NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD NOVEMBRE 2016

Acad Pediatr. 2015 Nov;15:658-65.
SCREENING FOR ADOLESCENT PROBLEMATIC INTERNET USE: VALIDATION OF THE PROBLEMATIC AND RISKY INTERNET USE SCREENING SCALE (PRIUSS).
Jelenchick LA, Eickhoff J, Zhang C, et al.
OBJECTIVE: Problematic Internet use (PIU) is an emerging health concern that lacks screening measures validated for use with adolescents and young adults. This study aimed to validate the Problematic and Risky Internet Use Screening Scale (PRIUSS) for use with older adolescents and to increase its clinical utility by determining scoring guidelines and assessing the relationship between PIU and other mental health conditions.
METHODS: This cross-sectional survey study took place at a large, public Midwestern university among 330 older adolescents aged 18 to 25 years. Confirmatory factor analysis and Spearman's correlations were used to assess the PRIUSS' structural and construct validity, respectively. A risk-based scoring cutoff was estimated using a Bayesian latent class modeling approach to computing a receiver operating characteristic curve.
RESULTS: The confirmatory factor analysis indices for the 3-factor model indicated an acceptable fit (goodness-of-fit index 0.89, root mean square error of approximation 0.07). A cutoff of 25 (sensitivity 0.80, 95% confidence interval [CI] 0.47-0.99; specificity 0.79, 95% CI 0.73-0.84) is proposed for identifying those at risk for PIU. Participants at risk for PIU were at significantly greater odds of also reporting symptoms of attention-deficit/hyperactivity disorder (odds ratio [OR] 2.36 95% CI 1.21-4.62, P = .009), depression (OR 3.25, 95% CI 1.65-6.42, P = .008), and social anxiety (OR 3.77, 95% CI 2.06-6.89, P < .000).
CONCLUSIONS: The PRIUSS demonstrated validity as a PIU screening instrument for adolescents and young adults. Screening for PIU may also help to identify those at high reciprocal risk for other mental health conditions

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

Acta Neurol Belg. 2016;1-5.

THE EFFECTS OF RISK FACTORS ON EEG AND SEIZURE IN CHILDREN WITH ADHD.

Kartal A, Aksoy E, Deda G.

Attention-deficit hyperactivity disorder (ADHD) is one of the most commonly seen developmental disorders in childhood. Its etiology, however, is not well known even though bio-psycho-social reasons have been thought to play a big role. The aims of this retrospective study are to identify the risk factors of ADHD in patients diagnosed with ADHD in childhood, analyze the relationship between clinical symptoms and risk factors to which they were exposed and determine their effects on prospective electrophysiological findings. Longitudinal cohort study of all children with ADHD treated at Ankara University Medical University during 2007ΓÇô2012, with follow-up to ascertain risk factors and seizure and EEG abnormalities outcome. Multinominal univariate logistic regression analysis was used to calculate adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for associations. Epileptiform discharges were found in 32 (22.9%) of the 140 ADHD patients. Of these, 71.9% had focal epileptiform discharges and 28.1% had generalized epileptiform discharges. The focal epileptiform discharges were most prevalent from the rolandic area. Among the 140 patients, 20 (14.3%) had a previous history of seizure, and all twenty had epileptiform discharges on EEG whereas none of the patients who had normal EEG had a seizure history. The rates of epileptiform discharges were significantly related to gestational age and asphyxia (RR: 1.8, 95% CI 0.3, 9.3; RR: 9.6, 95% CI 2.3, 40, respectively), whereas the rates of epilepsy were related to asphyxia but not gestational age. History of asphyxia and prematurity do seem to increase the risk of EEG abnormality in patients with ADHD. Modification of these environmental risk factors by evidence-based prevention programs may help to decrease the burden of ADHD

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Addiction. 2015 Nov;110:1811-24.

EARLY SECOND-HAND SMOKE EXPOSURE AND CHILD AND ADOLESCENT MENTAL HEALTH: EVIDENCE FROM HONG KONG'S 'CHILDREN OF 1997' BIRTH COHORT.

Leung CY, Leung GM, Schooling CM.

BACKGROUND AND AIMS: Second-hand smoke (SHS) exposure is associated negatively with childhood behavioural problems in western settings. In a developed non-western setting, we estimated the associations of early SHS exposure during the prenatal and postnatal periods with several aspects of adolescent mental health.

DESIGN: Multivariable linear regression was used to estimate the adjusted associations of pre- and postnatal SHS exposure with adolescent mental health.

SETTING: Hong Kong.

PARTICIPANTS: Population-representative "Children of 1997" birth cohort. Behavioural problems at ~11 years were available for 5598, self-esteem at ~11 years for 6937 and depressive symptoms at ~13 years for 5797.

MEASUREMENTS: SHS was categorized as no SHS exposure, occasional prenatal SHS exposure from non-parental sources, daily prenatal SHS exposure from non-parental sources, postnatal SHS exposure from non-parental sources, prenatal and postnatal SHS exposure from non-parental sources, occasional paternal smoking, daily paternal smoking and any maternal smoking. Behavioural problems were assessed from parent-reported Rutter score, self-esteem from self-reported Culture-Free Self-Esteem Inventory score and depressive symptoms from self-reported Patient Health Questionnaire-9 score.

FINDINGS: Prenatal SHS exposure from non-parental sources was associated with behavioural problems at ~11 years (1.24, 95% confidence interval 0.20-2.28) adjusted for sex, age of assessment, survey mode (for depressive symptoms only), socio-economic position (SEP), mother's birthplace, gestational age and parity; paternal smoking and maternal smoking were associated with more mental health problems but also with lower SEP.

CONCLUSIONS: In Hong Kong, prenatal second-hand tobacco smoke exposure appears to be a risk factor for behavioural problems at age 11 years independent of socio-economic position

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Addiction. 2015 Jan;110:49-50.
COMMENTARY ON ZHOU ET AL. (2015): TREATING PSYCHIATRIC COMORBIDITY IN ADOLESCENTS--AN IMPORTANT PROBLEM.
Nunes EV.

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ADHD Atten Deficit Hyperact Disord. 2016;1-12.
PRE-SERVICE TEACHERS' PERCEPTIONS OF SLUGGISH COGNITIVE TEMPO.
Meisinger RE, Lefler EK.
Sluggish cognitive tempo (SCT) is characterized by a passive form of inattention that may not overtly disrupt classroom goals. Due to the nature of these symptoms, children with SCT may be "falling through the cracks" in schools. The current study examined pre-service teachers' perceptions of SCT in the classroom. Undergraduate education majors (n = 161) read vignettes describing fictitious fourth-grade boys presenting with symptoms of SCT, attention-deficit/hyperactivity disorder (ADHD), or a non-ADHD-related control: social anxiety disorder (SA), and rated each of the vignettes in terms of their perceptions of the boy described. Results were analyzed using repeated measures ANOVAs and paired-sample t tests. Pre-service teachers viewed all three sets of symptoms as concerning, but viewed ADHD behaviors as the most problematic. These results are promising, as they suggest that pre-service teachers are concerned about both hyperactive (i.e., ADHD) and non-hyperactive behavioral problems (i.e., SCT and SA). Implications and future directions are discussed

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Adm Policy Ment Health. 2015 Nov;42:767-74.
RELATIONSHIPS OF SHARED DECISION MAKING WITH PARENTAL PERCEPTIONS OF CHILD MENTAL HEALTH FUNCTIONING AND CARE.
Butler AM, Weller B, Titus C.
Experts encourage parents and practitioners to engage in shared decision making (SDM) to provide high quality child mental health care. However, little is known regarding SDM among families of children with common mental health conditions. The objectives of this study were to examine associations between parental report of SDM and parental perceptions of (a) receiving child mental health care and (b) child mental health functioning. We analyzed cross-sectional data on children with a common mental health condition (attention-deficit hyperactivity disorder, oppositional-defiant or conduct disorder, anxiety, or depression) from the 2009/2010 National Survey of Children with Special Healthcare Needs (N = 9,434). The primary independent variable was parent-reported SDM, and the dependent variables were parental perception of (a) their child receiving all needed mental health care (b) their children's impairment in school attendance and extracurricular activity participation, and (c) severity of their children's mental health condition. Multivariate logistic and multinomial regression analyses were conducted. Greater parent-reported SDM was associated with parental perceptions of receiving all needed child mental health care and children not having school or extracurricular impairment. Greater SDM was also associated with perceptions of children having a mild mental health condition compared to children having a moderate or severe condition. Findings provide a basis for future longitudinal and intervention studies to examine the benefit of SDM for improving parental perceptions of the quality of child mental health care and mental health functioning among children with common mental health conditions

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Adm Policy Ment Health. 2015 Mar;42:229-43.

VALIDITY OF THERAPIST SELF-REPORT RATINGS OF FIDELITY TO EVIDENCE-BASED PRACTICES FOR ADOLESCENT BEHAVIOR PROBLEMS: CORRESPONDENCE BETWEEN THERAPISTS AND OBSERVERS.

Hogue A, Dauber S, Lichvar E, et al.

Developing therapist-report fidelity tools to support quality delivery of evidence-based practices in usual care is a top priority for implementation science. This study tested the reliability and accuracy of two groups of community therapists who reported on their use of family therapy (FT) and motivational interviewing/cognitive-behavioral therapy (MI/CBT) interventions during routine treatment of inner-city adolescents with conduct and substance use problems. Study cases (n = 45) were randomized into two conditions: (a) Routine Family Therapy (RFT), consisting of a single site that featured family therapy as its standard of care for behavioral treatment; or (b) Treatment As Usual (TAU), consisting of five sites that featured non-family approaches. Therapists and trained observational raters provided FT and MI/CBT adherence ratings on 157 sessions (104 RFT, 53 TAU). Overall therapist reliability was adequate for averaged FT ratings (ICC = .66) but almost non-existent for MI/CBT (ICC = .06); moreover, both RFT and TAU therapists were more reliable in reporting on FT than on MI/CBT. Both groups of therapists overestimated the extent to which they implemented FT and MI/CBT interventions. Results offer support for the feasibility of using existing therapist-report methods to anchor quality assurance procedures for FT interventions in real-world settings, though not for MI/CBT

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Allergol Immunopathol (Madr). 2016 Mar;44:120-24.

PSYCHIATRIC DISORDERS AND SYMPTOMS SEVERITY IN PRESCHOOL CHILDREN WITH ATOPIC ECZEMA.

Catal F, Topal E, Soylu N, et al.

BACKGROUND: To compare with a control group the frequency of psychiatric disorders and severity of psychiatric symptoms in preschool children with atopic eczema.

METHODS: The study included children between the ages of 3-5 who were diagnosed to have atopic eczema. The parents of the children with atopic eczema were interviewed in person and were asked to fill in "The Early Childhood Inventory-4" form. This form assesses the psychiatric disorders and symptoms severity in children between the ages of 3-5.

RESULTS: The atopic eczema group included 80 patients (38 male, 42 female) with a mean age of 48.4 +/- 15.7 months and the control group included 74 patients (41 male, 33 female) with a mean age of 49.9 +/- 15.19 months. It was established that 68.8% of the group with atopic eczema received at least one psychiatric diagnosis. Between the psychiatric disorders, ADHD (Odds ratio: 2.57, 95% CI: 1.049-6.298, p=0.035), enuresis and encopresis (Odds ratio: 2.39, 95% CI: 1.121-5.097, p=0.022) and attachment disorder (Odds ratio: 2.03, 95% CI: 1.046-3.953, p=0.035) were found to be significantly higher when compared with the healthy control group. When the groups were compared in terms of psychiatric symptom severity scores calculated by using ECI-4, ADHD severity (p=0.043), conduct disorder severity (p=0.001), anxiety disorders severity (p<0.001), eating disorders severity (p=0.011) and tic disorder severity (p=0.01) were found to be higher in the atopic eczema group.

CONCLUSION: Psychiatric illnesses are frequent in preschool children with atopic eczema

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Allergy. 2016 Apr;71:532-40.

EMOTIONAL AND BEHAVIORAL PROBLEMS IN ADOLESCENTS AND YOUNG ADULTS WITH FOOD ALLERGY.

Ferro MA, Van Lieshout RJ, Ohayon J, et al.

BACKGROUND: Adolescents with food allergy have poorer psychosocial outcomes compared with their nonallergic counterparts; however, few studies have prospectively examined the mental health of adolescents and young adults in this vulnerable population. Our objectives were to estimate the prevalence of emotional and behavioral problems in an epidemiological sample of adolescents and young adults with food allergy; determine whether food allergy is associated with adolescent and maternal reports of such

problems; and examine the patterns of change in emotional and behavioral problems from adolescence to young adulthood among individuals with and without food allergy.
METHODS: Data came from 1303 participants at 14 and 21 years of age in the Mater University Study of Pregnancy. Emotional and behavioral problems were measured using self- and maternal-reported symptoms of depression, anxiety, attention/deficit hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder.
RESULTS: Maternal, but not self-reports suggested that emotional and behavioral problems were higher among adolescents with food allergy. Food allergy was associated with increased odds of elevated levels of maternal-reported symptoms of depression [OR = 4.50 (1.83, 11.07)], anxiety [OR = 2.68 (1.12, 6.44)], and ADHD [OR = 3.14 (1.07, 9.19)] in adolescence. Food allergy was also associated with depressive symptoms that persisted from adolescence to young adulthood [OR = 2.05 (1.04, 4.03)].
CONCLUSIONS: Emotional and behavioral problems, particularly symptoms of depression, anxiety, and ADHD, are common among adolescents with food allergy in the general population and, in the case of elevated levels of depressive symptoms, persist into young adulthood. Healthcare professionals should seek adolescent and parental perspectives when assessing emotional and behavioral problems and monitor mental health during the transition to adulthood

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Am Indian Alsk Native Ment Health Res. 2015;22:23-40.
ADHD SYMPTOMS IN AMERICAN INDIAN/ALASKA NATIVE BOYS AND GIRLS.
Lefler EK, Hartung CM, Bartgis J, et al.
Despite the commonality of attention-deficit/hyperactivity disorder (ADHD), the diagnostic criteria are based largely on research with European American boys. Much less research is available regarding the prevalence of ADHD in other groups, specifically American Indian/Alaska Native (AI/AN) children. Moreover, research on sex differences in ADHD has typically not included AI/AN children. The current study examined parent- and teacher-reported ADHD symptoms in 72 AI children from one region in the Southern U.S., with a focus on sex differences. Data showed that AI children may have more pronounced sex differences in ADHD symptomology than is found in studies with primarily European American children. Implications, limitations, and future directions are discussed

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Am J Med Genet A. 2016 Apr;170A:918-29.
MUENKE SYNDROME: AN INTERNATIONAL MULTICENTER NATURAL HISTORY STUDY.
Kruszka P, Addissie YA, Yarnell CM, et al.
Muenke syndrome is an autosomal dominant disorder characterized by coronal suture craniosynostosis, hearing loss, developmental delay, carpal, and calcaneal fusions, and behavioral differences. Reduced penetrance and variable expressivity contribute to the wide spectrum of clinical findings. Muenke syndrome constitutes the most common syndromic form of craniosynostosis, with an incidence of 1 in 30,000 births and is defined by the presence of the p.Pro250Arg mutation in FGFR3. Participants were recruited from international craniofacial surgery and genetic clinics. Affected individuals, parents, and their siblings, if available, were enrolled in the study if they had a p.Pro250Arg mutation in FGFR3. One hundred and six patients from 71 families participated in this study. In 51 informative probands, 33 cases (64.7%) were inherited. Eighty-five percent of the participants had craniosynostosis (16 of 103 did not have craniosynostosis), with 47.5% having bilateral and 28.2% with unilateral synostosis. Females and males were similarly affected with bicoronal craniosynostosis, 50% versus 44.4% (P = 0.84), respectively. Clefting was rare (1.1%). Hearing loss was identified in 70.8%, developmental delay in 66.3%, intellectual disability in 35.6%, attention deficit/hyperactivity disorder in 23.7%, and seizures in 20.2%. In patients with complete skeletal surveys (upper and lower extremity x-rays), 75% of individuals were found to have at least a single abnormal radiographical finding in addition to skull findings. This is the largest study of the natural history of

Muenke syndrome, adding valuable clinical information to the care of these individuals including behavioral and cognitive impairment data, vision changes, and hearing loss

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Am J Med Genet A. 2016 Apr;170A:1035-39.

DISTINCTIVE FINDINGS IN A BOY WITH SIMPSON-GOLABI-BEHMEL SYNDROME.

Halayem S, Hamza M, Maazoul F, et al.

Simpson-Golabi-Behmel syndrome (SGBS) is an X-linked condition characterized by pre and post natal overgrowth, facial malformations, and visceral, skeletal, and neurological anomalies. The physical characteristics of SGBS have been well documented; however there is a lack of description regarding the behavioral phenotype. We report the case of a 6-year-old boy, with confirmed deletion of 6-8 exons of the glypican-3 gene (GPC3) who presents three distinctive findings: the persistence of the craniopharyngeal canal, an immune-allergic specificity, and a scarcely behavioral phenotype consisting in the association of Austim Spectrum Disorder with accompanying mild intellectual disability and language impairments. He also fulfilled the criteria of Attention Deficit Hyperactivity Disorder and Oppositional Defiant Disorder according to DSM 5 criteria. The specificities of the case are discussed in the light of recent pathophysiological data

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Am J Med Genet B Neuropsychiatr Genet. 2016 Mar;171B:153-59.

THE ASSOCIATION BETWEEN CHILDHOOD AUTISTIC TRAITS AND ADOLESCENT PSYCHOTIC EXPERIENCES IS EXPLAINED BY GENERAL NEUROPSYCHIATRIC PROBLEMS.

Cederlof M, Pettersson E, Sariaslan A, et al .

Studies suggest associations between childhood autistic traits and adolescent psychotic experiences. However, recent research suggests that a general neuropsychiatric problems factor predicts adverse outcomes better than specific diagnostic entities. To examine if the alleged association between autistic traits and psychotic experiences could rather be explained by a general neuropsychiatric problems factor comprising symptoms of ADHD, tic disorder, developmental coordination disorder, and learning disorder, we conducted a prospective cohort study based on the Child and Adolescent Twin Study in Sweden. In addition, we examined the genetic and environmental influences on the associations. A total of 9,282 twins with data on childhood autistic traits and other neuropsychiatric problems, and follow-up data on psychotic experiences at ages 15 and/or 18 years were included. First, psychotic experiences were regressed on autistic traits and second, the general neuropsychiatric problems factor was added to the model. Auditory hallucinations were analyzed separately from the other psychotic experiences. Finally, twin analyses were employed to disentangle genetic from environmental influences in the observed associations. Replicating prior research, significant associations were found between autistic traits in childhood and auditory hallucinations at ages 15 and 18. However, after controlling for the general neuropsychiatric problems factor, the associations between autistic traits and auditory hallucinations disappeared, whereas the association between the general neuropsychiatric problems factor and auditory hallucinations persisted after controlling for autistic traits. Twin analyses revealed that the association between the general neuropsychiatric problems factor and auditory hallucinations was driven by shared genetic influences. (c) 2015 Wiley Periodicals, Inc

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Am J Med Genet Part B Neuropsychiatr Genet. 2016.

PSYCHOPATHOLOGY IN 7-YEAR-OLD CHILDREN: DIFFERENCES IN MATERNAL AND PATERNAL RATINGS AND THE GENETIC EPIDEMIOLOGY.

Wesseldijk LW, Fedko IO, Bartels M, et al.

The assessment of children's psychopathology is often based on parental report. Earlier studies have suggested that rater bias can affect the estimates of genetic, shared environmental and unique environmental influences on differences between children. The availability of a large dataset of maternal as well as paternal ratings of psychopathology in 7-year old children enabled (i) the analysis of informant effects on these

assessments, and (ii) to obtain more reliable estimates of the genetic and non-genetic effects. DSM-oriented measures of affective, anxiety, somatic, attention-deficit/hyperactivity, oppositional-defiant, conduct, and obsessive-compulsive problems were rated for 12,310 twin pairs from the Netherlands Twin Register by mothers (N=12,085) and fathers (N=8,516). The effects of genetic and non-genetic effects were estimated on the common and rater-specific variance. For all scales, mean scores on maternal ratings exceeded paternal ratings. Parents largely agreed on the ranking of their child's problems (r 0.60-0.75). The heritability was estimated over 55% for maternal and paternal ratings for all scales, except for conduct problems (44-46%). Unbiased shared environmental influences, i.e., on the common variance, were significant for affective (13%), oppositional (13%), and conduct problems (37%). In clinical settings, different cutoffs for (sub)clinical scores could be applied to paternal and maternal ratings of their child's psychopathology. Only for conduct problems, shared environmental and genetic influences explain an equal amount in differences between children. For the other scales, genetic factors explain the majority of the variance, especially for the common part that is free of rater bias

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Ann Allergy Asthma Immunol. 2016;117:186-91.

ASSOCIATION BETWEEN MEDICATION PRESCRIPTION FOR ATOPIC DISEASES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

van der Schans J, Pleiter JC, De Vries TW, et al.

Background Data on the association between atopic diseases and attention-deficit/hyperactivity disorder (ADHD) have been inconclusive.

Objective To assess whether children with drug-treated ADHD are more likely to receive treatment for asthma, allergic rhinitis, or eczema before the start of ADHD medication use compared with controls and to examine the effect of parents receiving medication for ADHD and atopic diseases on ADHD medication use in their offspring.

Methods We conducted a retrospective nested case-control study among children (6-12 years of age) using the Groningen University prescription database. Cases were defined as children with at least 2 prescriptions of methylphenidate within 12 months. For each case, 4 controls were matched on age, sex, and regional area code. Parental prescription data were linked to cases and controls to assess the influence of parents receiving medication for ADHD and atopic diseases on ADHD medication use in their offspring.

Results We identified 4257 cases and 17,028 matched controls. Drug treatment for asthma, allergic rhinitis, and eczema was more common in cases than controls (adjusted odds ratios [aORs], 1.4 [95% confidence interval (CI), 1.3-1.6], 1.4 [95% CI, 1.1-1.8], and 1.3 [95% CI, 1.1-1.5], respectively). Medication for allergic rhinitis and asthma among parents was associated with ADHD treatment in their children (aORs, 1.3 [95% CI, 1.1-1.5] and 1.2 [95% CI, 1.1-1.3], respectively).

Conclusion This study provides further evidence to support the hypothesis that atopic diseases are associated with ADHD. The parental-offspring association suggests a possible genetic and/or environmental component

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Ann Neurol. 2016;80:S386.

ADHD IN AUTISM AND THEIR ASSOCIATION WITH OTHER TREATABLE COMORBIDITIES FROM A NATIONAL AUTISM REGISTRY.

Gordon-Lipkin E, Marvin A, Law J, et al.

