Disorders, and Disruptive Behavior Disorders). After adjusting for demographic variables, two dimensional measures showed significant inverse relationships with resting state connectivity, regardless of diagnosis: 1) PGBI-10M with amygdala-left posterior insula/bilateral putamen; and 2) depressive symptoms with amygdala-right posterior insula connectivity. Diagnostic categories showed no significant relationships with resting state connectivity. Resting state connectivity between amygdala and posterior insula decreased with increasing severity of behavioral and emotional dysregulation and depression; this suggests an intrinsic functional uncoupling of key neural regions supporting emotion processing and regulation. These findings support the RDoC dimensional approach for characterizing pathophysiologic processes that cut across different psychiatric disorders

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Psychiatry Res Neuroimaging. 2015.

ANTISACCADE-RELATED BRAIN ACTIVATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER - A PILOT STUDY.

Schwarz NF, Krafft CE, Chi L, et al.

While antisaccade paradigms invoke circuitry associated with cognitive control and attention-deficit/hyperactivity disorder (ADHD), there is a dearth of functional magnetic resonance imaging (fMRI) investigations using antisaccade tasks among children with ADHD. Neural correlates associated with antisaccade performance were examined with fMRI in 11 children with ADHD (10 medicated) matched to 11 typically developing children. Significantly greater brain activation in regions in right dorsolateral prefrontal cortex and caudate nucleus was observed in children with ADHD relative to the control group. This pattern separated the children into their respective groups in a taxonomic manner. Sensitivity analyses probing comorbidity and medication-specific effects showed that results were consistent; however, the caudate nucleus difference was only detectable in the full sample, or in subsets with a more relaxed cluster threshold. Antisaccade performance did not significantly differ between the groups, perhaps as a result of greater brain activation or medication effects in the ADHD group. Thus, antisaccade paradigms may have sensitivity and specificity for the investigation of cognitive control deficits and associated neural correlates in ADHD, and may contribute towards the development of new treatment approaches for children with the disorder

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Psychiatry Res. 2015 Oct;229:750-54.

ABNORMAL BRAINSTEM AUDITORY RESPONSE IN YOUNG FEMALES WITH ADHD.

Claesdotter-Hybbinette E, Safdarzadeh-Haghighi M, Råstam M, et al.

Studies have shown that the auditory brainstem response (ABR) is often affected in neurodevelopmental disorders. The aim of this study is to investigate possible differences in ABR between young females with ADHD compared to control subjects. This study focuses on young females, age 7–17 with ADHD, comparing the ABR of 43 young females with ADHD to 21 age- and gender-matched control subjects. Young females with ADHD have a significantly different ABR in a region between cochlear nucleus and superior olivary complex as well as in the thalamic region compared to control subjects. These data indicate specific

differences in ABR between girls with ADHD compared to female controls. (PsycINFO Database Record (c) 2015 APA, all rights reserved). (journal abstract)

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Psychiatry Res. 2015 Sep;229:310-17.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND OXIDATIVE STRESS: A SHORT TERM FOLLOW UP STUDY.

Guney E, Cetin FH, Alisik M, et al.

In this study, we aimed to investigate total antioxidative status (TAS) and total oxidative status (TOS) of plasma and antioxidant enzymes such as paraoxonase (PON), stimulated paraoxonase (SPON), arylesterase (ARES) and thiols in plasma of children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD). In the second step. this study aimed to reveal the possible effects of ADHD treatment on these parameters. Fifty-six patients with ADHD and 52 healthy controls were involved in this study. Venous blood samples were collected and oxidative and antioxidative parameter's were studied. In the second phase of the study, blood samples were taken from patients using medication. Pre-treatment oxidative stress index (OSI) values and the plasma TOS levels of the patients with ADHD were statistically higher than those of the control group. The plasma thiol levels of the patients with ADHD were significantly lower than the control group. The post-treatment plasma antioxidative parameter's levels were significantly higher than the pre-treatment levels. The post-treatment oxidative stress index value was significantly lower than the pre-treatment value. Therefore, oxidative metabolism was found to be impaired in children and adolescents with ADHD. It was also determined that methylphenidate repairs the oxidative balance by increasing antioxidant defence mechanisms.

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Psychol Rep. 2015 Jun;116:710-22.

MATERNAL RATINGS OF BULLYING AND VICTIMIZATION: DIFFERENCES IN FREQUENCIES BETWEEN PSYCHIATRIC DIAGNOSIS IN A LARGE SAMPLE OF CHILDREN.

Mayes SD, Calhoun SL, Baweja R, et al.

Little is known about psychiatric diagnoses that place children at risk for bullying and victimization. Mothers of 1,707 children 6-18 yr. rated their child as a bully and a victim (not at all, to very often a problem) on the Pediatric Behavior Scale. Children with psychiatric diagnoses were evaluated in an outpatient psychiatry clinic (M age = 9.2 yr., 68.4% male). Control children were community children not on psychotropic medication and with no neurodevelopmental disorder (M age = 8.7 yr., 43.5% male). Children with autism, intellectual disability, and ADHD-Combined type had higher victim and bully maternal ratings than children in the ADHD-Inattentive, depression, anxiety, eating disorder, and control groups. Eating disorder and controls were the only groups in which most children were not rated a victim or a bully. Comorbid oppositional defiant disorder accounted for the higher bully ratings for ADHD-Combined, autism, and intellectual disability. Victimization ratings did not differ between psychiatric groups. Except for eating disorders, victimization ratings were greater in all groups than in control children, suggesting that most psychiatric disorders place children at risk for victimization, as perceived by their mothers

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Psychol Addict Behav. 2015.

CHANGE OVER TIME IN ADOLESCENT AND FRIEND ALCOHOL USE: DIFFERENTIAL ASSOCIATIONS FOR YOUTH WITH AND WITHOUT CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) .

Belendiuk KA, Pedersen SL, King KM, et al.

Individuals with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for experiencing alcohol-related problems by adulthood. However, few studies have examined contextual factors that may contribute to this risk. The current study examined 1 widely investigated social-contextual risk factor, friend alcohol use, in a sample of adolescents with and without a history of ADHD. One hundred and 59 adolescents (14-17 years old) with childhood ADHD and 117 demographically similar youth without ADHD were interviewed

annually in the Pittsburgh ADHD Longitudinal Study. Adolescents reported the frequency of their own alcohol use in the prior 12 months and the number of friends who used alcohol regularly or occasionally (perceived friend alcohol use). Multiple-group parallel process models indicated that increases in friend alcohol use were more strongly associated with increases in adolescent alcohol use over time for individuals with ADHD (r = .15, SE = 0.04; 95% confidence interval [CI] = [0.08, 0.22]) than for those without ADHD (r = .06, SE = 0.03; 95% CI [0.00, 0.11]). These results suggest that social factors are an important part of escalating alcohol use among adolescents with ADHD histories, and they highlight the possibility that interventions focused on the peer context could be important for these at-risk youth. Additional social network research on adolescent alcohol use within the larger context of other relationships (e.g., family and romantic relationships) is indicated.

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Psychosomatics: Journal of Consultation and Liaison Psychiatry. 2015 Sep;56:495-503.

CLINICAL AND SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PATIENTS WITH CYSTIC FIBROSIS.

Eworuke E, Zeng QYL, Winterstein AG.

Background: There is scarce evidence on the epidemiology of attention-deficit/hyperactivity disorder (ADHD) in patients with cystic fibrosis (CF).
Objective: We employed stepwise logistic regression to examine the association between ADHD diagnosis and selected patient characteristics.
Methods: This was a cross-sectional analysis of inpatient and outpatient billing data for Medicaid beneficiaries with CF ages 3–18 years to obtain ADHD diagnosis prevalence and incidence estimates from 1999–2006.
Results: Annual ADHD prevalence increased 1.55-fold from 5.26% (95% CI: 5.25–5.27) to 8.16% (8.15–8.17), and annual ADHD incidence rose slightly from 1.70% (1.70–1.71) to 2.01% (2.00–2.01). As in the general population, males were significantly more likely to have a diagnosis of ADHD compared with females (odds ratio: 1.97 [CI: 1.49–2.60]), as were children with recent diagnoses of anxiety, emotional disorder, depression, adjustment disorder, and learning, motor, and communication disorders. Patients with ADHD diagnoses were also more likely to be in foster care (odds ratio = 4.36 [CI: 2.26–8.40]). Except for recent DNase use (odds ratio = 0.64 [CI: 0.43–0.93]), CF severity indicators and medications including pancreatic enzymes, inhaled tobramycin, inhaled or oral corticosteroids, inhaled bronchodilators, and oral antibiotics had no association with ADHD diagnosis.
Conclusion: ADHD prevalence in CF increased during the study period. Clinical and sociodemographic determinants of ADHD diagnosis were similar to the general population, whereas treatment and severity of CF appeared to have little influence. Our findings warrant future research evaluating diagnostic protocols and assessment of safety and efficacy of ADHD treatment in children with CF.

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Q J Exp Psychol (Hove). 2015;68:83-98.

IMPAIRMENT OF GAZE-DIRECTED SPATIAL CODING IN RECENT-ONSET SCHIZOPHRENIA.

Roder CH, Dieleman S, Mohr H, et al.

Patients with schizophrenia show deficits in core cognitive functions as well as in social cognition. The aim of the present study was to test whether deficits in social cognition influence nonsocial, "cold", cognition. Thirty-five patients with recent-onset schizophrenia (SC) and 30 healthy controls (HC) performed a Simon task with social and simple geometric stimuli. We investigated whether the Simon effect, the slowing of reaction times produced by stimulus incongruities in the task-irrelevant spatial domain, differs between patients and healthy participants as a function of the social nature of the cues. The Simon effect was generated by a schematic drawing of human eyes (social cues) or rectangles (nonsocial cues). Overall, patients had longer reaction times than HC. In the eye-like condition, the Simon effect was significantly stronger for HC than for SC. In HC the Simon effect was significantly stronger in the eye-like than in the rectangle condition. In patients, the Simon effect did not differ significantly between both conditions. Thus,

the influence of social cues was greatly reduced in the patient group. Current psychopathology or antipsychotic treatment did not influence results. The present study supports earlier findings of altered processing of schematic social cues in patients with schizophrenia, especially when gaze is task-irrelevant

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Q J Exp Psychol (Hove). 2015;68:99-128.

ENCODING ORDER AND DEVELOPMENTAL DYSLEXIA: A FAMILY OF SKILLS PREDICTING DIFFERENT ORTHOGRAPHIC COMPONENTS.

Romani C, Tsouknida E, Olson A.

We investigated order encoding in developmental dyslexia using a task that presented nonalphanumeric visual characters either simultaneously or sequentially--to tap spatial and temporal order encoding, respectively--and asked participants to reproduce their order. Dyslexic participants performed poorly in the sequential condition, but normally in the simultaneous condition, except for positions most susceptible to interference. These results are novel in demonstrating a selective difficulty with temporal order encoding in a dyslexic group. We also tested the associations between our order reconstruction tasks and: (a) lexical learning and phonological tasks; and (b) different reading and spelling tasks. Correlations were extensive when the whole group of participants was considered together. When dyslexics and controls were considered separately, different patterns of association emerged between orthographic tasks on the one side and tasks tapping order encoding, phonological processing, and written learning on the other. These results indicate that different skills support different aspects of orthographic processing and are impaired to different degrees in individuals with dyslexia. Therefore, developmental dyslexia is not caused by a single impairment, but by a family of deficits loosely related to difficulties with order. Understanding the contribution of these different deficits will be crucial to deepen our understanding of this disorder

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Res Dev Disabil. 2015 Feb;37:17-30.

COMPARING THE EXECUTIVE ATTENTION OF ADULT FEMALES WITH ADHD TO THAT OF FEMALES WITH SENSORY MODULATION DISORDER (SMD) UNDER AVERSIVE AND NON-AVERSIVE AUDITORY CONDITIONS.

Mazor-Karsenty T, Parush S, Bonneh Y, et al.

Certain behavioral expressions of sensory modulation disorder (SMD) such as distractibility, hyperactivity, and impulsivity are often similar to those of attention deficit/hyperactivity disorder (ADHD) in pediatric and adult populations. There is also a high comorbidity rate between these two diagnoses and absence of research regarding the objective neuropsychological differentiation between them. In the present study we employed a factorial design which enabled us to: (a) systematically examine the effects of SMD and ADHD on executive attention in a sample of adult females using a Stroop-like task, and (b) measure the effect of aversive conditions (sounds) on executive attention. The experimental measures used were the Stroop-like Location-Direction Task (SLDT) to assess executive attention and the battery of aversiveness to sounds (BAS), a standardized measure of aversive sounds that was developed for this study and enabled individual customization of aversive auditory sounds. Results revealed, as expected, a specific core deficit in executive attention for the ADHD factor. In addition to that, the present study provides an important, pioneering finding of SMD impairment in a unique combination of a cognitively demanding task with aversive sounds, providing preliminary objective evidence differentiating SMD from ADHD

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Res Dev Disabil. 2015;47:175-84.

AUTISM SPECTRUM DISORDER SYMPTOMS IN CHILDREN WITH ADHD: A COMMUNITY-BASED STUDY .

Green JL, Rinehart N, Anderson V, et al.

This study examined the prevalence of autism spectrum disorder (ASD) symptoms in a community-based sample of children with attention-deficit/hyperactivity disorder (ADHD) and non-ADHD controls. We also examined the relationship between ASD symptoms and ADHD subtype, ADHD symptom severity and child

gender. Participants were 6-10-year-old children (164 ADHD; 198 non-ADHD control) attending 43 schools in Melbourne, Australia, who were participating in the Children's Attention Project. ADHD was assessed in two stages using the parent and teacher Conners' 3 ADHD index and the Diagnostic Interview Schedule for Children IV (DISC-IV). ASD symptoms were identified using the Social Communication Questionnaire (SCQ). Unadjusted and adjusted linear and logistic regression examined continuous and categorical outcomes, respectively. Children with ADHD had more ASD symptoms than non-ADHD controls (adjusted mean difference = 4.0, 95% confidence interval (CI) 2.8; 5.3, p< 0.001, effect size = 0.7). Boys with ADHD had greater ASD symptom severity than girls with ADHD (adjusted mean difference = 2.9, 95% CI 0.8; 5.2, p = 0.01, effect size = 0.4). Greater ADHD symptom severity was associated with greater ASD symptom severity (regression co-efficient = 1.6, 95% CI 1.2; 2.0, p< 0.001). No differences were observed by ADHD subtype. Greater hyperactive/impulsive symptoms were associated with greater ASD symptoms (regression coefficient = 1.0; 95% CI 0.0; 2.0, p = 0.04) however, this finding attenuated in adjusted analyses (p = 0.45). ASD symptoms are common in children with ADHD. It is important for clinicians to assess for ASD symptoms to ensure appropriate intervention

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Res Dev Disabil. 2015;47:199-207.

"TURNING DOWN THE HEAT": IS POOR PERFORMANCE OF CHILDREN WITH ADHD ON TASKS TAPPING "HOT" EMOTIONAL REGULATION CAUSED BY DEFICITS IN "COOL" EXECUTIVE FUNCTIONS?

Van C, V, Sonuga-Barke EJS, Hoppenbrouwers K, et al.

Emotional dysregulation in daily life is very common in children with attention deficit hyperactivity disorder (ADHD). It is however not clear whether this reflects a specific deficit or that it may be the result of generic executive function (EF) deficits. The current study addresses this question by means of an emotional working memory (WM) task with 2 memory load conditions and four possible backgrounds (blank screen, neutral, positive or negative picture), which was administered to 38 typically developing children and 29 children with ADHD. Children responded slower on trials when negative pictures were presented at the background versus when neutral pictures were presented, indicating an emotional interference effect; however crucially, groups did not differ in this respect. Reaction times were also slower on trials with a neutral picture as background versus trials without a picture, with children with ADHD showing an enhanced interference effect. There was a main effect of WM load on performance, but it did not interact with interference or group effects. To summarize, the findings indicate a generic interference control deficit in the children with ADHD in the current sample, while they could not provide support for an emotional interference deficit

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Rev Neurol. 2015;61:289-94.

INFLUENCE OF THE MONTH OF BIRTH ON THE DEMAND FOR HEALTHCARE TO TREAT ATTENTION DEFICIT HYPERACTIVITY DISORDER. RESULTS OF A RETROSPECTIVE STUDY CONDUCTED IN A NEUROPAEDIATRIC CLINIC.

Rivas-Juesas C, Gonz+ílez de DJ, Benac-Prefaci M, et al.

INTRODUCTION: There is an increase in the child neurology attention and, specially in attention deficit hyperactivity disorder (ADHD). It's been proposed that the birth date affects the diagnosis of ADHD, so the youngest children more susceptible of being diagnosed.

AIMS: To analyse if there is a relationship between the birth date and the suspicion of ADHD, and to investigate the health demand of child neurology and its evolution regarding diagnostic categories.

PATIENTS AND METHODS: Retrospective study of patients been attended in a child neurology clinic between 1992 and 2012. Different diagnostic groups were compared considering epidemiologic variables and trimester and semester of birth to determine whether exists a seasonal pattern.

RESULTS: 3469 patients were included, 58.5% were male with a median age of 6 years old. The first reason of consultation was the headache, and the ADHD has experienced an increase of 350% in the last 10 years of the study. 61.6% of patients with ADHD suspicion were born in the second semester of the year. The difference was higher for girls. This pattern was not observed in other neurologic diseases when a comparative analysis was done.

CONCLUSIONS: There is an increase of child neurologic demand within the last years, mainly of ADHD patients. Children born in the last semester of the year have a higher risk of being sent to a neurology clinic for evaluation.

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Schizophr Res. 2015;168:161-67.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, METHYLPHENIDATE USE AND THE RISK OF DEVELOPING SCHIZOPHRENIA SPECTRUM DISORDERS: A NATIONWIDE POPULATION-BASED STUDY IN TAIWAN.

Shyu Y-C, Yuan S-S, Lee S-Y, et al.

This study estimated the risk of developing psychotic disorders by comparing children with ADHD to non-ADHD controls, and to examine whether methylphenidate (MPH) treatment influences the risks of psychotic disorders. A nationwide cohort of patients who were newly diagnosed with ADHD (n= 73,049) and age- and gender-matched controls (n= 73,049) were selected from Taiwan's National Health Insurance database from January 2000 to December 2011. All participants were observed until December 31, 2011. Cox regression models were used to estimate the effects of ADHD diagnosis and MPH use on subsequent outcomes. Having a diagnosis of any psychotic disorder and of schizophrenia were set as two different outcomes and were analyzed separately. Compared to the control group, the ADHD group showed significantly increased risk of developing any psychotic disorder (adjusted hazard ratio [aHR], 5.20; 95% confidence interval [CI], 4.30-6.30) and schizophrenia (aHR, 4.65; 95% CI, 3.59-6.04). Compared to ADHD patients without psychosis, patients with ADHD who developed psychosis had significantly older age at first diagnosis of ADHD (9.4. -¦. 3.3. years vs. 10.6. -¦. 4.0. years). Among patients with ADHD, MPH use significantly increased the risk of developing any psychotic disorder (aHR, 1.20; 95% CI, 1.04-1.40), but did not increase the risk of developing schizophrenia (aHR, 1.16; 95% CI, 0.94-1.42). The results indicated that previous diagnoses of ADHD are a powerful indicator of developing psychotic disorders. Nevertheless, the specific mechanisms of the relationships between ADHD, MPH use and psychotic disorders need further elucidation in future clinical studies

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Seizure. 2015 Feb;25:117-25.

ENCEPHALOPATHY WITH STATUS EPILEPTICUS DURING SLEEP: UNUSUAL EEG PATTERNS.

Caraballo RH, Fortini S, Flesler S, et al.

PURPOSE: To retrospectively analyze the electroclinical characteristics, etiology, treatment, and prognosis of patients with epileptic encephalopathy with status epilepticus during sleep (ESES) with unusual EEG features and to corroborate if this series of patients is part of the ESES syndrome.

METHOD: Charts of 17 patients with typical clinical manifestations of the ESES syndrome with focal ESES of non-REM sleep at onset and during the focal ESES phase, or bilateral synchronic and asynchronic ESES with a symmetric or asymmetric morphology, continuous or subcontinuous and sometimes multifocal paroxysms with or without slow-wave activity during slow sleep seen between 2000 and 2012 were analyzed.

RESULTS: Mean patient follow-up from onset was 7.5 years. An idiopathic cause was found in seven patients, a structural cause in eight, and etiology was unknown in the remaining two. The median age at onset of the unusual ESES syndrome was 7 years. During the ESES phase, 15 children developed new seizure types, negative myoclonus was observed in seven patients, positive myoclonus in five, and absences in nine. Six patients had motor impairment, two had auditory verbal agnosia, and two had motor speech impairment. Attention deficit hyperactivity disorder was observed in four, aggressiveness in six, memory deficit in two, and impaired temporospatial orientation in four. The patients with focal ESES in the frontal region showed behavioral disturbances and/or motor deterioration, and in those with temporo-occipital involvement the dominant clinical manifestations were language and/or behavioral disturbances.

CONCLUSION: Our patients with typical clinical manifestations of ESES syndrome but with unusual EEG patterns may be variants of this syndrome

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Seizure. 2015 Feb;25:95-98.

CO-MORBIDITIES AND OUTCOME OF CHILDHOOD PSYCHOGENIC NON-EPILEPTIC SEIZURES--AN OBSERVATIONAL STUDY.

Rawat VS, Dhiman V, Sinha S, et al .

PURPOSE: To assess the psychiatric diagnoses and outcome in children with psychogenic non-epileptic seizures (PNES).

METHODOLOGY: This hospital based observational study was performed on 44 children aged <16 years, who suspected to have psychogenic non-epileptic seizures based on video-EEG, from August 2005 to August 2012. The parameters noted were the psychiatric diagnosis, co-morbidities, management assessment and interventions (pharmacological and psychosocial), number and duration of follow-up visits, symptoms at follow-up, functioning as reflected by involvement in the social and scholastic work.

RESULTS: All forty four children completed the evaluation. Thirty four children were diagnosed as having PNES and the underlying psychiatric diagnosis was conversion disorder (n=34, 77.3%). Co-morbid psychiatric disorders were present in 17 children (50%). The common co-morbidities were intellectual disability (n=8, 23.5%), specific learning disorder (n=5, 14.7%), and depression (n=5, 14.7%). Co-morbid epilepsy was present in 8 (23.5%) children and family history of epilepsy was present in 10 (29.4%) cases. About 17 of 34 (50.0%) patients had a minimum follow-up of 6 months (13.9 +/- 4.8 months). Twenty six children (76.5%) remained symptom free at the follow-up of 9.8 +/- 7 months. The remaining 10 children (22.7%) had non-epileptic seizures with underlying diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), gratification disorder and other physiological conditions.

CONCLUSIONS: Conversion disorder is a common diagnosis underlying psychogenic non-epileptic seizures. Outcome was good in 76.5% children with PNES. A multidisciplinary approach is needed in the diagnosis and management of PNES

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Sleep Med. 2015;16:1192-97.

ASSOCIATION BETWEEN SLEEP AND WORKING MEMORY IN CHILDREN WITH ADHD: A CROSS-SECTIONAL STUDY.

Sciberras E, DePetro A, Mensah F, et al.

Objective/Background: This study aimed to examine the relationship between sleep problems and working memory in children aged 5-13 years with attention-deficit/hyperactivity disorder (ADHD).

Patients/Methods: Children with ADHD were recruited into a randomized controlled trial from 21 paediatric practices in VIC, Australia. Cross-sectional data for intervention and control children were pooled at 6 months post randomization for the current analyses (n=189). Children who met the Diagnostic Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for ADHD and had a parent-reported moderate/severe sleep problem that fulfilled diagnostic criteria for a behavioural sleep disorder were recruited into the study. Sleep was assessed by detailed parent (Children's Sleep Habits Questionnaire) and self-reports (Self-Sleep Report). Working memory was measured using the Working Memory Test Battery for Children (low and very low working memory defined as <25th and <10th percentiles, respectively). Analyses were adjusted for child age and gender, internalizing and externalizing comorbidities, and socio-economic status.

Results: Self-reported sleep problem severity was associated with poorer working memory; for each standard deviation increase in self-reported sleep problems, working memory scores decreased by -3.8 points (95% confidence interval (CI): 6.7, -0.8; p=0.01). , was some evidence that self-reported sleep problems were associated with low (p=0.06) and very low working memory (p=0.01). There was minimal evidence that parent-reported sleep problems were associated with poorer working memory with the exception of bedtime resistance problems.

Conclusions: Behavioural sleep problems and working memory are associated in children with ADHD, particularly when sleep is assessed by self-report

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Sleep Med. 2015;16:1377-80.

COMPARING SUBJECTIVE MEASURES OF BEHAVIORAL SLEEP PROBLEMS IN CHILDREN WITH ADHD: A CROSS-SECTIONAL STUDY.

Lycett K, Mensah FK, Hiscock H, et al.

Aim: Behavioral sleep problems are ideally measured using a combination of objective and subjective measures. However, this is not always feasible. Thus, a global subjective measure has been used to assess sleep problems in children with attention deficit hyperactivity disorder (ADHD), yet it is unclear how this relates to more detailed multidimensional measures of sleep problems. In children with ADHD, parent report of a global measure of sleep problem severity (classified no/mild versus moderate/severe) is compared with the following: (1) a 7-Day Sleep Log and (2) the validated Children's Sleep Habits Questionnaire (CSHQ).
Method: This study recruited 392 children with ADHD (aged 5-13 years) from 50 pediatric practices across Victoria, Australia. All caregivers completed the CSHQ, and 257 children prospectively completed the 7-Day Sleep Logs.
Results: Sleep log data identified distinct sleep patterns according to parent-reported sleep problem severity; children with moderate/severe sleep problems slept 30 min less per day, took longer to fall asleep, and experienced more night awakenings. This pattern was also repeated across the CSHQ, where children with moderate/severe sleep problems experienced more problematic sleep symptoms across all domains (effect sizes: 0.5-1.1; all $p < 0.001$).
Conclusion: A subjective, global measure of sleep problem severity appears to be a useful tool for the initial assessment of sleep problems in children with ADHD when more extensive measures are not feasible, as it is reflective of well-established multidimensional measures. However, further research is required to determine its validity

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Soc Neurosci. 2015;10:70-88.

AUTISTIC TRAITS INFLUENCE GAZE-ORIENTED ATTENTION TO HAPPY BUT NOT FEARFUL FACES.

Lassalle A, Itier RJ.

The relationship between autistic traits and gaze-oriented attention to fearful and happy faces was investigated at the behavioral and neuronal levels. Upright and inverted dynamic face stimuli were used in a gaze-cueing paradigm while event related potentials (ERPs) were recorded. Participants responded faster to gazed-at than to non-gazed-at targets, and this gaze orienting effect (GOE) diminished with inversion, suggesting it relies on facial configuration. It was also larger for fearful than happy faces but only in participants with high autism-spectrum quotient (AQ) scores. While the GOE to fearful faces was of similar magnitude regardless of AQ scores, a diminished GOE to happy faces was found in participants with high AQ scores. At the ERP level, a congruency effect on target-elicited P1 component reflected enhanced visual processing of gazed-at targets. In addition, cue-triggered early directing attention negativity and anterior directing attention negativity reflected, respectively, attention orienting and attention holding at gazed-at locations. These neural markers of spatial attention orienting were not modulated by emotion and were not found in participants with high AQ scores. Together, these findings suggest that autistic traits influence attention orienting to gaze and its modulation by social emotions such as happiness

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Soc Psychiatry Psychiatr Epidemiol. 2015 Mar;50:397-406.

ESTIMATING THE BURDEN OF PSYCHIATRIC DISORDERS IN ADOLESCENCE: THE IMPACT OF SUBTHRESHOLD DISORDERS.

Roberts RE, Fisher PW, Turner JB, et al.

PURPOSE: We examine the impact of including subthreshold disorders on estimating psychiatric morbidity burden in adolescents. To more fully understand this burden it is important to focus on both full syndrome and subthreshold disorders and the impairment associated with each, since evidence suggests prevalence of subthreshold disorders is substantial as is impairment.

METHODS: Data were analyzed from a probability sample of 4,175 youths 11-17 years of age. We examine the prevalence of DSM-IV disorders (FS) and subthreshold (SUB) disorders, with and without impairment. Diagnostic categories examined were anxiety, mood, attention deficit hyperactivity disorder, disruptive, and substance use disorders in the past year.
RESULTS: The prevalence of any FS disorders was 16.1 and 42.3 % for SUB. The combined prevalence was 58.4 %. By requiring impairment, the prevalence of any FS in the past year dropped to 8 % and for SUB to 15.7 %, with a combined overall rate of 23.7 %. For FS disorders, 49.6 % met criteria for moderate to severe impairment, compared to 37.8 % for SUB. One in four adolescents had either an FS or SUB disorder with impairment.
CONCLUSION: The results indicate that SUB disorders constitute a major public health burden in terms of psychiatric morbidity among adolescents. Given their substantial impairment and their high prevalence, consideration should be given to including SUB disorders in estimates of the public health burden psychiatric morbidity. Doing so would provide a more accurate estimate of psychiatric morbidity

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Subst Use Misuse. 2015 Jan;50:257-67.

A GENDER-SPECIFIC ANALYSIS OF ADOLESCENT DIETARY CAFFEINE, ALCOHOL CONSUMPTION, ANGER, AND VIOLENT BEHAVIOR.

James JE, Kristjansson AL, Sigfusdottir ID.

Self-reported dietary caffeine and alcohol consumption were examined in relation to anger and violent behavior in Icelandic tenth-graders. Structural equation modeling (SEM) was used to investigate direct and indirect effects of measured and latent variables in the population sample of 3,670, controlling for parental financial standing, family structure, ADHD, and peer delinquency. Gender differences were observed that have not been reported previously, especially in relation to anger as a possible mediator of violent behavior against a background of caffeine and alcohol consumption. Study findings suggest the need to take account of caffeine consumption in relation to adolescent anger and violence

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Tijdschr Psychiatr. 2015;57:508-16.

EFFICACY OF FREQUENCY-NEUROFEEDBACK AND COGMED JM-WORKING MEMORY TRAINING IN CHILDREN WITH ADHD.