Objective: To compare phenotype and comorbidity of Autism Spectrum Disorder (ASD) children with and without Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: Data was obtained from the Interactive Autism Network (IAN), an internet-mediated autism research registry containing parent-report data on >20,000 children with ASD. Eligibility criteria: professional diagnosis of ASD; IAN Child with ASD Questionnaire (CAQ) completed between ages 6-17 years; Social Communication Questionnaire with score 12 and Social Responsiveness Scale (SRS) T-Score 60 to verify ASD diagnosis. Information was obtained from CAQ regarding diagnosis or treatment of ADHD, anxiety

disorder, mood disorder (depression or bipolar), intellectual disability. ASD severity was measured by SRS Total Score.
Results: 3319 children met inclusion criteria; 45.3% had ADHD. Table 1 contains demographics. ADHD was associated with an increase in ASD severity ($p<0.001$) but with a small effect size (Cohen's $d=0.22$). Comparison of comorbid anxiety and mood disorders in ASD, with and without ADHD, are found in Figures 1 and 2, respectively. Comorbidity rates increased with age. Overall, a generalized linear model controlling for gender, race, ethnicity and intellectual disability showed that children with both ASD and ADHD had increased risk of anxiety disorder (Relative Risk=2.37, CI95[2.12,2.64]; $p<0.001$) and mood disorder (Relative Risk=3.17, CI95[2.65,3.79]; $p<0.001$) compared to children with ASD alone.
Conclusions: Children with both ASD and ADHD have an increased risk of comorbid anxiety and mood disorder, increasing with age. Physicians caring for children with ASD should be aware of the coexistence of these treatable conditions and monitor for them as the children age. (Table Presented)

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Ann Neurol. 2016;80:S387.

IMPROVING ACCESS TO SPECIALTY CARE FOR UNDERSERVED CHILDREN WITH NEURODEVELOPMENTAL DISORDERS USING TELEMEDICINE.

Menon D, Singh V, Lipkin P.

Objective: Children and youth with special healthcare needs (CYSHCN) residing in rural and medically underserved regions of the country experience a disparity in accessing specialty care due to both distance, poverty and transportation. The objectives in this study were to demonstrate the feasibility and reliability of conducting neurodevelopmental screening using telemedicine, to assess the acceptance of families to this new model of service, to assess the family benefits
Methods: Telemedicine clinic was started between Kennedy Krieger Institute (Tertiary Center) in Baltimore, MD and Atlantic General Hospital (AGH) to provide direct evaluation and developmental testing by a neurodevelopmental physician at KKI interacting directly with patients at the remote site using secure video conferencing . Referral reasons included DD, language delays, severe behaviors and possible autism. Standardized Developmental testing done for assessment of language, problem solving skills
Results: Total scheduled evaluations= 142 patients Show rate= 83 to 95%. Diagnoses=Autism, ADHD, Conduct/disruptive behavior disorder, language delay, Intellectual disability, specific learning disability Age +> 0-3 years (8%); 3-5 years (22%); 5 to 11 yo (55%) and>12 years (15%). Family satisfaction =75-80%. Average mileage =210 to 300 miles round trip
Conclusions: Telemedicine is a replicable and valid method for a comprehensive Neurodevelopmental examination for CYSHCN. Accepted by practitioners and families, improved access to care for families with CYSHCN, early diagnosis helped to improve the care provided to the CYSHCN

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Ann Neurol. 2016;80:S357.

RHOMBOENCEPHALOSYNAPSES AND NEURODEVELOPMENTAL OUTCOMES: A REVIEW OF 4 CASES.

Agarwal S, Clark G, Emrick L.

Objective: Rhomboencephalosynapses is a rare brain malformation characterized by fusion of cerebellar hemispheres and dentate nuclei and vermian hypogenesis. This case series discusses four children with rhomboencephalosynapses (RES) and their clinical presentation, thus highlighting a wide spectrum of neurodevelopmental profiles.
Methods: We discuss the imaging, clinical findings and genetic testing of four children with RES presenting with diverse neurological issues at a tertiary care Fetal Center and Neurology clinic.
Results: The study includes two children in the adolescent age group, one with behavioral disorders, ADHD, and gait and balance issues and the second with shunted hydrocephalus and developmental delay since an early age. The third infant is a 12 month old male with prenatally diagnosed RES and is developmentally normal with a prenatal amniocentesis showing unbalanced rearrangement of 18p11.3 chromosome. The fourth infant is a 13 month old female with multiple congenital anomalies in the VACTERL spectrum that

include aqueductal stenosis secondary to rhombencephalosynapsis, shunted hydrocephalus and has global developmental delay, with a normal chromosomal microarray.
Conclusions: Rhomboencephalosynapses is rare malformation of the posterior cranial fossa with characteristic imaging findings and is increasingly being diagnosed prenatally. The clinical presentation may be on a wide spectrum of neurological issues. The associated genetic aberration, other congenital malformations and the severity of the condition help prognosticate the neurodevelopmental outcomes

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Ann Neurol. 2016;80:S389.

EARLY MORNING FUNCTIONING IN SCHOOL-AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Sallee F, Komolova M, DeSousa N.

Objective: This study examined the temporal occurrence and severity of inadequate attention-deficit/hyperactivity disorder (ADHD) symptom control throughout the day, and related early morning functioning (EMF) impairments and their impact on caregivers in school-age children with ADHD currently treated with stimulant medications.
Methods: An on-line, primary caregiver-completed questionnaire (n=201) was designed to determine if inadequately controlled ADHD symptoms exist in stimulant-treated school-age children with ADHD. Caregivers who identified inadequately controlled ADHD symptoms (Likert severity rating 2) during the early morning routine (EMR) were asked to continue the survey by answering a series of questions.
Results: On a 10-point scale, with 1 denoting no ADHD symptoms and 10 denoting significant ADHD symptoms, inadequately controlled ADHD symptoms were rated as equally severe during the EMR (6.45) and evening homework time (6.46). The majority of caregivers reported early morning ADHD symptoms (74%) and impairment of EMF (76%) as moderate-to-severe (Likert rating score 5- 10). Easily distracted (74%) and does not listen (73%) were the ADHD symptoms reported most frequently during the EMR, and being impulsive (49%) and failing to finish things (49%) were the most frequent unwanted behaviors appearing during the EMR. Caregivers reported that they often: felt overwhelmed and exhausted (41%), raised their voice more (37%), and felt constantly stressed (30%) as a result of their child's ADHD symptoms during the EMR.
Conclusions: Despite early morning administration of stimulants, caregivers of school-age children with ADHD report a high prevalence of inadequately controlled early morning ADHD symptoms, which has a negative impact on caregivers

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Ann Neurol. 2016;80:S384.

VISUAL ART INTERVENTION IN THE NEURODEVELOPMENTAL DISABILITIES OUTPATIENT CLINIC.

Ley A, Turnacioglu S.

Objective: This study aims to determine if placement of visual art in the outpatient clinic helps ease fear and anxiety in patients with neurodevelopmental disabilities. Children with autism spectrum disorder and attention deficit hyperactivity disorder have increased risk for anxiety, and often experience greater stress in medical settings. Little is known about the effect of visual art on easing pediatric patient fear and anxiety, particularly in children with neurodevelopmental disabilities. However, research to date has shown that visual art in adult clinical environments reduces anxiety and perception of pain. We hypothesize that installing visual art in the clinic will reduce patient anxiety, and will result in improved behaviors with the ability to obtain vital signs more frequently. We also hope to see reductions in physiologic markers of stress and anxiety, such as elevated blood pressure and heart rate.
Methods: This is a prospective, non-randomized study. Participants evaluated before the art installation are the control group; participants evaluated after the installation are the intervention group. A caregiver questionnaire largely derived from the Screen for Child Anxiety Related Disorders will be scored and used for comparative analysis. Ability to obtain vital signs, vital sign values, other pertinent clinical exam findings, medication use and neurodevelopmental diagnosis will also be reviewed. The t-test will be the primary

statistical model used. RxArt, a non-profit organization that commissions visual art from contemporary artists, is sponsoring this project.
Results: Results pending: Art installation to be completed in Summer 2016.
Conclusions: Conclusions pending: We expect to have significant results by September 2016

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Ann Neurol. 2016;80:S314-S315.
DEFICIT ATTENTION HYPERACTIVITY DISORDER (ADHD) IN CHILDREN WITH EPILEPSY AND THEIR SIBLINGS.
Velez-van-Meerbeke A, Romero C, Taver L, et al.
Objective: Epilepsy is a high prevalent neurologic disease in our country (10.6 per 1000 habitants) but the real frequency of ADHD in those patients and its siblings is controversial. The purpose of this study was to stablish the prevalence and risk factors of ADHD in epileptic children and their siblings in Colombia.
Methods: Observational analytic study with 156 children with epilepsy and 51 siblings aged 6 - 18 years selected from different epilepsy clinics. We used the checklist of the DSM IV for ADHD and the Behavioral Assessment System for Children (BASC) applied to parents and teachers.
Results: ADHD prevalence was 35.9% in children with epilepsy and 13.7% in their siblings. Combined sub-type was the most common in both groups (44.6% and 42.8% respectively). There was a non-significant trend in patients with partial epilepsy (n=30) to have a higher prevalence of ADHD when compared to those with generalized epilepsy (n=26). There was no association when age was analysed but younger patients had a greater risk to present ADHD (OR=2,037 IC 95%51.943 - 3.978 p=0.035). 82.1% of children was taking antiepileptic drugs and only 24.4% were seizure free; nevertheless, there was no association between treatment of persistence of seizures and the presence of ADHD.
Conclusions: Epileptic patients and their siblings have a higher prevalence of ADHD than general population. We did not have a representative sample to find out what risk factors will explain this association

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Ann Neurol. 2016;80:S301.
RETT SYNDROME: ANALYSIS OF MEMORY AND ATTENTION.
Djukic A, Rose S, Jankowsk J, et al.
Objective: Rett syndrome (RTT), a severely disabling neurodevelopmental disorder caused by spontaneous mutations in the x-linked MECP2 gene, affects 1:10,000 females. Assessments of cognitive functioning have been extremely difficult because patients with RTT are nonverbal and have no or little purposeful hand use. We have pioneered using state-of-the-art eye-tracking technology to bypass these limitations and reveal the disorder's cognitive phenotype.
Methods: Testing more than 100 genetically confirmed RTT patients, and their typically developing counterparts (TD), we have: (1) established the feasibility of using this new technique with RTT, (2) examined the extent to which memory is affected (as shown by visual preference for a novel target over a familiar one) and (3) delineated aspects of attention that are compromised.
Results: Children with RTT were able to recognize simple patterns, faces, and some emotional expressions (i.e., novelty scores were significantly above chance), although their performance was significantly poorer than that of TD children. An especially striking finding were the atypical patterns of attention, characterized by fewer and longer fixations, poorly distributed looking, less looking to key target areas (e.g., over 40% totally ignored the lower part of the face, and a striking absence of anticipatory/predictive saccades. Deficits in attention correlated with poorer recognition.
Conclusions: This new work indicates that the cognitive world of those with RTT can be unlocked using visually-based tasks, and holds promise for the assessment of therapeutic interventions. Deciphering attentional processes has already led to the design of better attention training strategies which are showing promise in pilot studies with RTT

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Ann Neurol. 2016;80:S392.

A TREATMENT OPTIMIZATION STUDY OF HLD200 IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

McDonnell M, Wigal S, Childress A, et al.

Objective: This 11-week Phase III trial examined the safety and efficacy of HLD200, a novel delayed- and extendedrelease methylphenidate formulation designed to be taken in the evening to control early morning attention-deficit/hyperactivity disorder (ADHD) symptoms before school and throughout the day, in children.
Methods: Children (6-12 years) with ADHD were enrolled. At the start of the 6-week open-label, treatment optimization phase (Visit 2 [V2]), subjects received HLD200 at their previous methylphenidate dose equivalent for 1 week. Five subsequent weekly dose adjustments were permitted to determine optimal daily dose and evening dosage administration time prior to the double-blind phase at V8. Optimal dose and evening dosage administration time were defined as 30% improvement from baseline on the ADHD Rating Scale (ADHD-RS-IV) and Before School Functioning Questionnaire (BSFQ), respectively. ADHDRS- IV, BSFQ, and Daily Parent Ratings of Evening and Morning Behaviors-Revised (DPREMB-R) findings during open-label treatment are reported herein.
Results: Forty-three subjects were included in this analysis. Mean starting dose was 33.0 mg and mean optimal dose achieved was 65.6 mg. Modal evening administration time was 9 p.m. Mean ADHD-RS-IV and BSFQ scores (-¦SD) at V2 were 38.2-¦8.9 and 36.2-¦13.3, and 12.5-¦6.6 and 10.1-¦7.3 at V8, respectively ($p<0.0001$). DPREMB-R AM and PM scores (-¦SD) were 4.9-¦2.4 and 15.1-¦5.9 at V2, and 1.2-¦1.2 and 7.7-¦5.7 at V8, respectively ($p<0.0001$). The majority of TEAEs were mild or moderate in severity.
Conclusions: Evening administration of HLD200 demonstrated statistically significant improvements of ADHD symptoms and functioning in the early morning and throughout the day

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Ann Neurol. 2016;80:S391.

FRAGILE X CARRIER EPIDEMIOLOGY AND SYMPTOMATOLOGY DERIVED FROM INDEX CASES, FROM A TERTIARY CHILD DEVELOPMENTAL CENTER.

Gabis L, Gruber N, Berkenstadt M, et al.

Objective: Fragile X syndrome (FXS) is the most prevalent known genetically inherited cause for autism and intellectual disability. Carriers of the syndrome (premutation) were once thought to be clinically insignificant but it is now welldocumented that the premutation state can cause several clinical disorders. We aimed to perform a nesting approach to acquire data with regard to direct relatives from the index Fragile X cases.
Methods: Seventy-nine women were referred due to a related Fragile X Syndrome patient, mainly offspring or sibling.
Results: Of the women who were referred as carrier, 17% were proven to be full mutation and not premutation. The years of education were in the range of 12-17 years (average of 14-¦1.51 SD). Twenty-seven percent reported Tunisia as their country of origin, mainly from the island of Djerba. High incidence of prolonged pregnancy, above 41 weeks, was reported in 13% of the mothers. Of the premutated group, 22% reported symptoms consistent with learning difficulties, mainly dyscalculia, and 14% reported ADHD symptoms. Awareness of the clinical disorders of the carriers was documented in only 25% of the patients.
Conclusions: Increased awareness and knowledge dissemination in regard to premutation symptomatology and risks are warranted. We suggest a national registry to be installed in different countries that will accumulate genetic and clinical information in regard to Fragile X carrier state

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Ann Acad Med Singapore. 2016;45:S103.

THE QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ong SY, Goh TJ.

Background & Hypothesis: Children and adolescents with psychiatric disorders often experience lower quality of life (QoL) compared to healthy controls. Specifically, children with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) have been reported to have poor QoL in various domains.

However, few studies have examined the difference in QoL between individuals with ASD and ADHD. This study examines the QoL of children diagnosed with ASD and ADHD as they age.
Methods: A total of 160 parents provided information on the QoL of their child on the KIDSCREEEN-27. Demographic information was also collected. Children were aged 7 to 19 years (M = 11.9, SD = 3.25), and were grouped into children (12 years, n = 96) and adolescents (13 years, n = 64). Fiftyeight had a primary diagnosis of ASD and 102 had a primary diagnosis of ADHD.
Results: Children and adolescents with ASD showed significantly lower QoL in the social support and peers domain compared to those with ADHD ($F(1, 158) = 17.67$, $P < 0.01$). Adolescents were reported to have lower QoL in the physical ($F(1,158) = 22.7$, $P > 0.01$) and psychological domain ($F[1, 158] = 4.55$, $P = 0.03$).
Discussion & Conclusion: Unsurprisingly, individuals with ASD were reported to have a lower QoL in the social support and peers domain compared to those with ADHD. Interestingly, adolescents were found to have lower QoL than children. While adolescence is a developmental stage which is often associated with heightened stress and emotional reactivity, factors that impact QoL of adolescents need further exploration. Adolescents with ASD or ADHD can benefit from more support to promote better wellbeing

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Ann Acad Med Singapore. 2016;45:S282.

A REVIEW OF THE USE OF BUPROPION FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS.

Ng QX.

Background & Hypothesis: Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neuropsychiatric disorders of childhood and adolescence. ADHD is associated with significant impairment in academic and social functioning. Stimulants are usually the first choice of drug, however, 2%-4% of children cannot tolerate stimulant medication because of severe side effects. Stimulants may also worsen comorbid mood and anxiety disorders and lead to problems of misuse and diversion. Bupropion is a promising non-stimulant alternative. This study will review published clinical trials on the subject.
Methods: Using the keywords (bupropion or Wellbutrin or Zyban or Elontril) and (attention deficit hyperactivity disorder or ADHD or ADDH), a preliminary search on the PubMed database yielded 25,455 papers published in English between 1 January 1988 and 1 May 2016. Of these, there were only 6 clinical trials involving children.
Results: Several open and controlled trials have shown bupropion's efficacy in improving ADHD symptoms. The pooled mean change in Iowa-Conner Abbreviated Questionnaire (ICQ) and ADHD Rating Scale- IV score for parents and teachers in child and adolescent ADHD in the bupropion- and methylphenidate-treated groups were not significantly different, with a standardised mean difference of 0.41 (95% CI, -0.92-0.11) and -0.10 (95% CI, -0.57-0.38) respectively. The pooled response rate for child and adolescent was also comparable between the 2 treatment groups, with a relative risk of 1.08 (95% CI, 0.85-1.38).
Discussion & Conclusion: In general, amongst children with ADHD, bupropion appears to be less effective than stimulants, but more tolerable. It should be considered for use in the management of childhood ADHD

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Appl Psychophysiol Biofeedback. 2016 Mar;41:17-25.

EFFICACY OF NEUROFEEDBACK VERSUS PHARMACOLOGICAL SUPPORT IN SUBJECTS WITH ADHD.

Gonzalez-Castro P, Cueli M, Rodriguez C, et al.

Behavioral training in neurofeedback has proven to be an essential complement to generalize the effects of pharmacological support in subjects who have attention deficit with hyperactivity disorder (ADHD). Therefore, this investigation attempts to analyze the efficacy of neurofeedback compared with pharmacological support and the combination of both. Participants were 131 students, classified into four groups: control (did not receive neurofeedback or pharmacological support), neurofeedback group, pharmacological support group, and combined group (neurofeedback + pharmacological support). Participants' executive control and cortical activation were assessed before and after treatment. Results indicate that the combined group obtained more benefits and that the neurofeedback group improved to a greater extent in executive control than the

pharmacological support group. It is concluded that this kind of training may be an alternative to stimulate activation in subjects with ADHD

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Appl Psychophysiol Biofeedback. 2016 Mar;41:71-79.

EFFECT OF EEG BIOFEEDBACK ON COGNITIVE FLEXIBILITY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH AND WITHOUT EPILEPSY.

Bakhtadze S, Beridze M, Geladze N, et al.

Attention deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders in school-aged children. Symptoms consistent with ADHD have been observed in 8-77 % of children with epilepsy. Researchers have been motivated to search for alternative forms of treatment because 30 % of patients with ADHD cannot be treated by psychostimulants. Several studies support the use of a multimodal treatment approach that includes neurofeedback (NF) for the long-term management of ADHD. These studies have shown that NF provides a sustained effect, even without concurrent treatment with stimulants. We aimed to assess cognitive flexibility in ADHD children with and without temporal lobe epilepsy (TLE), and to evaluate the effects of NF on cognitive flexibility in these groups of children. We prospectively evaluated 69 patients with ADHD aged 9-12 years. The control group was 26 ADHD children without TLE who received no treatment. The first experimental group comprised 18 children with ADHD. The second experimental group comprised 25 age-matched ADHD children with TLE. This group was further divided in two subgroups. One subgroup comprised those with mesial temporal lobe epilepsy (16 patients, 9 with hippocampal sclerosis and 7 with hippocampal atrophy), and the other with lateral temporal lobe epilepsy (9 patients, 5 with temporal lobe dysplasia, 3 with temporal lobe cysts, and 1 with a temporal lobe cavernoma). We treated their ADHD by conducting 30 sessions of EEG NF. Reaction time and error rates on the Trail Making Test Part B were compared before and after treatment, and significant differences were found for all groups of patients except those who had mesial temporal lobe epilepsy with hippocampal atrophy. Our results demonstrate that in most cases, NF can be considered an alternative treatment option for ADHD children even if they have TLE. Additional studies are needed to confirm our results

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Arch Dis Child. 2016.

ATTENTION DEFICIT HYPERACTIVITY DISORDER: OVERDIAGNOSED OR DIAGNOSES MISSED?

Taylor E.

The prevalence of attention deficit hyperactivity disorder is about 5% of the child population, and it carries risks for mental health, educational and personal dysfunction, antisociality and death. The diagnosis in practice is made with remarkable differences in frequency between nations. Low rates in the UK, by comparison with research estimates, suggest that the condition may often be missed in clinical practice; the reasons are considered

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Archives of Medical Science. 2016;12:1279-85.

MIND CONDUCT DISORDERS IN CHILDREN WITH POOR ORAL HYGIENE HABITS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH EXCESSIVE TOOTH DECAY.

Dursun OB, engl F, Esin IS, et al.

Introduction: Dental caries and poor oral hygiene are among the major childhood public health problems. Although dental research frequently refers to the link between these conditions and behavioural issues, little attention has been paid to understanding the reason for oral health problems from a psychiatric point of view. The aim of this study was to examine the relationship between poor oral health and hygiene and parental attitudes towards child rearing, parents' and children's oral hygiene behaviours, and childhood psychiatric disorders.

Material and methods: This study included 323 children aged 3-15 years. Decayed, missing, filled and decayed, extracted, filled indices, the Simplified Oral Hygiene Index, the Strengths and Difficulties Questionnaire, and the Parent Attitude Research Instrument were used in the study.
Results: We found that the subjects' hyperactivity/inattention scores were positively correlated with poor oral health (p = 0.001) and heavy cariogenic food consumption (p = 0.040). Tooth brushing frequency was found to be significantly lower in children who have a risk for conduct/oppositional disorders than in their non-problematic peers (p = 0.001).
Conclusions: Dental health and oral hygiene behaviours have close links with psychiatric disorders and psychosocial issues. Improving cooperation between child psychiatrists and dentists seems to be important in the prevention of paediatric dental problems

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Asia-Pacific Psychiatry. 2016.

LOST IN TRANSITION: A REVIEW OF THE UNMET NEED OF PATIENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER TRANSITIONING TO ADULTHOOD.

Treuer T, Chan KLP, Kim BN, et al.

This review discusses the unmet needs of patients with attention deficit/hyperactivity disorder (ADHD) who are transitioning into adulthood. Although awareness and recognition of ADHD in children, adolescents, and adults have improved in recent years, there is often an interruption in management of the disorder when adolescent patients transition to adult health care services. This review has the following objectives: (1) to identify key issues patients with ADHD (with or without an early diagnosis) face during transition into adulthood; (2) to review the current clinical practice and country-specific approaches to the management of the transition into adulthood for patients with ADHD; (3) to discuss challenges facing clinicians and their patients when drug treatment for ADHD is initiated; (4) to review current ADHD guidelines on transition management in Hong Kong, Singapore, South Korea, Turkey, and Africa; and (5) to examine economic consequences associated with ADHD. The review suggests that the transition period to adult ADHD may be an underresearched and underserved area. The transition period plays an important role regarding how ADHD symptoms may be perceived and acted upon by adult psychiatrists. Further studies are needed to explore the characteristics of the transition period. If only a fraction of adolescents go on to have mental disorders during adulthood, especially ADHD, it is crucial to identify their characteristics to target appropriate interventions at the beginning of the course of illness. There continues to be low recognition of adult ADHD and a severe lack of medical services equipped to diagnose and care for patients with ADHD transitioning from child to adult services

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Asian J Psychiatry. 2017;25:16-21.

ADDITIVE EFFECTS OF NEUROFEEDBACK ON THE TREATMENT OF ADHD: A RANDOMIZED CONTROLLED STUDY.

Lee EJ, Jung CH.

Neurofeedback (NF) has been identified as a ΓÇ£possibly efficaciousΓÇØ treatment in current evidence-based reviews; therefore, more research is needed to determine its effects. The current study examined the potential additive effect of NF for children diagnosed with ADHD beginning a medication trial first. Thirty-six children (6ΓÇô12 years) with a DSM-IV-TR diagnosis of ADHD were randomly assigned to an NF with medication (NF condition) or a medication only condition. Children in the NF group attended 20 twice-weekly sessions. Outcome measures included individual cognitive performance scores (ADS, K-WISC-III), ADHD rating scores completed by their parents (ARS, CRS) and brainwave indices of left and right hemispheres before and after NF treatment. Significant additive treatment effect in any of the symptom variables was found and a reduction of theta waves in both the right and left hemispheres was recorded in NF condition participants. However our randomized controlled study could not demonstrate superior effects of combined

NF on intelligent functioning compared to the medication treatment only. This study suggested any possible evidence of positive and additive treatment effects of NF on brainwaves and ADHD symptomatology

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Atten Defic Hyperact Disord. 2016 Mar;8:45-52.

ADHD STIGMA AMONG COLLEGE STUDENTS.

Thompson AC, Lefler EK.

The current study examined ADHD stigma within a college-enrolled young adult population, including the debate regarding the cause of stigma: label or behavior. In Phase 1, 135 college students rated stigma toward one of the four fictitious partners described as having either: the label of ADHD alone, the behaviors associated with ADHD alone, the label of ADHD and a set of behaviors associated with ADHD, or neither the label nor behaviors. In Phase 2, 48 college students rated stigma toward one of the two assigned fictitious partners described as having either: the label of ADHD and a set of behaviors associated with ADHD, or the label of Depression and a set of behaviors associated with Depression. It was hypothesized that the interaction between the label and the behaviors would cause the highest levels of ADHD stigma and that ADHD would elicit more stigma than Depression. In Phase 1, stigma was associated with the behaviors of ADHD, but not the label. In Phase 2, ADHD and Depression were found to be equally stigmatized. Implications, limitations, and future directions are discussed

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Atten Defic Hyperact Disord. 2016 Mar;8:21-33.

EMOTIONAL SYMPTOMS AND THEIR CONTRIBUTION TO FUNCTIONAL IMPAIRMENT IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Morstedt B, Corbisiero S, Bitto H, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a severe neurodevelopmental disorder beginning in childhood and consisting of the core symptoms of inattention, hyperactivity, and impulsivity. The disorder is often accompanied by functional impairment in daily life. Research showed that severe impairment cannot be fully explained by the core symptoms of ADHD. Accordingly, emotional symptoms in ADHD and their influence on functional impairment have increasingly become the focus of research in recent years. The aim of the current study was to investigate the relationship between ADHD core symptoms, emotional symptoms, and functional impairment. We assumed that emotional symptoms might form part of adult ADHD and that the connection between ADHD core symptoms and functional impairment may be partly mediated by emotional symptoms. Data of 176 participants from an ADHD Special Consultations Unit were included. Of these participants, 146 were diagnosed with ADHD, while 30 received no such diagnosis. We developed a structural equation model which included core symptoms, emotional symptoms, and four domains of daily impairment (family life, social life, work, and organization). As predicted, results indicate that emotional symptoms are directly linked to adult ADHD and bear a strong negative influence on different domains of daily life. The results of different analyses showed a mediation of the relationship between ADHD core symptoms and impairment through emotional symptoms: While the connection between inattention and work and organization was partly mediated, the connections between impulsivity and family life and between inattention and social life were shown to be fully mediated through emotional symptoms

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Behav Res Ther. 2015 Dec;75:60-71.

COGNITIVE-BEHAVIORAL THERAPY FOR EXTERNALIZING DISORDERS: A META-ANALYSIS OF TREATMENT EFFECTIVENESS.

Battagliese G, Caccetta M, Luppino OI, et al.

Externalizing disorders are the most common and persistent forms of maladjustment in childhood. The aim of this study was to conduct a meta-analysis evaluating the effectiveness of Cognitive Behavioral Therapy (CBT) to reduce externalizing symptoms in two disorders: Attention Deficit Hyperactivity Disorder (ADHD)

and Oppositive Defiant Disorder (ODD). The efficacy of CBT to improve social competence and positive parenting and reduce internalizing behaviors, parent stress and maternal depression was also explored. The database PsycInfo, PsycARTICLES, Medline and PubMed were searched to identify relevant studies. Twenty-one trials met the inclusion criteria. Results showed that the biggest improvement, after CBT, was in ODD symptoms (-0.879) followed by parental stress (-0.607), externalizing symptoms (-0.52), parenting skills (-0.381), social competence (-0.390) and ADHD symptoms (-0.343). CBT was also associated with improved attention (-0.378), aggressive behaviors (-0.284), internalizing symptoms (-0.272) and maternal depressive symptoms (-0.231). Overall, CBT is an effective treatment option for externalizing disorders and is also associated with reduced parental distress and maternal depressive symptoms. Multimodal treatments targeting both children and caregivers' symptoms (e.g. maternal depressive symptoms) appear important to produce sustained and generalized benefits

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Behav Genet. 2015;45:654.

PRENATAL ALCOHOL EXPOSURE AND ADHD: A PROSPECTIVE EXTENDED CHILDREN-OF-TWINS STUDY.

Eilertsen E, Gjerde L, Reichborn-Kjennerud T, et al.

Several epidemiological studies have suggested an association between maternal drinking during pregnancy and offspring risk for developing ADHD. That is, children of mothers who consume alcohol during pregnancy are more likely to develop ADHD or ADHD like symptoms than children of mothers who do not consume alcohol during pregnancy. Similarly, parents of children with ADHD have been shown to consume more alcohol than parents of children without ADHD. While these studies are important for descriptive purposes, they are not suited for identifying causal pathways underlying intergenerational transmissions of risk. Any unmeasured variable that affects both maternal drinking during pregnancy and children's ADHD would be included, and inseparable in these designs. Both ADHD and alcoholism are considered to be highly genetically influenced traits, with heritability estimates in the range of 70-80 and 40-70 %, respectively. While not directly informative to the genetic covariance between maternal drinking during pregnancy and offspring ADHD, these estimates highlights the importance of considering the influence of shared genetic risk within families. At the same time, shared environmental factors may also contribute to the relationship between maternal drinking and offspring ADHD. For instance, both alcoholism and ADHD have been linked to low socioeconomic status. The current study seeks to deal with many of the problems associated with unmeasured confounders when studying intergenerational transmission of risk by using an extended children-of-twins design. This design allows us investigate the relationship between prenatal alcohol exposure and ADHD, while controlling for important genetic and environmental confounders both between and within families. We will utilize a population based Norwegian birth cohort, The Norwegian Mother and Child Study (MoBa), that includes more than 108.000 pregnancies, and where longitudinal data from both parents and children have been collected prospectively from first trimester of pregnancy and onwards

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Behav Genet. 2015;45:647.

GENETIC AND ENVIRONMENTAL INFLUENCES ON THE RELATION BETWEEN ADHD-LIKE TRAITS AND INTERNALIZING PROBLEMS: A CHINESE CHILD TWIN STUDY.

Chen TJ, Ji C, Wang S, et al.

Several twin studies have investigated the overlap between attention deficit hyperactivity disorder (ADHD) and externalizing problems; however, limited information is known regarding the genetic and environmental contribution to the overlap between ADHD and internalizing problems. This study examined the genetic and environmental influences on the variation in and covariation between ADHD symptoms and internalizing problems by using the Child Behavior Checklist (CBCL). We investigated 1316 child and adolescent twins, including 780 monozygotic twins and 536 dizygotic twins, aged 6 years to 18 years from the Chinese Child and Adolescent Twin Registry. ADHD symptoms and internalizing problems were quantified through parent rating by using the Attention Problems Scale and other three scales, which include Anxious/Depressed, Withdrawn, and Somatic Complaints of CBCL. Genetic and environmental susceptibilities common to ADHD

symptoms and internalizing problems were examined through bivariate twin modeling. Results showed that genetic factors substantially influenced the ADHD symptoms with a heritability of 72 %. Modest genetic influences and substantial shared environmental influences (20 to 77 %) were observed in the three internalizing problem scales. Common genetic and shared environmental influences were essential for the overlap between ADHD and the three internalizing problems respectively. Approximately one-fifth of the genetic variance of ADHD symptoms was shared with anxiety/depression. In conclusion, substantial genetic and shared environmental influences on ADHD symptoms and internalizing problems were observed in Chinese children and adolescents. Our finding supports a common etiology between ADHD and internalizing problems. This finding can also help explain the co-existence of these behavior problems

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Behav Genet. 2016;46:813-14.

DIFFERENCES IN MATERNAL AND PATERNAL RATINGS OF PSYCHOPATHOLOGY AND THE GENETIC EPIDEMIOLOGY IN 12,000 7-YEAR OLD TWIN PAIRS.

Wesseldijk L, Fedko I, Bartels M, et al.

Objective: The assessment of children's psychiatric disorders is often based on parental report. Earlier studies have suggested that rater bias can affect the estimates of genetic, shared environmental and unique environmental influences on differences between children. The availability of a large dataset of maternal as well as paternal ratings of psychopathology in 7-year old children enabled 1) the analysis of informant effects on these assessments, and 2) to obtain more reliable estimates of the genetic and non-genetic effects.

Method: DSM-oriented measures of affective, anxiety, somatic, attention-deficit/hyperactivity, oppositional-defiant, conduct, and obsessive-compulsive problems were rated for 12.310 twin pairs from the Netherlands Twin Register by mothers (N = 12.085) and fathers (N = 8.516). The effects of genetic and non-genetic effects were estimated on the common and rater-specific variance.

Results: For all scales, mean scores on maternal ratings exceeded paternal ratings. Parents largely agreed on the ranking of their child's problems (r .60-.75). The heritability was estimated over 55 % for maternal and paternal ratings for all scales, except for conduct problems (44-46 %). Unbiased shared environmental influences, i.e. on the common variance, were significant for affective (13 %), oppositional (13 %) and conduct problems (37 %).

Conclusions: In clinical settings, different cutoffs for (sub)clinical scores could be applied to paternal and maternal ratings of their child's psychopathology. Only for conduct problems, shared environmental and genetic influences explain an equal amount in differences between children. For the other scales, genetic factors explain the majority of the variance, especially for the common part that is free of rater bias

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Behav Genet. 2016;46:774.

FAMILIAL LIABILITY OF ADHD AND EPILEPSY: A NATIONWIDE COHORT STUDY.

Brikell I, Kuja-Halkola R, D'Onofrio B, et al.

Individuals with epilepsy have elevated levels of ADHD-symptoms and ADHD has been associated with an increased risk of seizures (Dunn, D., Williams, A., Giust, J., & Kronenberger, W., 2016. Epilepsy and attention-deficit hyperactivity disorder: links, risks, and challenges. Neuropsychiatric Disease and Treatment, 12, 287-296). However, the extent to which ADHD and epilepsy co-occur, and why, is poorly understood. This study aimed to estimate the association between ADHD and epilepsy and the degree of familial co-aggregation between the disorders. We identified a birth-cohort of 1899602 individuals, born 1987-2006, via Swedish national registers. The cohort was followed from age seven until 31/12/2013. We obtained ADHD and epilepsy status for each individual and linked every person to their biological parents, full-siblings, half-siblings and cousins. The association between ADHD and epilepsy was estimated using logistics regression at the individual-level and across different groups of relatives. At the individual-level, individuals with epilepsy had a significantly increased risk of ADHD (OR 3.47, 95 % CI 3.33-3.62). At the family-level, children of mothers with epilepsy also had a significantly increased risk of ADHD (OR 1.85, 95 % CI 1.75-1.86), as did children of fathers with epilepsy (OR 1.64, 95 % CI 1.54-1.74) and individuals whose full-siblings had epilepsy

(OR 1.56, 95 % CI 1.46-1.67). Risk estimates were attenuated in second-degree relatives, i.e. individuals with a maternal half-sibling (OR 1.28, 95 % CI 1.14-1.43), a paternal half-sibling (OR 1.09, 95 % CI 0.96-1.25) or a cousins with epilepsy (OR 1.15, 95 % CI 1.10-1.20). Our results suggest that individuals with epilepsy and their relatives have an increased risk of ADHD. The pattern of familial coaggregation suggests that familial risk factors, primarily genetic, contribute to the association between ADHD and epilepsy. These findings have implications for nosology and research on pathophysiology, as they imply shared familial liability between two conditions not traditionally considered within the same diagnostic spectrum

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Behav Sleep Med. 2016 Nov;14:677-86.

INCREASED SLEEP DISTURBANCES IN THAI CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER COMPARED WITH TYPICALLY DEVELOPING CHILDREN.

Chiraphadhanakul K, Jaimchariyatam N, Pruksananonda C, et al.

This study compares sleep disturbances in Thai children aged 5–12 years with attention-deficit hyperactivity disorder (ADHD) and typically developing children using the Children's Sleep Habits Questionnaire (CSHQ)–Thai version. Fifty-five children with ADHD and 110 typically developing children were enrolled. Their parents completed the CSHQ, the ADHD rating scales, and the Strengths and Difficulties Questionnaire (SDQ). Children with ADHD had significantly higher scores in all subscales of the CSHQ compared to controls. Among children with ADHD, children with higher SDQ scores (> 15) appeared to have more sleep disturbances than those with relatively lower SDQ scores. Moreover, fewer sleep-related behavioral problems were observed in the medication treated group, which is particularly new to the field and for some perhaps not unexpected clinically

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Biol Psychiatry. 2016;80:266-73.

AGE-DEPENDENT PLEIOTROPY BETWEEN GENERAL COGNITIVE FUNCTION AND MAJOR PSYCHIATRIC DISORDERS.

Hill WD, Davies G, Liewald DC, et al.

Background General cognitive function predicts psychiatric illness across the life course. This study examines the role of pleiotropy in explaining the link between cognitive function and psychiatric disorder.

Methods We used two large genome-wide association study data sets on cognitive functionΓÇöone from older age, n = 53,949, and one from childhood, n = 12,441. We also used genome-wide association study data on educational attainment, n = 95,427, to examine the validity of its use as a proxy phenotype for cognitive function. Using a new method, linkage disequilibrium regression, we derived genetic correlations, free from the confounding of clinical state between psychiatric illness and cognitive function.

Results We found a genetic correlation of.711 (p = 2.26e-12) across the life course for general cognitive function. We also showed a positive genetic correlation between autism spectrum disorder and cognitive function in childhood (rg =.360, p =.0009) and for educational attainment (rg =.322, p = 1.37e-5) but not in older age. In schizophrenia, we found a negative genetic correlation between older age cognitive function (rg = ΓêÆ.231, p = 3.81e-12) but not in childhood or for educational attainment. For Alzheimer's disease, we found negative genetic correlations with childhood cognitive function (rg = ΓêÆ.341, p =.001), educational attainment (rg = ΓêÆ.324, p = 1.15e-5), and with older age cognitive function (rg = ΓêÆ.324, p = 1.78e-5).

Conclusions The pleiotropy exhibited between cognitive function and psychiatric disorders changed across the life course. These age-dependent associations might explain why negative selection has not removed variants causally associated with autism spectrum disorder or schizophrenia

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BMC Health Serv Res. 2016 Apr;16:141.

"IT HAS TO BE FIXED": A QUALITATIVE INQUIRY INTO PERCEIVED ADHD BEHAVIOUR AMONG AFFECTED INDIVIDUALS AND PARENTS IN WESTERN AUSTRALIA.

Ghosh M, Fisher C, Preen DB, et al.

BACKGROUND: The use of stimulant medication for Attention Deficit Hyperactivity Disorder (ADHD) to improve classroom behaviour and sustained concentration is well known. Achieving a better academic grade has been reported as the prime motivation for stimulant use and is an increasingly discussed topic. The proliferation of stimulant use for ADHD has been a cause for public, medical and policy concern in Australia. This paper explores individuals' perceptions of ADHD, the meaning that the diagnosis carries for them and their attitudes to stimulant medication treatment.

METHODS: This qualitative study was underpinned by a social constructivist approach and involved semi-structured interviews with eight participants. The participants were parents of children with ADHD or were adults who themselves had been diagnosed with ADHD. Interviews were audiotaped, transcribed verbatim and thematically analysed.

RESULTS: There were three interrelated yet contradictory overarching themes: (i) An impairment to achieving success, which can be a double-edged sword, but has to be fixed; (ii) Diagnosis as a relief that alleviates fault and acknowledges familial inheritance; (iii) Responsibility to be normal and to fit in with societal expectations. Collectively, these perceptions and meanings were powerful drivers of stimulant use.

CONCLUSIONS: Paying attention to perceptions of ADHD and reasons for seeking or not seeking stimulant treatment is important when planning appropriate interventions for this condition

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BMC Psychiatry. 2016 Nov;16.

RELATIONSHIP BETWEEN EARLY LANGUAGE SKILLS AND THE DEVELOPMENT OF INATTENTION/HYPERACTIVITY SYMPTOMS DURING THE PRESCHOOL PERIOD: RESULTS OF THE EDEN MOTHER-CHILD COHORT.

Peyre H, Galera C, van der Waerden J, et al.

Background: This study aims to examine bidirectional relationships between children's language skills and Inattention/Hyperactivity (IH) symptoms during preschool.

Method: Children (N = 1459) from the EDEN mother-child cohort were assessed at ages 3 and 5.5 years. Language skills were evaluated using the WPPSI-III, NEPSY and ELOLA batteries. Children's behavior, including IH symptoms, was assessed using the parent-rated Strengths & Difficulties Questionnaire (SDQ). Using a Structural Equation Modeling (SEM) approach, we examined the relationship between language skills and IH symptoms, as well as potential mediating processes.

Results: SEM analyses indicated a small negative effect of language skills at 3 years on ADHD symptoms at 5.5 years after adjusting for IH symptoms at 3 years (ß =-0.12, SE = 0.04, p-value = 0.002). Interpersonal difficulties did not mediate the relationship between early language skills and later IH symptoms, nor was this association reduced after adjusting for a broad range of pre- and postnatal environmental factors and performance IQ. Among different language skills, receptive syntax at 3 years was most strongly related to IH symptoms at 5.5 years.

Conclusions: Poor language skills at age 3 may predict IH symptoms when a child enters primary school. Implications for the understanding and the prevention of the co-occurrence of language disorders and ADHD are discussed

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BMC Psychiatry. 2016 Oct;16.

COMPULS: DESIGN OF A MULTICENTER PHENOTYPIC, COGNITIVE, GENETIC, AND MAGNETIC RESONANCE IMAGING STUDY IN CHILDREN WITH COMPULSIVE SYNDROMES.

Naaijen J, de Ruiter S, Zwiers MP, et al.

Background: Compulsivity, the closely linked trait impulsivity and addictive behaviour are associated with several neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive compulsive disorder (OCD). All three disorders show impaired

fronto-striatal functioning, which may be related to altered glutamatergic signalling. Genetic factors are also thought to play an important role in the aetiology of compulsivity-related disorders.
Methods: The COMPULS study is a multi-center study designed to investigate the relationship between the traits compulsivity, impulsivity, and, to a lesser extent, addictive behaviour within and across the neurodevelopmental disorders ADHD, ASD, and OCD. This will be done at the phenotypic, cognitive, neural, and genetic level. In total, 240 participants will take part in COMPULS across four different sites in Europe. Data collection will include diagnostic interviews, behavioural questionnaires, cognitive measures, structural, functional and spectral neuroimaging, and genome-wide genetic information.
Discussion: The COMPULS study will offer the unique opportunity to investigate several key aspects of compulsivity across a large cohort of ADHD, ASD and OCD patients.

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BMC Public Health. 2016 Mar;16:209.

INDIVIDUAL-LEVEL PREDICTORS OF INPATIENT CHILDHOOD BURN INJURIES: A CASE-CONTROL STUDY.

Sadeghi-Bazargani H, Mohammadi R, Amiri S, et al.

BACKGROUND: Burn injuries are considered one of the most preventable public health issue among children; however, are a cause of significant morbidity and mortality in Iran. The aim of this study was to assess individual-level predictors of severe burn injuries among children leading to hospitalization, in East Azerbaijan Province, in North-West of Iran.
METHODS: The study was conducted through a hospital based case-control design involving 281 burn victims and 273 hospital-based controls who were frequency matched on age, gender and urbanity. Both bivariate and multivariate methods were used to analyze the data.
RESULTS: Mean age of the participants was 40.5 months (95 % CI: 37-44) with the majority of burns occurring at ages between 2 months-13.9 years. It was demonstrated that with increase in the caregiver's age there was a decrease in the odds of burn injuries (OR = 0.94, 95 % CI: 0.92-0.97). According to the multivariate logistic regression there were independent factors associated with burn injuries including childhood ADHD (OR = 2.82, 95 % CI: 1.68 - 4.76), child's age (OR = 0.73, 95%CI: 0.67 - 0.80), flammability of clothing (OR = 1.60, 95 % CI: 1.12 - 2.28), daily length of watching television (OR = 1.31, 95 % CI: 1.06 - 1.61), playing outdoors (OR = 1.32, 95 % CI: 1.16 - 1.50) and increment in the economic status (OR = 1.37, 95 % CI: 1.18 - 1.60).
CONCLUSION: Major risk predictors of burn injuries among the Iranian population included childhood ADHD, child's age, watching television, playing outdoors, high economic status and flammable clothing

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Br J Clin Psychol. 2016 Sep;55:305-19.

CONSUMER EVALUATION AND SATISFACTION WITH INDIVIDUAL VERSUS GROUP PARENT TRAINING FOR CHILDREN WITH HYPERKINETIC DISORDER (HKD).

Heubeck BG, Otte TA, Lauth GW.

OBJECTIVES: The objective of this study was to investigate the social validity of cognitive-behavioural parent training (CBPT) delivered in two formats to parents who have children with hyperkinetic disorder (HKD) with and without medication.
DESIGN: Compared individual with group treatment as part of a multicentre randomized controlled trial.
METHOD: Obtained a broad range of evaluations and satisfaction ratings post-treatment and related them to pre-treatment and treatment factors.
RESULTS: Attendance rates were high in the individual and slightly less in the group training. Levels of satisfaction were high in both treatment arms with large numbers rating the outcomes, the trainers and the overall training very favourably. Medication showed no effect on parental evaluations. Evaluation of outcomes and satisfaction with the trainer emerged as strong predictors of overall programme satisfaction.
CONCLUSION: The social validity of cognitive-behavioural parent training for hyperkinetic children was supported by high levels of treatment acceptability across a range of indicators and for children with and without medication.