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

BACKGROUND: The need for and the interest in non-pharmacological treatments for children with ADHD are increasing. The treatments include electro-encephalogram (EEG) frequency-neurofeedback and Cogmed working memory training. AIM: To investigate the efficacy of frequency-neurofeedback and Cogmed working memory training in children with ADHD.
METHOD: Forty-one children with ADHD (aged 8-15 years) were assigned to frequency-neurofeedback or to placebo-neurofeedback in a randomized double-blind trial. We took measurements to find out whether frequency-neurofeedback had reduced the severity of the ADHD-symptoms, and/or had improved neurocognitive ability and global clinical functioning. Fifty-one children with ADHD (aged 5-7 years) were assigned to the active Cogmed JM-working memory training or to the placebo working memory training in a randomised double-blind trial. We took measurements to find out whether Cogmed JM-working memory training had reduced the ADHD symptoms, and/or had improved neurocognitive ability, daily performance and global clinical functioning.
RESULTS: The ADHD symptoms and global clinical functioning of the children in both neurofeedback groups improved. However, frequency-neurofeedback did nor produce any significantly better treatment results than did the placebo neurofeedback. At the neurocognitive level, frequency-neurofeedback did not yield any measurements that were significantly superior to those achieved with placebo feedback. Various outcome measurements improved in both groups with memory training. However, the active working memory training was not found to have produced significantly better results than the placebo training with regards to the

ADHD symptoms, neurocognitive ability and daily and global functioning. Children from the active working memory training group showed improvements in trained working memory tasks but not on untrained tasks.
CONCLUSION: Neither study produced any conclusive evidence for the efficacy of the investigated treatments in children with ADHD. However, both types of treatments can be further improved. Furthermore, the controlled designs may have restricted the embedding of the treatments. Because of possible improvements in the treatments in the future and because of the design restrictions affecting the treatments in their present form, it is still too early to draw any definitive conclusions about the validity and advantages of the two treatment methods

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Trials. 2015;16.

PHYSICAL ACTIVITY INTERVENTION (MOVI-KIDS) ON IMPROVING ACADEMIC ACHIEVEMENT AND ADIPOSITY IN PRESCHOOLERS WITH OR WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Sánchez-López M, Pardo-Guijarro MJ, Del Campo DG, et al.

Background: The prevention of obesity and improvement of academic achievement in children are concerns of industrialized societies. Obesity has been associated with psychological disorders, including attention deficit hyperactivity disorder, whose prevalence has been estimated at 6.8 % in Spanish children and adolescents. It is known that physical activity is positively related to academic achievement and negatively related to the risk of obesity in children. However, studies to test the effectiveness of physical activity interventions in improving academic achievement in preschool children are scarce and have some weaknesses that threaten their validity. Moreover, very few studies have examined their effectiveness in improving symptoms of attention deficit hyperactivity disorder. This paper outlines a two-year multidimensional preschool intervention (Movi-Kids) aimed at preventing obesity and improving academic achievement in children with or without attention deficit hyperactivity disorder.
Methods/Design: Twenty-one schools from Ciudad Real and Cuenca, Spain, were randomized to intervention and control groups. In the first academic year, children in the third grade of preschool and the first grade of primary school in the intervention group received the Movi-Kids intervention. In the second academic year, schools were crossed over to the other group. The intervention included children, parents and teachers, and the school environment, and consisted of: (i) three hour-long sessions of recreational non-competitive physical activity after school, weekly, (ii) educational materials for parents and teachers addressing sedentary lifestyle risks and (iii) playground modifications to promote physical activity during breaks. Primary outcome measures of this study were academic achievement (intelligence, cognition, memory, attention and perception), assessed by the Battery of General and Differential Aptitudes, and adiposity measures (body mass index, waist circumference, triceps skinfold thickness and body fat percentage). Secondary outcome measures were: attention deficit hyperactivity disorder risk, motor skills, health-related quality of life and sleep quality. These variables will all be measured in both groups at baseline and at the end of the first and second academic years.
Discussion: It seems reasonable that an intervention to promote physical activity based on playground games will be useful for simultaneously improving academic achievement and controlling obesity.
Trial registration: ClinicalTrials.gov NCT01971827

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Tunis Med. 2015;93:302-07.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AT SCHOOLS IN SFAX-TUNISIA.

Khemakhem K, Ayadi H, Moalla Y, et al.

Background: Frequency, social impact, the negative effects of ADHD on personal development, make it a public health problem. Tunisian existing data confirm its frequency and severity in clinical population. The absence of data in student population has led us to develop this work.The objectives of our study were to study epidemiological profile of ADHD in school population.

Methods: The analysis involved a cross-sectional descriptive study conducted from April 2008 to October 2008 using a representative randomized multistage sample of schoolchildren between 6 and 12 years old. Measurement was performed in two stages first the parents and teachers of each children filled Conners questionnaire separately then students with the score in subscales inattention, hyperactivity with impulsivity higher than 70 were selected for psychiatric interview. Psychiatric interview was intended to confirm or refute the diagnosis of ADHD. The diagnoses were made according to DSM IV-TR. To study the possible associated factors with the disorder they were compared in children with ADHD and children without the disorder taken as controls.
Results: A total of 51 students out of 513 had ADHD. Prevalence was found to be 9,94%. For the study of factors associated with ADHD were found in males, neonatal hospitalization, psychiatric and family history of ADHD and the existence of a family dysfunctionment.
Conclusion: Our prevalence is similar to the majority of those reported by studies conducted through the same methodology as ours. The etiology of ADHD is not unequivocal. The disorder appears to be multifactorial

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Twin Res Hum Genet. 2015 Jun;18:290-97.

GENETIC AND ENVIRONMENTAL ETIOLOGY OF THE RELATIONSHIP BETWEEN CHILDHOOD HYPERACTIVITY/INATTENTION AND CONDUCT PROBLEMS IN A SOUTH KOREAN TWIN SAMPLE.

Hur YM.

Recently, there has been increased research into the etiology of the comorbidity between hyperactivity/inattention problems (HIP) and conduct problems (CP). However, the nature of the etiology of the comorbidity has remained unclear. Mothers of 507 pairs of twins, comprised of 221 monozygotic (MZ) and 286 dizygotic (DZ) twin pairs aged from 6 to 13 years (mean = 9.6 years; SD = 2.0 years), completed the HIP and the CP scale of the Strengths and Difficulties Questionnaire (SDQ) via a telephone interview. The phenotypic correlation between HIP and CP was 0.43 ($p < .01$). MZ and DZ twin correlations were, respectively, 0.48 (95%CI: 0.37-0.58) and 0.06 (95% CI: -0.06-0.19) for HIP and 0.38 (95% CI: 0.26-0.49) and 0.35 (95% CI: 0.25-0.45) for CP. The bivariate model-fitting results revealed additive genetic correlation of 1.0 (95% CI: 0.72-1.00), a complete overlap of additive genetic variance component between HIP and CP, supporting the importance of correlated additive genetic risk factors for the comorbid condition of HIP and CP. HIP was additionally influenced by non-additive genetic factors that did not contribute to the relationship between HIP and CP. There was a significant but moderate child-specific environmental correlation ($r_e = 0.37$) between HIP and CP. CP was additionally influenced by shared family environmental influences. While the results of the present study are generally consistent with the findings from Western twin studies of the relationship between HIP and CP, they add a new finding to the extant literature by showing that it is additive rather than non-additive genetic factors that are responsible for the co-occurrence of HIP and CP

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Value Health. 2015;18:824-31.

DEVELOPING A RISK SCORE TO GUIDE INDIVIDUALIZED TREATMENT SELECTION IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Setyawan J, Yang H, Cheng D, et al.

Objective To develop a risk score for treatment failure that could potentially be used to individualize treatment selection between lisdexamfetamine dimesylate (LDX) and osmotic-release oral system methylphenidate (OROS-MPH) in children and adolescents with attention deficit/hyperactivity disorder (ADHD).
Methods The study used data from patients with ADHD receiving LDX (N = 104) or OROS-MPH (N = 107) in a phase III randomized clinical trial. A prediction model was developed to estimate risk scores for failing OROS-MPH, where treatment failure was defined as less than 25% improvement in the ADHD Rating Scale IV total score from baseline. Patients were ranked by their predicted risks of OROS-MPH failure to define high-risk subpopulations. Outcomes of LDX and OROS-MPH were compared within subpopulations.

Results The prediction model for OROS-MPH failure selected seven predictors (age, disease duration, and five ADHD Rating Scale IV item scores) and had an in-sample C statistic of 0.860. Among all patients, LDX had a 17% (95% confidence interval 7.1%-27.8%) lower treatment failure rate than that of OROS-MPH; differences in failure rates ranged from 17% to 43% across subpopulations, increasingly enriched for high-risk patients. Similar heterogeneity across subgroups was observed for other efficacy measures.
Conclusions In the overall trial population, LDX was associated with a lower rate of treatment failure compared with OROS-MPH in patients with ADHD. A more pronounced benefit of LDX over OROS-MPH was observed among subpopulations with a higher predicted risk of failing OROS-MPH. The present study showed the feasibility of individualizing treatment selection. Future research is needed to prospectively verify these results

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World J Biol Psychiatry. 2015.

VARIATION IN SEROTONIN NEUROTRANSMISSION GENES AFFECTS NEURAL ACTIVATION DURING RESPONSE INHIBITION IN ADOLESCENTS AND YOUNG ADULTS WITH ADHD AND HEALTHY CONTROLS .

Van RD, Hartman CA, van Donkelaar MMJ, et al.

Objectives. Deficits in response inhibition have been associated with attention-deficit/hyperactivity disorder (ADHD). Given the role of serotonin in ADHD and impulsivity, we postulated that genetic variants within the serotonin pathway might influence response inhibition.
Methods. We measured neural activation during stop-signal task performance in adolescents with ADHD (N = 185), their unaffected siblings (N = 111), and healthy controls (N = 124), and investigated the relationship of two serotonin gene polymorphisms (the rs6296 SNP of the HTR1B gene and HTTLPR variants of the 5-HTT gene) with the neural correlates of response inhibition.
Results. The whole-brain analyses demonstrated large scale neural activation differences in the inferior and medial frontal and temporal/parietal regions of the response inhibition network between the different variants of both the HTR1B and 5HTT genes. Activation in these regions was significantly associated with stop-task performance, but not with ADHD diagnosis or severity. No associations were found between HTR1B and 5HTT variants and ADHD or ADHD-related neural activation.
Conclusions. These results provide novel evidence that serotonin may play an important role in the neurobiology of response inhibition. Although response inhibition is strongly linked to ADHD, serotonin linked genetic variants associated with response inhibition and its neural correlates do not explain variance of the ADHD phenotype

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SCHOOL WELL-BEING OF STUDENTS WITH AND WITHOUT SPECIAL EDUCATIONAL NEEDS--A COMPARISON OF STUDENTS IN INCLUSIVE AND REGULAR CLASSES.

Schwab S, Rossmann P, Tanzer N, et al.

OBJECTIVE: The present study examines the academic well-being of students with and without special educational needs (SEN) in inclusive classes compared to students from regular classes in which no child with SEN is taught. In addition, the relationships between the school well-being and emotional problems, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behavior are analyzed.
METHOD: A total of 1115 students from the 4th and 7th grade (37 % 4th graders, 63 % 7th graders) participated in the survey, 126 of whom had been diagnosed as having SEN. The subscale Well-Being at School taken from the FEESS 3-4 (Rauer & Schuck, 2004) and the SDQ (Goodman, 1997) were used for measurement.
RESULTS: Results indicate high reliabilities for the subscale Well-Being in School for students both with and without SEN for both grades 4 and 7. Furthermore, it could be shown that the variance explained for school well-being can be connected to elements on the students' individual level as well as on the class-specific level. Significant predictors of school well-being were sex, behavioral difficulties and strengths as well as the

school grade. The SEN status (no SEN vs. SEN) and the class setting (regular vs. inclusive class) did not influence the school well-being significantly

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AN INCLUSIVE MISUNDERSTANDING--WHY NONCATEGORIZATION IN SPECIAL EDUCATION FOR PEOPLE WITH EMOTIONAL AND SOCIAL BEHAVIOR DISORDERS COMPLICATES THE COOPERATION WITH CHILD AND ADOLESCENT PSYCHIATRY.

Ahrbeck B, Fickler-Stang U.

The welcomed coeducation of children and adolescents with and without disabilities is going into dangerous territory since it has become burdened with a number of illusionary expectations. The constraints applied by real-life and meaningful circumstances should be taken into account, especially for children with emotional and social behavior disorders. Practicable prevention and intervention measurements cannot be generated without profound knowledge about disorders among this heterogeneous group of people. Abandoning all previously relevant terminology (<<noncategorization>>), demanded by some radical inclusion advocates, leads to a situation that is helplessly confronted with its duties but lacks the basic skills and the necessary support stemming from an interdisciplinary dialogue. The contact with child and adolescent psychiatry is threatened to the disadvantage of the profession

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Review

Mental disorders and transition to adult mental health services: A scoping review

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ABSTRACT

Background: Data are progressively accumulating regarding the transition to adult services.
Methods: A comprehensive search using the MEDLINE, Embase, PsycINFO, and Cochrane databases up until 16 March 2015 was conducted in order to summarize recent evidence on the transition from child to adult mental health services for patients with mental disorders. Authors extracted data and assessed study quality independently.
Results: The main findings of the 33 included studies were discussed taking into consideration four aspects: experiences of patients, carers, and clinicians, accounts of transition, current services models and protocols, and outcomes of transition. Of the 33 studies, 17 focused on a specific mental disorder: seven on attention deficit hyperactivity disorder, four on intellectual disability, three on eating disorders, two on serious emotional disorders and one on autism spectrum disorder. An attempt was also made to integrate the studies' conclusions in order to improve transitional care.
Conclusions: The review reveals an evident need for longitudinal, controlled, health services research to identify and evaluate optimal service models with systematic and seamless transition protocols for patients with mental disorders requiring continuity of care into adult mental services.

1. Introduction

Improving the transition from pediatric to adult services is an emerging healthcare need [36]. Although many agree that transition is as a key component of care [1,24,25,94], there is little empirical data on which health services can be based. Most studies on health care transition address chronic illness or physical disability, delineating guidelines and good practice models [74,55,72,17]. A comprehensive analysis of the literature is beyond the scope of this review, which focuses on mental disorders. While evidence from physical health services may not be entirely generalizable to mental health services, there are certain lessons that can be learned. Studies evaluating chronic conditions identified various factors involved in successful transition, including the importance of continuity and relationships with familiar health professionals and better information and involvement in care management. Although good practice models have been described, there is still no consensus on what constitutes successful transitions and positive outcomes [112]. Potentially more effective transition arrangements such as illness peer support groups, web-based approaches, joint-working, and closer coordination, have been recommended [77,49,4,95,32].

There is increasing evidence that mental disorders lead to a range of different clinical outcomes, as well as to outcomes related to service use, in adulthood, resulting in the need for care continuity [99,92]. Cross-sectional studies have shown a decline in the use of services by adolescents and young adults, despite the documented continuation into adulthood for several mental disorders [86,87,107,33,104,65,56,47,52,44,3,85,90,58]. This inconsistency between needs and services may be partly caused by the different types of gaps in the transition process from pediatric to adult services [18]. Paul et al. recently discussed some of these gaps, analyzing heterogeneous studies on transitional care modalities and, more broadly, concerns about transition from adolescence to adulthood, and confirmed the need for more primary research on the effectiveness of different models to ensure a good quality care continuity [82].

The transition from adolescence to adulthood is also a challenging time with profound physiological, psychological, and social changes [8,64]. Adolescents with mental disorders face greater challenges as they transition to adulthood than their peers with or without other disabilities; overall, rates of mental health

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0924-9338/

problems increase during adolescence, problems become more complex, and serious disorders, such as psychosis, emerge [99,22,109,50,53]. Most adolescent disorders are often undifferentiated, with polysymptomatic presentations, that, later in life, progress to more traditional, differentiated types [59,68]. Emerging knowledge about psychopathology and brain development in adolescence is, both, of great relevance and crucial to improving and guiding prevention and public health engagement. The highest dropout rates are in young adults, suggesting that it is not sufficient to simply engage them and ensure transition to adult services; the latter also needs to be effective and developmentally appropriate for these young adults [30,28].

Despite the presence of relevant policy statements and documents concerning mental health care continuity in various countries [11,37,111,46,83,20,38], transition problems occur in health care systems in different continents [23,101]. A US study found that continuity of care was hampered by separate access policies, lack of clarity in access procedures, and lack of shared transition planning [21]. An Australian study found that many young people referred to adult mental health providers were not accepted, despite their continuing mental health needs [15]. Although England and Wales have also implemented several policy initiatives for child and adolescent mental health services, they, too, have had problems in ensuring optimal transition of care [101,57]. The most recent Annual Report of the England Chief Medical Officer reiterates, indeed, that a main focus should be on an improvement in the transition to adulthood through better access to health services, particularly those concerning mental health [20]. Even The International Declaration on Youth Mental Health contains target measures that young people and their families should expect from mental health services, and states that "transitions from one service to another will always involve a formal, face-to-face transfer of care meeting, that involves the young person, his or her family/carers, and every service involved in his or her care" [16]. The UK recently developed transition guidelines based on all the existing resources, policy documents, and initiatives that relate to transition from child to adult services [97], and in the US a report by the Institute of Medicine and National Research Council summarized recommendations to improve the child to adult medical and behavioral health care transition [48].

Moreover, although the two terms are used almost interchangeably, transition needs to be distinguished from transfer. Transfer refers to the termination of care by a children's health care service, which is re-established with an adult provider. Transition is a lengthy and seamless process with a beginning, middle, and end marked by joint responsibilities in multidimensional and multidisciplinary work to ensure a way to enable and support young patients continuing on into adult care. In this study we consider both terms. Overall, the importance of maintaining continuity of care in mental health care has been well documented, but there is a limited amount of research addressing this problem. This review aims to scope the extent of current and upcoming literature and research studies, specifically analyzing, documenting, or aiming to study the transition of young people with mental disorders from child and adolescent to adult mental health services.

2. Methods

2.1. Definition and inclusion/exclusion criteria

The review was restricted to studies evaluating the transition from child to adult mental health services. The search was limited to humans and only original articles were considered. Studies were eligible if they analyzed experiences, rates, service model descriptions or outcomes related to the transition from child to adult care for people with mental disorders. Book chapters, editorials, comments or letters, congresses, reviews, or published errata were excluded.

2.2. Search strategy

The search was performed independently by the 2 authors using the Medline, Embase, PsycINFO, and Cochrane databases, and all articles published up until 16 March 2015 were considered.

The search strategy used, both, terms included in the title/abstract and in the subject headings, i.e. Medical Subject Headings (MeSH) (Medline, Cochrane), Emtree (Embase), and thesaurus (PsycINFO). The search strategy used was: ["transition*" or "transfer*" or "continuity of care" or "transition to adult care" or "continuity of patient care"] and ["mental disorder*" or "mental health service*" or "child and adolescent mental health service*" or "CAMHS" or "psychiatric service*"] and ["adolescent*" or "young" or "young adult" or "youth*"]. No language restriction was applied. The two authors independently screened the titles and abstracts of each study and excluded studies not pertinent to the study population or to transition within mental health services for patients with diagnosed mental disorder. The full text of the remaining articles was obtained and evaluated by the authors independently to decide whether to include or exclude the studies. Disagreements on the eligibility of a study were resolved by discussion until consensus was reached.

Moreover, a review of the references of the included studies was performed. Complete references were downloaded and stored using Reference Manager 2011.0.1 software (Thompson ResearchSoft, Carlsbad, CA, USA).

2.3. Quality assessment

The quality of studies was assessed independently by the authors using the "Methodology checklist: qualitative studies" checklist proposed in The Guidelines manual published by the National Institute of Health and Clinical Excellence [75] and based on criteria suggested in the literature [103,88,51]. This tool includes the following main information relating to methodological quality: theoretical approach, study design, data collection, validity, analysis, and ethical concerns (Table 1). Both authors assessed each study according to the 14 criteria in the scale and the average of the scores was calculated to obtain the methodological quality ("high": $\geq$ 12 criteria, "medium": 8–11 criteria, or "low": $<$ 8 criteria) based on the information retrieved from the papers [41].

Table 1
Methodology checklist.

Criteria used to assess the methodological quality of the studies
Theoretical approach
1. Is the research approach appropriate?
2. Is the study clear in what it seeks to do?
Study design
3. How defensible/rigorous is the research design/methodology?
Data collection
4. How well was the data collection carried out?
Validity
5. Is the role of the researcher clearly described?
6. Is the context clearly described?
7. Were the methods reliable?
Analysis
8. Is the data analysis sufficiently rigorous?
9. Are the data "rich"?
10. Is the analysis reliable?
11. Are the findings convincing?
12. Are the findings relevant to the aims of the study?
13. Are the conclusions adequate?
Ethics
14. How clear and coherent is the reporting of ethical considerations?

2.4. Data synthesis

For each study, data concerning year, country, setting, target disorder, and involved population were extracted. To summarize the findings, the results of all included studies were presented in tables according to four main aspects: experiences of patients, carers and clinicians, accounts of transition, description of services models, and outcomes of transition.

3. Results

3.1. Search results

A complete trial flow chart is shown in Fig. 1. A total of 1845 titles were retrieved: 787 in Pubmed, 778 in Embase, 212 in PsycINFO, and 68 in Cochrane. A total of 590 (32%) studies were duplicates and were excluded. In all, 55 full-text articles were thus assessed for eligibility. Authors agreed on 48 of 55 papers (86.4%) reviewed for eligibility (K = 0.727). Twenty-six studies addressing the research question were included. To make the search more complete, the references of the 26 included articles were scrutinized and a further 7 relevant publications were identified. Overall, 33 studies were included (Fig. 1). The included studies were published in 21 journals, 4 in the *Journal of Behavioral Health Services and Research*, 2 in the *BMC Psychiatry*, 2 in the *BMC Health Service Research*, and the rest in 13 different journals. The papers were published between 1999 and 2015: 30 (91%) in the 2008–2015 period. Thirteen studies were performed in the US, 13 in the UK, 5 in other European countries and 2 in Canada. The participants in the studies were parents in nine cases, patients in seven, and clinicians in 15; three studies included all three together. For seven studies, data sources were national or health organization databases. The mean quality score of all included studies was of medium level: six reached a high score, 22 a medium one, and

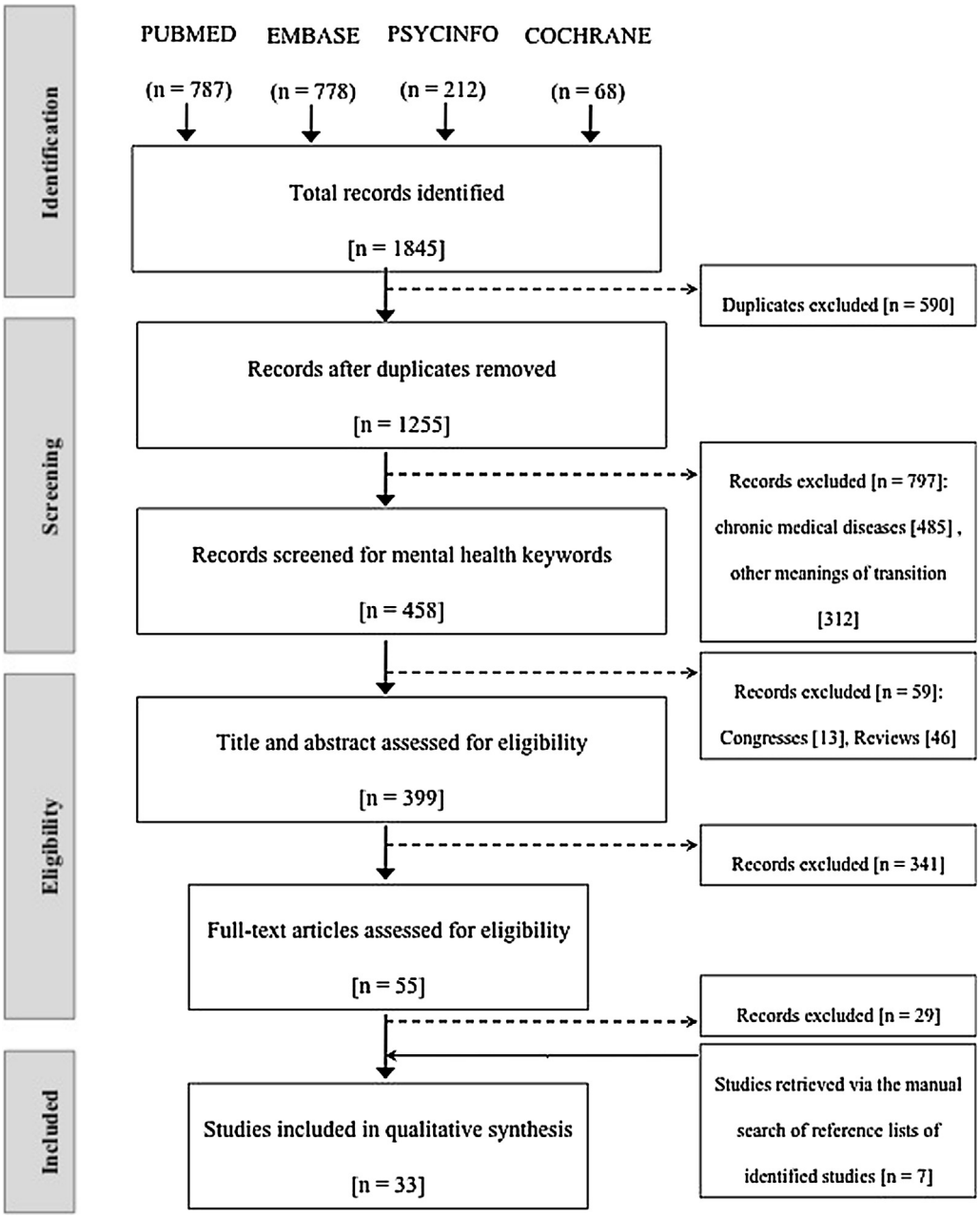

Fig. 1. Flow chart of the retrieved studies.

three a low score (Table 2). Seventeen studies were conducted with the use of a survey questionnaire, nine with semi-structured qualitative interviews, and two with focus groups, whereas 10 studies involved data analysis from clinical databases (Table 3).

3.2. Experience of patients, carers and clinicians

Eleven studies discussed the experience of patients, carers and clinicians on transition to adult services (Table 3).

In a study evaluating transition experiences for subjects with intellectual disability (ID) [5], findings showed that more than half of parents were not aware of a transition plan, only 26% were satisfied with the transition care their child had received, and at least 50% had had various difficulties in accessing services. These problems were mostly due to a lack of information about the transition plan and to poor staff attendance at meetings. Similar experiences were reported by parents of young people with ID in the Netherlands [7]. Also a US study found that the main barriers for ID youth were difficulty in finding adult services to transition to, with a consequent desire to continue care through the pediatric service, and difficulty in defining the timing of the transition process [84].

The perspectives of service providers were also sought to understand the challenges affecting the transition service process for young patients with eating disorders. Three main obstacles emerged: the influence of illness related factors such as ambivalence towards recovery, effect of the illness on normal developmental processes, and a decline in parental involvement during service transition [26].

Table 2
Main characteristics of included studies.

Ref.	Year	Country	Setting	Target disease	Involved population [n]	Studied patients		Quality score
						[n]	[Age]	
[26]	2015	Canada	Adult and paediatric eating disorder services	ED	Patients [32]	15	17–21	9
[40]	2015	UK	National mental health services	ADHD	Clinicians [22]	-	-	9
[13]	2014	US	Statewide transition support program	ID	(Case notes review)	139	11–22	10
[34]	2014	US	National alliance on mental illness	MDs	Parents [87]	19	18–25	8
[54]	2014	US	Transitional living programs	MDs	Patients [85]	29	19–24	8
[91]	2014	Italy	Regional ADHD paediatric centres	ADHD	Clinicians [86]	52	18–21	11
[7]	2013	Netherlands	South-Holland region hospitals and patient organizations	ID	Parents [131]	131	20,4 ± 2,9[a]	9
[13]	2013	US	Health care transition services	ASD	(Database analysis)	18,198	12–17	9
[39]	2013	UK	National mental health services, community paediatric services	ADHD	Clinicians' teams [10]	-	-	11
[60]	2013	Sweden	Child and adolescent psychiatry and general psychiatry units	MDs	Clinicians [65]	-	-	8
[70]	2013	UK	National mental health services	MDs	Health and social care professionals [8]	-	-	12
[71]	2013	Ireland	National mental health services	MDs	Clinicians [97]	-	-	10
[81]	2013	UK	National mental health services	MDs	(Case notes review)	154	18,1 ± 0,8[a]	12
[105]	2013	UK	Child and adolescent mental health services	ADHD	Patients [112]	10	17–18	10
[9]	2012	Spain	National mental health services	HD	(Database analysis)	2274	≥18	11
[26]	2012	Canada	Adult and paediatric eating disorder services, paediatric services	ED	Clinicians [-]	-	-	9
[35]	2012	US	Transition-age mental health service, national adult mental health service	MDs	(Database analysis)	2505	18–24	10
[45]	2012	UK	National mental health services	MDs	Clinicians [112], patients [77], parents [74]	11	16–21	10
[5]	2011	UK	National mental health services, paediatric services, social services	ID	Parents [62]	79	16–19	11
[78]	2011	US	National mental health services	MDs	(Database analysis)	26,336	9–17	7
[113]	2011	US	Specialist transition service for patients with childhood conditions	MDs	Parents [13]	63	11–22	7
[84]	2010	US	Urban, suburban and rural community services	ID	Clinicians [32], patients [99], parents [92]	16	13–23	10
[102]	2010	UK	National mental health services	MDs	Clinicians [23], patients [77], parents [74]	155	16–21	12
[106]	2010	UK	Paediatric neurodevelopment service	ADHD	(Database analysis)	139	14–19	8
[2]	2008	UK	Adult eating disorder service	ED	Patients [206]	206	16–25	11
[42]	2008	US	Tennessee Medicaid data	SED	(Database analysis)	134,569	14–17	12
[62]	2008	US	Community-based mental health services	SED	Clinicians [37]	8484	14–22	9
[63]	2008	UK	Community paediatric services	ADHD	Community paediatricians [42]	-	Children	7
[86]	2008	US	National mental health services	MDs	(Database analysis)	6326	6–35	12
[101]	2008	UK	National mental health services	MDs	Clinicians' teams [30]	155	16–21	12
[21]	2005	US	National mental health services	MDs	Parents [23]	-	14–25	8
[93]	2004	UK	National mental health services, pediatric services, social service	MDs	Health managers [86], clinicians [33]	-	16–19	9
[96]	1999	US	Specialist transition health services	MDs	Clinicians' teams [126]	-	-	10

ASD: autism spectrum disorders; HD: hyperkinetic disorder; ED: eating disorder; MDs: mental disorders; ID: intellectual disability; ADHD: attention deficit hyperactivity disorder; SED: severe emotional disorder; -: not reported.