PRACTITIONER POINTS: Both forms of treatment delivery lead to high rates of consumer satisfaction. Consumer evaluations of CBPT appear independent of medication for HKD. Course satisfaction is clearly associated with two factors that trainers can affect: The parent-trainer relationship and parents' sense of achievement.
LIMITATIONS INCLUDE THE FOLLOWING: Far more mothers than fathers attended the trainings. Attitudes may differ in other cultures

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Brain Sciences. 2016;6.

LANGUAGE PROBLEMS AND ADHD SYMPTOMS: HOW SPECIFIC ARE THE LINKS?

Hawkins E, Gathercole S, Astle D, et al.

Symptoms of inattention and hyperactivity frequently co-occur with language difficulties in both clinical and community samples. We explore the specificity and strength of these associations in a heterogeneous sample of 254 children aged 5 to 15 years identified by education and health professionals as having problems with attention, learning and/or memory. Parents/carers rated pragmatic and structural communication skills and behaviour, and children completed standardised assessments of reading, spelling, vocabulary, and phonological awareness. A single dimension of behavioural difficulties including both hyperactivity and inattention captured behaviour problems. This was strongly and negatively associated with pragmatic communication skills. There was less evidence for a relationship between behaviour and language structure: behaviour ratings were more weakly associated with the use of structural language in communication, and there were no links with direct measures of literacy. These behaviour problems and pragmatic communication difficulties co-occur in this sample, but impairments in the more formal use of language that impact on literacy and structural communication skills are tied less strongly to behavioural difficulties. One interpretation is that impairments in executive function give rise to both behavioural and social communication problems, and additional or alternative deficits in other cognitive abilities impact on the development of structural language skills

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Cardiol Young. 2014;24:S68-S69.

EFFECTS OF METHYLPHENIDATE TREATMENT ON THE HEART RATE VARIABILITY IN PATIENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.

Kocabas A, +çetin I, Ekici F, et al.

Introduction: Methylphenidate (MPH) is a psychostimulant drug and commonly used for attention deficit and hyperactivity disorder (ADHD). It has been reported that the sympathomimetic effects of methylphenidate may cause disturbances in cardiac rhythm.
Methods: Heart rate variability (HRV) analyses were performed to all patients before and at the end of first month of MPH treatment by 24-hr rhythm Holter. Control group consisted of age and gender matched healthy children. Heart rates, maximal QTand QTc durations were analyzed. The time-domain analysis included average heart rate, standard deviation of all normal sinus RR intervals over 24 h (SDNN), standard deviation of average NN intervals (SDANN), SDNN-index, percentage of successive normal sinus RR intervals >50 ms (pNN50) and root-meansquare of the successive normal sinus RR interval difference (rMSSD). The following frequency domain analysis indices were obtained: total power (TP), low frequency (LF) power, high frequency (HF) power, and LF/HF ratio.
Results: A total of 33 patients (24 boys, 9 girls) and 36 healthy control subjects (21 boys, 15 girls) were enrolled in this study. The mean age of the patients and controls were 9.7-¦2.6 years and 9.5-¦2.8 years, respectively (p>0.05). The mean average heart rate before and after MPH treatment was 93.9-¦8.5 and 95.9-¦9.3, respectively. While the minimum, maximum and average heart rate were similar between two groups before MPH treatment (p>0.05) only maximal QTc duration was significantly increased under MPH treatment in the ADHD patients (mean 452.8-¦19.1 ms and 442.9-¦14 ms, respectively; p=0.02) (Table). The comparison of pre- and post-treatment 24-h HRV analyses with the values of control group demonstrated no significant

differences both in all time and frequency domain parameters (p>0.05). Also, no significant arrhythmia was detected in the Holter recordings.
Conclusions: ADHD seems not to have a significant effect on HRV in children. Also, in contrast to majority of the previous studies, MPH treatment did not affect the HRV significantly in our study. However, increase in maximal QTc duration was statistically significant after MPH treatment. (Table Presented)

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Cardiol Young. 2015;25:S172.

INCREASE OF FREQUENCY IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH RHEUMATIC FEVER: PRELIMINARY STUDY.

Hallioglu O, Gumus G, Yildirim V, et al.

Introduction: Genetically, susceptible children who are infected by Group A +¦-hemolytic streptococci may develop a systemic autoimmune disorder known as rheumatic fever (RF). Several psychiatric disorders, in particular obsessive-compulsive spectrum disorders (OCD), attention deficit/hyperactivity disorder (ADHD), and tic disorders have been described in RF. This study aims to examine neuropsychiatric symptoms which are determined in pediatric patients with RF.
Methods: Thirty consecutive patients with RF (mean age 12.8-¦ 1.9 (9-16) years; M/F; 16/14) were studied for a structured psychiatric evaluation according to DSM-IV-TR by a child and adolescent psychiatrist. Also, Yale-Brown obsessive compulsive scale (Y-BOCS), Yale global tic severity scale (YGTSS), and Turgay Attention-Deficit/Hyperactivity Disorder (ADD/ ADHD) DSM-IV-Based Diagnostic Screening and Rating Scale were performed to the patients.
Results: According to DSM-IV-TR criteria, 20 (66.6%) cases had at least one psychiatric disorder. The most frequent diagnosis by the cases is found to be ADHD (n =16). Other diagnoses were OCD (n= 4), anxiety disorder (n = 4), tic disorder (n =3), and enurezis nocturna (n = 1). Parents have declared fewer ADHD symptoms (n= 6) by using the ADD/ADHD DSM-IV-Based Diagnostic Screening and Rating Scale than the clinician as usual in the literature. The mean total score of Y-BOCS was 2.3 -¦6.2; the mean obsession subscale score was 1.3 -¦3.6 and the mean compulsion subscale score was 0.96-¦3.6. The mean score of YGTSS was 0.5-¦ 2.2 in our study group.
Conclusions: On the basis of our results, especially ADHD symptoms seem to be more frequent in patients with RF. Thus, clinicians should not only deal with the treatment of RF but also be aware of the neuropsychiatric manifestations for early diagnosis

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Child Adolesc Ment Health. 2016.

IS EMOTIONAL LABILITY A MARKER FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER, ANXIETY AND AGGRESSION SYMPTOMS IN PRESCHOOLERS?

Maire J, Galéra C, Meyer E, et al.

Background: Emotional lability (EL) is frequent in school-aged children with attention deficit hyperactivity disorder (ADHD) and is associated with more frequent comorbidities and more severe impairment. However, little research has investigated the association between EL, ADHD and comorbid symptoms in preschoolers. This study assessed dimensional EL in preschoolers and its link with ADHD symptoms (e.g. hyperactivity-impulsivity and inattention) and behavioural and emotional problems (e.g. aggression and anxiety).
Method: One hundred and fifty-four preschoolers aged 3-6 years old were rated on questionnaires by parents. EL was assessed with the index from the Conners Rating Scale-Revised and behavioural and emotional problems with an adapted version of the Social Behavior Questionnaire. Multiple linear regressions analyses were conducted.
Results: Higher EL was associated with higher hyperactivity-impulsivity, inattention, anxiety and aggression problems. After controlling for other behavioural and emotional problems and sociodemographic variables, EL remained associated with hyperactivity-impulsivity and anxiety.
Conclusions: Emotional lability seems to be a potential marker for ADHD symptoms with internalizing problems in preschoolers and could be a target for diagnosis and early interventions. This finding should be

treated with caution as the study was limited by the low response rate of the participants and consequently the small sample size

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Child Adolesc Ment Health. 2016;21:217-24.

A PILOT RANDOMIZED CONTROLLED TRIAL COMPARING COMPUTER-ASSISTED COGNITIVE REHABILITATION, STIMULANT MEDICATION, AND AN ACTIVE CONTROL IN THE TREATMENT OF ADHD.

Azami S, Moghadas A, Sohrabi-Esmrood F, et al.

Background This research aimed to compare computer-assisted cognitive rehabilitation (CACR) psychostimulants (MED) and placebo CACR (PCACR) in the treatment of ADHD using a multiarm parallel design.

Methods Thirty-four boys with ADHD, aged 7–12, were randomly assigned to either CACR (n = 12), MED (n = 11), or PCACR (n = 11). However, the study was not blinded and medication doses might be suboptimal given the lack of titration. Continuous performance test, Tower-of-London, forward/backward digit span, span board, Raven's progressive matrices, and SNAP-IV were completed at baseline, posttest, and follow-up.

Results Computer-assisted cognitive rehabilitation outperformed both MED and PCACR on backward digit span at posttest and PCACR at follow-up. CACR outperformed PCACR and MED on forward digit span at posttest and PCACR at follow-up. CACR outperformed MED on span board at posttest. CACR outperformed PCACR and MED on Raven's matrices at posttest. CACR and PCACR scored lower than MED on ADHD-PHI at posttest. CACR scored lower than MED on ADHD-C at posttest.

Conclusions Immediately after interventions, CACR improved certain simple executive functions (EFs) as much as active stimulant medication. On complex EFs, CACR was superior to active stimulant medication and PCACR. CACR reduced behavioral symptoms of ADHD more than active stimulant medication. However, at 3-month follow-up, maintenance of the CACR gains was weak

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Child Psychiatry Hum Dev. 2016 Apr;47:317-25.

ADVERSE PRENATAL, PERINATAL AND NEONATAL EXPERIENCES IN CHILDREN WITH ANXIETY DISORDERS.

Johnco C, Lewin AB, Salloum A, et al.

This study examined the incidence of adverse prenatal, perinatal, and neonatal experiences amongst children with anxiety disorders, and the relationship to clinical symptomology and functional impairment in treatment-seeking children (N = 107) with a primary anxiety disorder. Anxious children had higher rates of reported maternal prescription medication use during pregnancy, maternal smoking and illness during pregnancy and neonatal complications (including neonatal intensive care and feeding issues) compared with population base rates and non-affected children. Almost one-third had early problems with sleep. Developmental problems were common with more than half having at least one area of delay. More than three quarters of anxious children had a first-degree family member with a psychiatric history. There were several associations between neonatal complications and subsequent clinical symptomology, including attention deficit hyperactivity disorder and depressive comorbidity, anxiety severity and functional impairment. Findings suggest higher rates of perinatal complications in anxious children

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Clin Child Fam Psychol Rev. 2015 Mar;18:77-97.

A SYSTEMATIC REVIEW OF META-ANALYSES OF PSYCHOSOCIAL TREATMENT FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Fabiano GA, Schatz NK, Aloe AM, et al.

The present report synthesizes outcomes across meta-analyses of psychosocial (i.e., non-pharmacological) treatments for ADHD. A total of 12 meta-analyses were identified that met search criteria. The meta-analyses were notable in that there was surprisingly little overlap in studies included across them (range of overlap was 2-46 %). Further, there was considerable diversity across the meta-analyses in terms of the

inclusion/exclusion criteria, types of psychosocial treatments reviewed, methodological characteristics, and magnitude of reported effect sizes, making it difficult to aggregate findings across meta-analyses or to investigate moderators of outcome. Effect sizes varied across the outcomes assessed, with meta-analyses reporting positive and significant effect sizes for measures of some areas of child impairment (e.g., social impairment) and small and more variable effect sizes for distal and/or untargeted outcomes (e.g., academic achievement). Results are reviewed in light of the larger literature on psychosocial interventions for ADHD, and specific recommendations for future meta-analyses of psychosocial treatments for ADHD are offered

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Clin Drug Investig. 2016 May;36:341-56.

LISDEXAMFETAMINE DIMESYLATE: PRODRUG DELIVERY, AMPHETAMINE EXPOSURE AND DURATION OF EFFICACY.

Ermer JC, Pennick M, Frick G.

Lisdexamfetamine dimesylate (LDX) is a long-acting d-amphetamine prodrug used to treat attention-deficit/hyperactivity disorder (ADHD) in children, adolescents and adults. LDX is hydrolysed in the blood to yield d-amphetamine, and the pharmacokinetic profile of d-amphetamine following oral administration of LDX has a lower maximum plasma concentration (Cmax), extended time to Cmax (Tmax) and lower inter- and intra-individual variability in exposure compared with the pharmacokinetic profile of an equivalent dose of immediate-release (IR) d-amphetamine. The therapeutic action of LDX extends to at least 13 h post-dose in children and 14 h post-dose in adults, longer than that reported for any other long-acting formulation. Drug-liking scores for LDX are lower than for an equivalent dose of IR d-amphetamine, which may result from the reduced euphorigenic potential associated with its pharmacokinetic profile. These pharmacokinetic and pharmacodynamic characteristics of LDX may be beneficial in the management of symptoms in children, adolescents and adults with ADHD

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Clin Neuropharmacol. 2016.

NO SUPERIORITY OF TREATMENT WITH OSMOTIC CONTROLLED-RELEASE ORAL DELIVERY SYSTEM□ÇôMETHYLPHENIDATE OVER SHORT/MEDIUM-ACTING METHYLPHENIDATE PREPARATIONS IN THE RATE AND TIMING OF INJURIES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Golubchik P, Kodesh A, Weizman A.

OBJECTIVES: Methylphenidate (MPH) treatment in patients with attention-deficit/hyperactivity disorder (ADHD) is reported to reduce the risk for injuries. In the present study, the rate and timing of injuries were compared among the various MPH preparations (4 and 6ΓÇô8 vs 12 hour-acting) in children with ADHD.

METHODS: This real-world retrospective study covered the years 2011 to 2013. Participants included 2042 youngsters (aged 4–18 years, 13.01 -¦ 3.2 years; 71.8% males and 28.2% females) diagnosed with ADHD according to the International Statistical Classification of Diseases, 10th Revision criteria and treated with various MPH preparations. They were divided into 2 groups by their treatment preparation as follows: MPH-immediate release (MPH-IR) 4 hour-acting pooled with MPH-slow release/long-acting (MPH-SR/LA) 6 to 8 hour-acting versus osmotic controlled-release oral delivery system-MPH (OROS-MPH; Concerta) 12 hour-acting that consisted of pooling of OROS-MPH only and OROS-MPH combined with the other MPH preparations. The monthly rates of injury, specifically, late injury (occurrence between 4:00 p.m. to midnight) and for multiple injuries, the time interval between injuries, were assessed.

RESULTS: No significant differences in monthly rate of nonfatal injuries were found between OROS-MPH with or without 4/6 to 8 hour-acting MPH-formulations versus only 4/6 to 8 hour-acting MPH-preparations (P = 0.53). Neither were differences found in the between-injury time interval (P = 0.83) or in late-injury-rates (P = 0.37) between those groups.

CONCLUSIONS: This real-world-naturalistic study in the community demonstrates that, in ADHD pediatric populations, OROS-MPH preparation is not superior to short/medium-acting (4/6ΓÇô8 hours) MPH preparations regarding the rate and timing of injuries

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Clin Pediatr. 2016;55:1197-201.

NOT ALL GENERIC CONCERTA IS CREATED EQUAL: COMPARISON OF OROS VERSUS NON-OROS FOR THE TREATMENT OF ADHD.

Lally MD, Kral MC, Boan AD.

Treatment effectiveness between equivalent doses of non-OROS (osmotic controlled release oral delivery system) methylphenidate ER and OROS methylphenidate ER (brand name Concerta) was examined in a clinical case series of children and adolescents followed for treatment of attention-deficit/hyperactivity disorder (ADHD). The Conners-Third Edition: Parent Rating Scale was used to compare ADHD symptoms when patients were taking non-OROS versus OROS at follow-up visits. A repeated-measures mixed-model approach was used to compare treatment effectiveness. The entire sample (N = 14) demonstrated a reduction in the mean score on the Inattention Scale from clinically significant (T-score > 65) to not clinically significant (T-score < 65) when patients were changed from non-OROS to OROS at the same dosage (mean T-score reduction = 23, p <.0001). The reduction in mean T-score after changing from non-OROS to OROS at the same dosage is indicative of improvement in symptoms of ADHD. Results provide empirical support for US Food and Drug Administration concerns regarding the therapeutic equivalence of non-OROS versus OROS for the treatment of ADHD

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Clin Psychol Rev. 2016;50:159-74.

SLEEP DISTURBANCES IN ADOLESCENTS WITH ADHD: A SYSTEMATIC REVIEW AND FRAMEWORK FOR FUTURE RESEARCH.

Lunsford-Avery JR, Krystal AD, Kollins SH.

Background Biological mechanisms underlying symptom and prognostic heterogeneity in Attention-Deficit/Hyperactivity Disorder (ADHD) are unclear. Sleep impacts neurocognition and daytime functioning and is disrupted in ADHD, yet little is known about sleep in ADHD during adolescence, a period characterized by alterations in sleep, brain structure, and environmental demands as well as diverging ADHD trajectories.

Methods A systematic review identified studies published prior to August 2016 assessing sleep in adolescents (aged 10 ΓÇô19-áyears) with ADHD or participating in population-based studies measuring ADHD symptoms.

Results Twenty-five studies were identified (19 subjective report, 6 using actigraphy/polysomnography). Findings are mixed but overall suggest associations between sleep disturbances and 1) ADHD symptoms in the population and 2) poorer clinical, neurocognitive, and functional outcomes among adolescents with ADHD. Common limitations of studies included small or non-representative samples, non-standardized sleep measures, and cross-sectional methodology.

Conclusions Current data on sleep in adolescent ADHD are sparse and limited by methodological concerns. Future studies are critical for clarifying a potential role of sleep in contributing to heterogeneity of ADHD presentation and prognosis. Potential mechanisms by which sleep disturbances during adolescence may contribute to worsened symptom severity and persistence of ADHD into adulthood and an agenda to guide future research are discussed

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Clin Psychopharmacol Neurosci. 2016;14:357-64.

THE EFFECTS OF EQUINE-ASSISTED ACTIVITIES AND THERAPY ON RESTING-STATE BRAIN FUNCTION IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A PILOT STUDY.

Yoo JH, Oh Y, Jang B, et al.

Objective: Equine-assisted activities and therapy (EAA/T) have been used as adjunct treatment options for physical and psychosocial rehabilitation. However, the therapeutic effects on resting-state brain function have not yet been studied. The aim of this study is to investigate the effects of EAA/T on participants with attention-deficit/hyperactivity disorder (ADHD) by comparing resting-state functional magnetic resonance imaging (rs-fMRI) signals and their clinical correlates.

Methods: Ten participants with ADHD participated in a 12-week EAA/T program without any medication. Two rs-fMRIs were acquired for all participants before and after EAA/T. For estimating therapeutic effect, the regional homogeneity (ReHo) method was applied to capture the changes in the regional synchronization of functional signals.
Results: After the EAA/T program, clear symptom improvement was found even without medication. Surface-based pairwise comparisons revealed that ReHo in the right precuneus and right pars orbitalis clusters had significantly diminished after the program. Reduced ReHo in the right precuneus cluster was positively correlated with changes in the scores on DuPaul's ADHD Rating Scale-Korean version.
Conclusion: Our results indicate that EAA/T is associated with short-range functional connectivity in the regions related to the default mode network and the behavioral inhibition system, which are associated with symptom improvement

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Codas. 2016 Apr;28:123-31.
SPELLING PERFORMANCE OF STUDENTS WITH DEVELOPMENTAL DYSLEXIA AND WITH DEVELOPMENTAL DYSLEXIA ASSOCIATED TO ATTENTION DEFICIT DISORDER AND HYPERACTIVITY.
Alves DC, Casella EB, Ferraro AA.
Purpose to analyze and classify the spelling performance according to the semiology of spelling error of children with developmental dyslexia (DD) and with developmental dyslexia associated to attention deficit disorder and hyperactivity(DD and ADHD) comparing them to a group of children without learning process complaints. Methods Seventy students, from the third to fifth grade, participated in this study divided as follows: 32 children without complaints of learning difficulties (GI), mean age 9.5 years; 22 students with developmental dyslexia (GII), mean age 10 years; 16 scholars with developmental dyslexia associated to attention deficit disorders and hyperactivity (GIII), mean age 9.9. Spelling skills were assessed through a standardized word dictation task. Results Data indicated that GII and GIII children presented lower performance when compared with typically developed children. There was no statistical difference between the performance of GII and GIII children regarding the score reached in spelling, although GIII children presented the lowest performance. We observed differences between GII and GIII only in the type of misspelling. Conclusion Data from this research contribute to develop better programs for intervention in the studied population

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Comput Intell Neurosci. 2016;2016:8450241.
MEG ANALYSIS OF NEURAL INTERACTIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Khadmaoui A, Gomez C, Poza J, et al.
The aim of the present study was to explore the interchannel relationships of resting-state brain activity in patients with attention-deficit/hyperactivity disorder (ADHD), one of the most common mental disorders that develop in children. Magnetoencephalographic (MEG) signals were recorded using a 148-channel whole-head magnetometer in 13 patients with ADHD (range: 8-12 years) and 14 control subjects (range: 8-13 years). Three complementary measures (coherence, phase-locking value, and Euclidean distance) were calculated in the conventional MEG frequency bands: delta, theta, alpha, beta, and gamma. Our results showed that the interactions among MEG channels are higher for ADHD patients than for control subjects in all frequency bands. Statistically significant differences were observed for short-distance values within right-anterior and central regions, especially at delta, beta, and gamma-frequency bands ($p < 0.05$; Mann-Whitney U test with false discovery rate correction). These frequency bands also showed statistically significant differences in long-distance interactions, mainly among anterior and central regions, as well as among anterior, central, and other areas. These differences might reflect alterations during brain development in children with ADHD. Our results support the role of frontal abnormalities in ADHD pathophysiology, which may reflect a delay in cortical maturation in the frontal cortex

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Congenit Heart Dis. 2016 Jan;11:26-33.

DOES CONGENITAL HEART DISEASE AFFECT NEURODEVELOPMENTAL OUTCOMES IN CHILDREN WITH DOWN SYNDROME?

Alsaied T, Marino BS, Esbensen AJ, et al.

OBJECTIVE: The impact that congenital heart disease (CHD) has on the neurodevelopment of children with Down syndrome (DS) is unknown and potentially has implications for targeted early intervention. This study assessed the relationship between CHD that required surgery in the first year of life and neurodevelopmental, behavioral and emotional functioning outcomes in children with DS.

METHODS: A retrospective chart review of 1092 children (0-18 years) with DS who visited a single institution from 8/08-8/13 was performed. Children who underwent at least one of nine neurodevelopmental (cognitive, language, developmental) or academic tests were included in the analysis (N = 178). Cohort was age-divided into infants/toddlers (0-2 years), preschoolers (3-5 years), and school age/adolescent (6-18 years). Test scores of children with DS who underwent cardiac surgery in the first year of life were compared to children with DS without CHD. T test, chi-square and Mann Whitney U tests were used where appropriate.

RESULTS: Infants/toddlers with cardiac surgery had lower scores for receptive (P = .01), expressive (P = .021) and composite language (P < .001) compared to those with no CHD. Preschoolers with cardiac surgery had lower language scores and lower visual motor scores, although not statistically significant. In school age children with cardiac surgery there were no differences in IQ scores, language scores, or academic achievement scores compared to those without CHD. Also at school-age there was no difference in the incidence of ADHD, executive function or on internalizing and externalizing behavior scores.

CONCLUSION: Children with DS undergoing cardiac surgery during the first year demonstrated poorer neurodevelopmental outcomes as infants/toddler but had no difference at school age compared to children with DS without CHD. These results will guide early interventions to optimize neurodevelopmental outcomes in children with DS and will help with family counseling after CHD repair

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Crisis. 2015;36:55-60.

SUICIDE IDEATION AND ATTEMPTS IN CHILDREN WITH PSYCHIATRIC DISORDERS AND TYPICAL DEVELOPMENT.

Dickerson MS, Calhoun SL, Baweja R, et al.

BACKGROUND: Children and adolescents with psychiatric disorders are at increased risk for suicide behavior. AIMS: This is the first study to compare frequencies of suicide ideation and attempts in children and adolescents with specific psychiatric disorders and typical children while controlling for comorbidity and demographics.

METHOD: Mothers rated the frequency of suicide ideation and attempts in 1,706 children and adolescents with psychiatric disorders and typical development, 6-18 years of age.

RESULTS: For the typical group, 0.5% had suicide behavior (ideation or attempts), versus 24% across the psychiatric groups (bulimia 48%, depression or anxiety disorder 34%, oppositional defiant disorder 33%, ADHD-combined type 22%, anorexia 22%, autism 18%, intellectual disability 17%, and ADHD-inattentive type 8%). Most alarming, 29% of adolescents with bulimia often or very often had suicide attempts, compared with 0-4% of patients in the other psychiatric groups.

CONCLUSION: It is important for professionals to routinely screen all children and adolescents who have psychiatric disorders for suicide ideation and attempts and to treat the underlying psychiatric disorders that increase suicide risk

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Dent Traumatol. 2015 Apr;31:140-43.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN WITH TRAUMATIC DENTAL INJURIES.

Herguner A, Erdur AE, Basciftci FA, et al.

AIM: The aim of this study was to compare the symptoms of attention-deficit/hyperactivity disorder (ADHD) in children with TDIs with to non-injured children.

MATERIAL AND METHODS: Children between 7 and 16 years old who were admitted to the Selcuk University, Faculty of Dentistry, for treatment of dental trauma were included in the study group (SG). As a control group (CG), children with no reported history of dental trauma were recruited. The Conners' Parent Rating Scale-Revised: Short Form (CPRS-R: S) was used to assess ADHD symptoms.
RESULTS: Both groups, SG and CG, composed of 55 children. There were no significant differences in age, gender, and duration of education between SG and CG. Children with TDIs had significantly higher CPRS-R: S Hyperactivity scores. Hyperactivity level was positively correlated with the history of previous dental trauma. There were no associations between number of injured teeth, type of injury, and ADHD symptoms.
CONCLUSIONS: These findings suggest that children with TDIs have more hyperactive symptoms than children without dental trauma. Clinicians should screen ADHD symptoms in children with TDIs and refer them for treatment when necessary

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Dev Neurorehabil. 2016 Aug;19:238-45.
CHILD OUTCOMES OF A PILOT PARENT-DELIVERED INTERVENTION FOR IMPROVING THE SOCIAL PLAY SKILLS OF CHILDREN WITH ADHD AND THEIR PLAYMATES.
Wilkes-Gillan S, Bundy A, Cordier R, et al.
OBJECTIVE: This pilot study examined the effectiveness of a parent-delivered intervention for improving: the social play skills of children with attention deficit hyperactivity disorder (ADHD) and their typically developing playmates and the empathy of children with ADHD.
METHODS: Participants were children with ADHD and their typically developing playmates (n = 9/group). The intervention was primarily parent-implemented and involved: parent-training, weekly home-modules, three clinic play-sessions, therapist-parent phone consultations and a one-month follow-up. The Test of Playfulness (ToP) was the primary outcome measure. Cohen's-d and paired sample t-test calculations were used to measure effect.
RESULTS: Social play outcomes of children with ADHD improved significantly from: pre- to post-test (t = 3.2; p = 0.02; d = 1.0) and post-test to follow-up intervention (t = 2.7; p = 0.02; d = 1.1). Playmate's improved significantly from pre- to post-intervention (t = 3.9; p = 0.03; d = 1.2). Children with ADHD improved significantly on 4/7 ToP empathy items (t = 2.31-3.16; p = 0.02).
CONCLUSION: The intervention successfully improved the social play skills of children with ADHD and their playmates

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Dev Psychopathol. 2016 May;28:517-26.
FAMILIAL INFLUENCES ON THE FULL RANGE OF VARIABILITY IN ATTENTION AND ACTIVITY LEVELS DURING ADOLESCENCE: A LONGITUDINAL TWIN STUDY.
Peng CZ, Grant JD, Heath AC, et al.
To investigate familial influences on the full range of variability in attention and activity across adolescence, we collected maternal ratings of 339 twin pairs at ages 12, 14, and 16, and estimated the transmitted and new familial influences on attention and activity as measured by the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale. Familial influences were substantial for both traits across adolescence: genetic influences accounted for 54%-73% (attention) and 31%-73% (activity) of the total variance, and shared environmental influences accounted for 0%-22% of the attention variance and 13%-57% of the activity variance. The longitudinal stability of individual differences in attention and activity was largely accounted for by familial influences transmitted from previous ages. Innovations over adolescence were also partially attributable to familial influences. Studying the full range of variability in attention and activity may facilitate our understanding of attention-deficit/hyperactivity disorder's etiology and intervention

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Dev Psychopathol. 2016 Nov;28:1013-31.

PATHWAYS FROM NEUROCOGNITIVE VULNERABILITY TO CO-OCCURRING INTERNALIZING AND EXTERNALIZING PROBLEMS AMONG WOMEN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FOLLOWED PROSPECTIVELY FOR 16 YEARS.

Owens EB, Hinshaw SP.

Using a sample of 228 females with and without childhood attention-deficit/hyperactivity disorder followed prospectively across 16 years, we measured childhood neurocognitive vulnerability via executive dysfunction using teacher-reported cognitive and learning problems. We then ascertained relations between dimensionally measured internalizing and externalizing psychopathology during adulthood and showed that childhood neurocognitive vulnerability reliably predicted such associated psychopathology. We identified six serial mediation pathways from childhood neurocognitive vulnerability to adult psychopathology through three early- and late-adolescent domains: individual (self-control and delay of gratification), peer (rejection/conflict and acceptance/friendship), and school (academic performance and school failure). The serial indirect effects occurred for the pathways from childhood neurocognitive vulnerability through early-adolescent academic performance, to late-adolescent school failure, to adult associated psychopathology, and from neurocognitive vulnerability through adolescent self-control and then the ability to delay gratification, to adult psychopathology. Furthermore, these indirect effects, plus two others, were moderated by parental distress during childhood and early adolescence, such that under conditions of high distress, the serial indirect effects were weaker than when parental distress was low. We discuss the potential importance of behavioral self-regulation and educational success for later psychological functioning, especially among girls, as well as implications for ontogenic process models of psychopathology

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Dev Med Child Neurol. 2016;58:22-23.

IDENTIFYING ATTENTION DEFICITS IN TYPICAL PRESCHOOL CHILDREN AND NEURODEVELOPMENTAL DISORDERS: A NEW IPAD APP OF THE EARLY CHILDHOOD ATTENTION BATTERY (ECAB).

Atkinson J, Breckenridge K, Kaplicz P, et al.

Background: Attention is a key area of cognitive competence, depending on multiple functional brain subsystems (for selective attention, sustained attention, attentional control/executive function). The ECAB is the first instrument designed to give an individual profile of abilities across these subsystems in preschool children and individuals of equivalent developmental age (Breckenridge et al., 2013).

Aim: To examine attention with the ECAB in Williams and Down Syndrome (WS/DS), and evaluate an iPad ECAB app for mental ages (MA) 3-6 years.

Method: (i) WS and DS children (n=32 each) were tested with ECAB and subtests from the WPPSI. MAs were between 3-6 yrs for each group - chronological age 5-15 yrs. (ii) Typically developing preschool children (N=31) were tested with the ECAB selective attention visual search task and two iPad versions of the test varying in items per screen.

Results: (i) both WS and DS groups showed significant impairments relative to MA in visual selective attention and attentional control, but not in sustained attention. WS performance on spatial attentional control reflected non-verbal better than verbal MA. DS children differed in the relation between spatial and nonspatial tests of attentional control. (ii) 3-6 yr old children adapted well to iPad use, with results on the iPad and original ECAB correlated r=0.68. Performance on the iPad was significantly better ($p<0.02$) when the number of search items was low (3 screens x 60 items compared to 180 in the original), but equivalent for 2 screens x 90 items.

Conclusion: ECAB shows attention deficits beyond general cognitive impairment, and distinctive profiles of ability across subsystems, for different neurodevelopmental disorders. 3-6 yr old children respond well to touchscreen testing, which replicates results from original tests. The iPad app offers a portable, child-friendly test for identifying specific attention deficits in individuals with acquired or genetic developmental disorders

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Dev Neurorehabilitation. 2016;19:389-97.

ATTENTIONAL NETWORK DEFICITS IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Mutreja R, Craig C, O'Boyle MW.

Statement of purpose: Individuals with autism spectrum disorder (ASD) often demonstrate deficient attentional ability, but the specific nature of the deficit is unclear. The Attention Networks model provides a useful approach to deconstruct this attentional deficit into its component parts. Method: Fifty-two neurotypical (NT) children and 14 children with ASD performed the child version of the Attention Network Test (ANT). The latter requires participants to indicate the direction of a centre target stimulus, which is presented above/below fixation and sometimes flanked by either congruent or incongruent distractor stimuli. Results: Relative to NT children, those with ASD were: (1) slower to react to spatially cued trials and (2) more error prone on executive (conflict) attention trials. Conclusions: Young children with ASD have intact alerting attention, but less-efficient orienting and executive attention

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Düsünen Adam: Journal of Psychiatry and Neurological Sciences. 2016 Sep;29:271-74.

ATTENTION DEFICIT HYPERACTIVITY DISORDER COMORBIDITY IN AN ADOLESCENT DIAGNOSED WITH L-2 HYDROXYGLUTARIC ACIDURIA AND RESPONSE TO ATOMOXETINE TREATMENT: A CASE REPORT.

Yektas C, Tufan AE.

L-2-hydroxyglutaric aciduria (L-2 HGA) is a rare, neurodegenerative, slowly progressing and autosomal recessively inherited metabolic disorder. The disease progresses with mental retardation, behavioral disorder, ataxia, extrapyramidal signs and epileptic seizures. Diagnosis is made by detection of increased levels of L-2-hydroxyglutaric acid in urine, plasma or cerebrospinal fluid. In this report, we presented a 13 year old male patient diagnosed with L-2 HGA and had seizures, intellectual disability, attention deficit hyperactivity disorder (ADHD) symptoms and failure in school performance. Here we discussed this rare disease with ADHD symptoms and the response to atomoxetine treatment

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Dyslexia. 2016;22:362-78.

SELECTIVE IMPAIRMENTS IN COVERT SHIFTS OF ATTENTION IN CHINESE DYSLEXIC CHILDREN.

Ding Y, Zhao J, He T, et al.

Reading depends heavily on the efficient shift of attention. Mounting evidence has suggested that dyslexics have deficits in covert attentional shift. However, it remains unclear whether dyslexics also have deficits in overt attentional shift. With the majority of relevant studies carried out in alphabetic writing systems, it is also unknown whether the attentional deficits observed in dyslexics are restricted to a particular writing system. The present study examined inhibition of return (IOR)ΓÇöa major driving force of attentional shiftsΓÇöin dyslexic children learning to read a logographic script (i.e., Chinese). Robust IOR effects were observed in both covert and overt attentional tasks in two groups of typically developing children, who were age- or reading ability-matched to the dyslexic children. In contrast, the dyslexic children showed IOR in the overt but not in the covert attentional task. We conclude that covert attentional shift is selectively impaired in dyslexic children. This impairment is not restricted to alphabetic writing systems, and it could be a significant contributor to the difficulties encountered by children learning to read.

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East Mediterr Health J. 2016;22:586-95.

ROLE OF SCHOOL TEACHERS IN IDENTIFYING ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG PRIMARY SCHOOL CHILDREN IN MANSOURA, EGYPT.

Awadalla NJ, Ali OF, Elshaer S, et al.

There is a knowledge gap in primary school teachers that affects their ability to detect attention deficit hyperactivity disorder (ADHD). This study measured primary school teachersΓÇÖ knowledge about ADHD, and implemented a training programme to improve early detection of ADHD. The prevalence and risk factors

of ADHD were also studied. The training programme was implemented through a 2-day workshop for 39 primary school teachers who completed a validated Arabic version of the ADHD Rating Scale for 873 primary school children. The childrenΓÇÖs parents completed the questionnaire to explore ADHD risk factors. The teachersΓÇÖ pre-training knowledge scores of ADHD ranged from 17.9 to 46.2%. Post-training, their scores improved significantly to 69.2-94.9%. Prevalence rate of ADHD was 12.60%. On logistic regression, independent predictors of ADHD were female gender, unemployed fathers and rural residence. In conclusion, ADHD is a significant health problem among primary school children in Mansoura, Egypt. Efforts should be made to improve teachersΓÇÖ knowledge about ADHD and control modifiable risk factors

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Educ 3 13. 2016 Nov;44:591-603.

THE EFFECTS OF PHYSICAL ACTIVITY ON CHILDREN DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A REVIEW.

Reeves MJ, Bailey RP.

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental psychiatric disorder among children. Despite the noted positive aspects of the disorder, it is often associated with a range of negative outcomes for that are detrimental to children's education and wider well-being. This comprehensive scoping review examined empirical literature from seven academic journal databases and specialist journals, published over 10 years, in relation to the benefits of sport/physical activity upon the effects of ADHD. The databases and time frame were chosen to give the 'ideal [scenario] … that could answer the review question', within the limitations of journal database access and resource available; searches of grey literature were also conducted. Ten articles were included in the final review. Due to the variation of methodological approach, sample size, and, most importantly, the form of physical activity measured, it is difficult to identify the 'best' form of physical activity to mediate symptoms of ADHD. However, it can be plausibly claimed that physical activity interventions may provide an alternative, non-pharmaceutical approach to management of ADHD in children

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Emot Behav Difficulties. 2016;21:387-402.

SOCIAL FUNCTIONING AMONG COLLEGE STUDENTS DIAGNOSED WITH ADHD AND THE MEDIATING ROLE OF EMOTION REGULATION.

Ryan J, Ross S, Reyes R, et al.

Despite the many studies that have documented the association between symptoms of ADHD and social difficulties in children and adolescents, few have examined this phenomenon in college students. In addition, the underlying factors contributing to such social difficulties are still poorly understood. We hypothesised that college students with symptoms of ADHD, namely inattention and hyperactivity/impulsivity, would continue to display social behavioural difficulties, and that emotion regulation would play a mediating role in that relationship. Ninety-nine 17ΓÇô24-year-old college students filled out three questionnaires to assess Inattentive and Hyperactivity/Impulsivity Symptoms, Social Skills, and Emotion Regulation abilities. Analysis revealed that emotion regulation is a significant mediator between Inattentive Symptoms and Social Skills for female students. There was no significant correlation between ADHD symptoms and Social Skills for males. Female college students report social functioning difficulties associated with their inattentive and hyperactive symptoms, and impaired emotion regulation abilities mediate this relationship for inattentive symptoms only

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Epilepsy Behav. 2016 Apr;57:151-54.

HEALTH RESOURCE UTILIZATION VARIES BY COMORBIDITIES IN CHILDREN WITH EPILEPSY.

Puka K, Smith ML, Moineddin R, et al.

OBJECTIVES: Comorbidities in adults with epilepsy have been shown to significantly increase health resource utilization (HRU). The current study aimed to determine whether a similar association exists among children with epilepsy in a universal health insurance system.
METHODS: Health administrative databases in Ontario, Canada were used to evaluate the frequency of neurologist visits, emergency department (ED) visits, and hospitalizations. We evaluated the association between HRU and comorbidities, including depression, anxiety, learning disability, attention deficit hyperactivity disorder (ADHD), and autistic spectrum disorder (ASD), adjusting for age, sex, residence, and socio-economic status.
RESULTS: The frequency of neurology visits was increased by comorbid depression, ASD, and learning disability (adjusted relative risk [aRR]=1.29-2.07; p<.01). The frequency of ED visits was increased by all comorbidities (aRR=1.26-2.83; p<.0001). The frequency of hospitalizations was increased by comorbid depression, anxiety, ASD, and learning disability (aRR=1.77-7.20; p<.0001). Learning disability had the largest impact on HRU. For each additional comorbidity, the frequency of neurology visits, ED visits, and hospitalizations increased by 1.64 to 3.16 times (p<.0001).
CONCLUSIONS: Among children with epilepsy, mental health and developmental comorbidities were associated with increased HRU, and different comorbidities influenced different types of HRU. In addition, we highlight the importance of identifying and managing these comorbidities, as they increased the risks of costly HRU such as ED visits and hospitalizations

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Eur J Paediatr Neurol. 2016 May;20:361-67.

LONG-TERM MOTOR, COGNITIVE AND BEHAVIORAL OUTCOME OF ACUTE DISSEMINATED ENCEPHALOMYELITIS.

Shilo S, Michaeli O, Shahar E, et al.

OBJECTIVE: The purpose of this study was to evaluate the long-term motor and neurocognitive outcome of children with acute disseminated encephalomyelitis and to identify prognostic risk factors.
METHODS: The study included 43 children who were hospitalized due to acute disseminated encephalomyelitis during the years 2002-2012. The children underwent full neurological examinations, along with comprehensive neurocognitive and behavioral assessments.
RESULTS: Twenty-six (61%) children had different degrees of neurological sequelae after a mean follow-up of 5.5 +/- 3.5 years. The most common residual impairment included attention-deficit hyperactivity disorder (44%), behavioral problems (32%), and learning disabilities (21%). Five (12%) children had a full-scale IQ of 70 or less, compared to 2.2% in the general population.
CONCLUSIONS: Neurocognitive sequelae were found even in children who were considered as fully recovered at the time of discharge. Risk factors for severe neurological sequelae were older age at diagnosis and male gender. We suggest neuropsychological testing and long-term follow-up for all children with acute disseminated encephalomyelitis, even in the absence of neurological deficits at discharge

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Eur Rev Med Pharmacol Sci. 2016 Apr;20:1373-78.

RELATIONSHIP BETWEEN THE DAT1 GENE AND THE EFFECTS OF METHYLPHENIDATE ADMINISTRATION IN ADULT ATTENTION DEFICIT HYPERACTIVITY DISORDER: A MAGNETIC RESONANCE SPECTROSCOPY STUDY.

Inci Kenar AN, Unal GA, Guler H, et al.

OBJECTIVE: This study investigated the relationship between DAT1 gene polymorphisms and the effects of methylphenidate (MPH) administration on N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho) levels in the anterior cingulate cortex, prefrontal cortex, striatum, and cerebellum in adult patients with attention deficit hyperactivity disorder (ADHD). This was the first study to investigate the relationship between DAT gene variable number tandem repeat (VNTR) polymorphisms and the responses of brain metabolites to MPH.
PATIENTS AND METHODS: Samples in this study were collected from 60 patients aged between 18 and 60 years with ADHD according to DSM-IV criteria. Genetic analysis of DAT1 gene polymorphisms was carried out using blood samples obtained after a detailed clinical evaluation. Levels of NAA, Cr, and Cho

were measured in the anterior cingulate cortex, prefrontal cortex, striatum, and cerebellum by magnetic resonance spectroscopy. After this evaluation, 10 mg of MPH was given orally to patients, and the levels of the same metabolites were measured 30 min later.
RESULTS: No marked difference in NAA, Cr, or Cho levels was detected before and after MPH administration with respect to the DAT1 gene VNTR polymorphisms. A considerable increase in Cr levels in the cerebellum was identified after MPH administration in individuals with the 10/10 repeat genotype as the DAT1 VNTR polymorphism (p=0.008).
CONCLUSIONS: An increase in the previously decreased blood flow after MPH therapy may induce an increase in creatine levels in patients with the 10/10 repeat genotype. Our results thus suggest that the 10R allele as the DAT1 gene VNTR polymorphism might be associated with MPH-related changes in brain metabolites in adults with ADHD

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Eur Child Adolesc Psychiatry. 2016;1-9.
TOURETTE SYNDROME INCREASES RISK OF BONE FRACTURES: A POPULATION-BASED COHORT STUDY.
Lu YY, Wang MY, Wei IH, et al.
This study assesses the risk of fractures among children with Tourette syndrome (TS), and identifies the effects of comorbidities and antipsychotics. We randomly sampled the claims data of 1 million enrollees in the National Health Insurance program of Taiwan, and identified 1258 children with TS diagnosed between 2000 and 2010. Additionally, 12,580 children without TS who were frequency matched for sex, age, residential area, parental occupation, and index year were identified for comparison. The children's cases were followed until December 31, 2010, or censored to ascertain incident fractures cases and associations with comorbidities of attention-deficit/hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD) and treatments with antipsychotics, antidepressants, or clonidine. The TS cohort had a 1.27-fold higher incidence of fractures than did the comparison cohort (190.37 vs. 149.94 per 10,000 person-years), with an adjusted hazard ratio (HR) of 1.28 [95% confidence interval (CI) 1.06-1.55] based on multivariable Cox regression analysis. This increased risk of fractures was apparent for fractures of the skull, neck, and spine. Comorbid ADHD and OCD did not result in an additional risk of fractures. The children without both ADHD and OCD were also at a higher risk of fractures, indicating that TS alone increases the risk of fractures. The children taking antipsychotics had a reduced risk of fractures, and the adjusted HR decreased to 1.17 (95% CI 0.90-1.52). Children with TS have an increased risk of fractures. ADHD and OCD do not increase the risk further

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Eur Child Adolesc Psychiatry. 2016;1-10.
LEARNING CURVES OF THETA/BETA NEUROFEEDBACK IN CHILDREN WITH ADHD.
Janssen TWP, Bink M, Weeda WD, et al.
Neurofeedback is widely applied as non-pharmacological intervention aimed at reducing symptoms of ADHD, even though efficacy has not been unequivocally established. Neuronal changes during the neurofeedback intervention that resemble learning can provide crucial evidence for the feasibility and specificity of this intervention. A total of 38 children (aged between 7 and 13 years) with a DSM-IV-TR diagnosis of ADHD, completed on average 29 sessions of theta (4ΓÇô8 Hz)/beta (13ΓÇô20 Hz) neurofeedback training. Dependent variables included training-related measures as well as theta and beta power during baseline and training runs for each session. Learning effects were analyzed both within and between sessions. To further specify findings, individual learning curves were explored and correlated with behavioral changes in ADHD symptoms. Over the course of the training, there was a linear increase in participantsΓÇÖ mean training level, highest obtained training level and the number of earned credits (range b = 0.059, ΓêÆ0.750, p < 0.001). Theta remained unchanged over the course of the training, while beta activity increased linearly within training sessions (b = 0.004, 95% CI = [0.0013ΓÇô0.0067], p = 0.005) and over the course of the intervention (b = 0.0052, 95% CI = [0.0039ΓÇô0.0065], p < 0.001). In contrast to the group analyses, significant individual learning curves were found for both theta and beta over the course of the intervention in 39 and 53%,

respectively. Individual learning curves were not significantly correlated with behavioral changes. This study shows that children with ADHD can gain control over EEG states during neurofeedback, although a lack of behavioral correlates may indicate insufficient transfer to daily functioning, or to confounding reinforcement of electromyographic activity. Clinical Trials Registration: This trial is registered at the US National Institutes of Health (ClinicalTrials.gov, ref. no: NCT01363544); https://clinicaltrials.gov/show/NCT01363544

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Eur Child Adolesc Psychiatry. 2016;1-13.