[a] Mean ± SD.

Table 3
Studies included: aims, instruments and main conclusions.

Ref.	Year	Main aim	Instruments	Findings
Studies evaluating the experience of patients, carers and clinicians				
[26]	2015	To evaluate experiences of patients with eating disorders who had transferred to adult services	Qualitative interviews	Young people advocated for better coordination and communication between paediatric and adult providers to bridge the gap between two different systems of care
[34]	2014	To explore mothers' perspectives of transitional-age (18–25) youths with mental disorders	Survey questionnaire	Services' providers did not meet youth's needs for emotional support, preparing for independent living, practical advice, collaborative and case planning, and information about their illness
[54]	2014	To survey experiences of young adults with mental disorders before and after transition	Qualitative interviews	Descriptions of adult services were vague and superficial in comparison to the lengthy descriptions provided for child service, (i.e.) job searches, and the relationship with clinician
[7]	2013	To explore parents' experiences and to collect their recommendations for transfer to adult care	Survey questionnaire	Parents pointed out lack of information, lack of coordinated planning, difficulties in accessing services, and unmet needs in multiple areas
[60]	2013	To describe professionals' views of the transition process from child to adult psychiatry	Focus groups	A gap could occur due to different perspectives, lack of knowledge, a mutual understanding, and cooperation. Child and adult psychiatry had different care cultures towards family- vs individual-care
[105]	2013	To explore the experiences of young people with ADHD during transition to adult mental services	Qualitative interviews	Timely preparation, joint-working, good clinician relationships and parental support serve to facilitate the process of transition for young people with ADHD
[26]	2012	To evaluate clinicians' perspectives on the service transition process for eating disorders	Qualitative interviews	Clinical factors associated with eating disorders may interfere with a successful transition
[45]	2012	To evaluate needs of patients, parents, and clinicians on transition to adult mental services	Qualitative interview	Transfer planning meetings and parallel care were valued by all parties and should be standard practice in transition. Services need to work jointly to improve the transition
[5]	2011	To evaluate carers' perceptions and unmet needs of the transition process to adult services	Survey questionnaire, qualitative interviews	Recommendations are that both standardized tools for transition planning and integrated referral systems be developed, and that individual outcomes be monitored
[84]	2010	To survey barriers of intellectual disability youths when transitioning to adult healthcare	Focus groups	The timing of the transition process for youths with ID should be individualized. Education of both paediatric and adult providers to improve transition for these patients is needed
[63]	2008	To evaluate the experiences of pediatricians when transferring ADHD patients to adult care	Survey questionnaire	There is a gap in provision of services for young people with ADHD when they leave paediatric care, with many paediatricians struggling to find appropriate ongoing care
Studies evaluating the accounts of transition				
[40]	2015	To investigate the transition process and current services for adults with ADHD in England	Survey questionnaire	There was a lack of accurate data on the number of young people with ADHD transitioning to, and being seen by, adult services. Young people with ADHD were prematurely discharged
[91]	2014	To investigate the care continuity from child to adult mental services for young adults with ADHD	Survey questionnaire	70% of patients who turned 18 were monitored by the general practitioner. One fifth of patients continued to use mental health services, the majority was still monitored by the RAPC
[12]	2013	To compare youth with ASD who receive transition services to youth with other SHCN	Case note review	Whereas half of youth with other special health care needs received health care transition services, less than a quarter of youth with ASD did
[71]	2013	To obtain information on annual transition numbers and existing transition policies	Survey questionnaire	The number of young people suitable for transfer was higher than the number of those who actually transferred to adult services, with lack of transition policies, standardized practice and interaction between services
[81]	2013	To evaluate concepts of transfer and transition between child and adult mental health services	Case note review	Of 154 cases, 102 (66%) were referred, 90 (58%) were accepted, and 76 (49%) transferred to the adult mental service
[9]	2012	To evaluate factors predicting adult service use of adults diagnosed with ADHD in childhood	Case note review	A fifth of ADHD cases need to be followed up to an adult mental health system
[78]	2011	To examine the role of the health care system in the transition to young adulthood	Case note review	A lower rate of patients with mental disorders receives services necessary to make transition to adult service compared to those with only physical conditions
[105]	2010	To identify the service's needs of young adults with ADHD transitioning from paediatric care	Case note reviews	36% of young people with ADHD were likely to have ongoing symptoms and would require continuing support from adult services, while 50% had good symptom control
[2]	2008	To evaluate young adults with eating disorders with previous involvement with a child service	Case note review, self-report questionnaires	Approximately 30% of patients continue to require care in adulthood, but few of them are referred to an adult service by the child and adolescent mental health service
[42]	2008	To evaluate youths at high risk of transition difficulties, shifting from child to adult services	Case note review	SED subjects with previous diagnoses of ADHD, CD, or ODD are at increased risk of experiencing gaps in transitioning to adult service systems

Table 3 (*Continued*)

Ref.	Year	Main aim	Instruments	Findings
[101]	2008	To determine the annual transition rates from child to adult mental health services	Survey questionnaire	There is discontinuity of care provision for some patients who need transition, but are not accepted by adult services
[62]	2008	To evaluate needs and services use of transition-aged youth with severe emotional disorders	Survey questionnaire	Differences in the severity and types of problems experienced by transition-age youths and changes in the use of services indicate the need for youth- and family-centred approaches
[86]	2008	To evaluate needs and services' use of transition-age youths by patient age	Case note review	A precipitous decline in mental health service utilization was observed at the ages of 18–19
Studies describing services models				
[13]	2014	To describe the development of ambulatory consultative transition support services	Case note review	Service models include routine and focused comorbidity screening and recommendations, care coordination of complex health and community service needs, and support for families
[39]	2013	To examine the provision of services and the transition process for ADHD patients	Survey questionnaire	Findings indicate lack of structured guidelines and limited communication between child and adult services as main barriers. Adult services often feel ill-prepared to deal with ADHD
[70]	2013	To identify the organisational factors which facilitate or impede transition to adult services	Qualitative interviews	There are some positive approaches to collaborative working across services and agencies, involving joint posts, parallel working, shared clinics and joint meetings
[35]	2012	To compare service use after offering transition-age-specific, versus standard, adult programs	Case note review	Age-specific services are associated with increases in outpatient service use and this, in turn, seems to be one of the factors related to a better outcome
[113]	2011	To assess the health, functional characteristics, and health care service needs of young adults	Survey questionnaire	Transition programs should assess patient health characteristics and service needs to design effective patient-centered services
[21]	2005	To explore needs and transition supports available within state child mental health systems	Survey questionnaire	There is a long way to go before patients can count on a comprehensive, age-appropriate and appealing service in the transition stage
[93]	2004	To explore needs and transition supports available within state child mental health systems	Qualitative interviews	The findings support the need for specialist transitional services and the adoption of an inter-professional service model incorporating education and social services
[96]	1999	To identify and characterize programs providing transition health services for adolescents	Survey questionnaire	For transition health services, the barriers to providing health care continuity are not the resistance of adolescents or their parents, but limitations of the health care system itself
Studies evaluating outcomes of transition				
[81]	2013	To describe the outcomes of transition from child to adult mental health services	Case note review	The elements of optimal transition were more often the continuity of care, having had at least one transition planning meeting, good information transfer, and a period of parallel care
[102]	2010	To evaluate process and patients' and parents' needs in transition to adult mental health services	Case note review, qualitative interviews	The transition process is poorly planned and executed and is a poor experience, highlighting the need to improve the interface between services

The TRACK study described, among its other findings, the experiences of patients, clinicians, and parents [45]. From the young patients' perspective the following activities were seen as key components of a good transition: at least one transition planning meeting with both the child and adult clinicians; a continuity in the therapeutic relationship with their CAMHS key-workers before, during, and after the transition; limited waiting time to initiation of treatment at the adult service; communication between services; and flexibility concerning transition-age thresholds. Parents, on the other hand, requested more involvement in their child's care and more flexibility regarding age boundaries. Lastly, clinicians identified working more closely between pediatric and adult services as important, although many thought this was difficult to achieve in practice. Similar needs and experiences for people with mental disorders emerged from other studies involving patients, parents and clinicians [34,54,60]. On the other hand, the perspective of patients with eating disorders who had completed the transition was that the transition to adult care services may be improved with increased coordination, communication, and collaborative partnerships between pediatric and adult providers [27]. Regarding the pediatricians' perspective, a UK study found that at least 40% of young patients with attention deficit hyperactivity disorder (ADHD) would need referral to adult services and, although 22% of pediatrician respondents were aware of a service for adults, many more found that services did not exist in their area or were difficult to access [63]. Contrarily, the experience of ADHD patients in transition, explored by Swift et al., suggested that, often, timely preparation and joint-working could facilitate the process [105].

The main issue that emerged from the included studies shows that patients', parents' and clinicians' perspectives differ slightly between them. The transition to adult services often results in poor patient and parent satisfaction and loss to follow-up for young adults with mental disorders. The experiences of young people, parents, and clinicians suggest joint-working as a common and shared need, given the reported lack of two-way communication as a major impediment to a successful transition process.

3.3. Accounts of transition

Thirteen studies evaluated the accounts of transition from child to adult services (Table 3).

Adolescents with a mental health condition, compared to those with chronic physical conditions, are especially likely to experience gaps in access to, and quality of, transitional care [78]. The TRACK study [101], involving 42 child and adolescent mental

health services (CAMHS) in the UK evaluating the population served and referral rates to adult services, showed that the annual number of cases considered suitable for transfer to adult mental services was greater than the number accepted, and that some patients continued to be seen by the CAMHS teams beyond the transitional boundary [81]. An investigation of process and operational practice in Ireland showed that the number of young people transferred was lower than the number considered suitable for transfer, suggesting the presence of critical gaps, nationwide, related to the lack of standardized practices, policies and protocols, with a minimal interaction between child and adult mental health services [71]. In the US, Heflinger and Hoffman showed that 23% of a sample of Medicaid enrolled transitional-age youths could be considered at risk of falling through the gap in transitioning to the adult service system, and that 79% had serious emotional disturbances (SED) [42]. Of these, youth with behavioral disorders such as ADHD, conduct disorders (CD), or oppositional defiant disorder (ODD) were at greater risk of not transitioning to needed adult services. Another national US study, examining the needs of transition-aged youth with SED, indicated specific service needs, in particular for those with more severe impairment, including ADHD, mood disorders, and physical aggression. Despite this, less than 10% of youths transitioned to adult services [62].

It is now acknowledged that ADHD is a lifelong disorder that commonly persists into adulthood [114]. A Spanish study retrospectively evaluated adult subjects diagnosed with ADHD in childhood to identify factors predicting adult service use. In total, 18.7% were followed up by adult mental health services and, among these, older age of diagnosis, female gender, psychiatric comorbidities, and pharmacological or combined treatment resulted as predictors of the need for continuity into adult mental services [9]. An Italian study also showed low rates of transfer to adult services for young ADHD people. ADHD subjects with comorbidity and those treated with pharmacological therapy were more likely to require care continuity after the age of 18, but the majority remained with the ADHD pediatric service that was already providing them with care [91]. Similar rates have been shown by Taylor et al. who found that 36% of young people with ADHD were likely to have ongoing symptoms and would require continuing support from adult services, while 50% had good symptom control and could be monitored by the general practitioner alone [106]. The fact that transition is considered to be a difficult process, particularly for individuals with neurodevelopmental disorders such as ADHD also emerged in the UK context. Findings concerning clinicians' perspectives highlight the need to provide a better transition service underpinned by clear, structured guidelines and protocols, routine data collection, and information sharing across child and adult services [40].

Investigating the prevalence of receipt of Health Care Transition (HCT) services among youth with Autism Spectrum Disorders (ASDs), compared with youth with other special health care needs, Cheak-Zamora et al. estimated that less than a quarter of youths with ASDs received HCT services and that this was less than those with other difficulties [12].

A UK adult eating disorders service evaluating patients aged between 16 and 25 years found that 27.7% of them had previously been in care at a child mental health service. Half of these patients were referred to the adult service by their general practitioner rather than by the child mental health service [2].

Pottick et al. studied the characteristics of the use of services by young people with psychiatric problems across a large transition-age period, from 16 to 25 years old, reporting that the rate of mental health service utilization at age 18–19 years is about half that of people aged 16–17 years, with rates that remained low among those aged 20–25 years. The difference in utilization was due to a 48% decline in the rate of admission to outpatient services and a 100% decline in admission to residential care [86].

Overall, young patients with neurodevelopmental disorders such as ADHD and autism spectrum disorders, and emotional disorders, were most likely to fall through the care gap between child and adult health services. According to the literature, this group would be expected to more often include subjects with ongoing needs, but who are either not referred to, or not accepted by, adult health services. This, in turn, could lead to a lack of policy services on management of transition that are disorder-specific.

3.4. Description of current services models and protocols

Eight studies described services models and protocols providing transition health services (Table 3).

Ciccarelli et al. developed and described a transition model that utilizes a developmental approach to youth's readiness through the following activities and according to a holistic approach: identifying and addressing the family needs, providing emotional support, providing information on eligible services, speaking on behalf of the family to other agencies or services, and coordinating clinical care [13]. From a multi-professional perspective exploring transition supports available within the child mental health system in the UK, four main issues have been identified with regard to transition: older adolescents have multi-faceted needs, statutory mental health services are not geared towards this age group, communication between services is variable, and there are no formal transfer arrangements [93]. A more recent study reported similar findings also for people with ADHD, showing that the lack of written protocols, poor communication between services and the feeling of being ill-prepared for assessing and managing ADHD patients in adult services emerged as main barriers [39]. A study exploring the transition process support available within the child mental health service of the 50 US states and the District of Columbia found that 70% of the states had at least one kind of transition support service, although only 5 states specifically reported a transition plan. Continuous case management (18%) and cross training of clinicians (38%), as mechanisms for bridging child and adult services, were also provided at different rates among included services [21]. A similar UK study identified collaborative work and working in parallel, shared clinics, and joint meetings as the organizational factors facilitating transition [70].

When comparing service transition among youths enrolled in age-specific services with those receiving standard adult mental health services, Gilmer et al. suggested that youth-specific programs are associated with an increase in outpatient service engagement and a decrease in emergency admissions [35]. Analyzing transition health service programs for youths with chronic or disabling disorders, the barriers to providing continuity of care were not the resistance of adolescents or their parents, but limitations of the healthcare system itself [96]. The Center for Youth and Adults with Conditions of Childhood, a specific service oriented to the transition-age, was described by Woodward, Swigonski, and Ciccarelli and recognized the frequent gaps that occur in cases of youths with mental disorders in the transition process, such as the poor rates of referral by child mental health providers [113].

Overall, the studies' findings showed that there are two main approaches to the care management for young people in transition: improving the interface between child and adult services and developing new service models as integrated youth mental health services. Each has its own advantages and limitations, but both with the common commitment to consider the developmental needs of this age range as a key care component.

3.5. Outcomes of transition

Two studies described the outcomes of the transition process from child to adult services (Table 3).

As part of the TRACK study [102], Singh et al. described the outcomes of transition from CAMHS to AMHS of 154 subjects who crossed the transition boundary. The transition process is poorly planned and executed and is a poor experience, highlighting the need to improve the interface between services, since an optimal transition was experienced by less than 5% of those who made a transition. Patients with a history of severe mental illness, those on medication, or those who had been admitted for in-patient care were more likely to make a transition than those with neurodevelopmental disorders [102]. According to Paul et al., the elements of optimal transition were more often the continuity of care, having had at least one transition planning meeting, good information transfer, and a period of parallel care [81].

With some exceptions described above, our review confirms the paucity of research on effectiveness of transitional care programs; indeed, while qualitative and quantitative improvement of studies addressing the transition process was observed, evaluating the relationships between the approach used to manage the transition and the patient outcomes is still limited.

4. Discussion

The aim of this paper was to review the current literature, updating findings on the transition process for young people with mental health disorders who are leaving child services and transitioning to adult services.

4.1. Open challenges and suggestions from the studies' findings to improve transitional care

4.1.1. Differences in setting and organization of the health systems

The research available comes from different, scattered settings. The TRACK study group conducted an independent research report on the needs and barriers in the transition between CAMHS and AMHS, from which recommendations to promote good continuity of care emerged [102]. Unfortunately, because of the large differences in health systems and in the approach and organization of mental care services, generalization of available information is difficult. Furthermore, the interpretation of the studies' findings, originating from different countries that have markedly different systems (e.g. US), may differ.

Recently, guidelines and initiatives addressing transition planning guidelines to adult care have been summarized in a New Zealand Ministry of Health report to promote consistent practice across services and to guide clinical practitioners [73], also in mental health [97]. We believe that this is an important index of greater, global attention paid to the issue [36,99,18,10,110]. Although the gaps in transition are common worldwide and the barriers to ensure care continuity are similar, because of the large differences in health systems and in the organization of mental care services, specific practice service approaches and interventions should be also developed at a national level. However, the findings of the present review also reveal scant data from international, cooperative studies comparing the effectiveness of the transition approach between countries. It would thus be useful to provide evidence-based support worldwide for shareable recommendations.

4.1.2. Diagnostic and symptomatological continuity

Several studies provide additional proof that there is a phenomenological continuity in mental disorders from childhood to the adult age [107,44,3,85,58,78,31,6]. A key question remains as to how so much observed data on symptomatological continuity could help to set up consistent service continuity and to define the management of the transition process towards the adult mental service. Only a few of the retrieved studies involved patients with only one specific mental disorder, such as ADHD, intellectual disability, ASDs, and eating disorders [21,12,2,39], or patients with disorders that differ slightly, such as severe emotional disorders [42,62]. This result may be related to the fact, as recently documented, that some disorders that seemed to be confined to an earlier developmental age actually persist into adulthood, stimulating new interests and needs for the mental health services system, such as a disorder-based approach. This is the case with ADHD [31]. The remaining majority of the studies involved patients with various mental disorders and often did not report the frequency of the different disorders in the sample nor whether patients with specific diagnosis showed different outcomes compared to the findings of the total sample. This methodological approach probably reflects the organizational system of the mental services care, which is usually not disorder-based.

4.1.3. Multiperspective needs evaluation

The transition to adult services can result in poor patient and parent satisfaction and loss to follow-up for young adults with mental disorders [84,45]. Identifying the needs and barriers of the different figures involved is of particular importance so that effective and shared referral interventions can be designed. Experiences of young people, parents, and clinicians suggest joint-working as a common and shared need, reporting the lack of two-way communication as a major impediment to a successful transition process [84,45,39].

4.1.4. Transition-age thresholds

The concept of transition should be considered as a process during development rather than as something that happens strictly at a fixed age, as healthcare system policies consider it. One key issue is the lack of consensus on age cut-offs for service use since the cut-off defining when "adulthood" is reached is difficult to define. Instead of rigid age demarcations between services, it is therefore better for services to be flexible and consider the developmental needs of individuals [57,100,66]. Moreover, flexibility regarding transition-age thresholds is seen as a key component of good transition by both patients and parents [84,45].

4.1.5. Health insurance

The challenges of transitioning into adulthood have also been related to health insurance, so the Affordable Care Act in the US plans to extend insurance coverage to people with severe mental disorders emphasizing, however, service integration and evidence-based care as key elements to fully reach the purpose [77].

4.1.6. Parental involvement in young adult care

Studies evaluating parents' perspectives show that parents would like greater involvement in their child's care as their child transitions into adult services. These needs could also be related to the different levels of complexity between child and adult systems, with the first being more family-oriented, inclusive, and holistic, and the latter being focused mainly on the individual patient (her/his symptoms/disorders) [73].

4.1.7. Cultural influence

Recent interest has focused on the possible relationship between organizational culture, quality outcomes, and the potential for reshaping cultures as a level for health care improvement. Despite this, supporting evidence and generalizable strategies are limited [98,61,79]. Recent findings from McLaren et al. have demonstrated evidence of a cultural divide between child and adult mental health

services, at least in the UK context, marked by different beliefs, attitudes, and understanding, as well as some negative misperceptions [70].

4.1.8. Service models and protocols

There are mainly two contrasting potential approaches to managing the transition to adult care: improving the interface between services as they currently exist [86,21,62,102] and developing new service models of integrated youth mental health services [42,35,96,19,89]. Findings from a review assessing similar studies on chronic physical diseases showed that the presence of specific transition clinics, often seen as a solution, can result in a double transition: a temporary solution before accessing adult services [18]. The TRACK findings suggesting that services' use of protocols to guide the transition process that are based on the key criterion of an enduring mental health condition would be of reference. This is true also for neurodevelopmental conditions such as ADHD, autism spectrum disorders, and emotional disorders, which are likely to not be accepted by adult mental health services [21,15,12]. A study described innovative services, present in three different countries, that had been redesigned to better meet the needs of young people according to national mental health policies, evidence-based mental healthcare, and patient needs [69]. These services included, for example, a closer integration with physical health care, whose adequate implementation is often denied [76].

4.1.9. Effectiveness evaluation

There is clear evidence of a need for studies not only describing, but also evaluating, the transition process through specific and appropriate outcome measures [29]. A review on the evidence of effectiveness of transition processes for young people with chronic illness identified, as successful components, the use of educational programs, joint pediatric/adult clinics, and specific young adult clinics. The conditions involved varied, and outcome measures varied accordingly. Studies that showed significant improvements evaluated patients with diabetes mellitus; it is difficult to generalize these successful studies to other conditions such as mental disorders [18]. The TRACK study suggested engagement rates, progression of mental illness, education level, and employment status as possible outcome measures [102], and continuity of care, at least one transition planning meeting, good information transfer, and a period of parallel care, as elements of successful transition [81]. Another important challenge that needs to be met is the evaluation of the effectiveness of the services and their care transition modalities, focusing on the outcome of health care transition [14,43].

4.2. Limitations

Results should be interpreted taking into consideration the limitations. First, results are limited by the heterogeneous methodologies and instruments used to explore similar aims by the studies. This, in turn, has led to difficulties in drawing conclusions. Second, despite the recent substantial increase in the number of available studies on transition, it is not possible to generalize the results to a worldwide level due to the geographic location of the studies, limited to a few countries and groups/centers. Third, too few studies evaluated long-term outcomes to allow an evaluation of the effectiveness of the different service models on transition process or clinical outcomes.

5. Conclusions

The present review focused on studies specifically targeting mental health service-based transition in practice. The main finding of this review is that studies confirm that problems occur during transition in diverse settings and countries. These problems are likely due to different reasons and comprise different aspects. First of all, although child psychiatry has not emerged recently as a sub-specialty, cultural approaches and professional education often differ between and within countries. This concern, and the specific focus on adolescent mental health that has become of increasingly growing interest worldwide [80,67], led to consider a continuous, evidence-based, updated training for professionals involved in the care of adolescents with mental disorders an essential tool to improve management and outcome of transition [108]. Moreover, paediatric and adult mental services often differ in their theoretical and conceptual views on diagnosis, aetiology, and treatment focus and have quite different service organization [67]. These differences accentuate the problems at their interface, creating barriers in transition that cut through local healthcare policies. Efforts are therefore needed at different levels and should involve governments, national and local services, regulatory agencies, child and adult mental health clinicians, and parents, to ensure the seamless continuity of care from pediatric to adult mental health services.

Disclosure of interest

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An Integrated Model of Executive Functioning is Helpful for Understanding ADHD and Associated Disorders

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Abstract

Objective: The aim of this study is to test the discriminative capacity of executive function (EF) tasks to better define the cognitive functioning of children with ADHD and comorbidities. **Method:** One hundred four children were presented with a battery of new EF tasks and a rating scale filled out by parents. **Results:** Preliminary analysis of the neuropsychological tasks revealed the presence of five factors: Speed of Processing, Inhibition, Planning, Execution, and Retrospective Memory. All children with ADHD were impaired in Execution (a measure describing the capacity to achieve a goal). ADHD-only children were specifically impaired in Planning, while ADHD + reading disorder (RD) children were impaired in Speed of Processing and Retrospective Memory. Children with ADHD + oppositional defiant disorder (ODD) did not show impairment in any other EF domains. The five EF processes correlated with the EF Questionnaire. **Conclusion:** The present study describes different cognitive profiles in children with ADHD with or without comorbid disorders using neuropsychological EF measures. *(J. of Att. Dis. 2015; 19(6) 455-467)*

Keywords

ADHD, executive function, comorbidity

Introduction

Executive functions (EFs) encompass the cognitive processes that underlie goal-directed behavior and are orchestrated by activity within the prefrontal cortex (PFC; for example, Olson & Luciana, 2008; Shimamura, 2000).

ADHD is a neurodevelopmental disorder that emerges during the early stages of development in which deficits at three different levels arise together: attention deficit, difficulty in inhibition (impulsivity), and disorder of motor activity control. These deficits are serious enough that they prohibit the normal performance of daily activities and compromise family and peer relationships (American Psychiatric Association [APA], 2000).

ADHD is frequently associated (50%-70% of patients) with other psychopathological disorders (Biederman, 2005). According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; APA, 2013), oppositional defiant disorder (ODD) co-occurs in 50% of children with the combined type of ADHD, whereas conduct disorder (CD) is observed to a lesser extent (25% with the combined type). The *DSM-5* does not provide any statistics about the association between ADHD and learning disorders (LDs), but studies have determined association rates that range from 8% to 39% (Bloom, Miller, Garcia, & Hynd, 2005). Different neurocognitive models have been proposed to explain why so many children with ADHD present a comorbid disorder.

Historically, there has been some debate over the specificity of EF deficits in ADHD (Sergeant, Geurts, & Oosterlaan, 2002). However, one meta-analysis (Pennington & Ozonoff, 1996) indicated a clear deficit in the EF domain associated with ADHD, particularly for working memory, planning, and inhibition. These results were confirmed 10 years later by a second meta-analysis conducted by Willcutt, Doyle, Nigg, Faraone, and Pennington (2005).

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Regarding comorbidity, De Jong, Oosterlaan, and Sergeant (2006) discussed several studies that test for a double dissociation between ADHD and reading disorder (RD), suggesting three hypotheses of comorbidity (phenocopy, cognitive subtype, and common etiology).

The phenocopy hypothesis proposes that one disorder may lead to a copy of the symptoms of another disorder (Pennington, Groisser, & Welsh, 1993). For example, children with RD could show hyperactivity or inattention at school because of frustration due to reading difficulty rather than because of neurocognitive problems resulting from ADHD (Marzocchi, Ornaghi, & Barboglio, 2009). However, the results of several neuropsychological double dissociation studies suggest that the phenocopy hypothesis regarding the nature of the comorbidity of ADHD and RD has little support.

The cognitive subtype hypothesis suggests that children with both ADHD and RD have a different or more severe form of ADHD or RD than children with either disorder alone (Rucklidge & Tannock, 2002). The cognitive subtype hypothesis was supported by Willcutt et al. (2001). In their study, the ADHD + RD group was more impaired on all measures than the group with ADHD-only, RD-only, and controls. Similar findings have been described by Seidman, Biederman, Monuteaux, Doyle, and Faraone (2001), who compared the performance of children with ADHD, LD (RD and dyscalculia), and both disorders on EF and non-EF tasks. The comorbid group performed poorest on all tasks, suggesting that comorbidity could worsen EF in children with ADHD.

Finally, some other studies provide evidence for the common etiology hypothesis, which suggests that ADHD and RD have common genetic origins. This hypothesis is supported when similar deficits are found in all the three groups. One common underlying deficit is thought to lead to different disorders (Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). Willcutt, Pennington and colleagues (2005) compared the performance of children with ADHD, RD, or ADHD + RD with healthy controls on tasks of language, reading, memory, EF, and speed of processing and described the different profiles characterizing the four groups. In particular, the ADHD + RD group showed a combination of the deficits observed in the ADHD group and in the RD group (reading disabilities and deficits in inhibition and information processing).

With respect to the comorbidity of ADHD and ODD/CD, it is not clear whether these disorders are two independent behavioral syndromes (Schachar, 1991) with different etiological correlates. In fact, ADHD seems to be due to cognitive deficits, and CD appears to be due to environmental deprivation (Schachar & Logan, 1990). According to Pennington and Ozonoff (1996), children with CD do not show an EF deficit but do show a deficit in impulse control. Clark, Prior, and Kinsella (2000) evaluated EF in four groups of adolescents, ADHD-only, CD-only, ADHD + CD, and healthy controls, using the Six Elements Test (SET) and the Hayling Sentence Completion Test. The ADHD-only group performed poorest on both tasks. The ADHD + CD group was impaired in problem solving and behavior monitoring, indicating that an EF deficit is associated with only ADHD and not CD. These findings were also supported by recent studies (Brocki, Nyberg, Thorell, & Bohlin, 2007; Oosterlaan, Scheres, & Sergeant, 2005; Wahlstedt, Thorell, & Bohlin, 2009). Thus, the study of EF could better define the cognitive functioning of children with ADHD and associated disorders, in particular with RD or with ODD.

The difficulty of studying EF in children concerns the limited number of specific tasks available to evaluate the executive domain with ecological validity (Burgess et al., 2006), which would allow researchers to formulate hypotheses regarding the daily functioning of ADHD children. Other studies have confirmed that classical EF tasks have low ecological validity when comparing children's task performance with the results of Executive Function Questionnaires (EFQs) completed by their parents (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Bodnar, Prahme, Cutting, Denckla, & Mahone, 2007; Mahone et al., 2002; Vriezen & Pigott, 2002). These findings have been confirmed by a recent review conducted by Toplak, West, and Stanovich (2013) on the association between performance-based and rating measures of EF. The authors scrutinized 20 studies examining this association and reported that only 24% of correlational comparisons were statistically significant, suggesting that the two types of measures (performance-based vs. ratings) appear to capture different aspects of cognitive functioning.