BELIEFS REGARDING MEDICATION AND SIDE EFFECTS INFLUENCE TREATMENT ADHERENCE IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Emilsson M, Gustafsson PA, Öhnström G, Marteinsdottir I.

Adherence to attention deficit hyperactivity disorder (ADHD) treatment is important because, when untreated, it may have serious consequences with lifelong effects. In the case of adolescents on long-term medicine prescription, more knowledge is needed regarding adherence and factors influencing adherence, which was the purpose of this study. Adolescents (n = 101) on ADHD medication ≥6 months were administrated questionnaires at a monitoring appointment: Medication Adherence Report Scale (MARS), beliefs about medicines (BMQ) and the Brief Illness Perception Questionnaire (B-IPQ). Adherence was high, the mean value was 88% of the maximum MARS score, and correlated positively with the "BMQ-necessity-concerns differential" but negatively with "BMQ-concerns" and "BMQ-side effects". Adolescents with more belief in the necessity of the medication, less concerns and less experience of side effects tended to be more adherent to medication prescription ("intentional non-adherence"), while "unintentional non-adherence" (forgetfulness) was associated with how much they perceived that their ADHD affected their lives. In a multiple regression model, the variance of MARS total (R 2 = 0.21) and "intentional non-adherence" (R 2 = 0.24) was explained by the "BMQ-necessity-concern differential" and "BMQ-experienced side effects". The variance of "unintentional non-adherence" (R 2 = 0.12) was explained by the "BMQ-necessity-concern differential" and "B-IPQ-consequences of ADHD". In conclusion, adolescents on long-term medication reported good adherence, mainly influenced by more beliefs in the necessity versus concerns of the medications, less experienced side effects and more perceived consequences of ADHD. BMQ could be useful to identify risks of low adherence, which should be counteracted by partially gender-specific interventions

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European Eating Disorders Review. 2017;25:36-43.

INFLUENCE OF PARENTAL EXPRESSED EMOTIONS ON CHILDREN'S EMOTIONAL EATING VIA CHILDREN'S NEGATIVE URGENCY.

Munsch S, Dremmel D, Kurz S, et al.

We investigated whether parental expressed emotion (criticism and emotional overinvolvement) is related to children's emotional eating and whether this relationship is mediated by children's negative urgency. One hundred children, aged 8 to 13 years, either healthy or have binge-eating disorder and/or attention-deficit/hyperactivity disorder, completed the questionnaires, along with their parents. Parental criticism and, to a lesser extent, parental emotional overinvolvement were both positively related to children's emotional eating, and this relationship was mediated by children's negative urgency. Further exploratory analyses revealed that the mediating role of children's negative urgency in the relationship between parental criticism and children's emotional eating was pronounced in the clinical group of children with binge-eating disorder and attention-deficit/hyperactivity disorder but almost absent in the healthy control group.

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Eur J Health Econ. 2016;1-12.

COMPARATIVE TREATMENT PATTERNS, HEALTHCARE RESOURCE UTILIZATION AND COSTS OF ATOMOXETINE AND LONG-ACTING METHYLPHENIDATE AMONG CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN GERMANY.

Greven P, Sikirica V, Chen YJ, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) imposes a substantial burden on patients and their families. Objective: A retrospective, propensity score-matched cohort study compared treatment patterns, healthcare resource utilization (HRU) and costs among children/adolescents with ADHD aged 6ΓÇô17 years at treatment initiation (index) in Germany who received atomoxetine (ATX) or long-acting methylphenidate (LA-MPH) monotherapy.

Methods: Patients received at least one prescription for their index medication (ATX/LA-MPH) during 2006ΓÇô2010; the first prescription marked the index date. ATX- and LA-MPH-indexed cohorts were matched 1:1 (n = 737); a patient subset was identified that had not received ADHD-indicated medications in 12 months prior to index (novel initiators: ATX, n = 486; LA-MPH, n = 488). Treatment patterns were evaluated among novel initiators, and HRU and costs among the matched cohorts in the 12 months after index.

Results: No significant differences in baseline characteristics were found between the novel initiator patient subsets. ATX-indexed novel initiators had significantly longer persistence to index medication [mean (standard deviation; SD) days: 222.0 (133.9) vs 203.2 (135.0), P = 0.029) but higher switching rates (8.8 vs 5.5 %, P = 0.045) than LA-MPH-indexed novel initiators. The total ATX-indexed cohort required more prescriptions [any medication; mean (SD): 20.9 (11.5) vs 15.7 (9.0), P < 0.001] and outpatient visits [mean (SD): 10.1 (6.3) vs 8.3 (5.3), P < 0.001], and incurred significantly higher total median healthcare costs (Γé¼1144 vs Γé¼541, P < 0.001) versus matched LA-MPH patients.

Conclusions: These real-world data indicate that, among children/adolescents with ADHD in Germany, ATX-indexed patients may require more prescriptions and physician visits, and incur higher total healthcare costs, than matched LA-MPH patients

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Eur J Psychiatry. 2016;30:173-82.

ADHD SYMPTOMS IN CHILDREN AGED 5 TO 15 YEARS IN ZHABEI DISTRICT, SHANGHAI.

Jin WL, Li GZ, Du YS, et al.

Background and Objectives: The prevalence of attention deficit hyperactivity disorder (ADHD) and its related factors remains unclear in Shanghai.The aim of this study was to investigate the positive rates of ADHD symptoms and the associated factors in a sample of children aged 5 to 15 years in Zhabei District, Shanghai.

Methods: The participants were selected by cluster-stratified sampling of the general information and responses gathered from questionnaires on ADHD symptoms. The questionnaires examined summed up to 9,627. The positive rates of inattention and hyperactivity-impulsivity symptoms and the socio-demographic factors were compared.

Results: The positive rates of most ADHD symptoms decreased with age. Children between 5 and 7 years and between 7 and 9 years exhibited the highest ADHD positive rates. Boys showed a higher positive rate of ADHD symptoms compared to girls. Children who were local residents showed a higher rate than nonlocal residents and those of other nationalities. This might be related to the integration of immigrants and those belonging to lower socioeconomic classes. The positive rates of ADHD symptoms decreased with the educational level of the parents, while the parents'; level of education was associated with the severity of the ADHD symptoms. Problems of inattention were more common than problems of hyperactivity, as indicated by the positive rates.

Conclusions: The improper educational guidance of ineffective parents, as well as simple and crude attitudes to education, may place children in such a conflicting state, gradually creating psychological problems and resulting in a lack of self-confidence and ADHD.

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Eur Psychiatry. 2017;39:11-16.

USE OF ATOMOXETINE AND SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS: RESULTS OF AN OBSERVATIONAL COHORT STUDY WITHIN GENERAL PRACTICE IN ENGLAND.

Davies M, Coughtrie A, Layton D, et al.

Aim To investigate the association between atomoxetine, a drug used in the treatment of Attention Deficit Hyperactivity Disorder (ADHD), and suicidal ideation, within a cohort of 2ΓÇô18-year-old patients in England.

Methods The study was conducted using the observational cohort technique of Modified prescription event monitoring (M-PEM). Patients prescribed atomoxetine were identified from dispensed prescriptions issued by primary care physicians. A customised postal GP questionnaire was used to capture outcome data for suicidal ideation. A matched pair cohort analysis was performed within patients to compare the risk of suicidal ideation in the period after starting atomoxetine with the risk prior to starting atomoxetine; this was stratified by age and concomitant use of methylphenidate. Additional information on patient characteristics, and events of interest was also collected; individual cases of suicidal ideation were qualitatively assessed for drug relatedness.

Results Of the final cohort (n = 4509); 85.5% male (n = 3857), median age 11 years (IQR: 9,14). Primary prescribing indication for atomoxetine was ADHD (n = 4261, 94.6%). Almost a quarter of the cohort had been co-prescribed methylphenidate. Results of the matched pair cohort analysis indicated that the period after starting atomoxetine was not associated with an increase in the incidence of suicidal ideation compared to the period prior to starting treatment (RR: 0.71; CI: 0.48ΓÇô1.07; P-value: 0.104). Individual case assessment of suicidal ideation suggested a causal association within a number of cases.

Conclusions This study found no evidence of an increased risk of suicidal ideation during treatment with atomoxetine, compared to the period prior to starting treatment. Amongst age specific subgroups, this risk may change. Nonetheless, individual case assessment suggested a causal relationship in some patients, hence physicians need to be aware of the possibility of developing this event, and furthermore consider how best to detect it in this paediatric population. This study demonstrates the importance of combining quantitative statistical analyses with a qualitative case series assessment

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Front Psychol. 2016 Sep;7.

COMPARING AUDITORY NOISE TREATMENT WITH STIMULANT MEDICATION ON COGNITIVE TASK PERFORMANCE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: RESULTS FROM A PILOT STUDY.

Söderlund GBW, Björk C, Gustafsson P.

Background: Recent research has shown that acoustic white noise (80 dB) can improve task performance in people with attention deficits and/or Attention Deficit Hyperactivity Disorder (ADHD). This is attributed to the phenomenon of stochastic resonance in which a certain amount of noise can improve performance in a brain that is not working at its optimum. We compare here the effect of noise exposure with the effect of stimulant medication on cognitive task performance in ADHD. The aim of the present study was to compare the effects of auditory noise exposure with stimulant medication for ADHD children on a cognitive test battery. A group of typically developed children (TDC) took the same tests as a comparison.

Methods: Twenty children with ADHD of combined or inattentive subtypes and twenty TDC matched for age and gender performed three different tests (word recall, spanboard and n-back task) during exposure to white noise (80 dB) and in a silent condition. The ADHD children were tested with and without central stimulant medication.

Results: In the spanboard- and the word recall tasks, but not in the 2-back task, white noise exposure led to significant improvements for both non-medicated and medicated ADHD children. No significant effects of medication were found on any of the three tasks.

Conclusion: This pilot study shows that exposure to white noise resulted in a task improvement that was larger than the one with stimulant medication thus opening up the possibility of using auditory noise as an alternative, non-pharmacological treatment of cognitive ADHD symptoms.

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Gesundheitswesen. 2015 Oct;77:814-19.

RELATIONSHIP BETWEEN INTELLIGENCE AND EXECUTIVE FUNCTION.

Daseking M, Melzer J, Rissling J, et al.

AIM OF THE STUDY: In this study the correlation between executive functions and intelligence as assessed by the BRIEF-P and WNV, respectively will be examined.

METHODS: A sample of 447 children at the 4;0-5;11 year age group was assessed with the WNV. Additionally, parents answered a questionnaire on executive functions (BRIEF-P) and a second questionnaire concerning family background. Partial correlations were calculated on the subtest and scale level and linear regression models were tested.

RESULTS: The primary scale Working Memory (BRIEF-P) contributes to an explanation of cognitive functions (WNV), as does the maternal educational level. WM an the Emergent Metacognition Index, which is incorporated the WM scale, shows significant correlation with subtests and with both of the higher order IQ scales of the WNV.

CONCLUSION: Already at the preschool age, executive functions play an important role in intelligence. Deficits in EF are related to ADHD and to negative school careers. Early programs for prevention or intervention should be implemented to improve conditions for academic learning

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Gesundheitswesen. 2015 Dec;77:908-15.

THE DEVELOPMENT OF QUALITY INDICATORS FOR MANAGEMENT OF PATIENTS WITH ADHD IN SOCIAL PAEDIATRICS.

Skrundz M, Borusiak P, Hameister KA, et al.

OBJECTIVE: Attention deficit/hyperactivity disorder (ADHD) with an estimated prevalence of 5% and its increased risk for comorbidities is of significant relevance for the health care system and is as well of socio-political significance. There is a lack of established methods for the evaluation of the diagnostic and therapeutic treatment of the patients. In this study, we have developed a set of evidence- and consensus-based meaningful indicators for the treatment of children with ADHD.

METHODS: Following a thorough examination of the literature and published Guidelines, a first set of 90 quality indicators was created after redundancy reduction and addition of newly developed indicators. The further development of the indicator set was based on a modified version of the 2-step RAND/UCLA expert evaluation method.

RESULTS: After assessment in 2 rounds of ratings, a set of 39 homogeneously positively rated indicators was established. 28 indicators apply to the quality of the diagnostic and therapeutic process, 4 to structural conditions and 3 rely on outcome.

CONCLUSION: This is the first study covering the aspect of quality measurement in children with developmental disorders, especially ADHD. For the next step a pilot evaluation is necessary to complete the evaluation of the quality indicators

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Human Psychopharmacology: Clinical and Experimental. 2016 Nov;31:427-32.

EFFECTIVENESS OF ATOMOXETINE AND METHYLPHENIDATE FOR PROBLEMATIC ONLINE GAMING IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Park JH, Lee YS, Sohn JH, et al.

Objective: There is a high prevalence of problematic online gaming in adolescents with attention deficit hyperactivity disorder (ADHD). In the current study, we compared the effectiveness of atomoxetine (ATM) and methylphenidate (MPH) on problematic online gaming in adolescents with ADHD.

Methods: We recruited 86 adolescents diagnosed with ADHD together with Internet gaming disorder. These participants were divided into two treatment groups: 44 participants were treated with MPH for 12 weeks, and 42 participants were treated with ATM for 12 weeks.

Results: During the 3-month study period, the MPH group showed greater improvement in Korean ADHD rating scale scores than the ATM group. The ATM group showed greater improvement in Child Depression

Inventory scores than the MPH group. However, Young Internet Addiction Scale and Behavioral Inhibition & Activation Scales score changes did not differ significantly between the MPH and ATM groups. In both groups, changes in Young Internet Addiction Scale scores were positively correlated with the changes in Behavioral Inhibition & Activation Scales scores.
Conclusions: Both MPH and ATM reduced the severity of Internet gaming disorder symptoms, and this reduction was correlated with impulsivity reduction, which also resulted from both ADHD medications. These findings suggest impulsivity plays a critical role in the development of problematic online gaming

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Indian J Pediatr. 2014 Dec;81 Suppl 2:S161-S164.
ADD-H-COMPREHENSIVE TEACHER'S RATING SCALE (ACTERS): A MEASURE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN WITH INTELLECTUAL DISABILITY IN INDIA.
Tsheringla S, Simon A, Russell PS, et al.
OBJECTIVE: There is no validated measure for assessing Attention Deficit Hyperactivity Disorder (ADHD) in India, and therefore, the authors validated the ADD-H Comprehensive Teacher's Rating Scale (ACTeRS).
METHODS: Teachers/parents/clinicians of 110 children with ADHD completed the ACTeRS. The diagnosis of ADHD was confirmed by an independent multi-disciplinary team using ICD-10 diagnosis for diagnostic accuracy and criterion validity. The convergent and divergent validity were assessed by another rater. The data was analyzed for diagnostic accuracy, reliability and validity appropriately.
RESULTS: An ACTeRS score of >/=61 [Sensitivity (Sn) =85.51%; Specificity (Sp) = 90.24%; Area under the curve (AUC) = 0.94] is appropriate for the diagnosis of ADHD. The test-re-test reliability [Intra-class correlation coefficient (ICC) = 0.87], internal consistency (Cronbach's alpha = 0.80; range of 0.89-0.93), section-total correlation, face and content validity for the ACTeRS were good. Convergent validity of attention deficit, hyperactivity and oppositional subscales of ACTeRS with the corresponding subscales of Swanson, Nolan & Pelham Rating Scale-Revised (SNAP-IV) was moderate (r = 0.60, P = 0.005; r = 0.49, P = 0.02; r = 0.58, P = 0.008 respectively), and negative correlation with the Childhood Autism Rating Scale (r = -0.36; P =0.1) for divergent validity was found. The criterion validity analysis showed a high concordance rate of 82.52% between ACTeRS and International Classification of Diseases, Edition10 (ICD-10) diagnosis of ADHD. A 4-factor structure was replicated.
CONCLUSIONS: The ACTeRS has adequate psychometric properties for use in the Indian population for identifying ADHD

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Int J Neuropsychopharmacol. 2015 Sep;19:yv094.
ATOMOXETINE TREATMENT STRENGTHENS AN ANTI-CORRELATED RELATIONSHIP BETWEEN FUNCTIONAL BRAIN NETWORKS IN MEDICATION-NAIVE ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL.
Lin HY, Gau SS.
BACKGROUND: Although atomoxetine demonstrates efficacy in individuals with attention-deficit hyperactivity disorder, its treatment effects on brain resting-state functional connectivity remain unknown. Therefore, we aimed to investigate major brain functional networks in medication-naive adults with attention-deficit hyperactivity disorder and the efficacy of atomoxetine treatment on resting-state functional connectivity.
METHODS: After collecting baseline resting-state functional MRI scans from 24 adults with attention-deficit hyperactivity disorder (aged 18-52 years) and 24 healthy controls (matched in demographic characteristics), the participants with attention-deficit hyperactivity disorder were randomly assigned to atomoxetine (n=12) and placebo (n=12) arms in an 8-week, double-blind, placebo-controlled trial. The primary outcome was functional connectivity assessed by a resting-state functional MRI. Seed-based functional connectivity was calculated and compared for the affective, attention, default, and cognitive control networks.
RESULTS: At baseline, we found atypical cross talk between the default, cognitive control, and dorsal attention networks and hypoconnectivity within the dorsal attention and default networks in adults with

attention-deficit hyperactivity disorder. Our first-ever placebo-controlled clinical trial incorporating resting-state functional MRI showed that treatment with atomoxetine strengthened an anticorrelated relationship between the default and task-positive networks and modulated all major brain networks. The strengthened anticorrelations were associated with improving clinical symptoms in the atomoxetine-treated adults.
CONCLUSIONS: Our results support the idea that atypical default mode network task-positive network interaction plays an important role in the pathophysiology of adult attention-deficit hyperactivity disorder. Strengthening this atypical relationship following atomoxetine treatment suggests an important pathway to treat attention-deficit hyperactivity disorder

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Int J Pediatr Otorhinolaryngol. 2016 May;84:12-20.
ASSOCIATIONS BETWEEN OTITIS MEDIA AND CHILD BEHAVIOURAL AND LEARNING DIFFICULTIES: RESULTS FROM A DANISH COHORT.
Niclasen J, Obel C, Homoe P, et al.
OBJECTIVES: Findings from studies investigating early childhood episodes of otitis media (OM) and developmental outcomes are inconclusive. This may in part be because large-scale prospective studies controlling for relevant confounding factors are sparse. The present study investigates associations between OM in early childhood and later behavioural and learning difficulties controlling for relevant confounding factors.
METHODS: The study applied data from the Aarhus Birth Cohort's 10-12-year-old follow-up (N=7578). Associations between retrospective parent-reported OM (no OM; 1-3 episodes of OM with/without tympanostomy tubes; 4+ OM episodes without tympanostomy tubes and; 4+ OM episodes with tympanostomy tubes) one the one hand, and parent- and teacher-reported scores on the Strengths and Difficulties Questionnaire (SDQ) and parent-reported academic difficulties on the other hand, were investigated. The following variables were controlled for: parental educational level, maternal and paternal school problems, parental post-natal smoking, breastfeeding, and age at which the child started walking. All analyses were stratified by gender.
RESULTS: Large differences in background characteristics were observed for the group of children with 4+ OM episodes with tympanostomy tubes compared to the no OM group. After controlling for relevant confounders, negative associations were consistently observed for the group of children with 4+ episodes of OM with tympanostomy tubes compared to the group of children without OM. This was particularly so for girls.
CONCLUSION: The findings suggest an association between 4+ episodes of early OM with tympanostomy tubes and behavioural and learning difficulties later in childhood. The large inter-group differences, i.e. impact of residual and unmeasured confounding factors, may in part explain the observed associations and underline the need to include these in future studies

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Int J Pediatr Otorhinolaryngol. 2016 May;84:151-55.
RISK FACTORS FOR PEDIATRIC POST-TONSILLECTOMY HEMORRHAGE.
Spektor Z, Saint-Victor S, Kay DJ, et al.
OBJECTIVES: To determine pre-operative risk factors for post-tonsillectomy secondary hemorrhage in children, and quantify the magnitude of their risk.
MATERIALS AND METHODS: Retrospective case-control study of all pediatric tonsillectomy patients experiencing post-operative bleeding from 2005 to 2010 in a community practice consisting of three fellowship-trained pediatric otolaryngologists were identified. The 91 cases were matched with 151 controls that underwent tonsillectomy by the same surgeon on the same day as each identified case. All charts were reviewed, and 41 pre-operative variables were extracted and statistically analyzed with contingency and regression analysis to calculate significance and odds ratios.
RESULTS: Three significant predictors of post-operative bleeding were identified. Performing a tonsillectomy on a child with recurrent tonsillitis (vs. other indications) increased the risk of post-operative hemorrhage by

4.5 times (p<0.0001, 95% confidence intervals 2.41-8.38). Performing a tonsillectomy on a child with attention deficit hyperactivity disorder (ADHD) increased the risk by 8.7 times (p=0.029, 95%CI 1.4-53.6). Older children were more predisposed to post-operative bleeding. For every increase in age by one year, the hemorrhage risk increased by 1.1 times (p=0.0025, 95%CI 1.032-1.162). Children 11 years of age and older had double the risk of bleeding compared to younger children (odds ratio 1.98, p=0.0381, 95%CI 1.04-3.79). None of the remaining 38 variables showed significant differences between cases and controls.
CONCLUSIONS: The risk of post-tonsillectomy hemorrhage is significantly increased in older children and those with recurrent tonsillitis and ADHD

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Isr Med Assoc J. 2016;18:652-54.

EXPLORING THE ASSOCIATION BETWEEN LEGG-CALV+®-PERTHES DISEASE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Berman J, Aran A, Berenstein-Weyel T, et al.

Background: Legg-Calv+®-Perthes disease (LCPD) is an idiopathic hip osteonecrosis prevalent in children < age 15 years. The etiology remains incompletely understood, partly because of multiple potential environmental risk factors and partly because of lack of genetic markers. It has been hypothesized that hyperactivity may induce mechanical stress and/or vascular damage at a fragile joint.
Objectives: To assess children with LCPD for markers of attention deficit hyperactivity disorder (ADHD) relative to their unaffected comparably aged siblings to exclude the contribution of hyperactive behavior versus environmental and/or genetic factors in LCPD.
Methods: All children followed in the Pediatric Orthopedic Clinic, and their comparably aged siblings, were recruited. ADHD was assessed using the TOVA computerized test and DSM-IV criteria. Quality of life and sleep disorders as ancillary tests were assessed using the Child Health Questionnaire (Parent Form 50), Pediatric Outcomes Data Collection Instrument, and Pediatric Daytime Sleepiness Scale.
Results: Sixteen children with LCPD (age 9.1 -¦ 3.3, 75% males) were compared with their closest-aged siblings (age 9.3 -¦ 2.6, 30% males). Mean TOVA scores of children with LCPD (-3.79 -¦ 2.6) and of their non-LCPD siblings (-3.6 -¦ 4.04) were lower relative to the general population (0 -¦ 1.8, P < 0.0001). Both group means were in the ADHD range (Γëñ -1.8) implying that 73% of this LCPD cohort and 53% of their non-LCPD siblings performed in the ADHD range, relative to 3.6% incidence expected in the general population (P < 0.0001). Other test results were similar in both groups.
Conclusions: Our findings in a small cohort of children with LCPD and their comparably aged siblings do not support an association between LCPD and ADHD. ADHD markers were equally high in the LCPD children and siblings

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Isr Med Assoc J. 2016;18:655-60.

SEASONALITY OF METHYLPHENIDATE ADMINISTRATION AMONG CHILDREN IN ISRAEL.

Cohen HA, Savitsky B, Ashkenas A, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention, impulsivity and hyperactivity. Recently, increases in ADHD prevalence and methylphenidate use have been reported. There is evidence that children and adolescents use ADHD medication only during the school year. Objectives: To investigate trends in methylphenidate dispensing over a period of 3 years (2010ΓÇô2012) at the monthly level and to investigate whether there is any monthly variation, especially during the summer season.
Methods: The database of Clalit Health Services (the largest of the four health funds in Israel) was used to identify (i) patients aged 6ΓÇô17 years with a diagnosis of ADHD, and (ii) methylpenidate dispensation during the period 2010–2012.
Results: Among children aged 6–17 years diagnosed with ADHD, 43% were treated with methylphenidate. For the period 2010 to 2012 there was an annual drop in methylphenidate dispensing, beginning in June and continuing through the 2 months of summer vacation, with a 2.5-fold reduction from July as compared to

May. This decline was consistently followed by a rise in medications dispensed starting August. A similar small drop was observed during the Passover school vacation. The summer drop decreased over the years. **Conclusions**: Our findings showed a decrease in the number of methylphenidate prescriptions dispensed during the summer months and Passover as compared to the rest of the year. However, this phenomenon appears to be decreasing. Given that ADHD is a chronic disease state that can effectively be managed with pharmacotherapy, discontinuation of treatment may be harmful for patients and should be considered only on a patient-by-patient basis

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J Abnorm Psychol. 2015 Feb;124:208-14.

DYSFUNCTIONAL MODULATION OF DEFAULT MODE NETWORK ACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Metin B, Krebs RM, Wiersema JR, et al.

The state regulation deficit model posits that individuals with attention-deficit/hyperactivity disorder (ADHD) have difficulty applying mental effort effectively under suboptimal conditions such as very fast and very slow event rates (ERs). ADHD is also associated with diminished suppression of default mode network (DMN) activity and related performance deficits on tasks requiring effortful engagement. The current study builds on these 2 literatures to test the hypothesis that failure to modulate DMN activity in ADHD might be especially pronounced at ER extremes. Nineteen adults with ADHD and 20 individuals without any neuropsychiatric condition successfully completed a simple target detection task under 3 ER conditions (2-, 4-, and 8-s interstimulus intervals) inside the scanner. Task-related DMN deactivations were compared between 2 groups. There was a differential effect of ER on DMN activity for individuals with ADHD compared to controls. Individuals with ADHD displayed excessive DMN activity at the fast and slow, but not at the moderate ER. The results indicate that DMN attenuation in ADHD is disrupted in suboptimal energetic states where additional effort is required to optimize task engagement. DMN dysregulation may be an important element of the neurobiological underpinnings of state regulation deficits in ADHD

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J Affect Disord. 2016 May;196:32-46.

A COMPARATIVE META-ANALYSIS OF TEMPS SCORES ACROSS MOOD DISORDER PATIENTS, THEIR FIRST-DEGREE RELATIVES, HEALTHY CONTROLS, AND OTHER PSYCHIATRIC DISORDERS.

Solmi M, Zaninotto L, Toffanin T, et al.

BACKGROUND: The Temperament Evaluation Memphis, Pisa, Paris and San Diego Auto-questionnaire (TEMPS) is validated to assess temperament in clinical and non-clinical samples. Scores vary across bipolar disorder (BD), major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), borderline personality disorder (BPD) and healthy controls (HCs), but a meta-analysis is missing.
METHODS: Meta-analysis of studies comparing TEMPS scores in patients with mood disorders or their first-degree relatives to each other, or to a psychiatric control group or HCs.
RESULTS: Twenty-six studies were meta-analyzed with patients with BD (n= 2025), MDD (n=1283), ADHD (n=56) and BPD (n=43), relatives of BD (n=436), and HCs (n=1757). Cyclothymic ($p<0.001$) and irritable TEMPS scores ($p<0.001$) were higher in BD than MDD (studies=12), and in MDD vs HCs (studies=8). Cyclothymic ($p<0.001$), irritable ($p<0.001$) and anxious ($p=0.03$) scores were higher in BD than their relatives, who, had higher scores than HCs. No significant differences emerged between ADHD and BD (studies=3);
CONCLUSION: Affective temperaments are on a continuum, with increasing scores ranging from HCs through MDD to BD regarding cyclothymic and irritable temperament, from MDD through BD to HC regarding hyperthymic temperament, and from HC through BD relatives to BD regarding cyclothymic, irritable and anxious temperament. Depressive and anxious temperaments did not differ between BD and MDD, being nonetheless the lowest in HCs. BD did not differ from ADHD in any investigated TEMPS domain. LIMITATIONS: Different TEMPS versions, few studies comparing BD with ADHD or BPD, no correlation with other questionnaires

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J Am Acad Child Adolesc Psychiatry. 2015 Nov;54:926-37.

CORRELATES AND CONSEQUENCES OF SUICIDAL COGNITIONS AND BEHAVIORS IN CHILDREN AGES 3 TO 7 YEARS.

Whalen DJ, Dixon-Gordon K, Belden AC, et al.

OBJECTIVE: Despite research documenting the existence of depression and other psychiatric disorders in early childhood, little is known about the nature and consequences of suicidal cognitions and behaviors (SI) in young children ages 3 to 7 years. The identification of trajectories of SI across childhood is a critical step toward preventing childhood suicide.

METHOD: Participants were 306 children enrolled in a prospective longitudinal investigation of young children and their families. Children and their families completed a baseline assessment between ages 3 and 7 years, and at least 1 follow-up assessment (ages 7-12 years). Child psychopathology, suicidal thoughts, plans, and behaviors were assessed via parent and trained interviewer report before age 9, and also with self-report after age 9. Data on maternal history of psychopathology, as well as maternal and family history of suicide attempts, were also obtained through parent report.

RESULTS: Controlling for a range of clinical and demographic variables, early-childhood SI (as defined as suicidal thoughts, behavior, or any expression of plans/attempts occurring before age 7) and suicidal themes in play were concurrently associated with childhood attention-deficit/hyperactivity (ADHD) and oppositional defiant/conduct disorders (ODD/CD). Early-childhood SI also predicted school-age depression and ODD/CD; however, these findings were no longer significant after controlling for the same diagnoses at the childhood baseline. Longitudinal analysis indicated that early-childhood SI was a robust predictor of school-age SI, even after accounting for psychiatric disorders at both time points.

CONCLUSION: Extending current research, these findings demonstrate that early-childhood SI confers significant risk for continuation into school-age SI and is concurrently associated with ADHD and ODD/CD. Although the meaning of early-childhood SI remains unclear, results suggest that it is a clinically important phenomenon that should be carefully assessed and taken seriously as a marker of risk for ongoing suicidal ideation/behavior. These findings suggest that early screening for SI in childhood is indicated in clinical settings, particularly in children less than 7 years of age with depression and externalizing disorders

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J Am Acad Child Adolesc Psychiatry. 2015 Sep;54:737-44.

SINGLE NUCLEOTIDE POLYMORPHISM HERITABILITY OF BEHAVIOR PROBLEMS IN CHILDHOOD: GENOME-WIDE COMPLEX TRAIT ANALYSIS.

Pappa I, Fedko IO, Mileva-Seitz VR, et al.

OBJECTIVE: Genetic factors contribute to individual differences in behavior problems. In children, genome-wide association studies (GWAS) have yielded the first suggestive results when aiming to identify genetic variants that explain heritability, but the proportion of genetic variance that can be attributed to common single nucleotide polymorphisms (SNPs) remains to be determined, as only a few studies have estimated SNP heritability, with diverging results.

METHOD: Genomic-relationship-matrix restricted maximum likelihood (GREML) as implemented in the software Genome-Wide Complex Trait Analysis (GCTA) was used to estimate SNP heritability (SNP h(2)) for multiple phenotypes within 4 broad domains of children's behavioral problems (attention-deficit/hyperactivity symptoms, internalizing, externalizing, and pervasive developmental problems) and cognitive function. We combined phenotype and genotype data from 2 independent, population-based Dutch cohorts, yielding a total number of 1,495 to 3,175 of 3-, 7-, and 9-year-old children.

RESULTS: Significant SNP heritability estimates were found for attention-deficit/hyperactivity symptoms (SNP h(2) = 0.37-0.71), externalizing problems (SNP h(2) = 0.44), and total problems (SNP h(2) = 0.18), rated by mother or teacher. Sensitivity analyses with exclusion of extreme cases and quantile normalization of the phenotype data decreased SNP h(2) as expected under genetic inheritance, but they remained statistically significant for most phenotypes.

CONCLUSION: We provide evidence of the influence of common SNPs on child behavior problems in an ethnically homogenous sample. These results support the continuation of large GWAS collaborative efforts to unravel the genetic basis of complex child behaviors

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J Am Acad Child Adolesc Psychiatry. 2015 Sep;54:697-98.
HERE/IN THIS ISSUE AND THERE/ABSTRACT THINKING: THE SECRET LIVES OF ADOLESCENTS: ARE WE ASKING THE RIGHT QUESTIONS?
Hong DS.

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J Am Acad Child Adolesc Psychiatry. 2015 Sep;54:728-36.
META-ANALYSIS: RISK OF TICS ASSOCIATED WITH PSYCHOSTIMULANT USE IN RANDOMIZED, PLACEBO-CONTROLLED TRIALS.
Cohen SC, Mulqueen JM, Ferracioli-Oda E, et al.
OBJECTIVE: Clinical practice currently restricts the use of psychostimulant medications in children with tics or a family history of tics for fear that tics will develop or worsen as a side effect of treatment. Our goal was to conduct a meta-analysis to examine the risk of new onset or worsening of tics as an adverse event of psychostimulants in randomized, placebo-controlled trials.
METHOD: We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of psychostimulant medications in the treatment of children with attention-deficit/hyperactivity disorder (ADHD). We used a fixed effects meta-analysis with risk ratio of new onset or worsening tics in children treated with psychostimulants compared to placebo. We used stratified subgroup analysis and meta-regression to examine the effects of stimulant type, dose, duration of treatment, recorder of side effect data, trial design, and mean age of participants on the measured risk of tics.
RESULTS: We identified 22 studies involving 2,385 children with ADHD for inclusion in our meta-analysis. New onset tics or worsening of tic symptoms were commonly reported in the psychostimulant (event rate = 5.7%, 95% CI = 3.7%-8.6%) and placebo groups (event rate = 6.5%, 95% CI = 4.4%-9.5%). The risk of new onset or worsening of tics associated with psychostimulant treatment was similar to that observed with placebo (risk ratio = 0.99, 95% CI = 0.78-1.27, z = -0.05, p = .962). Type of psychostimulant, dose, duration of treatment, recorder, and participant age did not affect risk of new onset or worsening of tics. Crossover studies were associated with a significantly greater measured risk of tics with psychostimulant use compared to parallel group trials.
CONCLUSION: Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use. Clinicians may want to consider rechallenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants

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J Am Acad Child Adolesc Psychiatry. 2015 Oct;54:787-88.
HERE/IN THIS ISSUE AND THERE/ABSTRACT THINKING: DOES IT ALWAYS START IN CHILDHOOD?
Rogers C.

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J Am Acad Child Adolesc Psychiatry. 2015 Apr;54:241-42.
HERE/IN THIS ISSUE AND THERE/ABSTRACT THINKING: ALONG A CONTINUUM.
Rogers CE.

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J Am Acad Child Adolesc Psychiatry. 2015 Nov;54:877-78.
HERE/IN THIS ISSUE AND THERE/ABSTRACT THINKING: NOT EVEN IN CARTOONS.
Vanderwal T.

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J Autism Dev Disord. 2016 Apr;46:1236-46.

SOCIAL-EMOTIONAL INHIBITION OF RETURN IN CHILDREN WITH AUTISM SPECTRUM DISORDER VERSUS TYPICAL DEVELOPMENT.

Antezana L, Mosner MG, Troiani V, et al.

In typical development there is a bias to orient visual attention to social information. Children with ASD do not reliably demonstrate this bias, and the role of attention orienting has not been well studied. We examined attention orienting via the inhibition of return (IOR) mechanism in a spatial cueing task using social-emotional cues; we studied 8- to 17-year-old children with ASD (n = 41) and typically developing controls (TDC) (n = 25). The ASD group exhibited a significantly stronger IOR effect than the TDC group, and the IOR effect correlated positively with social impairments but was unrelated to co-occurring ADHD or anxiety symptoms. The results provide evidence of an early altered attention mechanism that is associated with to core social deficits in ASD

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J Behav Health Serv Res. 2015 Oct;42:437-51.

THE COMORBIDITY OF ADHD AND EATING DISORDERS IN A NATIONALLY REPRESENTATIVE SAMPLE.

Bleck JR, Debate RD, Olivardia R.

Evidence suggests a comorbidity of childhood attention-deficit/hyperactivity disorder (ADHD) and subsequent eating disorders. However, most studies have assessed this comorbidity among patient populations as opposed to nationally representative samples and have not explored differences by subtype of each disorder. The current study aims to investigate the association between both clinical (i.e., diagnosed) and subclinical (i.e., presence of behaviors but not all diagnostic criteria) ADHD and eating disorders via a secondary data analysis of the National Longitudinal Study of Adolescent Health (n = 12,262). Results reveal that those with clinical ADHD are more likely to experience (a) clinical eating disorder, (b) clinical-level binging and/or purging behaviors, and (c) clinical-level restrictive behaviors. Those with subclinical ADHD (both inattentive and hyperactive/impulsive) were more likely to experience subclinical binging and/or purging behaviors but not subclinical restrictive behaviors. Implications of study findings pertain to both secondary/targeted prevention of eating disorders and tertiary prevention via patient-specific treatment plans

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J Behav Ther Exp Psychiatry. 2016 Jun;51:27-34.

ATTENTIONAL BIASES IN HIGH SOCIAL ANXIETY USING A FLANKER TASK.

Chen S, Yao N, Qian M, et al.

BACKGROUND AND OBJECTIVES: The existence of threat-related attentional bias has been well supported in social anxiety research. However, most previous studies investigated separately attentional bias toward targets or distractors. This study examined the selective attention of socially anxious individuals in the presence of both emotional targets and distractors.

METHODS: Participants with high vs. low social anxiety (HSA vs. LSA) took part in a modified flanker task. Participants initially focused on the center of the screen, and then were required to identify the emotion of the central face (target) regardless of the flanking faces (distractors). RESULTS: The response times (RTs) of the HSA and LSA groups did not differ significantly when responding to different central faces (targets), but the HSA group responded more slowly to central faces when the flankers (distractors) were negative faces as opposed to positive or neutral.

LIMITATIONS: The depression levels of participants in this non-clinical sample were not controlled.

CONCLUSION: The results support attention control theory and suggest impaired inhibition control in HSA.

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J Child Adolesc Psychiatr Nurs. 2015 Feb;28:3-13.

THE ROLE OF FAMILY PHENOMENA IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Paidipati CP, Deatrick JA.

TOPIC: Previous research suggests that families are integral to the understanding of children and adolescents with attention deficit hyperactivity disorder (ADHD).

PURPOSE: The purpose of this article is to identify family phenomena related to children and adolescents with ADHD and highlight research findings that intersect family phenomena with the care and treatment of ADHD in youth.

SOURCES: A literature review was conducted at the University of Pennsylvania in spring of 2014 using an online library system. The four major databases utilized are Cumulative Index to Nursing and Allied Health Literature (CINAHL), Ovid Medline, Scopus, and Psyc-INFO.

CONCLUSIONS: A wide array of family-related concepts are identified in the literature and represent a multifaceted and dynamic range of family phenomena related to ADHD youth. Four major themes emerged in the literature, including family stress and strain, parenting practices and caregiver health, family relationships, and family processes related to ADHD management. Different cultural and ethnic groups are reflected in the studies, but the majority of participants are self-identified Caucasian. As a collective, the research findings suggest family-related phenomena are essential and relevant to the investigation of children and adolescents with ADHD and worthwhile to explore in future research endeavors, especially in diverse populations

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J Child Adolesc Psychopharmacol. 2016 Feb;26:65-73.

PHARMACOTHERAPY OF AGGRESSION IN CHILD AND ADOLESCENT PSYCHIATRIC DISORDERS.

Gurnani T, Ivanov I, Newcorn JH.

OBJECTIVE: Aggression is a common, yet complex, behavioral complaint, and a frequent indication for referral to child and adolescent psychiatrist treatment. This article reviews the evidence supporting pharmacotherapy of aggression in youth, with a primary focus on impulsive aggression (the primary indication for this intervention). Relevant diagnostic considerations and consensus guidelines are discussed.

METHODS: Articles examining the role of medications in the treatment of aggression in youth with pathological aggression were identified using PubMed and MEDLINE(R) databases over the past 15 years (2000-2015); selected articles published prior to 2000 and deemed to be of high relevance were searched and also included. Search terms included: Aggression, aggressive, disruptive behavior, conduct, youth, children, and adolescents. Cited references were also searched for relevant articles.

RESULTS: There are a number of evidence-based medication treatments for aggression, which are generally best considered in the context of differential diagnosis and ongoing evidence-based psychosocial interventions. Impulsive aggression is generally considered the type of aggression most amenable to medication, but other aggression subtypes may also possibly respond to treatment. Medication classes with positive evidence include the psychostimulants and alpha-2 agonists (in the presence of attention-deficit/hyperactivity disorder [ADHD] and/or disruptive behavior disorders), mood stabilizing agents, and atypical antipsychotics. Published guidelines recommend systematic and adequate trials of medications in sequential order, to optimize response and minimize polypharmacy. Guidelines for safety monitoring are available for many of the medications used for aggression in youth, and are also discussed.

CONCLUSIONS: Aggression in children carries a high risk of poor outcomes, and, therefore, a better understanding of treatment options is a high priority. The available literature points to the importance of identifying the underlying disorder, when possible, and using this information to guide treatment selection. Future studies are needed to better inform the treatment of aggression across disorders, and the treatment of different aggression subtypes

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J Child Neurol. 2016 Apr;31:569-72.

VISUAL ATTENTION IN CHILDREN WITH MIGRAINE: THE IMPORTANCE OF PROPHYLAXIS.

Villa TR, Agessi LM, Moutran AR, et al.

This study aimed to compare the visual attention performance of children newly diagnosed with migraine, children undergoing migraine prophylaxis, and a healthy control group. Eighty-two children aged 8 to 12 years were divided into 3 groups: untreated migraine (n = 30), migraine prophylaxis (n = 22), and control (n = 30). All were subjected to a visual attention assessment with the Trail Making Test parts A and B, Letter-Cancellation Test, and the Brazilian Visual Attention Test 3rd edition. Although performance in attention tasks was within the normal range in all groups, children with untreated migraine performed significantly worse in some visual attention tests than did the control children or children undergoing migraine prophylaxis. The migraine prophylaxis group performed as well as the control group. The deregulation of the neurochemical mechanisms underlying the physiopathology of migraine might induce visual attention deficits, but an effective prophylactic treatment might reverse migraine symptoms

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J Child Psychol Psychiatry. 2016 Mar;57:353-68.

ANNUAL RESEARCH REVIEW: NEURAL CONTRIBUTIONS TO RISK-TAKING IN ADOLESCENCE--DEVELOPMENTAL CHANGES AND INDIVIDUAL DIFFERENCES.

Crone EA, van Duijvenvoorde AC, Peper JS.

BACKGROUND: Risk-taking, which involves voluntary choices for behaviors where outcomes remain uncertain, undergoes considerable developmental changes during childhood, adolescence, and early adulthood. In addition, risk-taking is thought to be a key element of many externalizing disorders, such as ADHD, delinquency, conduct disorder, and substance abuse. In this review, we will discuss the potential adaptive and nonadaptive properties of risk-taking in childhood and adolescence.

FINDINGS: We propose that the changes in brain architecture and function are a crucial element underlying these developmental trajectories. We first identify how subcortical and cortical interactions are important for understanding risk-taking behavior in adults. Next, we show how developmental changes in this network underlie changes in risk-taking behavior. Finally, we explore how these differences can be important for understanding externalizing behavioral disorders in childhood and adolescence.

CONCLUSIONS: We conclude that longitudinal studies are of crucial importance for understanding these developmental trajectories, and many of these studies are currently underway

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J Child Psychol Psychiatry. 2016 Mar;57:421-39.

ANNUAL RESEARCH REVIEW: DISCOVERY SCIENCE STRATEGIES IN STUDIES OF THE PATHOPHYSIOLOGY OF CHILD AND ADOLESCENT PSYCHIATRIC DISORDERS--PROMISES AND LIMITATIONS.

Zhao Y, Castellanos FX.

BACKGROUND: Psychiatric science remains descriptive, with a categorical nosology intended to enhance interobserver reliability. Increased awareness of the mismatch between categorical classifications and the complexity of biological systems drives the search for novel frameworks including discovery science in Big Data. In this review, we provide an overview of incipient approaches, primarily focused on classically categorical diagnoses such as schizophrenia (SZ), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), but also reference convincing, if focal, advances in cancer biology, to describe the challenges of Big Data and discovery science, and outline approaches being formulated to overcome existing obstacles.

FINDINGS: A paradigm shift from categorical diagnoses to a domain/structure-based nosology and from linear causal chains to complex causal network models of brain-behavior relationship is ongoing. This (r)evolution involves appreciating the complexity, dimensionality, and heterogeneity of neuropsychiatric data collected from multiple sources ('broad' data) along with data obtained at multiple levels of analysis, ranging from genes to molecules, cells, circuits, and behaviors ('deep' data). Both of these types of Big Data landscapes require the use and development of robust and powerful informatics and statistical approaches.