A growing body of research on the nature and development of EF mechanisms has demonstrated that EF can be separated into distinct processes. Letho, Juujarvi, Kooistra, and Pulkkinen (2003) confirmed the model of EF proposed by Miyake et al. (2000) using a battery of EF tasks with a sample of children aged 8 to 13 years. According to these authors, EFs are composed of three interrelated domains: Inhibition, Working Memory, and Shifting. Wu and colleagues (2011) supported this tripartite model using a different battery of Attention and EF tasks with a sample of children aged 7 to 14 years.

The main limitation of such models is that they consider human goal-directed behaviors as separable into distinct cognitive processes, although the functioning of the mind is more likely to involve a sequential flow of cognitions and behaviors. Burgess, Veitch, Costello, and Shallice (2000) argued that an ecological model of EF could be derived from a multitasking test of consecutive cognitive processes: rule learning, planning, executing or following a plan, retrieving the performance and recalling the rules. Similarly, Zelazo and Frye (1998) proposed a model of EF comprising four sequential steps: representation of the problem, planning,

executing, and evaluation of the behavior. Mackinlay, Charman, and Karmiloff-Smith (2006) designed a test of multitasking in children inspired by the Greenwich Test (Burgess et al., 2000) and the SET (Shallice & Burgess, 1991; Siklos & Kerns, 2004) to validate the EF model proposed by Burgess et al. (2000). Other attempts to devise more ecologically valid tasks to assess EF in patients with frontal lobe deficits have been made by Knight, Alderman, and Burgess (2002), who proposed a simpler version of the Multiple Errands Test (Schweiger & Marzocchi, 2008; Sgaramella, Bisiacchi, & Falchero, 1995; Shallice & Burgess, 1991).

The present study has different goals:

1. We aimed to test a model of EF in which the different components could be interpreted as sequential steps of a complex behavior aimed at achieving a goal because the tripartite models do not explain how inhibition, working memory, and shifting are related to each other.
2. We analyzed which component/s of EF could be impaired in children with ADHD, using an EF model in which cognitive processes are thought to be sequential and not fractionated.
3. Finally, we were interested to know whether children with ADHD and comorbid RD or ODD are more impaired than children with ADHD-only, using an EF framework.

Method

Participants

Children with ADHD were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; APA, 1994) criteria using the Parent Interview for Child Symptoms, revised for *DSM-IV* (PICS-IV; Ickowicz et al., 2006) by a medical doctor specialized in child neuropsychiatry. The PICS-IV requires verification of the presence of at least six inattention and hyperactivity–impulsivity symptoms in at least two contexts (e.g., school and home). The PICS-IV also allows for the exclusion of other psychopathologies such as psychosis or pervasive developmental disorders.

To verify children's impairment in several contexts, the Conners' (1997) Rating Scale or the "Sindrome da Deficit di Attenzione" questionnaire (SDA, an Italian version of the ADHD-Rating Scale; Marzocchi & Cornoldi, 2000) was also presented to parents and teachers. The teacher and parent versions of the SDA questionnaire include 18 items based on the *DSM-IV* criteria for diagnosing ADHD (9 items concerning inattention and 9 concerning hyperactivity–impulsivity) and 8 items relevant to ODD. Marzocchi and Cornoldi (2000) provided a detailed description of the psychometric characteristics of the questionnaires. In short, the interrater reliabilities for inattention and hyperactivity–impulsivity were .80 and .74, respectively. The test–retest reliabilities were .83 and .81 for inattention and hyperactivity–impulsivity, respectively.

Reading skills were assessed using an Italian standardized test, the *MT* (Memory Training) *Test of Text Reading* (Cornoldi, Colpo, & Gruppo, 1998). The MT test presents text passages of increasing length according to grade level (from 120 syllables for first graders to 500 syllables to eighth graders) and evaluates reading fluency according to two parameters: reading speed (syllables/seconds) and reading accuracy (number of errors). The diagnostic criterion for RD was a score at least two standard deviations (*SD*s) below the mean of the children of the same age on the *MT Test of Text Reading* (for speed or accuracy).

Children in the ADHD-only group had an average score above the 90th percentile on the Inattention and Hyperactivity–Impulsivity subscales, an average score below the 70th percentile on the ODD subscale for both parent and teacher questionnaires, and a score no worse than 1 *SD* below the mean on the reading test. Children in the ADHD + ODD group had an average score above the 90th percentile on the Inattention and Hyperactivity–Impulsivity subscales, an average score above the 90th percentile on the ODD subscale for both the parent and teacher questionnaires and a score no worse than 1 *SD* below the mean on the reading test. Children in the ADHD + RD group had an average score above the 90th percentile on the Inattention and Hyperactivity–Impulsivity subscales, an average score below the 70th percentile on the ODD subscale for both the parent and teacher questionnaires and a score worse than 2 *SD*s below the mean on the reading test. Children in the control group were recruited from primary schools in the same areas as ADHD children. The ADHD groups and normal controls were matched by age. Typically developing children were excluded from the study if their parent or teacher stated that the child had ever received a clinical diagnosis (e.g., a behavioral problem or a learning disability), their full-scale IQ (FSIQ) estimate was below 80 as measured with the short version of the Wechsler Intelligence Scale for Children–III (WISC-III), or their score on one of the behavioral questionnaires of the parent or the teacher exceeded the 75th percentile.

Two subtests of the WISC-III (vocabulary, block design; Wechsler, 2006) were administered to all children. The estimated FSIQ was used to match the four groups. These WISC subtests have a correlation of .93 to .95 with the FSIQ (Groth-Marnat, 1997). Children with an IQ score below 80 were excluded from the study. All children in the clinical groups underwent a comprehensive neurological and medical examination. The exclusion criterion for these groups was the presence of CDs or mood or anxiety disorders. No child had a history of brain damage, epilepsy, psychosis, or a specific language disorder.

According to these criteria, 104 children aged 7 to 12 years were selected to participate in this study and were divided into four groups: 68 normal controls, 11 ADHD-only, 12 ADHD + ODD, and 13 ADHD + RD.

Materials

The EF battery consisted of four tasks and a behavioral questionnaire chosen to investigate several variables within the EF domain: *Honk Test* (derived from the Change Task by Oosterlaan & Sergeant, 1998), *Daily Planning Test* (derived by Sgaramella et al., 1995), *Sentence Completion Test* (derived by Shallice et al., 2002), *Battersea Multitask Paradigm* (Mackinlay et al., 2006), and Executive Function Questionnaire (EFQ) *parent form* (Schweiger & Marzocchi, 2008). All tasks were specifically adapted by the authors for the present study from previously established tasks. The *EFQ* parent form was an adapted and modified version of the Behavior Rating Inventory for Executive Functions (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). Further details about task adaptation from the original version and scoring information are described below.

Honk Test. The *Honk Test* is a computerized task adapted from the Change Task paradigm that lasts approximately 15 min (Oosterlaan & Sergeant, 1998). In the present study, the type and number of the stimuli were changed from the original version, but the general paradigm remained the same as that reported by Oosterlaan and Sergeant (1998). This task is composed of three conditions (Go, Stop, and Change) and assesses three basic cognitive variables: vigilance, inhibition, and cognitive flexibility.

In three blocks, each with 160 consecutive trials, a visual stimulus (a red car) was shown on a computer screen for a maximum of 2 s, balanced for side of presentation (left or right). In the Go condition, children had to press a key according to the side where the stimulus appeared. The participants' response time and accuracy were recorded. In the Stop condition, children had to respond as in the Go condition on 75% of the trials but inhibit their response and refrain from pressing any key when a horn sounded during the visual stimulus during the other 25% of trials. Finally, in the Change condition, children had to respond as in the Go condition on 75% of the trials but use a different response key when a horn sounded in the remaining trials.

In the Stop and Change conditions, the horn tones were presented 50, 200, 350, or 500 ms before the expected response of the child. In the Stop condition, the children had to inhibit their primary response. In the Change condition, the children had to press a different button with the non-dominant hand. The next trial began 1 s after the child's response. The scoring of this task was fully computerized. The dependent variables of the Honk Test were as follows: (a) median reaction time (RT) for correct responses in the Go condition, (b) *SD* of RTs for correct responses in the Go condition, (c) number of errors due to lack of inhibition for the Stop Condition, (d) number of commission errors due to lack of inhibition, and (e) *SD* of the RTs for correct responses in the Change condition.

Daily Planning Test. The *Daily Planning Test* is a pencil-and-paper task designed to be completed in 20 min with the goal of evaluating the ability to plan daily activities in a simulated environment. This test is derived from the Multiple Errands Test (Shallice & Burgess, 1991) and used in frontal lesioned patients and older adults (Sgaramella et al., 1995). Participants have to carry out 10 errands in the correct order, using logical constraints (e.g., the errand "You should visit your grandmother—she asked you to buy bread" requires the participant to choose "buying bread" as the first errand) and choosing appropriate places to complete each errand (i.e., "at the bakery" for the errand "buying bread"). Moreover, children must draw the correct route on a map of an imaginary town provided by the examiner. The total score comprises the number of errands correctly reported in a logical sequence and the selection of appropriate places (maximum 10).

Sentence Completion Test. The Sentence Completion Test requires oral responses and investigates verbal inhibition, cognitive flexibility, and use of verbal strategies. The task is a modification of the Junior Hayling Sentence Completion Test (Shallice et al., 2002) and consists of 20 sentences in which the final word is missing. Children were presented with 10 sentences of each of two types (A and B). For Type A, children were asked to complete the sentence with a word that fits the phrase, earning a maximum score of 10. Following the procedure of the adult Hayling test (Burgess & Shallice, 1996) for Type B, children were asked to produce a word that made no sense at all in the context of the sentence. The children were told that the word had to be completely unrelated to the words in the sentence. The missing words were matched for frequency and age of acquisition. The sentences were presented alternately (Type A, Type B, Type A, etc.). The scoring of the Type B sentences is as follows:

0. if the child said a word unrelated to the sentence and used a strategy, for example, by naming objects in the room (*us*-type responses).
1. if the child said a word unrelated to the sentence without using a strategy (*u*-type responses).
2. if the child said a word related to the sentence or to the related answer (*s*-type responses).
3. if the child said a word that completed the sentence (*c*-type responses).

The total score for this task comprises the sum of scores for Type B sentences. Thus, a high score for Type B

sentences indicates poorer performance. (The maximum value is 30.)

Battersea Multitask Paradigm. The *Battersea Multitask Paradigm* requires the child to plan and execute a number of tasks simultaneously to gain as many points as possible given a set of rules. This task is a modified version of a test set up by Mackinlay et al. (2006), inspired by the Greenwich Test (Burgess et al., 2000) and the SET (Shallice & Burgess, 1991; Siklos & Kerns, 2004). The paradigm consists of three independent tasks: bead sorting, counter sorting, and caterpillar sorting. Participants have to achieve the most effective strategy to perform these three tasks simultaneously and score the most points within a 6-min time limit (which is not long enough to complete all three tasks). The task performance is constrained by four simple rules, which are learned before the beginning of the test and used by the experimenter to compute the child's score in different test stages. The Battersea Multitask Paradigm is divided into a practice game, where the experimenter explains the single tasks, and six stages, which represent the dependent variables of the test: (a) learning the four rules, with free and cued recall; (b) planning, where participants describe an executive plan; (c) performance of the three tasks in 6 min, a multifaceted dimension that relies upon executive strategy formation, cognitive flexibility, and mostly on inhibitory skills; (d) evaluation of coherence between planning and real performance; (e) performance retrieval; and (f) retrieval of rules learned at the beginning of the paradigm. For further details, the reader is referred to Mackinlay et al. (2006).

EFQ. The *EFQ* parent form is an adapted and modified version of the BRIEF (Gioia et al., 2000) that investigates children's behavior in a familiar context, providing a heterogeneous profile of executive functioning. The modified version was created according to the following steps: (a) we selected the four most correlated items to the eight subscales (according to the Factor Analysis presented in the original BRIEF manual); (b) we transposed the original items of the BRIEF into a positive form (e.g., "the child is able to") and translated them into Italian; and (c) a pilot study was carried out to check the quality and the clarity of the items.

The EFQ consists of 32 items describing children's behavior in many circumstances, divided into eight subscales (4 items per scale): Inhibition, Shifting, Emotional Control, Initiative, Attention, Planning/Organization, Organization of Materials, and Self-Monitoring. Parents score each single item on a 5-point Likert-type scale (from "never" to "often"), and each subscale score is the sum of the single-item scores. A total score can be derived by adding together every subscale score. The maximum score (indicating excellent EF) is 20 for each scale.

For the parent version of the EFQ, Cronbach's alpha was .92.

Procedure

The EF battery was administered to all participants individually in a single session. The total duration of the testing session varied from 50 to 75 min. The tasks were always administered in the same order: *Honk Test, Daily Planning Test, Sentence Completion Test*, and *Battersea Multitask Paradigm*. The parents completed the *EFQ*. The EF tasks were interesting enough to ensure the full motivation and compliance of all participants, and no oppositional behaviors were observed during task completion across groups.

Statistical analysis. First, a chi-square analysis was conducted to examine group differences in gender distribution, and univariate ANOVA was used to individually examine group differences in age and IQ. When significant differences arose, preliminary analyses (ANOVA) were conducted to examine the role of these factors in dependent measures.

Second, an exploratory factor analysis was conducted on the 13 neuropsychological measures of the EF battery to identify latent dimensions of neurocognitive functioning and to clarify the relations between tasks. Principal-axis extraction and Varimax rotation with Kaiser normalization were used on control group scores to extract factors with eigenvalues greater than 1. The standardization of the measures normalized the variance, and the kurtosis and skewedness values were less than 1.

Next, after checking that the assumptions (multivariate linearity, homogeneity of covariance matrices, independence of observations) were not violated, a MANOVA was carried out to compare the four groups of children (ADHD-only, ADHD + RD, ADHD + ODD, controls) on all factors extracted from the EF battery and all measures of EFQ. The alpha level was set to .05 for all data analyses. Effect sizes for MANOVAs are reported using partial eta squared (η_p^2). Where appropriate, post hoc comparisons were conducted using the Tukey HSD (Honestly Significant Difference) ($p < .05$) procedure.

Because this study was exploratory, a priori power analysis was not conducted; however, Cohen's *d* effect size for contrasts between groups and 95% confidence intervals for *d* were calculated to appropriately indicate the statistical power for significant results.

Results

Gender was not balanced across groups, as there was 1 female in the ADHD + ODD group, 1 female in the ADHD + RD group, and 24 females in the normal control group, $\chi^2(3) = 11.365$; $p = .010$. Preliminary analysis using gender

Table 1. Participant Characteristics: Age, IQ, ADHD, and ODD Symptoms.

	NC (*n* = 68)		A (*n* = 11)		A + O (*n* = 12)		A + R (*n* = 13)		One-way ANOVA		
Measures	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*(*df* = 3,101)	*p*	Tukey post hoc
Age	10.40	2.04	9.00	1.67	10.00	1.65	9.46	1.33	2.304	.081	*ns*
FSIQ	112.02	21.66	104.64	16.73	99.67	25.25	102.67	18.46	1.295	.281	*ns*
Parent ratings (CRS or the SDA questionnaire)											
Inattention	0.50	0.20	2.22	0.55	2.07	0.82	1.88	0.60	139.65	**<.001**	NC < A + R,A + O < A
Hyperactivity–impulsivity	0.49	0.20	1.65	0.87	1.91	1.06	1.29	0.82	48.25	**<.001**	NC < A + R,A + O < A
ODD	0.52	0.21	1.70	0.60	2.13	0.23	1.55	0.74	63.42	**<.001**	NC < A,A + R < A + O
Teacher ratings (CRS or the SDA questionnaire)											
Inattention	0.59	0.43	2.00	0.86	2.16	0.95	1.78	0.91	35.54	**<.001**	NC < A,A + O,A + R
Hyperactivity–impulsivity	0.54	0.33	1.77	0.67	1.83	0.65	1.06	0.96	37.70	**<.001**	NC,A + R < A,A + O

Note. IQ was obtained from the WISC-III (Wechsler, 2006). Inattention, Hyperactivity–impulsivity, and ODD are adjusted values obtained from CRS (Conners, 1997) or the SDA questionnaire (Marzocchi & Cornoldi, 2000). The adjustment was made to report raw values of CRS and SDA on a 0-3 scale (0 = minimum, 3 = maximum). Contrasts are significant at alpha = .05 (Tukey post hoc test). ODD = oppositional defiant disorder; RD = reading disorder; NC = normal controls; A = ADHD-only; A + O = ADHD + ODD; A + R = ADHD + RD; FSIQ = full-scale IQ; SDA = Sindrome da Deficit di Attenzione. WISC-III = Wechsler Intelligence Scale for Children–III; CRS = Conners' Rating Scale. Contrasts in bold are significant at alpha = .05.

as a factor revealed that the difference between boys and girls was significant only on the *SD* of the RTs for the Honk Test's Go condition, $F(1, 100) = 4.551$; $p = .036$; $\eta_p^2 = .05$). The Group × Gender interaction was not significant for any neuropsychological measure ($p > .10$). The groups did not significantly differ with respect to age or FSIQ ($p > .20$).

Table 1 presents behavioral and cognitive characteristics of the children included in the study.

Data Reduction

The results from the exploratory factor analysis on neuropsychological measures revealed five factors (explaining 69% of the variance) with eigenvalues greater than 1; these factors were labeled as Speed of Processing, Inhibition, Planning, Execution, and Retrospective Memory. Measures of general processing speed, namely, the Honk Test Go condition RT, Honk Test Go condition *SD* of RTs, and Honk Test Change condition *SD* of RTs, loaded on Speed of Processing, with loadings ranging from 0.76 to 0.85. The number of errors on the Honk Test Stop condition and the number of errors on the Honk Test Change condition loaded on the Inhibition factor, with loadings of 0.82 and 0.80, respectively; additionally, the performance score of the Battersea Multitasking Paradigm loaded primarily on the Inhibition factor, with a loading of 0.46, most likely because this test requires the participant to avoid responding repeatedly to the same task to achieve the most effective performance. The Planning score and Coherence score on the Battersea Multitasking Paradigm loaded on the Planning factor, with loadings of 0.88 to 0.65, respectively. The total scores on the Daily Planning Test and Sentence Completion Test loaded on the Execution factor, with loadings of 0.68 to 0.78, respectively. All measures involved in retrospective memory demands of the Battersea Multitasking Paradigm, namely, the Rule Learning score, Performance Retrieval, and Rule Retrieval, loaded together the Retrospective Memory factor, with loadings ranging from 0.45 to 0.62. Table 2 shows the results of the exploratory factor analysis.

A second exploratory factor analysis was carried out on the eight subscales of the parents' EFQ. Two factors that explained 73.5% of the total variance were extracted. Five subscales (Initiative, Attention, Plan/Organize, Organization of Materials, and Self-Monitoring) loaded on Factor 1, labeled Metacognition; three subscales (Inhibition, Shifting, and Emotional Control) loaded on Factor 2, labeled Inhibitory Control. Table 3 presents saturation values of the eight subscales of the EFQ on the two factors.

Comparison Between Groups

Table 4 presents the unadjusted means of each group on the five factor scores.

The group effect was significant for the Speed of Processing factor score because children with ADHD + RD were slower than normal controls. For the Inhibition factor score, the difference between groups did not reach statistical significance. The group effect was significant for the Planning Factor score, with the normal control group outperforming the ADHD-only group. The group effect on the Execution Factor score was significant because all of the ADHD groups performed worse than the normal controls. The group effect on Retrospective Memory factor score was

Table 2. Principal-Axis Factor Analysis of Executive Function Tasks.

	Factor loadings on the five extracted factors				
Measures	Speed of Processing	Inhibition	Planning	Execution	Retrospective Memory
Honk Test—Go mean RT	**0.85**	—	—	—	—
Honk Test—Go *SD* of mean RT	**0.78**	—	—	—	—
Honk Test—Change *SD* of mean RT	**0.76**	0.39	—	—	—
Honk Test—Stop Errors	—	**0.82**	—	—	—
Honk Test—Change Errors	—	**0.80**	—	0.39	—
Battersea Multitasking Paradigm—Performance	—	**0.46**	—	0.26	—
Battersea Multitasking Paradigm—Planning	—	—	**0.88**	—	—
Battersea Multitasking Paradigm—Coherence	0.48	—	**0.65**	—	0.24
Daily Planning Test—Total Score	—	—	0.38	**0.68**	—
Sentence Completion Test—Total Score	—	—	0.21	**0.78**	—
Battersea Multitasking Paradigm—Rule Learning	0.42	—	0.41	0.32	**0.45**
Battersea Multitasking Paradigm—Performance Retrieval	—	—	—	0.24	**0.82**
Battersea Multitasking Paradigm—Rule Retrieval	0.36	—	0.30	0.25	**0.60**
Eigenvalue	2.57	1.75	1.72	1.55	1.34
Percentage of variance explained	19.75	13.46	13.26	11.92	10.29

Note. A dash (—) indicates a factor loading of less than .20. Loadings in bold type indicate primary factor loadings.

Table 3. Principal-Axis Factor Analysis of EFQ subscales.

EFQ subscale	Metacognition	Inhibitory control
Inhibition	.425	.784
Shifting	—	.830
Emotional Control	—	.876
Initiative	.792	.290
Attention	.886	—
Planning/Organization	.902	—
Organization of Materials	.689	—
Self-Monitoring	.702	.472

Note. EFQ = Executive Function Questionnaire; RT = Reaction Time. Dash (—) indicates a factor loading less than .20.

significant, as the ADHD + RD group performed worse than the normal controls.

Moreover, the average group scores on the eight EFQ subscales and two factors were compared. Children in the ADHD-only and ADHD + ODD groups were judged by their parents as having more Inhibitory Control difficulty than were normal controls ($p < .001$). Moreover, all groups with ADHD (ADHD-only, ADHD + ODD, and ADHD + RD) were rated by their parents as having lower metacognitive skills than their peers in the control group ($p < .001$). On seven of the eight subscales, all groups with ADHD were rated as more problematic than were controls (all $ps <$ .001). Only for the Organization of Materials subscale did the post hoc analysis find no significant difference between groups. This null result was due to the lower scores of the normal controls on this subscale compared with the other scales (Table 5).

Finally, to study the ecological validity of the new EF battery, a Pearson correlation analysis was performed between the EFQ and the five factor scores of the EF measures. The factor of the EF battery labeled Execution significantly correlated with almost all measures of the EFQ (only Organization of Materials did not correlate with Execution), with correlations ranging from .30, $p = .01$ to

Table 4. Group Means and Standard Deviations for Executive Function Tasks.

	NC (*n* = 68)		A (*n* = 11)		A + O (*n* = 12)		A + R (*n* = 13)						*d* Cohen's effect size (95% CI)		
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*(3, 101)	*p*	η_p^2	Tukey post hoc	ADHD-only vs. NC	ADHD + ODD vs. NC	ADHD + RD vs. NC
Processing speed	0.00	1.00	0.73	1.24	0.09	0.91	1.18	1.14	5.67	**.001**	.145	NC < A + R	0.71 [0.49, 0.94]	0.09 [0.00, 0.31]	1.12 [0.89, 1.33]
Inhibition	0.00	1.00	0.76	1.52	0.23	1.13	0.69	1.08	2.63	.054	.073	ns	0.71 [0.48, 0.95]	0.23 [0.01, 0.45]	0.69 [0.48, 0.91]
Planning	0.00	1.00	−1.01	0.89	−0.46	1.28	−0.62	1.38	3.70	**.014**	.100	NC > A	1.04 [0.82, 1.26]	0.45 [0.22, 0.67]	0.59 [0.36, 0.82]
Execution	0.00	1.00	−1.49	0.83	−1.78	1.32	−0.89	0.88	16.06	**.000**	.327	NC < A,A + O,A + R	1.54 [1.33, 1.75]	1.71 [1.49, 1.95]	0.92 [0.71, 1.13]
Retrospective memory	0.00	1.00	−0.45	1.09	−0.44	0.81	−1.17	1.42	4.86	**.003**	.127	NC > A + R	0.45 [0.23, 0.67]	0.46 [0.24, 0.67]	1.10 [0.87, 1.33]

Note. Contrasts in bold are significant at alpha = .05. ODD = oppositional defiant disorder; RD = reading disorder; NC = normal controls; A = ADHD-only; A + O = ADHD + ODD; A + R = ADHD + RD. CI = confidence interval.

Table 5. Group Means and Standard Deviations for the EFQ.

	Groups										
	NC (*n* = 68)		A (*n* = 11)		A + O (*n* = 12)		A + R (*n* = 13)		One-way ANOVA		
EFQ subscales	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*(*df* = 3,102)	*p*	Tukey post hoc
Inhibitory Control factor	0.00	1.00	−1.61	1.05	−1.44	1.34	−0.86	0.94	12.832	**<.001**	A,A + O < NC
Inhibition	15.60	3.12	9.00	3.38	9.73	4.10	11.92	4.81	19.178	**<.001**	A,A + O,A + R < NC
Shifting	15.99	3.12	11.45	3.50	12.55	4.34	12.33	4.14	9.832	<.001	A,A + O,A + R < NC
Emotional Control	14.59	3.12	9.82	3.60	9.91	3.78	11.50	3.06	13.024	<.001	A,A + O < NC
Metacognitive factor	0.00	1.00	−1.28	1.22	−1.07	1.07	−1.53	0.96	12.513	**<.001**	A,A + O,A + R < NC
Initiative	16.53	2.84	13.00	3.98	13.27	2.61	12.75	3.44	10.359	**<.001**	A,A + O,A + R < NC
Attention	15.84	3.52	9.55	3.45	10.64	3.20	9.00	2.92	24.780	**<.001**	A,A + O,A + R < NC
Planning/ Organization	15.79	3.36	11.09	3.56	11.45	4.03	10.00	2.76	16.592	**<.001**	A,A + O,A + R < NC
Organization of Materials	13.01	3.79	9.73	3.23	11.18	4.77	10.25	4.71	3.588	**=.016**	
Self-Monitoring	15.69	2.68	11.55	2.58	12.00	4.38	12.08	2.54	13.302	**<.001**	A,A + O,A + R < NC

Note. Contrasts are significant at alpha = .05 (Tukey post hoc) in bold. EFQ = Executive Function Questionnaire; NC = normal controls; A = ADHD-only; ODD = oppositional defiant disorder; A + O = ADHD + ODD; A + R = ADHD + RD; RD = reading disorder.

.46, $p = .001$. The Inhibitory Control factor of the EFQ significantly correlated with the Inhibition factor, $r = -.29$, $p = .01$, and the Execution factor, $r = .36$, $p = .01$, of the EF tasks, whereas the Metacognition factor of the EFQ significantly correlated with the Speed of Processing factor, $r = -.22$, $p = .05$, and the Execution factor, $r = .33$, $p = .01$, of the EF battery. Overall, 23 (46%) of a total of 50 correlational comparisons between EFQ measures and the five factors extracted by EF performance-based task were statistically significant ($p < .05$).

Discussion

The purpose of the present study was threefold. Our first aim was to test a model of EF in which the different components could be interpreted as sequential steps of a complex behavior to achieve a goal. Second, we aimed to analyze which components of EF could be impaired in children with ADHD. Finally, we intended to determine whether children with ADHD and comorbidity with ODD or with RD are more impaired than children with ADHD-only, using an EF framework. To achieve these goals, four groups of participants (ADHD-only, ADHD + ODD, ADHD + RD, and typically developing children) were presented with a battery of new EF tasks inspired by neuropsychological models (Burgess et al., 2000; Zelazo & Frye, 1998), and parents rated their everyday life EF skills using the EFQ. Five cognitive factors (Speed of Processing, Inhibition, Planning, Execution, and Retrospective Memory) were extracted from EF tasks via exploratory factor analysis. Similarly, two cognitive factors (Metacognition and Inhibitory Control) were extracted from the EFQ using factor analysis. Two distinct group comparisons were performed on the EF battery and on the questionnaire results to test the discriminative capacity of the new EF measures. Afterward, a Pearson correlation analysis was performed between the EFQ subscales and the five factor scores of the EF tasks to examine the ecological validity of the EF battery.

With regard to the first goal of our study—to test a model of EF comprised of a sequential flow of cognitive processes—the exploratory factor analysis conducted on the neuropsychological measures of the EF battery identified five latent dimensions of neurocognitive functioning that support a unified model of EF in children: Inhibition, Planning, Execution, and Memory of Performance, sustained by Speed of Processing. In fact, our data support a "sequential" EF model, wherein EF could represent consecutive cognitive processes (see, for example, Burgess et al., 2000; Zelazo & Frye, 1998) rather than other neurocognitive models that have proposed a division of EF into distinct and fractionated domains (see, for example, Letho et al., 2003; Wu et al., 2011). More specifically, the present results are consistent with the "ecological" EF model proposed by Burgess et al. (2000). According to this neurocognitive model, performing a goal-directed behavior requires a child to pass through sequential steps: controlling impulsive responses (Inhibition), learning the rules of the activity to be performed (Memory), establishing a working plan (Planning), performing the action scheme (Execution) and, finally, verifying the accomplishment of the goal of the behavior by recalling the rules of the task.

With regard to the other two major aims, the neurocognitive EF battery used in the present study has been shown to be more sensitive to between-group differences than the classic EF measures used in other studies investigating EF in children with ADHD with or without comorbidities (Barnett, Maruff, & Vance, 2009; Klorman et al., 1999; Qian, Shuai, Cao, Chan, & Wang, 2010). In fact, with respect to our examination of between-group differences, the present results yield evidence for the existence of a specific executive profile for each group of children with ADHD. Children with ADHD + RD demonstrated impairment on cognitive factors representing the Speed of Processing and Retrospective Memory factors, which is consistent with previous studies (Shanahan et al., 2006; Willcutt, Pennington, et al., 2005), and on the Executive factor. Children with ADHD + ODD showed a unique deficit in the Executive factor. This finding is consistent with Clark et al. (2000), who used the SET and Hayling Test. Thus, ADHD + ODD children could be described by parents as displaying severe executive dysfunction in everyday activities (e.g., reporting more externalizing symptoms in clinical interviews), even though such a dysfunction may not be evident during performance-based tests (Gioia & Isquith, 2004). Finally, ADHD-only children showed a specific deficit in the Planning factor and in the Executive factor. This finding is consistent with the work of Clark et al. mentioned above and with a previous Italian study (Marzocchi et al., 2008). The present study provides evidence for the existence of a common deficit across all groups with ADHD regarding the Executive factor, the most relevant component in the executive domain. It is worth remembering that the Executive factor was included in the total scores on the Daily Planning Task and the Sentence Completion Test. Moreover, these deficits in performance-based tests were confirmed by parental ratings on an EFQ.

Finally, with regard to the ecological validity of the neuropsychological tests of EF, the literature on the relationship between EFQs and classic EF tests yields conflicting findings. Some studies have reported no significant correlations between the BRIEF and classical performance-based EF tests (Anderson et al., 2002; Bodnar et al., 2007; Mahone et al., 2002; Vriezen & Pigott, 2002), whereas other studies have shown weak to moderate correlations between BRIEF and classical EF tests (McCandless & O'Laughlin, 2007; Toplak, Bucciarelli, Jain, & Tannock, 2009). Furthermore, a recent review by Toplak et al. (2013) on the correlations between performance-based versus ratings of EF reported that only 24% of correlational comparisons were statistically significant, suggesting that the two types of measures could assess different aspects of cognitive functioning. In the present work, however, moderate associations were obtained between performance on the EF measures and EFQ scores. The Inhibitory Control factor of the EFQ significantly correlated with the Inhibition and Executive factors of the EF tasks, and the Metacognitive factor of the EFQ significantly correlated with the Speed of Processing and Executive factors of the EF tasks. Moreover, 46% of the correlational comparisons between EFQ measures (parent ratings of EF) and the five factors extracted by the EF performance-based tasks reached significance in the present study. Our results therefore indicate a relative but significant overlap between EF performance-based tests and executive dysfunction in everyday activities as rated by parents, showing that the EF battery used in the present study demonstrates sufficient ecological validity.

In summary, the present study separates and describes different cognitive profiles of children with ADHD-only and those with ADHD and comorbid disorders using neuropsychological EF measures. These tests show good ecological validity, significantly correlating with parent ratings of EF in everyday activities. Moreover, our work yields meaningful information about EF in children aged 7 to 12 years (i.e., a system of consecutive cognitive processes), supporting the hypothesis that an integrated model of executive functioning, in which different components are interpreted as sequential processes, could be helpful in understanding ADHD and associated disorders.

From a neuroanatomical point of view, it is interesting to note that the components of EF extracted from the EFQ (Metacognition and Inhibitory Control) could reflect the different functional organization within the PFC in children with ADHD that has been described in the literature. Indeed, the Inhibitory Control, or "hot" affective aspect of EF (Zelazo & Müller, 2002), is reported to activate inferior frontal regions (Ardila, 2008; Fuster, 2002), while the Metacognitive, or "cool" cognitive aspects of EF (Zelazo & Müller, 2002), could involve the dorsolateral PFC bilaterally (Ardila, 2008; Fuster, 2002). Future neuropsychological studies of ADHD should document the association of the dorsolateral and inferior frontal cortices more thoroughly.

Limitations and Future Directions

Despite our promising results, some limitations of the present study should be considered. The main limitation is related to the small sample sizes of the clinical groups; the present results therefore require replication in a larger scale study. Moreover, an analysis of concurrent validity and construct validity between the new EF tests (Multitask, Daily Planning Task, Sentence Completion Test) and the classic EF tasks (Tower of London, Wisconsin Card Sorting Test, Trail Making Test, Verbal Fluency) could be useful for clarifying which cognitive dimensions are effectively evaluated by these new EF tests.

Finally, it should be noted that there was a disproportionate gender distribution between the clinical subgroups (one

female in the ADHD + ODD group, one female in the ADHD + RD group) and the healthy control group (24 females). Although a Group × Gender effect was not observed for any neuropsychological measure in this study, consistent with previous findings not supporting any effect of gender on impairment or development of EF (for a review, see Rucklidge, 2010), future studies in which the samples are large enough to study gender differences by means of the present EF battery and questionnaire could be fruitful.

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Clumsiness in fine motor tasks: evidence from the quantitative drawing evaluation of children with Down Syndrome

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Abstract

Introduction Drawing tests are commonly used for the clinical evaluation of cognitive capabilities in children with learning disabilities. We analysed quantitatively the drawings of children with Down Syndrome (DS) and of healthy, mental age-matched controls to characterise the features of fine motor skills in DS during a drawing task, with particular attention to clumsiness, a well-known feature of DS gross movements.
Methods Twenty-three children with DS and 13 controls hand-copied the figures of a circle, a cross and a square on a sheet. An optoelectronic system allowed the acquisition of the three-dimensional track of the drawing. The participants' posture and upper limb movements were analysed as well.
Results Results showed that the participants with DS tended to draw faster but with less accuracy than controls.
Discussion While clumsiness in gross movements manifests mainly as slow, less efficient movements, it manifests as high velocity and inaccurate movements in fine motor tasks such as drawing.

Keywords ADHD, Down Syndrome, drawing, fine motor skills

Introduction

A pervasive feature of motor skill performance in participants with Down Syndrome (DS) is 'clumsiness', which commonly implies an ample set of movement characteristics, such as slow movements with unusual, less efficient patterns of co-ordination and high rates of failure (Galli *et al.* 2010; Rigoldi *et al.* 2011a), slower reaction times, lower muscle tone and ligament laxity (Morris *et al.* 1982; Galli *et al.* 2008). The evaluation of 'clumsiness' has since now taken into account gross motor tasks, mainly walking and slowness of movements seems to be one of the main, omnipresent features of DS movements. This phenomenon has been largely related to the biomechanical features of DS's movements, such as muscular weakness and ligament laxity (Cioni *et al.* 2001; Rigoldi *et al.* 2011a). Recent literature, however, points out that clumsiness may be mainly a product of limitations at

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central nervous system level, more than a product of biomechanical constraints alone (Virji-Babul & Brown 2004; Latash 2007). In this sense, biomechanical aspects are recently beginning to be linked together with the specific sensory, motor, cognitive and perceptual impairments of DS, but it remains unclear how these localised deficits impact on perceptual-motor processing and function (Virji-Babul & Brown 2004; Vimercati *et al.* 2013).

Behavioural disorders in DS include decreased attention, hyperactivity and impulsivity, which are frequently reported in DS. The exact prevalence of attention-deficit/hyperactivity disorder (ADHD) has not been clearly estimated in this population, yet a recent study (Ekstein *et al.* 2011) indicates that 43.9% of the evaluated participants with DS was affected by ADHD. The possible presence of ADHD in DS population is supported also by several studies addressing the presence of a deficit in the frontal lobes function in DS (Rowe *et al.* 2006; Kittler *et al.* 2008; Lanfranchi *et al.* 2009, 2010). Sensory deficits are present as well, such as increased risk of hearing loss and eye diseases (Ekstein *et al.* 2011). The general picture of DS thus presents itself as a very complicated picture, in which aspects of co-morbid psychiatric disorders interplay with the cognitive, motor and perceptual impairment caused by the syndrome itself. Some aspects of this picture have been more in-depth studied, such as the gross motor functions of walking and posture (Galli *et al.* 2010; Rigoldi *et al.* 2011a,b), which allowed an in-depth study of the biomechanics of movement in DS, whereas some other aspects are only recently beginning to be considered by literature. For instance, drawing ability, which has been since now almost completely omitted from the analysis, could provide important information about the cognitive state of DS. The study of drawing, in fact, allows analysing the perceptual-motor skills of the participant (in particular visual-spatial and grapho-motor abilities), together with the presence of ADHD disturbances. Simple drawing tests are commonly used for the clinical evaluation of cognitive capabilities in children with learning disabilities. Among several graphic tests that have been developed for the cognitive evaluation of children, the Denver Developmental Screening Test (DDST) (Frankenburg *et al.* 1992) is one of the most used. The test comprises a drawing session in which the child is asked to copy the figures of a circle, a square and a cross. Copying a figure requires the child to consider the visual form (figure) as well as the neuromuscular adjustments for line control, direction, speed and pressure (Khalid *et al.* 2010), together with appropriate management of the ocular-motor co-ordination. Thus, drawing a figure can give insight on both the biomechanical control and some of the neural mechanisms underlying this control.

Graphic tests have been administered to evaluate the performance of children with a wide range of pathologies and/or difficulties, such as children at risk for school problems (Perera 2005; Bayoglu *et al.* 2007), children with developmental co-ordination disorders (Smits-Engelsman *et al.* 2003), children with autism (Sheppard *et al.* 2007, 2009) and children with learning disabilities (Galli *et al.* 2011) but, to the best of our knowledge, only one study (Clements & Barrett 1994) addressed the characterisation of drawings in children with DS, though by a qualitative visual evaluation. This study analysed the drawing performance of children and young people with DS compared with verbal-mental-age-matched children without learning difficulties. The drawing task required the participants to depict the partial occlusion of one object by another object. The drawings were given a visual score, which was then correlated with the verbal mental age of the participants. Children with DS obtained significantly lower scores than children without learning disabilities and, more interestingly, they employed different drawing strategies on individual drawing tasks. While the control group's performance correlated strongly with the verbal mental age, the performance of DS did not show the same correlation. Consequently, the authors suggested that the differences between the drawings of children with and without DS reflected a developmental difference in the underlying processes of drawing production and development rather than a delay in development.

Most of the drawing evaluation in clinical routine is nowadays still based on visual scoring systems, such as for the DDST. However, some quantitative methods have been developed and applied in research settings in the last years. In particular, a three-dimensional (3D) method for graphic gesture acquisition with the use of an optoelectronic system

was developed by Galli *et al.* (2011) to allow a quantitative, detailed description of drawings. The method was successfully applied to children with learning disability (Galli *et al.* 2011), participants with Parkinson Disease (Galli *et al.* 2012) and with dementia (De Pandis *et al.* 2010). In the present study, and based on the previous work of Galli *et al.* (2011) on the acquisition of drawings with an optoelectronic system, we analyse quantitatively the drawings of a group of children with DS and of a group of healthy, mental age-matched controls. The aim of the study was to characterise the features of fine motor skills in DS during a drawing task taken from the DDST.

Methods

Participants

Two groups of participants were enrolled for this study at the IRCCS San Raffaele Pisana, in Rome, where the acquisitions took place. The participants and their legal tutors gave their informed written consent to the study. The study was approved by the ethical committee of IRCSS San Raffaele Pisana, Tosinvest Sanità, Rome, Italy, in accordance with the ethical principles of the Declaration of Helsinki.

The DS group was composed of 23 children with DS. Their chronological mean age was 14.9 ± 4.6 years old, whereas their mean mental age, estimated from the quotient of intelligence index, was 8.1 ± 2.9 years old. The inclusion criteria for DS were right-handedness, a regular school frequency and education, no orthopaedic problems that could restrict upper limbs motion.

The control group (N) was composed of 13 children, whose mean age (9.0 ± 2.1 years old) was matched to the mental age of the DS group. Inclusion criteria for N were right-handedness, no physical or psychological dysfunction and a regular school education.

Methods

The graphic gesture was acquired with an optoelectronic system with six cameras (SMART-D BTS; Italy), at a frequency of 200 Hz, and with an integrated video system (Vixta, BTS, Italy) for video-recording. The optoelectronic system is an equipment that measures the 3D co-ordinates (X, Y, Z) of reflective markers through time. The markers were of diameter = 10 mm and were used in the configurations described here following (Fig. 1a,b).

Before every acquisition, a calibration was performed to define a global reference system frame for all the cameras and compute the extrinsic and intrinsic parameters for each camera. The calibrated volume (around 0.6 × 0.4 × 0.6 m) was defined

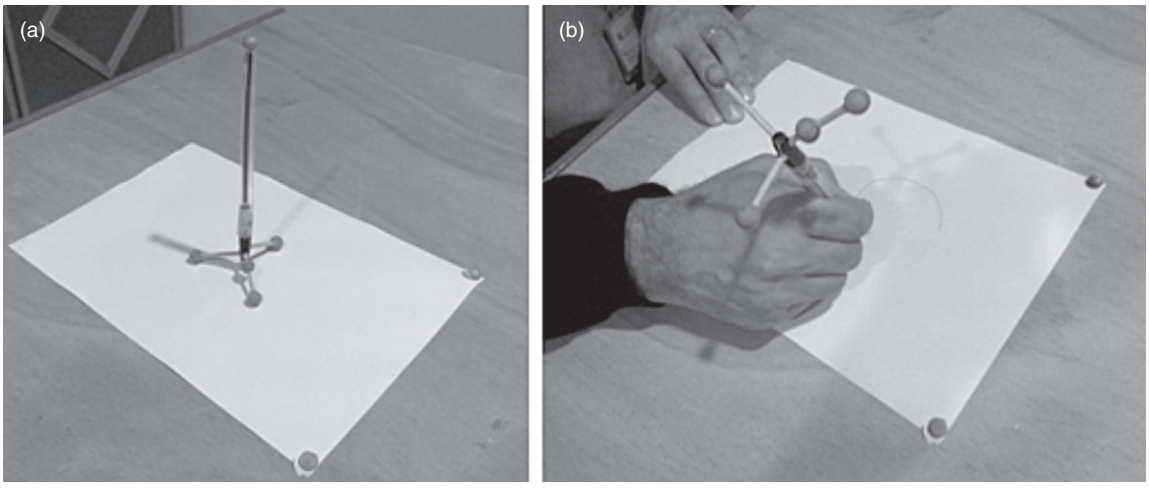

Figure 1 (a) Markers configuration for the pen during the static acquisition, (b) markers configuration for the pen and sheet during the dynamic acquisition.

considering that the volume had to include the whole motion and it had to be as small as possible, in order to obtain a high accuracy. At the end of the process, calibration was considered acceptable if the mean error on the computation of the difference between the measure and actual distance of two markers fixed on the extremities of a rigid bar at the distance of 150 mm was within 0.20 mm (standard deviation: 0.20 mm).

The children seated comfortably on an adjustable chair, in front of a desk. Their height respect to the desk was regulated to allow easy and comfortable drawing. They were given a paper sheet with a printed figure (a circle, an equilateral cross and a square) and were asked to '*copy the illustrated figure*' with their dominant hand. The figures were presented one per time. After drawing the first figure, the child was presented with the second and then with the third. Three acquisitions (one for each drawing) were recorded for each child. Children were given a modified ink pen with markers on the cap that allowed the reconstruction of the trace drawn by the children, as described following.

Two acquisitions were necessary for each participant: a static acquisition of the markers on the pen, and a dynamic acquisition during which the participant drew. The first markers configuration, shown in Fig. 1 on the left, was used for the static acquisition, in which the participant did not take part. The pen was positioned on the table with the four markers on the cap and a maker on the tip, and the markers were acquired for five seconds, in order to calculate the position of the tip of the pen and allow the calculation of its position during the dynamic acquisition, in which the graphic test was executed by the participant. Figure 1 on the right shows the markers configuration for the drawing trials: the marker on the tip was removed, and the participant drew on the sheet. Two markers were also placed on the sheet to define a system of reference on the sheet during the dynamic acquisition. This marker configuration is a further adaptation and improvement of the method by Galli *et al.* (2011).

As shown in Fig. 2, starting from the co-ordinates of the markers on the pen cap, a system of reference (Xp, Yp, Zp) was defined on the pen. In this way, during the dynamic acquisition, the pen tip co-ordinates were reconstructed

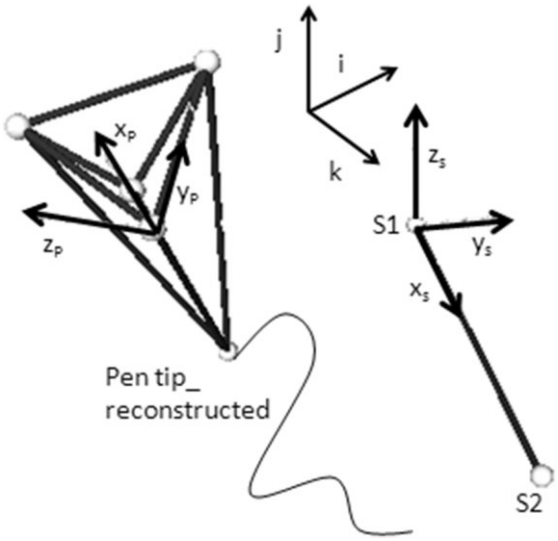

Figure 2 Pen tip reconstruction during the drawing trials and reference system on the sheet to allow rotation of the sheet during the drawing.

(Pen tip_reconstructed) and it was possible to obtain the digitalised drawing trace (i.e. the drawn figure) and the trace of the pen lifts. Another system of reference (Xs, Ys, Zs) was defined starting from the markers on the sheet and from the laboratory reference system (i, j, k). In this way, the sheet could be rotated by the participant during the drawing without interfering with the measurements, allowing free and natural movements of the participants.

Markers were also put on the body of the participant. Landmarks on the body were chosen in order to minimise the effect of the skin artefacts. In particular, markers were put on the head, shoulders, trunk, elbow, wrist and hand on the side of hand dominance. The protocol for markers placement is shown in Fig. 3 for a right-handed participant.

Tests and parameters

After reconstructing the 3D co-ordinates of the markers, the following parameters were computed. To characterise the position of the participant's head during the drawing, the maximum and minimum projections of the c_head marker on the table were computed and the difference between these two values was named head-table distance (*head-table_dist*) (m).

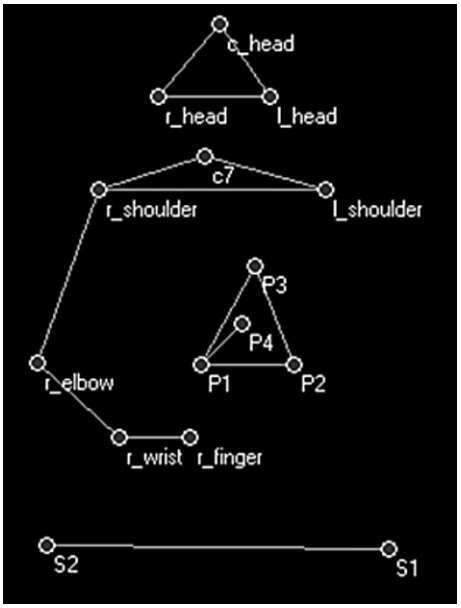

Figure 3 Protocol for markers placement; r, right; l, left; c, central.

To characterise the movement of the upper limb, the elbow angle was defined as the acute angle between the markers positioned on the shoulder, elbow and wrist. The wrist angle was defined as the acute angle between the markers positioned on the elbow, wrist and hand. The ranges of motion (ROMs) of these two angles were computed from the co-ordinates of the external markers.

To characterise the drawing traces of the different figures the following parameters were calculated.

Circle drawing

The drawing features of the circle were characterised by:
• length of the drawing track (*Length*) (m), drawing time (*Time*) (s) and drawing peak of velocity (*Max Vel*) (m/s);
• horizontal and vertical diameters lengths (*H_Dm*, *V_Dm*) (m);

Drawing accuracy was evaluated by the parameter of eccentricity:

• eccentricity (*Ecc*): $Ecc = \left|1 - \frac{V\_Dm}{H\_Dm}\right|$

The more the drawn figure is close to a perfect circle, the more the parameter approaches a 0 value.

Cross drawing

The drawing features of the cross were characterised by:
• drawing time (*Time*) (s) and drawing peak of velocity (*Max Vel*) (m/s);
• length of the horizontal and vertical sides (*H_side*, *V_side*) (m);

Drawing accuracy was evaluated by the cross side error parameter, chosen to assess the tendency to draw irregular cross bars:

• cross side error (*side-ε*): $side\_\varepsilon = \left|1 - \frac{H\_Side}{V\_Side}\right|$

The closer the value is to 0, the more precise is the drawing, i.e. the sides have more similar lengths (equilateral cross);

Square drawing

The drawing features of the square were characterised by:
• drawing time (*Time*) (s) and drawing peak velocity (*Max Vel*) (m/s);
• length of the upper, lower, left and right sides (*S1*, *S2*, *S3*, *S4*) (m);

Drawing accuracy was evaluated by two parameters, chosen to assess the tendency to draw an irregular polygon:
• square sides error ($s - \varepsilon$) (m): $s - \varepsilon = |S1 - S2| + |S3 - S4|$
the closer the value is to 0, the more precise is the drawing, that is, the sides have more similar lengths.
• square to rectangle error ($str - \varepsilon$): $str - \varepsilon = \left|1 - \frac{W}{H}\right|$
where W is the square's width, calculated as Max(S1, S2) and H is the square's height, calculated as Max(S3, S4). The closer the parameter is to 0, the closer the drawing is to a square.

These parameters were chosen to assess the tendency to draw irregular parallelepiped rather than squares.

Figure 4 illustrates some of the analysed parameters.

Statistical analysis

Data were collected for each participant and tabulated in order to compare overall results from pathological group and control group. The median,

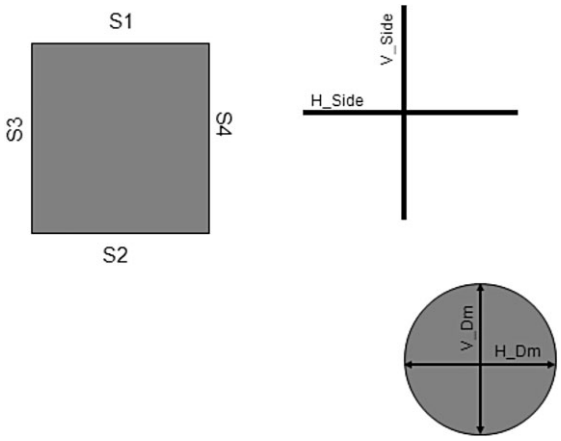

Figure 4 Representation of some of the parameters.

25° and 75° percentile values were computed for each group and parameter. The non-parametrical Mann–Whitney *U*-test was used to verify the presence of statistically significant differences between the DS and N groups. Differences were considered significant at a *P*-value < 0.05.

Results

The kinematic parameters of upper limb motion did not reveal any statistically significant difference between groups.

Table 1 presents the results for the characterisation of the drawing features and drawing accuracy in DS and N participants and for the head-table distance parameter.

For the circle, although the length of the track and the diameters' lengths were similar (similar drawing dimensions among groups) duration of the drawing was shorter for DS than for N. In agreement with this, maximum velocity was higher in DS. The eccentricity parameter was not statistically different for N compared with DS, meaning that a comparable degree of accuracy was present in the drawings of the two groups in terms of eccentricity.

For the cross, duration of the drawing was shorter in DS. The horizontal side of the cross was shorter in DS as well, whereas dimensions were comparable among groups for the vertical side. Maximum velocity was higher for DS. The accuracy parameter highlighted the presence of more inaccuracy in DS: the side-error parameter revealed in fact that DS's crosses were further from being equilateral crosses, with the centre of the cross being more off-centred, decentralised from the ideal position in DS respect to N.

For the square, no duration differences were found. Dimensions were similar and just some slight difference was found in the two vertical sides of the square, with DS drawing slightly longer sides. The side error was slightly higher for DS, whereas the tendency to draw rectangles instead of squares was more pronounced for DS.

The head-table distance was lower for DS in both the circle and cross drawing, whereas it was comparable for the square. Thus, the DS drew with a

Table 1 Median (25° percentile, 75° percentile) values for the drawing features and drawing accuracy parameters for the Down Syndrome (DS) and control (N) groups

Parameter	DS Median (25°, 75°)	N Median (25°, 75°)	*P*-value < 0.05
Circle drawing			
Length (m)	0.14 (0.10, 0.15)	0.15 (0.11, 0.18)	
Time (s)	2.92 (2.11, 5.70)	6.48 (5.12, 9.07)	*
Max Vel (m/s)	0.08 (0.06, 0.10)	0.05 (0.04, 0.07)	*
H_Dm (m)	0.04 (0.03, 0.05)	0.05 (0.04, 0.05)	
V_Dm (m)	0.04 (0.03, 0.05)	0.05 (0.04, 0.05)	
Ecc	1.16 (0.98, 1.24)	0.99 (0.96, 1.04)	
Head-table_ dist (m)	0.02 (0.01, 0.02)	0.03 (0.03, 0.08)	*
Cross drawing			
Time (s)	3.31 (2.07, 4.88)	6.66 (4.94, 8.35)	*
Max Vel (m/s)	0.09 (0.07, 0.18)	0.05 (0.05, 0.13)	*
H_side (m)	0.04 (0.03, 0.05)	0.06 (0.05, 0.06)	*
V_side (m)	0.06 (0.05, 0.07)	0.06 (0.05, 0.07)	
s_ε	0.26 (0.12, 0.39)	0.15 (0.07, 0.19)	*
Head-table_ dist (m)	0.01 (0.01, 0.03)	0.0.5 (0.03, 0.07)	*
Square drawing			
Time (s)	7.87 (4.68, 12.53)	10.01 (9.14, 11.95)	
Max Vel (m/s)	0.10 (0.08, 0.11)	0.07 (0.05, 0.07)	*
S1 (m)	0.05 (0.04, 0.06)	0.05 (0.04, 0.05)	
S2 (m)	0.05 (0.04, 0.06)	0.05 (0.05, 0.05)	
S3 (m)	0.05 (0.04, 0.06)	0.04 (0.04, 0.05)	*
S4 (m)	0.05 (0.04, 0.06)	0.04 (0.04, 0.05)	*
s_ε	0.01 (0.01, 0.02)	0.00 (0.00, 0.01)	*
str_ε	0.21 (0.11, 0.23)	0.06 (0.01, 0.11)	*
Head-table_ dist (m)	0.03 (0.02, 0.06)	0.03 (0.02, 0.06)	

* *P*-value < 0.05.

closer position of the head respect to the sheet in the circle and cross drawings.

Discussion

Drawing tests are commonly administered to children with a wide range of cognitive impairments. Surprisingly, drawing tests have not been applied in literature to DS, with the exception of the work by Clements & Barrett (1994), who analysed drawings from a qualitative point of view. The aim of the study was therefore to characterise the features of fine motor skills in DS by a quantitative 3D analysis of drawing.

Literature has proven how clumsiness is a pervasive feature of DS gross movements, and how it manifests mainly as slow, less efficient movements (Galli *et al.* 2010; Rigoldi *et al.* 2011a). Traditionally, this phenomenon has been largely related to the biomechanical features of DS's movements (Cioni *et al.* 2001; Rigoldi *et al.* 2011a). On the other hand, recent literature points out that clumsiness may be mainly a product of the limitations at the central nervous system level, more than a product of biomechanical constraints alone (Virji-Babul & Brown 2004; Latash 2007). The results of the present study support this latter hypothesis. The present results, in fact, highlight shorter durations and higher peaks of velocity (with comparable drawing dimensions) in the drawings of DS compared with mental aged-matched participants without cognitive disability. An increased velocity would not be *per se* a proof of clumsiness, but it is in fact a proof of clumsiness if we consider velocity results together with accuracy results. The general accuracy in drawing, in fact, appears to be lower in DS than in controls if we take into account the cross and square drawings, whereas it is comparable in the circle drawing. The cross and square drawings, in fact, are less regular, with the square often depicted as a rectangle and the cross often depicted with a decentralised centre and uneven sides. Thus, our participants with DS tend to draw faster but with less accuracy than controls. For what concerns the circle, higher velocity peaks were found whereas accuracy seems comparable among groups. This may be attributable to the higher complexity of drawing curved lines instead of straight lines as required in the circle drawing, which caused lower accuracy in both groups. Anyway, the percentile ranges for the two groups (DS: 0.26, N: 0.08), calculated by subtracting the 25° percentile value to the 75° percentile value, suggest the presence of a higher variability in DS, so it is possible that a significant difference could be found just by increasing the participants' number. Thus, a first comment on the results is that DS's clumsiness in fine movements such as drawing manifests itself in a different way than it does for gross movements. The fact that clumsiness acquires different features based on the kind of motor task involved (gross vs. fine motor tasks) suggests that this central characteristic of DS movement is not mainly related to muscular weakness and/or ligament laxity problems (i.e. problems at the 'effector system'), yet it is principally due to a problem at a central level, in agreement with recent studies (Virji-Babul & Brown 2004; Latash 2007). Thus, biomechanical aspects such as slowness of movement, or velocity of movement in our case, should probably be interpreted in light of the specific sensory, motor, cognitive and perceptual impairments of DS.

The fact that kinematic parameters of the upper limb did not reveal significant differences, and nevertheless drawing accuracy was lower and velocity was higher in DS, provides further evidence for the prevalence of cognitive aspects in the performance of drawing. Our results in fact show that in children with DS a psycho-motor delay, more than a biomechanical constrain, is present, which causes difficulties to represent, programme and activate correct motor sequences, manifesting motor clumsiness and lower levels of accuracy in drawings. This is in agreement with the study by Clements & Barrett (1994), who suggested that the differences between the drawings of children with and without DS reflected a developmental difference in the underlying processes of drawing production and development rather than a delay in development.

Limitations and future developments

Attentive inefficiency may have also contributed to the decreased ability of modifying the performed and the to-be-performed action of drawing. One limitation of our study is that participants were not evaluated for ADHD, so we cannot draw conclusions about the presence of ADHD in our specific

group of participants. However it is known that inattention, excessive motor hyperactivity or restlessness, and poor impulse control could lead to an impulsive drawing characterised by high speed and low accuracy, and it is known that DS has a high prevalence of attention disorders. The different posture of DS during the drawing, which led to a closer distance between their head and the sheet, may be an attempt to focus on the drawing by increasing the visual field directed on the drawing, consecutively reducing distracting factors. The analysis of drawing could be used to evaluate the presence of ADHD in DS, and future research should be addressed at evaluating and correlating the drawing performance of DS with ADHD evaluation scores. A deeper neuropsychological evaluation, together with an increase in the number of participants involved in the study, may give interesting falls out on the use of drawing tests as diagnostic tools in DS.

Conflict of interest

All authors have no conflicts of interest and no financial interest. All authors attest and affirm that the material within has not been and will not be submitted for publication elsewhere.

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Safety and tolerability of atomoxetine in treatment of attention deficit hyperactivity disorder in adult patients: An integrated analysis of 15 clinical trials

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Abstract

The safety profile of atomoxetine in the treatment of attention deficit hyperactivity disorder has been studied in many clinical trials. We performed an integrated safety analysis of 15 clinical trials in adults with attention deficit hyperactivity disorder. The analysis pooled patient data into three groups: acute placebo-controlled trials; long-term placebo-controlled trials; all trials. In total, 4829 adults (18–77 years, median: 36 years) were exposed to atomoxetine. Statistically significantly more atomoxetine-treated than placebo-treated patients experienced treatment-emergent adverse events (81.3% vs. 68.3% acute; 90.6% vs. 76.8% long term) and discontinued due to adverse events (8.9% vs. 4.0% acute; 17.9% vs. 6.3% long term). No statistically significant differences were observed in the proportion of patients experiencing serious adverse events. No previously unknown adverse events were identified. The most common adverse events included nausea, dry mouth, decreased appetite, insomnia and erectile dysfunction. Mean increases in heart rate (+5.2 beats per min) and blood pressure (systolic +2 mmHg, diastolic +1.9 mmHg) were modest. The proportion of patients experiencing clinically significant increases in blood pressure and heart rate at any time was statistically significantly higher with atomoxetine (systolic blood pressure 13–17%, diastolic blood pressure 37–40%, heart rate 42–43%) compared to placebo (systolic blood pressure 8–13%, diastolic blood pressure 29–34%, heart rate 21–26%). There was no increased risk of suicidal ideation or behaviour. Our findings confirm atomoxetine's known safety profile. From a safety perspective, atomoxetine is a useful treatment option for adults with attention deficit hyperactivity disorder.

Keywords

Atomoxetine, safety, attention deficit hyperactivity disorder, adult, integrated analysis

Background

Attention deficit hyperactivity disorder (ADHD) is widely recognized as a psychiatric disorder in childhood and adolescence, potentially related to genetic factors (Faraone et al., 2005) and it has become more widely recognized that ADHD frequently persists into adulthood (Asherson, 2005; Faraone et al., 2006; Wender et al., 2001).

Current estimates suggest that ADHD may affect 4.4% of the adult population in the USA (Faraone et al., 2005; Kessler et al., 2005, 2006); estimates for European countries range from 1.0% to 7.3%, depending on diagnostic criteria (Bitter et al., 2010; Fayyad et al., 2007; Kooij et al., 2005; Simon et al., 2009) and the worldwide prevalence in adults is estimated to be 3.4% (Fayyad et al., 2007).

ADHD in adults is often associated with comorbid psychiatric disorders, such as mood and anxiety disorders, or substance abuse (Fayyad et al., 2007; Kessler et al., 2006). Furthermore, adult patients with ADHD tend to suffer from major socioeconomic and functional impairment (Sobanski et al., 2007), as well as diminished quality of life (Able et al., 2007; Biederman and Faraone, 2006; de Graaf et al., 2008).

Treatment guidelines for adult ADHD (Kooij et al., 2010; NICE, 2008) recommend a multimodal approach. A comprehensive treatment programme should include both pharmacological and non-pharmacological interventions, addressing psychological, behavioural, educational and occupational needs. Pharmacological treatment includes stimulant and non-stimulant options. Stimulants (such as methylphenidate) act primarily by enhancing the neurotransmission of dopamine and, to a lesser extent, norepinephrine (Biederman and Spencer, 2008). Atomoxetine is a non-stimulant and a potent and selective inhibitor of the presynaptic noradrenaline transporter. Preclinical data suggest that atomoxetine has minimal affinity for either the serotonin or dopamine transporters or other neurotransmitter receptors (Bymaster et al., 2002). However,

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Table 1. Analysis groups.

Analysis groups	Number of trials included	Treatment group(s)	Drug exposure, mean dose of atomoxetine and duration of treatment
Acute controlled group (*N*=932)	6 trials	• Atomoxetine • Placebo	• Atomoxetine (*n*=926): 89.0 mg/day, 71 days • Placebo (*n*=931): 73 days
Long-term controlled group (*N*=765)	3 trials	• Atomoxetine • Placebo	• Atomoxetine (*n*=765): 84.3 mg/day 127 days. • Placebo (*n*=617): 133 days
Overall group (*N*=4892)	15 trials	• Atomoxetine	• Atomoxetine: 85.6 mg/day (*n*=4829), 163 days.

N: number of patients in analysis set; *n*: number of enrolled patients who received at least one dose of study drug.

in the forebrain of the rat, dopaminergic levels are also increased by atomoxetine (Bymaster et al., 2002), perhaps because of non-specific reuptake of dopamine by the noradrenaline transporter in that brain region (Carboni et al., 1990). Atomoxetine does not increase dopamine, either in the striatum or in the nucleus accumbens in rats (Bymaster et al., 2002). In contrast to methylphenidate, the pharmacological profile of atomoxetine indicates that it is less likely to have drug abuse potential. Drug abuse liability studies have provided evidence that atomoxetine is unlikely to be abused (Bymaster et al., 2002; Carboni et al., 1990; Heil et al., 2002; Jasinski et al., 2008; Upadhyaya et al., 2013a; Wee and Woolverton, 2004). Thus, atomoxetine is pharmacologically distinct from stimulants.

The efficacy of atomoxetine for ADHD in adults has been consistently demonstrated in various clinical trials, including six placebo-controlled short-term trials of 10–16 weeks duration, three placebo-controlled 6-month trials and one long-term maintenance of response trial of 1 year duration (Adler et al., 2008, 2009a, 2009b; Durell et al., 2013; Hirata et al., 2012; Michelson et al., 2003; Upadhyaya et al., 2013b; Wilens et al., 2008; Young et al., 2011).

Atomoxetine is metabolized by the cytochrome P450 2D6 (CYP2D6) pathway. Approximately 7% of Caucasians have a genotype corresponding to a non-functional CYP2D6 enzyme (called CYP2D6 poor metabolizers). Patients with this genotype have a higher exposure to atomoxetine when compared to patients with a functional enzyme. Poor metabolizers are therefore potentially at higher risk of adverse events (AEs). For patients with a known poor metabolizer genotype or for patients who are concomitantly receiving CYP2D6 inhibitors (selective serotonin-reuptake inhibitors (e.g. fluoxetine, paroxetine), quinidine, terbinafine), a lower starting dose and slower up titration of the dose may be considered.

To be able to assess the clinical value of atomoxetine for ADHD in adults, a comprehensive understanding of its efficacy and safety profiles is required. While the efficacy of atomoxetine for ADHD in the adult patient population is discussed elsewhere (see references above), the objective of this paper is to provide a comprehensive assessment of the safety and tolerability of atomoxetine for treatment of adult patients with ADHD. This is of particular interest as the indication of atomoxetine for adult patients with ADHD has recently been granted in the European Union and other countries worldwide. The potential association between medications approved for treating patients with ADHD and the risk of serious cardiovascular problems is still being investigated (Martinez-Raga et al. 2013; Olfson et al. 2012), and recent guidance on the management of the most common AEs during treatment with ADHD medications in children and adolescents has been published (Cortese et al. 2013). However, an overview of all safety data including cardiovascular parameters and their relevance in adult patients for this drug – as presented in this paper – has not yet been published and will improve the current knowledge on atomoxetine's safety in adults and help physicians make informed decisions in their clinical practice.

Methods

In the present analysis, 15 trials were included, all sponsored by Eli Lilly, studying atomoxetine in adult patients (≥18 years) with a diagnosis of ADHD (see Table 1 in Supplementary Material).

Trial designs

Six of the 15 trials were acute, double-blind trials evaluating acute efficacy as primary end-point and safety as secondary, with durations between 10 and 16 weeks. Two of these acute trials included a comorbid condition (alcohol abuse and social anxiety disorder). Three of the 15 trials were long-term, evaluating long-term efficacy as primary end-point and safety as secondary; they included double-blind phases and had durations of at least 6 months. In addition, there was one long-term maintenance of response trial evaluating efficacy as primary end-point and safety as secondary, with a duration of up to 49 weeks (data from a subsequent 2 year extension study were not included here because the extension study had not been completed at the time of this analysis). Safety was also evaluated in four open-label trials ranging in duration from 8 weeks to nearly 4.5 years and in another double-blind trial comparing two atomoxetine dose regimens.

Patients

Inclusion criteria. All 15 trials required patients to have ADHD as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) or 4th edition, text revision (DSM-IV-TR) as assessed through a structured diagnostic interview, such as the Conners' Adult ADHD Diagnostic Interview for DSM-IV. Patients were required to have ADHD symptoms or overall illness disturbance of at least moderate severity across all trials (e.g. at least four on the Clinical Global Impressions-Severity scale).

Two trials were designed to compare atomoxetine and placebo with regard to relapse to alcohol abuse or worsening of anxiety, therefore one trial required patients to have comorbid alcohol abuse problems (Wilens et al., 2008) and the other required patients to have comorbid social anxiety disorder (Adler et al., 2009a).

Table 2. Clinically significant criteria for DBP, SBP, HR and weight.

Parameter	Low	High
DBP (mmHg)	Decrease of ≥10 to a value ≤50	Increase of ≥10 to a value of ≥100
SBP (mmHg)	Decrease of ≥20 to a value ≤90	Increase of ≥20 to a value ≥160
HR (bpm)	Decrease of ≥15 to a value <50	Increase of ≥15 to a value >120
Weight (kg)	Decrease of ≥7%	Increase of ≥7%

DBP: diastolic blood pressure; SBP: systolic blood pressure; HR: heart rate.

Exclusion criteria

All trials used a core set of exclusion criteria, of which most were intended to ensure patient safety and minimize risk in a research setting. Patients with serious acute medical conditions were generally excluded, as were patients with a history of a seizure disorder, patients with uncontrolled hypertension and patients at serious risk for suicide. Women who were pregnant or breast-feeding were also generally excluded. A number of medications were grounds for exclusion, including primarily medications with psychoactive effects that could confound efficacy analyses (e.g. antidepressants or antipsychotics) and medications that could have unwanted pharmacodynamic or other interactions with atomoxetine, such as additive sympathomimetic effects. Patients with relevant psychiatric disorders such as bipolar or psychotic disorder were generally excluded. Most trials (except for the Adler and colleagues trial (Adler et al., 2009a)) excluded patients who met DSM-IV diagnostic criteria for current major depression or a current anxiety disorder (including generalized anxiety disorder, panic disorder and social phobia).

Statistical analyses

An integrated analysis of individual patient-level data (or pooled analysis) was performed. An integrated analysis can be viewed as a meta-analysis of individual patient-level data as opposed to trial-level summary data used in meta-analyses. This allows investigation of patient characteristics using within-subgroup analyses that were not part of the original trial analyses.

Analysis groups

As detailed in Table 1, three analysis groups were established:

- The 'acute controlled group' comprising all six acute, double-blind, placebo-controlled trials with a length of 10–16 weeks.
- The 'long-term controlled group' comprising all three long-term, double-blind, placebo-controlled trials with 6 months duration.
- The 'overall group' comprising all 15 trials (i.e. the trials in the two above groups and six other trials with varying durations, from 7 months up to nearly 4.5 years).

Single-trial results for safety in comorbid conditions

Safety data from the two trials in patients with comorbid anxiety and comorbid alcohol abuse were part of the integrated analysis to address the overall safety profile. In addition, results specifically related to safety and tolerability in the comorbid conditions are presented as single-trial results.

Safety measures

Treatment-emergent AEs (TEAEs) were collected as spontaneously reported (i.e. no solicited reporting using check-lists of potential AEs) at each study visit. Vital signs were measured according to the procedures specified in the respective study protocols.

All analyses were done on the safety population (i.e. all enrolled patients receiving at least one dose of atomoxetine as study drug). The following analyses were performed on the overall group: duration of exposure; modal dose by geographic region; demographics, disposition; AEs; laboratory tests; vital signs and weight; electrocardiogram (ECG). Subgroup analyses (age, gender, ethnic origin, dose regimen and CYP2D6 genotype) were conducted for atomoxetine exposure, TEAEs, serious AEs (SAEs), AEs leading to discontinuation, laboratory analyses, vital signs and weight, and ECG parameters.

For the analysis of continuous measures, unless otherwise specified, when an analysis of variance (ANOVA) model was used, it contained the main effects of treatment and trial. An analysis of covariance model consists of the terms used in the ANOVA with baseline added as a covariate. The last observation carried forward method was used for these analyses.

Within treatment group comparisons were conducted using the Wilcoxon signed-rank test.

For categorical/frequency data, the significance of overall treatment group differences was assessed using Fisher's exact test.

Clinically significant criteria for diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) and weight are defined as shown in Table 2. The criteria for blood pressure (BP) and HR in Table 2 were chosen for our analyses because, although from an individual patient management perspective it is appropriate to consider values of ≥140/90 mmHg for BP and >100 for HR, when determining in clinical trials the occurrence of an adverse phenomenon whose measurement is subject to significant random variability (such as an increase in BP or HR), it is advisable to use a threshold or reference limit that will improve specificity for a given number of patients and incur fewer false positives.

Suicide-related events were analysed using the Mantel–Haenszel incidence difference test, stratified by trial and Mantel–Haenszel risk ratio.

Regarding first occurrence and persistence of TEAEs, a TEAE was considered to be a persistent occurrence at a time-point if it first occurred prior to the time-point and was not yet resolved. For each time-point, patients who had not discontinued the trial prior

Table 3. Baseline demographics and illness characteristics.

Demographic parameter	Acute controlled group		Long-term controlled group		Overall group
	ATX (*N*=932)	Placebo (*N*=943)	ATX (*N*=765)	Placebo (*N*=617)	ATX (*N*=4892)
Age, years					
Mean	35.2	34.7	38.7	38.7	35.6
Median	33.1	32.1	39.4	39.7	35.7
Range	18.2–76.7	17.6–67.5	18.2–58.7	18.5–62.2	17.6–76.7
Age category, *n* (%)					
<18	0	1 (0.1)	0	0	10 (0.2)
18–30	416 (44.6)	444 (47.1)	158 (20.7)	134 (21.7)	1769 (36.2)
31–50	415 (44.5)	400 (42.4)	553 (72.3)	432 (70.0)	2835 (58.0)
51–65	99 (10.6)	97 (10.3)	54 (7.1)	51 (8.3)	276 (5.6)
>65	2 (0.2)	1 (0.1)	0	0	2 (0.04)
Gender, n (%)					
Male	545 (58.5)	553 (58.6)	398 (52.0)	316 (51.2)	2820 (57.7)
Female	387 (41.5)	390 (41.4)	367 (48.0)	301 (48.8)	2072 (42.4)
Ethnic origin, *N*=4890, n (%)					
White	610 (65.5)	609 (64.6)	652 (85.2)	525 (85.1)	3868 (79.1)
Asian	214 (23.0)	213 (22.6)	8 (1.1)	6 (1.0)	463 (9.5)
Hispanic	62 (6.7)	64 (6.8)	53 (6.9)	45 (7.3)	336 (6.9)
Black or African American	41 (4.4)	46 (4.9)	35 (4.6)	31 (5.0)	177 (3.6)
Other	5 (0.5)	10 (1.1)	17 (2.2)	10 (1.6)	40 (0.8)
American Indian or Alaska Native	0	1 (0.1)	0	0	6 (0.1)
ADHD subtype, *n* (%)	*N*=930	*N*=943	*N*=765	*N*=616	*N*=4875
Mixed	603 (64.8)	599 (63.5)	527 (68.9)	437 (70.9)	3366 (69.1)
Inattentive	314 (33.8)	326 (34.6)	233 (30.5)	175 (28.4)	1424 (29.2)
Hyperactive/Impulsive	13 (1.4)	18 (1.9)	5 (0.7)	4 (0.7)	85 (1.7)
Vital signs, mean (SD)	*N*=907	*N*=919	*N*=760	*N*=617	*N*=4727
Systolic BP (mmHg)	117.7 (11.7)	118.0 (12.1)	118.2 (11.6)	118.2 (11.2)	118.9 (11.7)
Diastolic BP (mmHg)	74.6 (8.9)	74.5 (8.7)	74.9 (8.6)	74.7 (8.6)	75.3 (8.9)
Heart rate (bpm)	73.1 (10.5)	72.7 (10.3)	71.9 (10.1)	71.4 (10.4)	72.8 (10.3)
CYP2D6 genotype, *n* (%)	*N*=716	*N*=715	*N*=264	*N*=232	*N*=3802
Extensive metabolizer	687 (96.0)	684 (95.7)	254 (96.2)	218 (94.0)	3599 (94.7)
Poor metabolizer	29 (4.1)	31 (4.3)	10 (3.8)	14 (6.0)	203 (5.3)

ADHD: attention deficit hyperactivity disorder; ATX: atomoxetine; BP: blood pressure; bpm: beats per minute; CYP: cytochrome P450; *N*: number of enrolled patients who received at least one dose of study drug; *n* (%): number/percentage of patients in each category.

to the time-point were included. For male sexual events, time to event analysis was conducted using Kaplan–Meier estimates. Between-treatment comparison was tested using Wilcoxon's test.

Results

Patient characteristics

A total of 4829 adult patients from the 15 source studies, exposed to atomoxetine for a mean of 163 days and 2152 patient-years of exposure, were included.

In general, demographic characteristics of patients across the trials were comparable; however, there were differences for a few trials (for example, one trial only included patients aged 18–30 years; two trials that included patients with comorbidities). Key demographic information (age, gender, sample size) is listed in Table 3. Overall, the majority of atomoxetine-treated patients were white (79.1%) and male (57.7%); mean age was 35.6 years. The majority of atomoxetine-treated patients were CYP2D6 extensive metabolizers (94.7%) and were classified as combined ADHD subtype (69.1%).

Patient disposition

Discontinuation rates (due to any reason, lost to follow-up and AE) for all three analysis groups are presented in Table 4. Overall, 747 atomoxetine-treated patients (15.3%) discontinued because of an AE. Nausea (*n*=107, 2.2%) was the most frequently reported TEAE as a reason for discontinuation, followed by erectile dysfunction (ED; *n*=40, 1.4%), fatigue (*n*=33, 0.7%) and insomnia (*n*=28, 0.6%). Two AEs leading to discontinuation were considered serious and likely to be related to study drug by the investigators: one event in the acute placebo-controlled group (diverticulitis); one event in the long-term placebo-controlled group (atrial fibrillation). Both of these cases recovered from these events.

Table 4. Patient disposition.

	Acute controlled group			Long-term controlled group			Overall group
	Atomoxetine	Placebo	*p*-value	Atomoxetine	Placebo	*p*-value	Atomoxetine
	N=932 *n* (%)	*N*=943 *n* (%)		*N*=765 *n* (%)	*N*=617 *n* (%)		*N*=4892 *n* (%)
Discontinued due to any reason	318 (34.1)	262 (27.8)	.003	448 (58.6)	303 (49.1)	<.001	3209 (65.6)
Lost to follow-up	102 (10.9)	96 (10.2)	.600	99 (12.9)	75 (12.2)	.684	592 (12.1)
Adverse event	83 (8.9)	38 (4.0)	<.001	137 (17.9)	39 (6.3)	<.001	747 (15.3)

N: number of enrolled patients who received at least one dose of study drug; *n* (%): number/percentage of patients in each category.

Table 5. Overview of TEAEs with a frequency ≥5% in atomoxetine, all analysis groups.

System organ class preferred term	Acute controlled group			Long-term controlled group			Overall group
	Atomoxetine	Placebo	*p*-value	Atomoxetine	Placebo	*p*-value	Atomoxetine
	(*N*=932) *n* (%)	(*N*=943) *n* (%)		(*N*=765) *n* (%)	(*N*=617) *n* (%)		(*N*=4892) *n* (%)
Patients with ≥1 TEAE	758 (81.3)	644 (68.3)	<.001	693 (90.6)	474 (76.8)	<.001	4041 (82.6)
Nausea	194 (20.8)	46 (4.9)	<.001	249 (32.5)	47 (7.6)	<.001	1305 (26.7)
Dry Mouth	137 (14.7)	37 (3.9)	<.001	195 (25.5)	40 (6.5)	<.001	898 (18.4)
Headache	119 (12.8)	107 (11.3)	.357	124 (16.2)	121 (19.6)	.104	796 (16.3)
Decreased appetite	134 (14.4)	26 (2.8)	<.001	140 (18.3)	22 (3.6)	<.001	731 (14.9)
Insomnia	97 (10.4)	50 (5.3)	<.001	88 (11.5)	40 (6.5)	.001	554 (11.3)
Fatigue	57 (6.1)	39 (4.1)	.059	109 (14.2)	47 (7.6)	<.001	529 (10.8)
Erectile dysfunction*	37 (6.8)[a]	4 (0.7)[a]	<.001	38 (9.5)[b]	5 (1.6)[b]	<.001	254 (9.0)[c]
Dizziness	61 (6.5)	16 (1.7)	<.001	68 (8.9)	31 (5.0)	.006	425 (8.7)
Nasopharyngitis	58 (6.2)	68 (7.2)	.408	31 (4.1)	45 (7.3)	.009	384 (7.8)
Constipation	70 (7.5)	25 (2.7)	<.001	57 (7.5)	18 (2.9)	<.001	325 (6.6)
Hyperhidrosis	32 (3.4)	7 (0.7)	<.001	35 (4.6)	2 (0.3)	<.001	318 (6.5)
Somnolence	56 (6.0)	40 (4.2)	.094	49 (6.4)	21 (3.4)	.013	295 (6.0)
Irritability	35 (3.8)	22 (2.3)	.081	50 (6.5)	31 (5.0)	.251	264 (5.4)
Upper respiratory tract infection	39 (4.2)	61 (6.5)	.031	44 (5.8)	37 (6.0)	.908	222 (4.5)
Urinary hesitation	22 (2.4)	2 (0.2)	<.001	49 (6.4)	6 (1.0)	<.001	171 (3.5)
Abdominal discomfort	35 (3.8)	21 (2.2)	.058	42 (5.5)	15 (2.4)	.004	164 (3.4)
Ejaculation disorder*	6 (1.1)[a]	2 (0.4)[a]	.175	20 (5.0)[b]	0 (0.0)[b]	<.001	68 (2.4)[c]

N: number of enrolled patients who received at least one dose of study drug; *n* (%): number/percentage of patients in each category; TEAE: treatment-emergent adverse event.
*Event for males.
[a]*N*=545 (atomoxetine), *N*=553 (placebo).
[b]*N*=398 (atomoxetine), *N*=316 (placebo).
[c]*N*=2820 (atomoxetine).

The median duration of exposure in the acute controlled group was 74 days in the atomoxetine (*N*=932) and 75 days in the placebo (*N*=943) group. In the long-term controlled group, the median duration of exposure was 147 days in the atomoxetine (*N*=765) and 159 days in the placebo (*N*=617) group.

Adverse events

In both the acute and long-term controlled groups, statistically significantly more atomoxetine-treated patients than placebo-treated patients experienced at least one TEAE (81.3% vs. 68.3%, $p<0.001$ for acute; 90.6% vs. 76.8%, $p<0.001$ for long term). In the overall group, the most frequent TEAEs of atomoxetine-treated patients were nausea (26.7%), dry mouth (18.4%), headache (16.3%), decreased appetite (14.9%), insomnia (11.3%) and fatigue (10.8%). An overview of common TEAEs (defined as with a frequency ≥5%) in all three analysis groups is given in Table 5. Overall, all of the common TEAEs (with the exception of nasopharyngitis) occurred more frequently during the initial acute treatment with atomoxetine (within the first 5 weeks), with few new reports occurring during long-term treatment. Most of the TEAEs showed the pattern of persistence seen for nausea: the events were reported early and tended to resolve fairly consistently during ongoing atomoxetine treatment (see Figure 1).

Subgroup analysis of adverse events

Analyses of TEAEs by subgroups were performed on the overall group to determine whether a particular subgroup experienced differences when treated with atomoxetine.

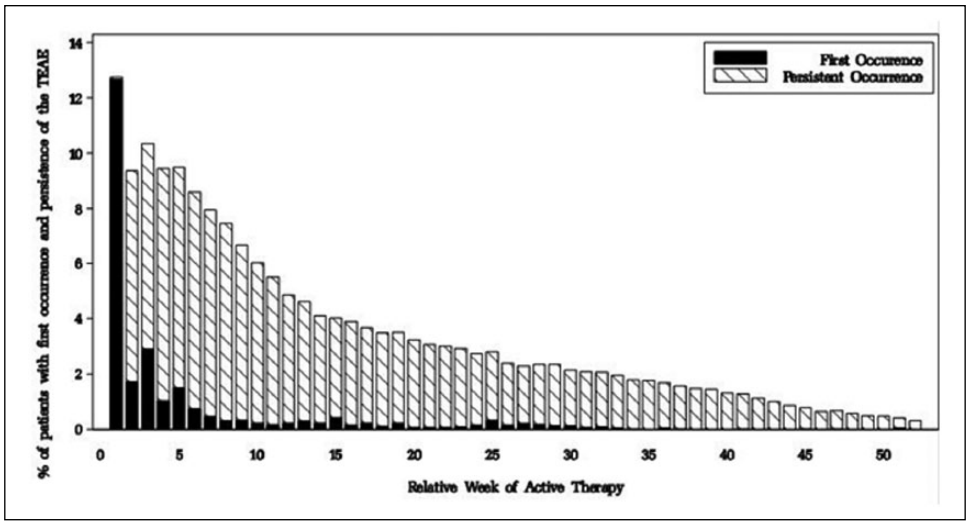

Figure 1. First occurrence and persistence of nausea.

Many of the common TEAEs were comparable or only slightly different in frequency among age, gender, once-daily (q.d.) or twice-daily (b.i.d.) dosing, and poor vs. extensive metabolizer subgroups. However, the following differences were noted: dry mouth (26.4% vs. 12.7%), constipation (12.3% vs. 4.1%) and ED (18.6% vs. 5.1%) were more than twice as likely in older patients (≥51 years) than in younger patients (18–30 years). The frequencies of nausea and dry mouth observed in females were notably higher than in males (33.4% vs. 21.7% and 22.6% vs. 15.2%, respectively). Dry mouth (34.5% vs. 17.4%), ED (20.9% vs. 8.9%) and hyperhidrosis (14.8% vs. 6.8%) were more than twice as likely to be reported in poor metabolizers relative to extensive metabolizers. Comparing q.d. and b.i.d. dosing showed that nausea was more than twice as likely to be reported in patients receiving atomoxetine q.d. (33.8%) compared to b.i.d. (16.7%). Somnolence was nearly twice as likely to be reported in patients receiving atomoxetine q.d. (8.8%) compared to b.i.d. (4.5%). On the other hand, insomnia was more frequently reported with b.i.d. (17.0%) than with q.d. (9.5%). Among the 13 most common AEs, six TEAEs were numerically higher in b.i.d. patients compared with seven in q.d. patients; therefore, no specific pattern was identified when comparing dose regimens.

Serious adverse events

In both the acute and long-term controlled groups, no statistically significant differences in the proportion of patients experiencing SAEs were observed between patients receiving atomoxetine and those receiving placebo (0.8% vs. 0.7% for acute, 0.5% vs. 1.3% for long term). No single event was predominant and the events did not fit into a pattern and did not suggest systemic drug toxicity.

Overall, 81 atomoxetine-treated patients (1.7%) experienced at least one SAE, with some patients experiencing more than one SAE. Among all reported SAEs, 12 events were considered likely to be related to study drug by the investigators. Of these, the outcome for seven events were reported as recovered following atomoxetine discontinuation (atrial fibrillation, restlessness, alcohol abuse, bradykinesia, haemorrhage, auditory hallucination, and diverticulitis), one was reported as recovering/resolving (palpitations), three were reported as not recovered (suicidal ideation, paresthesia, and palpitations) and one was reported as unknown (headache).

In all 15 trials, one death (suspected myocardial infarction) was reported. It occurred in the long-term maintenance of response trial (Upadhyaya et al., 2013b) in a 38-year-old male patient, 220 days after the initiation of atomoxetine treatment. The investigator was unable to assess the relatedness between this event and blinded study drug. The patient had very minor above-normal limits values at baseline for creatine phosphokinase and cholesterol, and pre-existing partial right bundle branch block. The patient had normal BP and HR at the beginning and throughout the trial. No conclusions could be drawn regarding possible causality.

Laboratory

In the acute treatment group, atomoxetine-treated patients experienced statistically significant mean changes in the following laboratory tests compared with placebo-treated patients: increased platelet count (+6.34 vs. –1.51); increased alkaline phosphatase (AP) (+0.84 vs. –1.74); decreased chloride (–0.61 vs. –0.03); less decreased albumin (–0.66 vs. –1.05); decreased uric acid (–2.44 vs. –5.84); increased prolactin (+2.68 vs. +0.42). In the long-term treatment group, statistically significant differences for increased monocytes (+0.01 vs. +0.03), decreased chloride (–1.01 vs. –0.66), and decreased uric acid (–2.20 vs. –8.69) were found. The changes and rates of treatment-emergent abnormal values were small and not clinically relevant and these differences in the laboratory data do not appear to be representative of systemic drug toxicities or of safety issues. These findings are consistent with laboratory value findings in paediatric trials with atomoxetine, which similarly were not clinically relevant.

Weight

As expected from the known safety profile of atomoxetine and its pharmacology, mean decreases in weight were observed in atomoxetine-treated patients (overall −1.01 kg). In both the acute

and the long-term controlled groups, the proportion of atomoxetine-treated patients experiencing significant weight loss (≥7%) at any time post-baseline was statistically significantly greater compared to placebo-treated patients (5.6% vs. 0.9% for acute; 10.0% vs. 3.3% for long term). In the long-term treatment analysis (patients from the overall group who received atomoxetine for at least 1 year, *N*=269), approximately one-third of patients experienced a significant weight loss. However, the stratified analysis of weight and body mass index (BMI) showed that on average they were overweight at baseline (BMI 27.6) and that those who experienced significant weight loss during treatment were actually heavier at baseline (BMI 29.8) than those who did not (BMI 26.6).

Safety measures of special interest

Cardiovascular events and parameters. In the acute controlled group, palpitations (2.9% vs. 1.0%, p=0.002), tachycardia (1.3% vs. 0.3%, p=0.020) and HR increased (2.0% vs. 0.2%, p<0.001) were reported statistically significantly more often in atomoxetine-treated patients compared to placebo. In the long-term controlled group, HR increased was the only AE reported statistically significantly more in atomoxetine-treated patients compared to placebo (2.1% vs. 0%, p<0.001).

The continuous analysis of mean baseline-to-end-point changes in SBP, DBP and HR showed that they were statistically significantly greater in atomoxetine-treated patients compared to placebo in both the acute and long-term controlled groups (see Table 6). To assess cardiovascular parameters in patients with a higher age, the mean changes for the 51–65 year old atomoxetine patients (*N*=268) in the overall atomoxetine group were SBP +3.90 mmHg, DBP +3.18 mmHg and HR +5.31 beats per minute (bpm). The respective values for patients of all age groups in the overall atomoxetine group were: SBP: +1.96 mmHg; DBP: +1.87 mmHg; HR: +5.23 bpm.

In order to analyse the pattern during treatment, mean changes over time were also calculated for the overall group, with patients with at least 1 year of atomoxetine treatment being included in the analysis. Mean baseline SBP (*N*=308, 118.1 mmHg, SD=11.0), DBP (*N*=308, 75.9 mmHg, SD=8.7) and HR (*N*=229, 73.4 bpm, SD=9.6) started to increase early after treatment initiation up to 3– 6 months and then remained substantially stable for up to 12 months, with slight further increases for DBP and SBP in the long-term period of more than 12 months.

In both the acute and long-term controlled groups, the categorical analysis of the clinically significant criteria as defined in Table 2 did not show statistically significant differences between atomoxetine and placebo for the three haemodynamic parameters. Also, no statistically significant differences compared to placebo were observed in the proportion of atomoxetine-treated patients exceeding clinically significant absolute value limits for SBP (160 mmHg), DBP (100 mmHg) and HR (120 bpm). However, the proportion of patients exceeding the clinically significant change from baseline at any time was statistically significantly different compared to placebo (Table 6). Of the overall atomoxetine group patients of 51–65 years of age, 2.6% (7/268) showed clinically significant higher SBP, 4.9% clinically significant higher DBP and no patient showed a clinically significant change in HR. The respective values for patients of all age groups in the overall atomoxetine group were: SBP: 1.2%; DBP: 2.9%; HR: 0.3%.

With regard to ECGs, for the data-derived QTc correction method (QTcD), proportions of atomoxetine-treated patients with important prolongation did not statistically significantly differ between atomoxetine and placebo groups in either the acute or long-term controlled groups. Overall, assessment of mean (SD) change in QTcD of atomoxetine-treated patients showed statistically significant increases from baseline (1.92 msec (15.55), p<0.001), but the resulting mean QTcD interval value remained within normal limits (404.51 (19.30) msec at baseline, 406.43 (18.37) msec at end-point).

In both the acute and long-term controlled groups, mean changes in cardiac- and vascular-related laboratory values were minimal and not considered clinically meaningful.

Hepatic safety. In both the acute and long-term controlled groups, mean changes in hepatic-related laboratory values were minimal and not considered clinically meaningful. In the acute controlled group, there were statistically significant differences in mean changes in alkaline phosphatase (ALP) (+0.88 vs. –1.74, p<0.001) and albumin (–0.66 vs. –1.05, p=0.003) when comparing atomoxetine-treated patients to placebo. Mean changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total bilirubin showed no statistically significant differences between atomoxetine and placebo groups. In the long-term controlled group, mean changes in ALT, AST, GGT, ALP, total bilirubin and albumin showed no statistically significant differences between atomoxetine and placebo groups.

In terms of hepatic-related TEAEs, no statistically significant differences between treatment and placebo groups were found in controlled trials. Overall, in all trials, a total of 28 hepatic-related TEAEs were reported for atomoxetine-treated patients. Of these, three events were serious (one case reported alcoholic hepatitis in a patient with a history of heavy alcohol binges several times per year, and two cases reported cholelithiasis and biliary dyskinesia, with resultant cholelithotomy and cholecystectomy, respectively). All three cases recovered, had normal laboratory values and were considered not related to study drug. The remaining 25 events were non-serious and mild to moderate in severity. Most of them represented increases in hepatic-related laboratory values with no associated hepatic-related TEAEs.

Aggression and hostility. In both the acute and long-term controlled groups, few aggression- and hostility-related TEAEs were reported. Six events were reported in acute trials: four in atomoxetine-treated patients (all anger); two in placebo patients (aggression and anger). Four events were reported in long-term trials: two in atomoxetine-treated patients (both anger); two in placebo patients (both aggression). No statistically significant differences between atomoxetine and placebo groups were observed. In the overall group, the incidence of aggression- and hostility-related TEAEs in atomoxetine-treated patients reported was low, with a total of 16 patients (0.3%) reporting aggression, 17 (0.3%) reporting anger, one reporting disinhibition, one reporting disturbance in social behaviour and one reporting violence-related symptoms.

A risk ratio (relative risk) analysis of aggression related terms in both the acute and long-term controlled groups has shown that aggression/hostility events, although not statistically different, are reported more frequently in the atomoxetine than in the placebo arm (risk ratio of 1.38 (95% confidence interval (CI): 0.39, 4.88; p=0.756)).

Table 6. Blood pressure and heart rate values at baseline and endpoint, relative changes and % patients with clinically relevant changes.

Vital sign		Acute controlled group			Long-term controlled group			Overall group
		ATX mean (SD)	Placebo mean (SD)	*p*-value	ATX mean (SD)	Placebo mean (SD)	*p*-value	ATX mean (SD)
SBP	*N*	907	919		760	612		4727
(mmHg)	Baseline	117.7 (11.65)	118.0 (12.11)	–	118.2 (11.64)	118.2 (11.23)	–	118.9 (11.65)
	End-point	119.6 (11.82)	118.0 (12.40)	–	120.0 (13.09)	118.2 (11.73)	–	120.9 (12.54)
	Change to end-point	1.86 (10.22)	–0.02 (10.28)	<.001	1.86 (10.30)	-0.04 (9.35)	<.001	1.96 (10.77)
DBP	*N*	907	919		760	612		4727
(mmHg)	Baseline	74.6 (8.93)	74.5 (8.71)	–	74.9 (8.62)	74.7 (8.59)	–	73.5 (8.89)
	End-point	76.6 (9.51)	74.7 (10.21)	–	76.5 (8.62)	74.9 (8.44)	–	77.2 (9.15)
	Change to end-point	2.00 (8.65)	0.01 (10.02)	<.001	1.65 (8.39)	0.25 (7.58)	<.001	1.87 (8.81)
HR	*N*	907	919		760	612		4726
(bpm)	Baseline	73.1 (10.53)	72.7 (10.28)		71.9 (10.10)	71.4 (10.35)		72.8 (10.31)
	End-point	78.6 (11.98)	72.7 (10.21)		76.2 (11.04)	71.7 (9.96)		78.0 (11.66)
	Change to end-point	5.50 (11.78)	0.01 (10.02)	<.001	4.32 (10.88)	0.30 (10.09)	<.001	5.23 (11.68)
Vital sign		ATX %	Placebo %	*p*-value	ATX %	Placebo %	*p*-value	ATX %
SBP	Absolute and change limits at any time (160 mmHg and 20 mmHg)*	0.33	0.33	1.000	0.79	0.65	1.000	1.16
	Absolute value limit at any time (160 mmHg)*	0.33	0.44	1.000	0.92	0.82	1.000	1.25
	Change limit at any time (20 mm Hg)*	13.45	7.83	<.001	16.58	13.07	.08	16.52
DBP[a]	Absolute and change limits at any time (100 mm Hg and 10 mmHg)*	1.76	0.87	.103	1.45	1.14	.812	2.94
	Absolute value limit at any time (100 mmHg)*	1.87	0.98	.117	1.84	1.47	.675	3.28
	Change limit at any time (10 mmHg)*	37.38	28.62	<.001	39.87	33.99	.028	41.80
HR	Absolute and change limits at any time (120 bpm and 15 bpm)	0.11	0.11	1.000	0.00	0.00	–	0.34
	Absolute value limit at any time (120 bpm)	0.33	0.11	.371	0.13	0.00	1.000	0.44
	Change limit at any time (15 bpm)	41.68	21.00	<.001	43.03	26.47	<.001	46.78

ATX: atomoxetine; bpm: beats per minute; DBP: diastolic blood pressure; HR: heart rate; *N*: number of patients with a baseline and at least one post-baseline result; SBP: systolic blood pressure.

*A cut-off of 160/100 mm Hg SBP/DBP was chosen as these values correspond to the 95 percentile of blood pressure (BP) observed in population-based studies and avoids reporting false positive values of high BP.

Suicidal or self-injurious behaviour. In general, patients at serious suicidal risk were excluded from the trials. A meta-analysis for unsolicited suicide-related events in all placebo-controlled trials of ADHD in adults using the combined FDA codes of 1–6 and 9 (Gassmann-Mayer et al., 2011), which involve all events related to either suicide-related ideation and/or possible suicide-related behaviours, identified four events meeting criteria for suicidal behaviour or ideation (categories 1–4), two in atomoxetine-treated patients and two in placebo-treated patients. The risk ratio (Mantel–Haenszel) was 0.96 (95% CI; 0.24, 3.79; p=0.953) and the incidence difference (Mantel–Haenszel) was −0.01 (95% CI; –0.27, 0.26; p=0.967) when the atomoxetine-treated group was compared with the placebo-treated group.

In addition, AEs potentially related to suicidality were analysed. Irritability was reported in the long-term placebo-controlled ADHD analysis by 6.5% patients in the atomoxetine and 5.0% in the placebo group (Fisher's exact test; p=0.251). Two patients (0.3%) in the atomoxetine group discontinued due to irritability vs. five patients (0.8%) in the placebo group (Mantel–Haenszel test; p=0.253). In the acute analysis, 3.8% of the patients in the atomoxetine group and 2.3% in the placebo group reported irritability (Fisher's exact test; p=0.081). }Two patients discontinued in the atomoxetine and none in the placebo group (Fisher's exact text; p=0.247).

Depression was reported in the long-term placebo-controlled ADHD analysis by 1.2% patients in the atomoxetine group vs. 1.8% in the placebo group (Fisher's exact test; p=0.373).

Depression was given as a reason for discontinuation in the long-term placebo-controlled ADHD analysis for three patients (0.4%) in the atomoxetine group and for two patients (0.3%) in the placebo group (Fisher's exact test; p=1.00). In the acute analysis, 1.3% of the patients in the atomoxetine group and 1.2% in the placebo group reported depression (Fisher's exact test; p=0.837). No patient discontinued due to depression in the acute analysis.

Mood swings were reported in the long-term placebo-controlled ADHD analysis by 0.8% of the patients in the atomoxetine group vs. 0.3% of the patients in the placebo group (Fisher's exact test; p=0.301. Mood swings were given as a reason for discontinuation for two patients (0.3%) in the atomoxetine group and for one patient (0.2%) in the placebo group (Fisher's exact test; p=1.00). In the acute analysis, 0.3% of the patients in the atomoxetine group and 0.1% in the placebo group reported mood swings (Fisher's exact test; p=0.372). No patient discontinued due to mood swings in the acute analysis.

These findings show that the risk of suicidal behaviour or ideation and other events potentially related to suicidality observed in adult patients treated with atomoxetine was not statistically significantly different from placebo.

Male sexual side effects. In the acute controlled group, among all male sexual dysfunction TEAEs included in the Medical Dictionary for Regulatory Activities high-level terms (erection and ejaculation conditions and disorders, orgasmic disorders and disturbances, reproductive tract disorders not elsewhere classified (NEC) (excluding neoplasms), sexual arousal disorders, sexual desire disorders, sexual function and fertility disorders NEC), ED was the only TEAE reported statistically significantly more frequently in atomoxetine-treated patients compared to placebo (6.8% vs. 0.7%, p<0.001). In the long-term controlled group, ejaculation disorder (5.0% vs. 0%, p<0.001), ejaculation delayed (2.3% vs. 0%, p=0.006) and ED (9.5% vs. 1.6%, p<0.001) were statistically significantly more frequent in atomoxetine patients.

A post hoc analysis of data from the long-term controlled group shows that more atomoxetine- than placebo-treated patients experienced male sexual dysfunction TEAEs (ejaculation disorder, ED, orgasm abnormal, male genital pain, priapism, ejaculation failure, libido decreased) (9.3% vs. 1.8%). However, there was no statistically significant difference in time to onset between atomoxetine and placebo groups, with most analysed events having onset in the first 1 to 2 months of treatment in both the atomoxetine and placebo groups (means of 20 days for atomoxetine and 27 for placebo; medians of 11 and 18). In the analysis of time to resolution, there was no statistically significant difference between atomoxetine and placebo groups. Approximately 50% of the analysed events in both the atomoxetine and placebo groups had resolved as of 3 months after event onset and 81.4% of the analysed events in the atomoxetine treatment group had resolved as of 6 months after event onset. Data for the placebo group at 6 months are limited because all placebo patients had discontinued or had already experienced resolution prior to that time. Mean time to resolution was 73 days for atomoxetine and 71 for placebo, with medians of 54 and 49. ED was the most frequently reported of all sexual dysfunction TEAEs. ED occurred more frequently during the initial acute treatment with atomoxetine, with few new reports occurring during long-term treatment.

Comorbidity. As mentioned above, one trial compared safety of atomoxetine with placebo in a population of adult patients who met DSM-IV-TR criteria for ADHD and social anxiety disorder after up to 16 weeks of treatment. No patients experienced a SAE that was anxiety related, and only two (0.9%) atomoxetine-treated and two (0.9%) placebo-treated patients discontinued due to 'anxiety'. Atomoxetine-treated patients did not experience worsening of anxiety compared to placebo-treated patients.

One placebo-controlled trial was conducted in patients with ADHD and comorbid alcohol abuse or dependence disorder. AEs were similar to those of other adult populations treated with atomoxetine.

Seizure. In atomoxetine trial protocols, patients with history or current seizure disorders were in general excluded from trials. In the acute controlled group, no seizure-related TEAEs were reported; in the long-term controlled group, convulsion was the only seizure-related TEAE reported, occurring in a placebo-treated patient. In the overall group, the incidence of seizure-related TEAEs reported was low, with a total of 4 (0.1%) atomoxetine-treated patients reporting convulsion.

Overdose. No fatal overdoses occurred in the clinical trials in adults.

Discussion

This is the first integrated analysis focusing on the safety of atomoxetine in adult patients with ADHD. It describes safety findings from 15 clinical trials in adult patients with ADHD, with a total of 4829 patients being exposed to atomoxetine for a mean of 163 days, or 2152 patient-years of exposure. Integrated analysis of data from these patients enabled us to further characterize and confirm the safety and tolerability of atomoxetine for treatment of adult patients with ADHD.

Most of the common AEs that occurred statistically significantly more in adult atomoxetine-treated patients compared to placebo (e.g. nausea, dry mouth, constipation, urinary hesitation and ED) were predictable, based on atomoxetine's noradrenergic pharmacology, and are listed in the approved label for atomoxetine. When comparing AEs between acute and long-term trials, there appear to be very few differences in the safety profile between acute and long-term treatment (see Table 5). A number of frequently occurring AEs were confirmed to be transient in the majority of patients, e.g. nausea, which is the most common AE and the AE most frequently leading to treatment discontinuation. In controlled trials, statistically significantly more atomoxetine-treated patients discontinued due to AEs compared to placebo. However, the number of events leading to discontinuations that were considered serious was very low.

Due to the known effects on BP and HR, the cardiac safety of drugs used to treat ADHD, including atomoxetine, may be important, particularly for patients with severe cardiovascular disorders whose condition would be expected to deteriorate in case of increases in BP or HR. In our dataset, mean changes in BP and pulse were modest and consistent with increased noradrenergic activity; however a higher proportion of atomoxetine-treated patients showed clinically relevant increases from baseline in BP and HR compared to placebo. This is consistent with a previous

analysis (MHRA, 2012) that was performed for an assessment of the UK Medicines and Healthcare Products Regulatory Agency in 2011. In this analysis, it was also shown that the proportion of atomoxetine patients who experienced clinically important increases in BP or HR ranged from 6 to 10% (increase in SBP ≥20 mmHg: 6%, in DBP ≥15 mmHg: 6.5%, in HR ≥20 bpm: 10%). Of those patients who simultaneously exceeded both clinically important changes from baseline and absolute value limits in BP and HR, approximately 30% had progressive or sustained increases while participating in the atomoxetine trials. The mean changes to end-point for all atomoxetine-treated patients were: SBP +2.0 mmHg; DBP +1.9 mmHg; HR +5.2 bpm. An interesting aspect for clinical practice in this regard is how increases in BP and HR evolve if atomoxetine treatment is stopped. In the 6-month double-blind randomized withdrawal phase of the long-term maintenance of response trial (Upadhyaya et al., 2013b), values were stable under continued atomoxetine treatment and decreased to baseline values when treatment was stopped. Data from our analysis support the current wording in the atomoxetine label regarding potential cardiovascular effects in patients, risk minimization activities (such as routinely monitoring BP before and while taking atomoxetine), as well as contraindications and warnings.

In our analysis, atomoxetine was not associated with adverse effects on cardiac repolarization (QT interval) and the mean QTcD interval value remained within normal limits. This finding is consistent with results of a TQT study in healthy volunteers (Loghin et al., 2013), which showed no clinically significant effect of atomoxetine on QT even at maximum therapeutic dosage. However, there is the possibility that atomoxetine might result in delayed repolarization in overdose (Barker et al., 2004; Kashani and Ruha, 2007; Sawant and Daviss, 2004). Thus, atomoxetine should be used with caution in patients with congenital long QT syndrome, acquired long QT syndrome (for example, due to concomitant use of a drug that prolongs the QT) or a family history of QT prolongation.

Overall, evidence indicates that atomoxetine use is not associated with an increased risk of cardiovascular or cerebrovascular adverse effects (Adler et al., 2008; Holick et al., 2009; Loghin et al., 2013; Wernicke et al., 2003). More recently, a retrospective study used electronic health care records of more than 440,000 patients aged 25– 64, more than 150,000 of whom were treated for ADHD with methylphenidate, amphetamine, atomoxetine, and pemoline (Habel et al., 2011). During more than 806,000 person-years of follow-up, the authors did not find any evidence of increased cardiovascular risk associated with current use of the aforementioned ADHD medications compared to non-use or remote use. This suggests that careful selection of patients for treatments and follow-up and management of AEs may decrease the theoretical risk of cardiovascular events in real life.

In terms of hepatic safety, clinical trial data did not identify any serious findings related to atomoxetine in adults. Despite these finding, very rarely liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported. Also very rarely, severe liver injury, including acute liver failure has been reported in patients taking atomoxetine. As noted in the product labelling, atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted.

In our integrated analysis, the overall incidence of reported aggression- and hostility-related TEAEs in atomoxetine-treated patients was low. Aggressive behaviour or hostility is often observed in patients with ADHD and has been reported in clinical trials and post-marketing experience of some ADHD medications. In our integrated analysis, aggression/hostility events were not reported with a statistically significantly increased frequency in atomoxetine-treated patients than in placebo-treated patients, but were slightly higher in the atomoxetine groups. Although there is no conclusive evidence that atomoxetine causes aggressive behaviour or hostility (Polzer et al., 2007), the atomoxetine label already comprises the warning that patients beginning treatment should be monitored for the appearance or worsening of aggressive behaviour or hostility.

The labelling for atomoxetine includes warnings and precautions to address the potentially increased risk of suicidal thoughts and behaviour. However, adult clinical trial meta-analyses and multiple reviews of spontaneous data sources have not identified an association of atomoxetine use with suicidal or self-injurious behaviour. Indeed, a recently published meta-analysis of adult (*N*=3365) and paediatric (*N*=3883) clinical trial data (Bangs et al., 2014), and in a recent randomized study of adults (*N*=524), using the Columbia Suicide-Severity rating scale (Camporeale et al., 2013), the risk of suicidal behaviour or ideation observed in those treated with atomoxetine is not significantly different from placebo. Data in our analysis do not show an increased risk of suicidal ideation or behaviour in adult patients treated with atomoxetine either. This is in contrast to some data from the paediatric clinical trial setting, where suicidal ideation was more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo (Bangs et al., 2008). However, there is evidence that those suffering from ADHD are at greater risk of suicide than the general population. ADHD appears to increase the risk of suicide, especially in males, via increasing severity of comorbid conditions, particularly conduct disorders and depression (Impey and Heun, 2012; James et al., 2004). In several unpublished post-marketing reviews, no inconsistencies in any trends of spontaneously reported events of suicidal ideation and behaviour, and of self-injurious ideation and behaviour, were identified between atomoxetine-treated patients and the general population for children, adolescents and adults.

More atomoxetine- than placebo-treated patients experienced treatment-emergent male sexual dysfunction AEs in our integrated analysis, but our post hoc analysis showed that more than three-quarters of the events in the atomoxetine treatment group had resolved as of 6 months after event onset. Despite the persistence of dysfunction events in some patients, it is notable that relatively few men discontinued atomoxetine trials for this reason. For example, although the most common sexual dysfunction event, ED, was reported as a TEAE in 9.0% of atomoxetine-treated men in the overall database, it was a reason for discontinuation in only 1.4%, indicating that for most men with this event, the perceived benefit of remaining in the trial outweighed the difficulty of tolerating the event.

A clinically useful finding is the difference in tolerability between q.d. and b.i.d. dosing. Both nausea and somnolence are relatively common AEs and both of these have lower incidences when atomoxetine is dosed in a b.i.d. regimen. On the other hand, insomnia, for example, was more frequent with the b.i.d. regimen. Atomoxetine can be taken once or twice daily. This gives the possibility for the clinician to treat each patient according to his or her needs and tolerability. q.d. dosing is the

recommended regimen, given the importance of patient convenience and adherence, especially for patients with ADHD who may be disorganized and inattentive to routine tasks. On the basis of the available data it does, however, remain appropriate that physicians consider the benefit of b.i.d. dosing in the case of patients with poor tolerability.

To date, the known atomoxetine safety profile has mainly been based on clinical trials and experience from children and adolescents. At present, the estimated number of worldwide exposures of atomoxetine is over 10 million patients, approximately 7 million of whom were children and adolescents and 3 million were adults. To a high degree, tolerability and safety of atomoxetine in adults is similar to its tolerability and safety in children and adolescents. However, some differences are seen between age groups. A post hoc analysis combining data from six randomized, placebo-controlled, parallel-arm atomoxetine trials with durations ranging from 6 to 9 weeks in adolescents (12–17 years) and three trials (10 weeks in duration) that studied young adults (18–30 years) found the AE profile to be similar in both age groups (Adler et al., 2012). Although there was the exception that nausea was significantly more frequent with atomoxetine compared to placebo in young adults (13.7% vs. 4.8%), in contrast to adolescents in which nausea occurred more frequently with placebo (4.5% vs. 10.2%) (Adler et al., 2012). The frequency of nausea observed in this analysis was lower than the 20.8% in our acute trial dataset, comprising patients from 18 years and over, with a mean age of 35.6 years. In our integrated analysis, we found some differences within the group of adult patients with dry mouth and constipation being more common among older adults than younger adults.

Limitations of our analysis are that despite the large number of patients included, the statistical power of the analysis was not suitable to detect differences in rare AEs between atomoxetine and placebo. As more patients on atomoxetine discontinued from the studies, as compared to patients on placebo, there might have been an attrition-bias that led to an underestimation of AEs for atomoxetine. However, the median exposure duration was comparable between both treatment groups. Moreover, the large majority of the possibly drug related AEs occurred in the first weeks of treatment, i.e. before most of the discontinuations happen, and therefore these TEAEs are taken well into account. Furthermore, compared to studies using solicited AE reporting for ADHD, the present study might have lower estimates for AEs because of their collection via spontaneous reporting. However, standard solicited AE questionnaires for ADHD are tailored for the typical side effects for stimulant medications, and might not have captured all atomoxetine-related side effects. In addition, the all-cause discontinuation rate in randomized controlled clinical trials, such as those included in the present analyses, cannot be considered as a proxy for a benefit-risk measurement, as study conduct-related reasons for discontinuation are frequent. As all studies included in this analysis were clinical trials and do not include results from non-interventional studies, the application of inclusion/exclusion criteria limits generalization of the results.

Conclusion

This integrated analysis confirmed atomoxetine's known safety profile. No new potential or identified important risks were found during treatment with atomoxetine in adults beyond those already known. The known risks are appropriately described in the atomoxetine label, and they can be managed through appropriate screening and monitoring of patients before and during treatment. No particular safety issues in patients with comorbid social anxiety disorder or alcohol abuse and the lack of abuse potential all suggest that, based on the published efficacy data and the current integrated analysis of safety data, atomoxetine is a useful treatment option for adults with ADHD.

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Child behaviour checklist emotional dysregulation profiles in youth with disruptive behaviour disorders: Clinical correlates and treatment implications

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ABSTRACT

Two Child Behaviour Checklist (CBCL) profiles were correlated to poor self-regulation, Deficient Emotional Self-Regulation (DESR) (elevation between 1 and 2 Standard Deviations (SD) in Anxiety/Depression, Aggression, Attention subscales), and Dysregulation Profile (DP) (elevation of 2 Standard Deviations or more). We explored youths with Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) whether these profiles are associated with specific clinical features. The sample included 57 patients with DESR profile and 41 with DP profile, ages 9 to 15 years, all assigned to a non-pharmacological Multimodal Treatment Program. No differences resulted between groups in demographic features, diagnosis ratio, and comorbidities with Attention Deficit Hyperactivity Disorder (ADHD), Bipolar Disorder (BD), and Anxiety Disorder. The DP group was associated with higher scores in Withdrawn, Social Problem, Thought, Rule Breaking, and Somatic CBCL subscales, and higher scores in Narcissism and Impulsivity (but not Callous–Unemotional (CU)), according to the Antisocial Process Screening Device (APSD). After treatment, patients with DESR improved their personality traits (Narcissistic and Callous–Unemotional, but not Impulsivity), while changes in CBCL scales were modest. Patients with DP improved scales of Attention, Aggression, Anxiety–Depression, Rule Breaking, Withdrawal, Social Problem and Thought, while personality features did not change. These results suggest diagnostic implications of CBCL profiles, and indications for targeted treatment strategies.

1. Introduction

Children with mood instability, severe irritability, aggression, temper outburst, hyper-arousal have become a challenging issue in the last two decades, as they do not completely fit any of the current diagnostic categories, including Attention Deficit Hyperactivity Disorder (ADHD), a disruptive behavior disorder (oppositional defiant disorder (ODD) or conduct disorder (CD)), and bipolar disorder (BD) (Carlson and Kelly, 1998), although they share features of all these domains. The core element in these patients is a severe dysregulation of emotions and behavior. The DSM 5 (American Psychiatric Association, 2013) has attempted to address this problem with the new diagnosis of Disruptive Mood Dysregulation Disorder (DMDD), but data are still inconclusive (Dougherty et al., 2014).

One of the most troublesome aspects in the exploration of the affective and behavioral dysregulation is the difficulty of reliable and cost-effective diagnostic measures. The Child Behavior Checklist (CBCL), one of the most frequently used instruments for assessment of developmental psychopathology (Achenbach and Rescorla, 2001), has been considered a possible diagnostic tool for identifying children with these features. A specific CBCL profile has been correlated to poor self-regulation in children and adolescents, the Deficient Emotional Self-Regulation (DESR), characterized by a moderate elevation, between 1 and 2 Standard Deviation (SD) in 3 syndrome scales (Anxiety/Depression, Aggression, Attention) (Hudziak et al., 2005). The DESR profile has been related to maladaptive behaviors in response to frustration or negative emotions, impulsivity, elevated irritability and anger, and high rates of anxiety and disruptive behaviour disorders (Biederman et al., 2009). This profile has been principally explored in youth with Attention Deficit Hyperactivity Disorder (ADHD), and a strong minority (44%) of them presented this specific profile, associated with more elevated rates of impairment in school adaptation and failure in peer relationship, when compared to youths without DESR (Biederman et al., 2012). In follow-up studies, the DESR

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profile correlated with a long-term risk of psychopathology, such as ADHD persistence in adolescence and adult age (Biederman et al., 2012), oppositional-defiant disorder (Biederman et al., 2012), bipolar disorder (Biederman et al., 2009; Faraone et al., 2005), suicidality (Holtmann et al., 2011), and poor global functioning (Biederman et al., 2009, 2012; Faraone et al., 2005). The DESR profile was thus associated with a subgroup of patients with a more severe clinical picture and poorer prognosis, but with different possible developmental trajectories.

More recently, a more severe form of the same profile has been described, with a greater elevation, more than 2 Standard Deviations (SD) in 3 syndrome scales (Anxiety/Depression, Aggression, Attention) of the CBCL, which may describe the more severe forms of dysregulated mood and behaviour. This profile was first more closely related to the pediatric bipolar disorder, and named CBCL-Pediatric Bipolar Disorder profile (CBCL-PBD) (Faraone et al., 2005; Biederman et al., 2009, 2013; Uchida et al., 2014). As several groups have questioned the relationship between this profile and the bipolar disorder diagnosis (Youngstrom et al., 2005; Volk and Todd, 2007; Holtmann et al., 2011; Mbekou et al., 2014), it has been lately named CBCL-Dysregulation Profile (CBCL-DP). The CBCL-DP profile has been explored also in youth without ADHD (i.e., general population, subjects at risk of various forms of psychopathology), and according to these studies it was associated with severe psychopathology, principally with Disruptive Behavior Disorders (DBDs) (Volk and Todd, 2007), suicidal behavior (Ayer et al., 2009), substance use disorders (Holtmann et al., 2011), with relevant affective storms, reactive aggression and often reduced need of sleep, and significant lower level of school adjustment and occupational stability (Hudziak et al., 2005; Volk and Todd, 2007). Perspective studies showed a stability of the profile and of its behavioral and affective correlates from childhood to young adult, had a greater risk for on-going comorbidity, including cluster B (borderline) and C (avoidant, dependent and obsessive–compulsive) personality disorders, and an impairment across a wide range of areas of functioning (Meyer et al., 2009; Halperin et al., 2011). Furthermore, the CBCL-DP was associated with specific temperamental features, including high novelty seeking, high harm avoidance, low reward dependence, and low persistence in tasks (Althoff et al., 2012). Another exploration of the personality traits in youth with CBCL-DP showed higher scores in hostility, impulsivity, emotional lability, callousness and grandiosity (DeCaluwè et al., 2013), indicating a possible proneness to antisocial or borderline personality disorders.

The clinical meaning of these profiles is still debated, as it can be considered a specific syndrome, or at least the early manifestation of this syndrome, based on its heritability, longitudinal stability, and consistency across countries and samples, although strong evidence is still lacking (Ayer et al., 2009). More likely, these behavioral phenotypes are not specific, and they are not due to the presence of a single disorder, but they represent a risk marker of a complex self-regulation disorder, which includes both internalizing and externalizing features (Stringaris and Goodman, 2009). This marker can give rise to personality traits and symptoms, in association with different specific disorders, predictive of later severe adult psychopathology, in which the dysregulation of affects and behavior persists at least up to young adulthood. It is debated whether the two profiles may be a useful diagnostic tool in distinguishing subgroups of youth with specific clinical and developmental features, or with different levels of deficits in an area of very high clinical importance. The role of an early and persisting deficit of self-regulation of affect and behavior as predictor of poorer outcome and a marker of severity is supported by longitudinal studies (Biederman et al., 2009; De Caluwè et al., 2013; Meyer et al., 2009; Holtman et al., 2010).

Emotional dysregulation can take different developmental trajectories, with independent associations with wide range of disorders (Holtmann et al., 2011), supporting the notion that it is not an early manifestation on a single disorder, but an antecedent and a vulnerability profile of a persisting and trans-diagnostic emotional and behavioral dysregulations. Thus, the timely detection and the exploration of these dysregulation profiles in different psychopathological domains may be helpful in distinguishing specific subgroups of patients with poorer prognosis and greater needs of intervention.

Other studies have related CBCL profiles to Disruptive Behavior Disorders (DBDs), such as oppositional defiant disorder and conduct disorder (Volk and Todd, 2007), as the emotional dysregulation is a core marker of these disorders (Frick et al., 2014, Masi et al., 2014a). However, specific studies on DESR and DP in DBDs are still lacking. The main aim of the current study is to further explore the potential clinical utility of the CBCL profiles DESR and DP in youth with DBDs, identifying two subgroups of DBDs patients, and individuating the specific clinical/personality features, socio-environmental characteristics, and specific response to a non-pharmacological multimodal treatment program. Among the personological traits, the study namely investigated the Callous–Unemotional (CU) traits, closely related with the new DSM 5 subtype of conduct disorder with limited prosocial emotions (Masi et al., 2013).

2. Methods

2.1. Sample

A consecutive sample of 108 patients referred to our hospital was included in the study: 90 males, ages 9 to 15 years, 70 with ODD diagnosis, 38 with CD diagnosis. Our hospital is a third level clinic with a national catchment for children and adolescents presenting a wide range of neuropsychiatric disorders. All patients were diagnosed according to a systematic evaluation, including historical information, prolonged observation of interactions with peers, parents and/or examiners, and a structured clinical interview according DSM-IV criteria, the Schedule of Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), administered by trained child psychiatrists. All the patients with current or past diagnosis of autism spectrum disorder, or any psychotic disorders, or with a Full Scale IQ below 85 according to Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991), were excluded from the study. The ethical committee of our Hospital approved the study. All patients and their families participated voluntarily in the study after written consent was obtained by parents/legal caregivers for assessment and treatments procedures.

2.2. Measures

All patients were assessed with the CBCL (Achenbach and Rescorla, 2001), a 118-item scale, completed by parents, with 8 different syndromes scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behaviour and Aggressive Behaviour), a Total Problem Score, and two broad-band scores designated as Internalizing Problems and Externalizing Problems. Regarding the CBCL profiles, 57 patients (52.7%) presented a DESR profile, defined as a score >180 but <210 resulting from the sum of Attention, Aggression and Anxious/Depressed CBCL scales (49 males, 17 [70%] with oppositional defiant disorder and 40 [30%] with conduct disorder, age range 9 to 15 years, mean age 10.3 ± 1.8 years). Forty-one patients (37.9%) presented a DP profile, defined as a score >210 on the same three scales (35 males, 14 [44%] with oppositional defiant disorder and 27 [66%] with conduct disorder, age range 9 to 15 years, mean age 10.2 ± 1.9 years). Ten patients (9.2%) did not present either DESR nor DP; the small percentage of patients not showing DESR or DP profiles did not allow any statistical analyses and then they were not included in the analyses.

As a measure of antisocial personality traits, the Antisocial Process Screening Device-Parent version (APSD) was used, it is a structured clinical interview with 20 items, with three main dimensions: Callous–Unemotional (6 items), Narcissistic (7 items), and Impulsivity (5 items) (19) (Frick and Hare, 2001). The APSD has been shown to have adequate reliability and validity in previous studies (Frick and White, 2008; McMahon et al., 2010).

The quality of familial relationships was explored using the Alabama Parenting Questionnaire (APQ) (Sheldon et al., 1996). The APQ is a 42-item measure on which parents indicate the frequency with which they implement the following parenting practices: Involvement, Positive Parenting, Poor Monitoring/Supervision, Inconsistent

Discipline, and Harsh Parenting. Items are rated on a 5-point scale, ranging from 1 (never) to 5 (always).

The severity of the clinical picture (based on clinician judgement) was assessed with the Clinical Global Impression, Severity (CGI-S) (Guy, 1976), a single item, recorded at the baseline, rating the severity of global symptomatology on a scale from 1 ("Normal") to 7 ("Extremely ill"). The level of functioning was assessed using the Children's Global Assessment Scale (C-GAS) (Shaffer et al., 1983), describing the severity of functional impairment on a scale from 0 (severe impairment) to 100 (superior functioning) in children from 4 to 16 years of age; scores above 70 indicate normal functioning. Family socio-economic status (SES) was evaluated according to Hollingshead and Redlich (1958).

Table 1 presents demographic and clinical characteristics of the DESR and DP groups.

2.3. Treatment

All patients were assigned to a Multimodal Treatment Program (MTP), a non-pharmacological treatment, conducted at our hospital, organized in once-a-week 4 h sessions, lasting one year, including individualized psychotherapy for youths and individual parent training. During each 4 h session, patients attend individual therapy, and parents participate in a parallel parent training. Individual therapy is focused on teaching children or adolescents to improve self-control and problem-solving skills, using modeling, positive reinforcements, assigning homeworks, and role-playing, modifying distorted perceptions and negative emotionality, and teaching social skills to improve interactions with peers. Parents' intervention first includes a definition and description of a selected number of children's behavioral problems, and a definition of techniques for modifying parent–child interaction, followed by monitoring of conflict situations on which to apply new rules. A weekly staff meeting based on case review is used to monitor the adherence of the intervention to the model. More details are reported elsewhere (Masi et al., 2014a). At the end of the treatment, one year from the baseline, the patients were re-assessed with the CBCL and the APSD. Tables 2–4.

2.4. Statistical analysis

Descriptive statistics were used to analyze demographic and clinical characteristics of the whole sample. Chi-square was performed on categorical variables, while ANOVA analyses (the skew and kurtosis indices of the distributions were acceptable) were performed on continuous variables to test differences between groups on all selected variables at the baseline. A paired *t*-test was used to assess the effect of the treatment in the two groups.

3. Results

3.1. Comparison between DESR (n=57) and DP (n=41): socio-demographic characteristics and psychiatric diagnoses

The patients with the two profiles were compared according to selected variables. No differences were found in age, gender ratio, socio-economic status, DBD diagnosis and comorbidities ratio. The two groups did not differ according to C-GAS and CGI-S scores.

Table 2
Comparison between CBCL DESR and DP profiles in youth with Disruptive Behavior Disorders: baseline clinical severity, functional impairment, and scores at the CBCL, Antisocial Process Screening Device-Parent version (APSD-parent) and Alabama Parenting Questionnaire (APQ) scores.

Baseline Mean (S.D.)	CBCL-DESR (*N*=57)	CBCL-DP (*N*=41)	*F* (ANOVA)
C-GAS	42.1 (6.0)	40.6 (6.9)	1.8
CGI-S	4.49 (0.9)	4.72 (1.0)	1.5
APSD-Callous–Unemotional	5.7 (2.0)	5.4 (2.3)	0.4
APSD-Narcissism	5.3 (2.6)	6.7 (2.8)	5.6*
APSD-Impulsivity	5.4 (1.7)	6.1 (1.6)	4.8*
CBCL-Withdrawn	60.0 (7.0)	68.0 (6.7)	32.1***
CBCL-Somatic	56.5 (7.0)	61.4 (7.7)	9.9**
CBCL-Social	63.9 (6.3)	71.0 (7.4)	27.2***
CBCL-Thought	59.4 (6.8)	67.4 (8.9)	25.5***
CBCL-Rule Breaking	63.9 (6.7)	70.0 (5.9)	22.1***
APQ-Inv.	35.3 (2.5)	34.8 (2.7)	0.4
APQ-P.P.	23.6 (2.2)	24.1 (1.8)	1.0
APQ-I.D.	15.5 (2.0)	15.1 (1.9)	0.6
APQ-Mon.	13.3 (3.5)	13.4 (3.4)	0.0
APQ-H.P.	5.7 (1.2)	6.2 (1.5)	1.9

CGI-S: Clinical Global Impression, Severity score; C-GAS= Children Global Severity Scale; APSD= Antisocial Process Screening Device; APQ= Alabama Parenting Questionnaire; Inv= Involvement; P.P= Positive Parenting, Mon= Poor Monitoring/ Supervision, I.D.= Inconsistent Discipline, H.P.= Harsh Parenting;

* $=p<0.05$;
** $=p<0.01$;
*** $=p<0.001$; Ns=not significant.

Table 3
Comparison between pre- and post-treatment scores according to CBCL and APSD in patients with DESR profile.

	Pre-intervention	Post-intervention	*t*
APSD-Callous–Unemotional	5.5 (2.1)	4.4 (1.9)	2.9**
APSD-Narcissism	5.7 (2.4)	4.3 (2.0)	3.9***
APSD-Impulsivity	5.4 (1.6)	4.9 (1.4)	1.6
CBCL-Withdrawal	60.0 (7.0)	60.5 (7.0)	0.7
CBCL-Anx/Depr	61.6 (6.8)	61.7 (7.5)	0.1
CBCL-Somatic	56.6 (6.8)	57.2 (6.8)	0.7
CBCL-Social	63.4 (7.1)	62.7 (8.1)	1.1
CBCL-Thought	59.4 (6.3)	59.1 (8.1)	0.3
CBCL-Attention	66.8 (5.7)	64.8 (6.1)	2.2*
CBCL-Aggressiv.	68.3 (5.4)	65.5 (6.8)	2.1*
CBCL-Rule Breaking	63.9 (6.7)	62.5 (6.2)	1.3

APSD=Antisocial Process Screening Device.

* $=p<0.05$;
** $=p<0.01$;
*** $=p<0.001$; Ns=not significant.

Table 1
Comparison between CBCL DESR and DP profiles in youth with Disruptive Behavior Disorders: baseline socio-demographic features and comorbidities.

	CBCL-DESR (*N*=57)	CBCL-DP (*N*=41)	$p\chi^2/F$
Age-months (S.D.)	124 (21.3)	122 (22.3)	Ns
Gender, Males(%)	49 (88%)	35 (85%)	Ns
SES 1–2 (%)/3–4(%)	14 (24%)/43(76%)	11 (27%)/30(73%)	Ns
CD(%)/ODD(%)	17 (30%)/40(70%)	14 (44%)/27(66%)	Ns
Comorbid ADHD	11 (19%)	8 (20%)	Ns
Comorbid BD	11 (19%)	11 (27%)	Ns
Comorbid ANX	3 (5%)	5 (12%)	Ns
Psychoterapy/psychoterapy+drugs	42 (74%)/15(26%)	16 (42%)/25(58%)	0.004

SES: socio-economic status; CD= Conduct Disorder; ODD= Oppositional Defiant Disorder; ADHD: Attention Deficit Hyperactivity Disorder; BD= Bipolar Disorder; ANX= Anxiety Disorders;

* $=p<0.05$;
** $=p<0.01$;
*** $=p<0.001$; Ns=not significant.

Table 4
Comparison between pre- and post-treatment scores according to CBCL and APSD in patients with DP profile.

	Pre-intervention	Post-intervention	*t*
APSD-Callous Unemotional	5.6 (2.1)	5.5 (1.9)	0.7
APSD-Narcissism	6.2 (2.7)	5.9 (2.7)	0.9
APSD-Impulsivity	6.1 (1.6)	5.5 (1.9)	1.5
CBCL-Withdrawal	68.0 (6.7)	63.0 (7.6)	5.0***
CBCL-Anx/Depres	69.8 (6.2)	65.6 (8.7)	2.9**
CBCL-Somatic	61.1 (6.8)	58.8 (6.8)	1.9
CBCL-Social	71.0 (8.4)	68.3 (9.4)	2.1*
CBCL-Thought	67.5 (8.2)	63.9 (9.1)	2.6*
CBCL-Attention	74.6 (6.7)	69.8 (9.4)	4.3***
CBCL-Aggressiv.	77.5 (6.4)	72.3 (8.6)	4.9***
CBCL-Rule Breaking	69.9 (5.9)	66.3 (5.9)	4.3***

APSD=Antisocial Process Screening Device.
* $=p<0.05$;
** $=p<0.01$;
*** $=p<0.001$; Ns=not significant.

3.2. Comparison between DESR (n=57) and DP (n=41): CBCL, APSD and APQ

The DP group was more severely impaired in the following CBCL syndrome scales: Withdrawn, Social Problem, Thought, Rule Breaking ($p<0.001$), and Somatic ($p<0.01$). Narcissistic and Impulsivity scores were higher in DP than in DESR at the APSD ($p<0.05$), while the Callous–Unemotional trait was similar in the two groups. No differences between groups in any of the parenting practices were found at the APQ.

3.3. Pre-post-treatment scores in the patients with DESR profile

When patients with the DESR profile were compared before and after the treatment, no differences were found in the CBCL syndrome scales, except for a modest effect in the Attention and Aggressive Behavior scales ($p<0.05$). A strong treatment effect was found in the Narcissistic ($p<0.001$) and Callous–Unemotional ($p<0.01$) scales of the APSD, but not in the Impulsivity scale.

3.4. Pre-post-treatment scores in the patients with DP profile

No treatment effect was found in any of the APSD scales. On the contrary, after the treatment, a significant effect was present in the following CBCL scales: Attention Problems, Aggressive Behavior, Rule Breaking, Withdrawal ($p<0.001$), Anxiety–Depression (d.f.: 40; $p<0.01$), Social Problem and Thought ($p<0.05$).

4. Discussion

It has been postulated that CBCL DESR and DP profiles may help identify subgroups of children with specific clinical and developmental features, partially independent of specific comorbid disorders (Mbekou et al., 2014). Even though they are both related with emotional dysregulation, they are partly different clinically, as the main clinical feature in DESR is the poor regulation (low tolerance of frustration, impatience, quickness to anger, and being easily excited to emotional reactions), and in DP the experience of strong emotions (Biederman et al., 2012). The relationship between DESR and DP is unclear, as they may represent different intensities of the same trait, or different clinical entities. In both the conditions, they can be found in different disorders, including ADHD, bipolar disorders and oppositional defiant disorder or conduct disorder.

In the present paper we first aimed at analyzing clinical, personological and socio-demographic correlates of both profiles in referred DBD youths. The first finding is that the great majority of the patients (90.7%) presented a DESR or a DP profile. Contrarily to youths with ADHD, in which emotional dysregulation has been identified in 44% of patients (Biederman et al., 2012), indicating an at-risk subgroup for future psychopathology, the DESR or DP profiles seem a key feature in the psychopathology of ODD/DC. These data parallel those reported by Biederman and coworkers in bipolar patients (Biederman et al., 2013), as the majority of bipolar patients without DP profile (still named Severe Dysregulation profile) were positive to DESR profile anyway, and DP or DESR profile were found in 80% of the patients.

Among the 98 DBD patients with DESR or DP profile, age, gender ratio and socio-economic status did not differ between the two groups. Of note, the two groups did not differ according to the ODD/CD ratio, in rates of ADHD, anxiety disorders and mood disorders, supporting the notion that the two profiles do not seem due to a single comorbid disorder. This is inconsistent with Biederman et al.'s, 2012 study, which compared the two profiles in ADHD patients. These authors found that DP was more frequently associated with ODD, CD, depression and bipolar disorder, while rates of anxiety, substance abuse and smoking did not differ between groups, when including only patients with ADHD.

Child Behaviour Check List syndrome scales were more severely impaired in the DP group, in both Externalizing (Rule Breaking), and Internalizing (Social and Withdrawn) scores. These findings are in line with the results reported by Biederman and colleagues in ADHD sample (Biederman et al., 2012), as DESR and DP groups significantly differed according to some CBCL syndrome scales, including Rule Breaking, Withdrawn, Somatic Complaints, Social Problems and Thought Problems. Youths with DP in this study had also more interpersonal, educational and family impairments, and higher rates of psychiatric hospitalizations.

Regarding personality features, Narcissism and Impulsivity were rated higher in the DP group, while the Callous–Unemotional trait did not differ between groups. Finally, regarding the familial relationships, parenting practices, including inconsistent or harsh discipline, did not differentiate the two groups.

In summary, our findings indicate that the baseline DP profile in youth with DBDs is associated with greater clinical severity, not accounted for by type of DBD (ODD or CD) and comorbidities. The greater severity is more clearly expressed by dimensional measures, such as the not AAA (Aggression, Anxiety–depression, Attention) CBCL scales, both internalizing and externalizing, and the personality traits, such as Narcissism and Impulsivity. These personality features may be related to a higher risk for subsequent personality disorders, antisocial or borderline, as reported in previous studies (De Caluwè et al., 2013). Our findings suggest that, as in ADHD (Biederman et al., 2012), in DBDs DESR and DP profiles are associated with a continuum in clinical severity. Whereas in ADHD they may represent a subset of high risk patients for future psychopathology, in oppositional defiant disorders and/or conduct disorder, as well as in bipolar patients (Biederman et al., 2013), they could be used as a severity index, a further aid to diagnosis and, specifically for DP, It could be associated to clinically relevant personality traits.

Regarding these personality features, DP children showed higher level of Narcissism traits than DESR children, but the same level of Callous–Unemotional traits. The clinical relevance in this finding is still unclear. Within the Callous–Unemotional traits, two main variants have been disentangled on the basis of anxiety (Skeem et al. 2007), with “primary” callous–unemotional with lower anxiety level, and “secondary” callous–unemotional with high anxiety level (Fanti et al., 2013). The high anxious, secondary variant, is characterized by lower self-esteem, associated with high narcissism, impulsivity, poor emotional regulation and severe conduct problems (Skeem et al., 2007; Hicks et al., 2004; Kimonis et al., 2012). We

can postulate that DP can help in identifying children at risk for developing the "secondary" variant, in which mood and behavioral dysregulation and impaired peer relationships (Biederman et al., 2012; Dougherty et al., 2014) may lead to secondary psychopathy through environmental insult, particularly social exclusion or victimization (Barker and Salekin, 2012). A possible further research perspective may be the exploration of the effects of environmental risk factors in affecting the developmental pathways of early dysregulation and secondary psychopathy traits. More intense treatment strategies may be implemented in those higher-risk subjects to contrast negative development, but currently no evidence is available about treatment strategies targeted for those patients. We can hypothesize that a cognitive-behavioral intervention more focused on internalizing symptoms, and especially on ameliorating pathological anxiety and strengthening low self-esteem, may improve youths' vulnerability to environmental insults, and reduce their potential for aggressive behaviors (Masi et al., 2014b). We have explored in our sample the one-year stability of the clinical picture in the two profiles, assessing the changes after a multimodal treatment. Two different patterns of change were found. In the DESR profile two dimensions of personality resulted significantly improved, the Callous–Unemotional and the Narcissistic, while only mild changes were found in the syndrome scales of the CBCL. It may be argued that the lesser severity of the clinical syndromes and personality traits makes these patients more sensitive to an intensive multimodal treatment, specifically aimed to improve both Callous–Unemotional and Narcissistic traits, through training and group discussions to increase insight about emotions of self and others, empathy, and sense of guilt, mostly related to a possible antisocial outcome.

On the contrary, in patients with the DP, none of the personality dimension improved, although the treatment strategy was the same as for DESR patients. The greater severity of these patients may have decreased the changeability of their personality dimensions, while some syndromes including both Externalizing (aggressive an Rule Breaking) an Internalizing (Anxious/Depressive and Withdrawn) significantly improved.

Our findings should be considered preliminary, in the light of important limitations. A selection bias limiting the generalization of the conclusions may be the severity of our sample, as our third-level university hospital may have selected the more severe and help-seeking patients, with the highest rates of comorbidities. For example, almost all our patients presented a score above 180 in the three CBCL dysregulation scales. As a consequence, it was not possible to compare patients with DESR and DP profiles with DBD patients without these profiles. Future studies may include data from community samples, and comparison between clinical and community findings may better highlight the clinical implications of the DESR profile.

Another limitation is that the CBCL, APSD and APQ scores were based on parent ratings. Other measures with different sources of information, such as the patient or the clinician, may have added new data.

However, our findings describe an unselected sample of children and adolescents with DBD as primary diagnosis, followed-up in an ordinary clinical setting, which may actually be one of the strengths of our study. These data may allow new information and broader inferences on the effectiveness of treatments over extended periods of time under ordinary clinical conditions. The two CBCL profiles seem to represent a sort of early marker of severity, associated with an increased risk of poorer outcome, with different developmental pathways, even though it is not possible to predict the typology of the risk, neither in terms of axis I disorders, nor in terms of specific personality dimensions and disorders.

In summary, the assessment of the self-regulation of emotions through CBCL DESR and DP profiles could be integrated in a comprehensive child psychiatric assessment. Although these dimensions lack specificity, their assessment and timely detection in clinical populations may help to disentangle specific high risk subgroups with need of more intense interventions, and to target specific treatment strategies, and to contrast negative development. Our finding may represent a first contribution for treatment strategies targeted for those patients.

Conflict of interest

Dr. Masi was in the advisory boards for Eli Lilly and Shire, has received research grants from Eli Lilly and Shire, and has been speaker for Eli Lilly, Shire, Lundbeck, and Novartis. All the other authors do not have conflicts of interest to declare.

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3 dicembre 2015

8.30-9.00
Registrazione

9.00-9.30
Indirizzo di benvenuto

Massimo Egidi
Presidente AIRA
e Rettore LUISS Guido Carli

Luigi Nicolais
Presidente Consiglio Nazionale delle Ricerche

Venera Padua
Senatrice, Commissione Igiene e Sanità

9.30-10.00
Main Lecture
Disturbi dello Spettro Autistico
Stefano Vicari

10.00-11.00
Simposio: Ricerca clinica e preclinica

Moderatori: Laura Ricceri e Fabio Benfenati

Autism and synaptic vesicle proteins: the case of synapsins
Fabio Benfenati

Basi neurobiologiche dei deficit di connettività nell'autismo
Alessandro Gozzi

Assenza di preferenze per alcuni stimoli visivi sociali nei neonati ad alto rischio di autismo
Giorgio Vallortigara

11.00-11.30
Coffee break

11.30-13.00
Simposio: Ricerca clinica
Moderatori: Stefano Vicari e Maria Luisa Scattoni

Autismo ed epilessia
Federico Vigevano

Autismo X-linked
Ginevra Zanni e Enrico Bertini

Indagini metaboliche nei Disturbi dello Spettro Autistico
Vincenzo Leuzzi

Gene expression and imaging
Michael Lombardo

13.00-14.00
Lunch

14.00-14.30
Main Lecture
Progetti italiani ed europei dedicati alla diagnosi precoce
Maria Luisa Scattoni

14.30-15.30
Simposio: Diagnosi Precoce
Moderatori: Filippo Muratori e Massimo Molteni

Diagnosi precoce: tra mito e realtà
Giovanni Valeri

Prospettiva storico-metodologica degli studi del riconoscimento precoce dei segni di autismo nei primi 12-18 mesi di vita
Fabio Apicella

Movimento spontaneo e dell'emergenza del movimento volontario: razionale ed iniziali evidenze di una loro alterazione nell'ASD
Andrea Guzzetta

Interazione tra sistema immunitario e predisposizione genetica nell'autismo
Stefano Gabriele

15.30-16.00
Coffee break

16.00-17.00
Simposio: Intervento precoce
Moderatori: Giovanni Valeri e Fabio Apicella

Implementazione di interventi intensivi precoci nel mondo reale: efficacia, sostenibilità, e indicatori prognostici
Giacomo Vivanti

Lavorare in rete: un modello di intervento intensivo e precoce per bambini con ASD
Paola Venuti

Risultati di un modello di intervento precoce (EIBI) e empowerment sui caregivers effettuato nel SSN
Laura Villa

Intervento intensivo precoce per i disturbi dello spettro autistico secondo il modello ESDM
Liliana Ruta

4 dicembre 2015

9.30-11.00
Simposio: Percorsi di inclusione scolastica e sociale
Moderatori: Fiorenzo Laghi e Donata Vivanti

Ricomporre il dilemma "speciale-normale" per un`inclusione scolastica efficace
Dario Ianes

Le nostre scuole dell'inclusione sono adeguate per gli allievi con autismo?
Lucio Cottini

Costruire collaborazioni tra scuola, famiglia e servizi come modo per dare un seguito concreto alla Legge sull'Autismo
Giuseppe Maurizio Arduino

11.00-11.30
Coffee break

11.30-12.30
Simposio: L'autismo e comorbilità psichiatriche
Moderatori: Angelo Picardi e Paolo Curatolo

Comorbilità psichiatriche in età evolutiva
Luigi Mazzone

Comorbilità psichiatriche e vita adulta
Paolo Girardi

Terapia delle comorbilità psichiatriche nell'autismo
Roberto Canitano

12.15-13.00
'Lia Vassena' Young Investigators Award
Verranno selezionati tre talks dagli abstract che arriveranno da ricercatori Under 40

13.00-14.00
Lunch

14.00-15.00
Simposio: Interventi farmacologici
Co-chairs: Antonella Costantino e Luigi Mazzone

Terapie farmacologiche "tradizionali"
Alessandro Zuddas

Terapie farmacologiche "innovative"
Antonio M. Persico

15.00-15.30
Coffee break

15.30-16.30
Simposio: Nuove tecnologie
Co-chairs: Giovanni Pioggia e Maurizio Arduino
L'impatto delle tecnologie mobili quale supporto al trattamento ed alla genitorialità
Alberto Tozzi

Il paradigma di interazione con robot sociali quale nuova metodologia di valutazione e stimolo del coinvolgimento sociale
Giovanni Pioggia

Conoscere il cervello autistico tramite le nuove tecnologie: DTI, EEG e l'eye tracking
Lucia Billeci

Orizzonti della Magnetoencefalografia (MEG) per lo studio e la diagnosi dei disturbi dello spettro autistico
Giuseppe Sorrentino

16.30-17.00
Discussione e conclusione lavori

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INFORMAZIONI GENERALI

Sede: Consiglio Nazionale delle Ricerche, Aula Convegni
Piazzale Aldo Moro 4.
Ingresso: Entrata angolo Via dei Marrucini

Destinatari e numero massimo partecipanti:
Il convegno è rivolto in particolare ai referenti regionali per la salute mentale, ai responsabili e agli operatori dei centri, alle associazioni di familiari/utenti e alle società scientifiche operanti nel settore. Numero massimo di partecipanti: 200.
L'iscrizione è obbligatoria fino ad esaurimento posti e puo' essere effettuata compilando ed inviando via email il modulo di iscrizione unitamente all'attestazione di pagamento.
Non sono previsti crediti ECM
Le spese di viaggio e soggiorno sono a carico del partecipante.

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La quota di iscrizione è di 50 euro e include la Tessera da Socio Sostenitore di AIRA.
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Specificare nella causale: congresso AIRA Roma 3-4 dicembre 2015
Per finalizzare l'iscrizione inviare copia del bonifico effettuato e scheda di iscrizione alla e-mail: convegno.aira@gmail.com

Le domande di partecipazione saranno accettate fino al raggiungimento della capienza massima dell'Aula.

Attestati
Al termine della manifestazione, sarà rilasciato un attestato di partecipazione a chi ne farà richiesta.

BORSA "Lia Vassena' Young Investigators Award"

Aira istituisce un premio destinato ai ricercatori Under 40: il "Lia Vassena' Young Investigators Award", una borsa di studio e la possibilità di esporre oralmente al convegno il contributo scientifico più meritevole e innovativo tra gli abstract presentati alla commissione scientifica.
La borsa è intitolata alla memoria della ricercatrice Lia Vassena, biotecnologa, prematuramente scomparsa. La scienziata italiana che si è formata presso i laboratori del San Raffaele di Milano ha lavorato diversi anni presso il National Institute of Health di Bethesda negli USA proseguendo la sua attività di ricerca dal 2012 presso l'ospedale pediatrico Bambino Gesù di Roma. I suoi studi sono stati focalizzati sulla comprensione del ruolo dell'interleuchina 7 (IL-7) come fattore protettivo nei confronti delle cellule immunitarie bersaglio del virus HIV.
Dal punto di vista sociale si è caratterizzata per una fervida attività di supporto nei confronti di persone affette da disturbo dello spettro autistico.

La deadline per l'invio degli Abstract è il **20 Novembre 2015.**
Il numero massimo di caratteri (spazi inclusi) per il testo è di 2300 caratteri (esclusi titolo, autori e affiliazioni). Non è possibile inserire immagini, tabelle o figure.
Devono essere citate tre parole chiave.
Per l'invio utilizzare esclusivamente il form on-line disponibile sul sito di AIRA.
Abstract inviati con modalità diversa da quella predisposta NON saranno presi in considerazione.
Il primo autore deve essere iscritto al Congresso.
Il Comitato Scientifico di AIRA valuterà gli abstract e ne comunicherà l'esito entro il 25 novembre 2015.

Per ogni informazione attinente alla manifestazione, si prega di contattare la Segreteria Tecnica

WebCenter

Questionario per la valutazione della Newsletter ADHD

Gent.mi lettori,

questo è un invito alla compilazione del questionario on-line sulla Newsletter ADHD.

Tale operazione Vi impegnerà per 2 minuti al massimo accedendo al seguente link:

http://givitiweb.marionegri.it/Centres/Customs/adhd/Publics/ValutazioneNewsletter.aspx?project=adhd

Si confida nella Vs preziosa collaborazione.

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

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