Thus, we describe Big Data analysis pipelines and the promise and potential limitations in using Big Data approaches to study psychiatric disorders.
CONCLUSIONS: We highlight key resources available for psychopathological studies and call for the application and development of Big Data approaches to dissect the causes and mechanisms of neuropsychiatric disorders and identify corresponding biomarkers for early diagnosis

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J Child Psychol Psychiatry. 2016 Mar;57:321-49.
ANNUAL RESEARCH REVIEW: TRANSDIAGNOSTIC NEUROSCIENCE OF CHILD AND ADOLESCENT MENTAL DISORDERS--DIFFERENTIATING DECISION MAKING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, CONDUCT DISORDER, DEPRESSION, AND ANXIETY.
Sonuga-Barke EJ, Cortese S, Fairchild G, et al.

BACKGROUND: Ineffective decision making is a major source of everyday functional impairment and reduced quality of life for young people with mental disorders. However, very little is known about what distinguishes decision making by individuals with different disorders or the neuropsychological processes or brain systems underlying these. This is the focus of the current review.
SCOPE AND METHODOLOGY: We first propose a neuroeconomic model of the decision-making process with separate stages for the prechoice evaluation of expected utility of future options; choice execution and postchoice management; the appraisal of outcome against expectation; and the updating of value estimates to guide future decisions. According to the proposed model, decision making is mediated by neuropsychological processes operating within three domains: (a) self-referential processes involved in autobiographical reflection on past, and prospection about future, experiences; (b) executive functions, such as working memory, inhibition, and planning, that regulate the implementation of decisions; and (c) processes involved in value estimation and outcome appraisal and learning. These processes are underpinned by the interplay of multiple brain networks, especially medial and lateralized cortical components of the default mode network, dorsal corticostriatal circuits underpinning higher order cognitive and behavioral control, and ventral frontostriatal circuits, connecting to brain regions implicated in emotion processing, that control valuation and learning processes.
FINDINGS AND CONCLUSION: Based on clinical insights and considering each of the decision-making stages in turn, we outline disorder-specific hypotheses about impaired decision making in four childhood disorders: attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), depression, and anxiety. We hypothesize that decision making in ADHD is deficient (i.e. inefficient, insufficiently reflective, and inconsistent) and impulsive (biased toward immediate over delayed alternatives). In CD, it is reckless and insensitive to negative consequences. In depression, it is disengaged, perseverative, and pessimistic, while in anxiety, it is hesitant, risk-averse, and self-deprecating. A survey of current empirical indications related to these disorder-specific hypotheses highlights the limited and fragmentary nature of the evidence base and illustrates the need for a major research initiative in decision making in childhood disorders. The final section highlights a number of important additional general themes that need to be considered in future research

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J Clin Psychopharmacol. 2016 Apr;36:187-89.
SOMNAMBULISM DURING MONOTHERAPY WITH MIXED AMPHETAMINE SALTS.
Pinnaka S, Gosai K, Czekierdowski C, et al.

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J Exp Child Psychol. 2015 Nov;139:51-70.

THE ATTENTIONAL BLINK IN TYPICALLY DEVELOPING AND READING-DISABLED CHILDREN .

de Groot BJ, van den Bos KP, van der Meulen BF, et al.

This study's research question was whether selective visual attention, and specifically the attentional blink (AB) as operationalized by a dual target rapid serial visual presentation (RSVP) task, can explain individual differences in word reading (WR) and reading-related phonological performances in typically developing children and reading-disabled subgroups. A total of 407 Dutch school children (Grades 3-6) were classified either as typically developing (n = 302) or as belonging to one of three reading-disabled subgroups: reading disabilities only (RD-only, n = 69), both RD and attention problems (RD+ADHD, n = 16), or both RD and a specific language impairment (RD+SLI, n = 20). The RSVP task employed alphanumeric stimuli that were presented in two blocks. Standardized Dutch tests were used to measure WR, phonemic awareness (PA), and alphanumeric rapid naming (RAN). Results indicate that, controlling for PA and RAN performance, general RSVP task performance contributes significant unique variance to the prediction of WR. Specifically, consistent group main effects for the parameter of AB(minimum) were found, whereas there were no AB-specific effects (i.e., AB(width) and AB(amplitude)) except for the RD+SLI group. Finally, there was a group by measurement interaction, indicating that the RD-only and comorbid groups are differentially sensitive for prolonged testing sessions. These results suggest that more general factors involved in RSVP processing may explain the group differences found

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J Health Soc Behav. 2015 Sep;56:415.

JHSB POLICY BRIEF. DOES MEDICAL TREATMENT OF CHILDREN'S BEHAVIORAL PROBLEMS LOWER FOSTER CARE RATES?

Fallesen P, Wildeman C.

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J Int Neuropsychol Soc. 2015 Sep;21:573-83.

ALZHEIMER DISEASE CEREBROSPINAL FLUID BIOMARKERS MODERATE BASELINE DIFFERENCES AND PREDICT LONGITUDINAL CHANGE IN ATTENTIONAL CONTROL AND EPISODIC MEMORY COMPOSITES IN THE ADULT CHILDREN STUDY.

Aschenbrenner AJ, Balota DA, Fagan AM, et al.

Cognitive measures that are sensitive to biological markers of Alzheimer disease (AD) pathology are needed to (a) facilitate preclinical staging, (b) identify individuals who are at the highest risk for developing clinical symptoms, and (c) serve as endpoints for evaluating the efficacy of interventions. The present study assesses the utility of two cognitive composite scores of attentional control and episodic memory as markers for preclinical AD pathology in a group of cognitively normal older adults (N = 238), as part of the Adult Children Study. All participants were given a baseline cognitive assessment and follow-up assessments every 3 years over an 8-year period, as well as a lumbar puncture within 2 years of the initial assessment to collect cerebrospinal fluid (CSF) and amyloid tracer Pittsburgh compound-B scan for amyloid imaging. Results indicated that attentional control was correlated with levels of Abeta42 at the initial assessment whereas episodic memory was not. Longitudinally, individuals with high CSF tau exhibited a decline in both attention and episodic memory over the course of the study. These results indicate that measures of attentional control and episodic memory can be used to evaluate cognitive decline in preclinical AD and provide support that CSF tau may be a key mechanism driving longitudinal cognitive change

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J Int Neuropsychol Soc. 2015 Jan;21:22-33.

WHITE MATTER INTEGRITY DISSOCIATES VERBAL MEMORY AND AUDITORY ATTENTION SPAN IN EMERGING ADULTS WITH CONGENITAL HEART DISEASE.

Brewster RC, King TZ, Burns TG, et al.

White matter disruptions have been identified in individuals with congenital heart disease (CHD). However, no specific theory-driven relationships between microstructural white matter disruptions and cognition have been established in CHD. We conducted a two-part study. First, we identified significant differences in fractional anisotropy (FA) of emerging adults with CHD using Tract-Based Spatial Statistics (TBSS). TBSS analyses between 22 participants with CHD and 18 demographically similar controls identified five regions of normal appearing white matter with significantly lower FA in CHD, and two higher. Next, two regions of lower FA in CHD were selected to examine theory-driven differential relationships with cognition: voxels along the left uncinate fasciculus (UF; a tract theorized to contribute to verbal memory) and voxels along the right middle cerebellar peduncle (MCP; a tract previously linked to attention). In CHD, a significant positive correlation between UF FA and memory was found, r(20)=.42, p=.049 (uncorrected). There was no correlation between UF and auditory attention span. A positive correlation between MCP FA and auditory attention span was found, r(20)=.47, p=.027 (uncorrected). There was no correlation between MCP and memory. In controls, no significant relationships were identified. These results are consistent with previous literature demonstrating lower FA in younger CHD samples, and provide novel evidence for disrupted white matter integrity in emerging adults with CHD. Furthermore, a correlational double dissociation established distinct white matter circuitry (UF and MCP) and differential cognitive correlates (memory and attention span, respectively) in young adults with CHD

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J Int Neuropsychol Soc. 2015 Apr;21:271-84.

ALTERED RESTING-STATE FRONTOPARIETAL CONTROL NETWORK IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lin HY, Tseng WY, Lai MC, et al.

The frontoparietal control network, anatomically and functionally interposed between the dorsal attention network and default mode network, underpins executive control functions. Individuals with attention-deficit/hyperactivity disorder (ADHD) commonly exhibit deficits in executive functions, which are mainly mediated by the frontoparietal control network. Involvement of the frontoparietal control network based on the anterior prefrontal cortex in neurobiological mechanisms of ADHD has yet to be tested. We used resting-state functional MRI and seed-based correlation analyses to investigate functional connectivity of the frontoparietal control network in a sample of 25 children with ADHD (7-14 years; mean 9.94 +/- 1.77 years; 20 males), and 25 age-, sex-, and performance IQ-matched typically developing (TD) children. All participants had limited in-scanner head motion. Spearman's rank correlations were used to test the associations between altered patterns of functional connectivity with clinical symptoms and executive functions, measured by the Conners' Continuous Performance Test and Spatial Span in the Cambridge Neuropsychological Test Automated Battery. Compared with TD children, children with ADHD demonstrated weaker connectivity between the right anterior prefrontal cortex (PFC) and the right ventrolateral PFC, and between the left anterior PFC and the right inferior parietal lobule. Furthermore, this aberrant connectivity of the frontoparietal control network in ADHD was associated with symptoms of impulsivity and opposition-defiance, as well as impaired response inhibition and attentional control. The findings support potential integration of the disconnection model and the executive dysfunction model for ADHD. Atypical frontoparietal control network may play a pivotal role in the pathophysiology of ADHD

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J Korean Acad Nurs. 2015 Apr;45:169-82.

EFFECTS OF COGNITIVE BEHAVIORAL THERAPY ON ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG SCHOOL-AGED CHILDREN IN KOREA: A META-ANALYSIS.

Park WJ, Park SJ, Hwang SD.

PURPOSE: This study was a meta-analysis designed to identify effects of Cognitive Behavioral Therapy (CBT) interventions in alleviating main symptoms of Attention Deficit Hyperactivity Disorder (ADHD) among school-aged children in Korea.

METHODS: Examination of several databases including Research Information Sharing Service, Korean Studies Information Service System, Data Base Periodical Information Academic and hand-searched article references, resulted in identification of 1,298 studies done between 2000 and 2013 of which 21 met the inclusion criteria. Comprehensive Meta-Analysis version 2.0 was used to analyze effect sizes, explore possible causes of heterogeneity, and check publication bias with a funnel plot and its trim-and-fill analysis.

RESULTS: Overall effect size of CBT intervention was large (g=1.08) along with each outcome of self-control (g=1.26), lack of attention (g=1.02), social skills (g=0.92), and hyperactivity (g=0.92). For heterogeneity, moderator analysis was performed, but no significant differences were found between the RCT (Randomized Controlled Trials) group and the NRCT (Non RCT) group. Also, meta-regression was performed using sample size, number of sessions, and length of session as predictors, but no statistically significant moderators were found. Finally, a funnel plot along with trim-and-fill analysis was produced to check for publication bias, but no significant bias was detected.

CONCLUSION: Based on these findings, there is clear evidence that CBT intervention has significant positive effects on the main symptoms of school-aged children suffering ADHD. Further research is needed to target diverse age groups with ADHD along with more RCT studies to improve the effectiveness of the CBT intervention

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J Learn Disabil. 2015 Jul;48:359-68.

ACADEMIC ACHIEVEMENT AMONG JUVENILE DETAINEES.

Grigorenko EL, Macomber D, Hart L, et al.

The literature has long pointed to heightened frequencies of learning disabilities (LD) within the population of law offenders; however, a systematic appraisal of these observations, careful estimation of these frequencies, and investigation of their correlates and causes have been lacking. Here we present data collected from all youth (1,337 unique admissions, mean age 14.81, 20.3% females) placed in detention in Connecticut (January 1, 2010-July 1, 2011). All youth completed a computerized educational screener designed to test a range of performance in reading (word and text levels) and mathematics. A subsample (n = 410) received the Wide Range Achievement Test, in addition to the educational screener. Quantitative (scale-based) and qualitative (grade-equivalence-based) indicators were then analyzed for both assessments. Results established the range of LD in this sample from 13% to 40%, averaging 24.9%. This work provides a systematic exploration of the type and severity of word and text reading and mathematics skill deficiencies among juvenile detainees and builds the foundation for subsequent efforts that may link these deficiencies to both more formal, structured, and variable definitions and classifications of LD, and to other types of disabilities (e.g., intellectual disability) and developmental disorders (e.g., ADHD) that need to be conducted in future research

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J Neurosurg Pediatr. 2016 May;17:564-68.

QUESTIONING THE NEED FOR ICU LEVEL OF CARE IN PEDIATRIC PATIENTS FOLLOWING ELECTIVE UNCOMPLICATED CRANIOTOMY FOR BRAIN TUMORS.

Gabel BC, Martin J, Crawford JR, et al.

OBJECTIVE The object of this study is to address what factors may necessitate the need for intensive care monitoring after elective uncomplicated craniotomy in pediatric patients who are initially managed in a non-intensive care unit setting postoperatively.

METHODS A retrospective chart review was undertaken for all patients who underwent elective craniotomy for brain tumor between April of 2007 and April of 2012 and who were directly admitted to the floor postoperatively. Factors such as age, tumor type, craniotomy location, neurological comorbidities, reason for transfer to intensive care unit (ICU) level of care (if applicable), time between admittance to floor and transfer to ICU level of care, and reason for transfer to ICU level of care were assessed.
RESULTS Adjusted logistic regression found 2 significant positive predictors of postoperative transfer to the ICU after initial admission to the floor: primitive neuroectodermal tumor pathology (OR 44.10, 95% CI 1.24-1572.16, p = 0.04), and repeat craniotomy during the same hospitalization (OR 13.97, 95% CI 1.21-160.66, p = 0.03). Conversely, 1 negative factor was found: low-grade glioma pathology (OR 0.05, 95% CI 0.00-0.87, p = 0.04).
CONCLUSIONS Select pediatric patients may not require ICU level of care after elective uncomplicated pediatric craniotomy. Additional studies are needed to adequately address which patients would benefit from initial ICU admittance following elective craniotomies for brain tumors

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J Pediatr Nurs. 2015 Jan;30:227-35.
SECONDHAND SMOKE EXPOSURE, PARENTAL DEPRESSIVE SYMPTOMS AND PRESCHOOL BEHAVIORAL OUTCOMES.
Bauer NS, Anand V, Carroll AE, et al.
Little is known about the association of secondhand smoke (SHS) exposure and behavioral conditions among preschoolers. A cross-sectional analysis was used to examine billing and pharmacy claims from November 2004 to June 2012 linked to medical encounter-level data for 2,441 children from four pediatric community health clinics. Exposure to SHS was associated with attention deficit-hyperactivity disorder/ADHD and disruptive behavior disorder/DBD after adjusting for potential confounding factors. Assessment of exposure to SHS and parental depressive symptoms in early childhood may increase providers' ability to identify children at higher risk of behavioral issues and provide intervention at the earliest stages

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J Pediatr Nurs. 2015 Jul;30:568-79.
ANXIETY, DECISION CONFLICT, AND HEALTH IN CAREGIVERS OF CHILDREN WITH ADHD: A SURVEY.
Chen JY, Clark MJ, Chang YY, et al.
The purpose of this study was to test a theoretical model to determine the effect of caregiver anxiety and decision conflict on the health of caregivers of children with ADHD. Cross-sectional analyses were conducted on data derived from caregivers (aged 24-70). Participants completed the Decision Conflict Scale, the Zung Anxiety Scale, the Duke Health Profile, and a demographic form. A path model that fit well indicated that anxiety and decision conflict had direct and indirect effects on the caregivers' health. Future study is needed to clarify factors contributing to uncertainty and to decrease emotional symptoms for caregivers, thus promoting their mental health

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J Relig Health. 2015 Jun;54:817-28.
DEVELOPMENTAL DEPRESSION IN ADOLESCENTS: A POTENTIAL SUB-TYPE BASED ON NEURAL CORRELATES AND COMORBIDITY.
Miller L, Barton YA.
Diagnosis of depression has low reliability (kappa = 0.28) due to "covert heterogeneity," making the identification of sub-types a focus of research. Very high rates of moderate or sub-threshold depression among adolescents (35-45 % beyond the 20-25 % with MDD), prompt consideration of a potential sub-type of moderate sub-threshold depression, linked to adolescent development. Previously, developmental depression (DD) has been proposed as sub-type of moderate depression that is a normative developmental process of spiritual individuation, the integration of existential and spiritual experience. DD as a potential sub-type is supported both by clinical observation and by an emerging body of research identifying a common

physiology to underlie both depression and spirituality (neurotransmitters, structural MRI and long-term clinical course), as well as research showing a surge of spirituality in adolescence (concomitant with window of risk of depression). We test for unique patterns of comorbidity and neural correlates as support for a sub-type. Based upon existing literature, we propose that DD will be (1) associated with the unique neural correlate of increased volume in the occipital region and (2) co-morbid with symptoms of affected regulation and processing. A sample of 125 adolescents (64 girls and 61 boys; ages 15-19 years) from the larger National Institute of Health Magnetic Resonance Imaging (MRI) Study of Normal Brain Development (Evans in Neuroimage 30(1):184-202, 2006) was assessed using the Cloninger Self-Transcendence Scale to examine correlates of sub-threshold mild to moderate symptoms of depression. Findings lend support to the possibility of a DD. Sub-threshold depression was associated with greater volume in the occipital region, as well as comorbidity with symptoms of affected regulation and processing (mania, ADHD, anxiety). By contrast, in adolescents with a low level of transcendence, sub-threshold depression was associated with conduct disorder and heavy substance use, both of which previous research have found to be associated with low levels of personal spirituality

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J Speech Lang Hear Res. 2016 Feb;59:133-42.

LANGUAGE IMPAIRMENT IN THE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CONTEXT.

Redmond SM.

PURPOSE: Attention-deficit/hyperactivity disorder (ADHD) is a ubiquitous designation that affects the identification, assessment, treatment, and study of pediatric language impairments (LIs).

METHOD: Current literature is reviewed in 4 areas: (a) the capacity of psycholinguistic, neuropsychological, and socioemotional behavioral indices to differentiate cases of LI from ADHD; (b) the impact of co-occurring ADHD on children's LI; (c) cross-etiology comparisons of the nonlinguistic abilities of children with ADHD and specific LI (SLI); and (d) the extent to which ADHD contributes to educational and health disparities among individuals with LI.

RESULTS: Evidence is presented demonstrating the value of using adjusted parent ratings of ADHD symptoms and targeted assessments of children's tense marking, nonword repetition, and sentence recall for differential diagnosis and the identification of comorbidity. Reports suggest that the presence of ADHD does not aggravate children's LI. The potential value of cross-etiology comparisons testing the necessity and sufficiency of proposed nonlinguistic contributors to the etiology of SLI is demonstrated through key studies. Reports suggest that children with comorbid ADHD+LI receive speech-language services at a higher rate than children with SLI.

CONCLUSION: The ADHD context is multifaceted and provides the management and study of LI with both opportunities and obstacles

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JAMA Psychiatry. 2016;73:955-62.

AGE-DEPENDENT EFFECTS OF METHYLPHENIDATE ON THE HUMAN DOPAMINERGIC SYSTEM IN YOUNG VS ADULT PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED CLINICAL TRIAL.

Schrantee A, Tamminga HGH, Bouziane C, et al.

IMPORTANCE Although numerous children receivemethylphenidate hydrochloride for the treatment of attention-deficit/hyperactivity disorder (ADHD), little is known about age-dependent and possibly lasting effects of methylphenidate on the human dopaminergic system.

OBJECTIVES To determine whether the effects of methylphenidate on the dopaminergic system are modified by age and to test the hypothesis that methylphenidate treatment of young but not adult patients with ADHD induces lasting effects on the cerebral blood flow response to dopamine challenge, a noninvasive probe for dopamine function.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled trial (Effects of Psychotropic Drugs on Developing Brain-Methylphenidate) among ADHD referral centers in the greater

Amsterdam area in the Netherlands between June 1, 2011, and June 15, 2015. Additional inclusion criteria were male sex, age 10 to 12 years or 23 to 40 years, and stimulant treatment-naive status.
INTERVENTIONS Treatment with either methylphenidate or a matched placebo for 16 weeks.
MAIN OUTCOMES AND MEASURES Change in the cerebral blood flowresponse to an acute challenge with methylphenidate, noninvasively assessed using pharmacological magnetic resonance imaging, between baseline and 1 week after treatment. Data were analyzed using intent-to-treat analyses.
RESULTS Among 131 individuals screened for eligibility, 99 patients met DSM-IV criteria for ADHD, and 50 participants were randomized to receivemethylphenidate and 49 to placebo. Sixteen weeks of methylphenidate treatment increased the cerebral blood flow response to methylphenidate within the thalamus (mean difference, 6.5; 95%CI, 0.4-12.6; P = .04) of children aged 10 to 12 years old but not in adults or in the placebo group. In the striatum, the methylphenidate condition differed significantly from placebo in children but not in adults (mean difference, 7.7; 95%CI, 0.7-14.8; P = .03).
CONCLUSIONS AND RELEVANCE We confirm preclinical data and demonstrate age-dependent effects of methylphenidate treatment on human extracellular dopamine striatal-thalamic circuitry. Given its societal relevance, these data warrant replication in larger groups with longer follow-up

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J Abnorm Child Psychol. 2016 Nov;44:1503-13.

WHICH TYPE OF PARENT TRAINING WORKS BEST FOR PRESCHOOLERS WITH COMORBID ADHD AND ODD? A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL COMPARING GENERIC AND SPECIALIZED PROGRAMS.

Forehand R, Parent J, Sonuga-Barke E, et al.

The present study examined whether the presence of comorbid ODD differentially moderated the outcome of two Behavioral Parent Training (BPT) programs in a sample of preschoolers with ADHD: One designed specifically for ADHD (NFPP: New Forest Parenting Programme) and one designed primarily for ODD (HNC: Helping the Noncompliant Child). In a secondary analysis, 130 parents and their 3–4 year-old children diagnosed with ADHD were assigned to one of the two programs. 44.6 % of the children also met criteria for ODD. Significant interactions between treatment conditions (NFPP vs. HNC) and child ODD diagnosis (presence vs. absence) indicated that based on some parent and teacher reports, HNC was more effective with disruptive behaviors than NFPP but only when children had a comorbid diagnosis. Further, based on teacher report, NFPP was more effective with these behaviors when children had a diagnosis of only ADHD whereas HNC was equally effective across ADHD only and comorbid ODD diagnoses. Comorbidity profile did not interact with treatment program when parent or teacher reported ADHD symptoms served as the outcome. Implications for clinical interventions are discussed and directions for future work are provided

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J Abnorm Child Psychol. 2016 Nov;44:1487-501.

DOES THE ENVIRONMENT HAVE AN ENDURING EFFECT ON ADHD? A LONGITUDINAL STUDY OF MONOZYGOTIC TWIN DIFFERENCES IN CHILDREN.

Livingstone LT, Coventry WL, Corley RP, et al.

Environmental factors play a key role in the development of Attention-Deficit/Hyperactivity Disorder (ADHD), but the long-term effects of these factors are still unclear. This study analyses data from 1024 monozygotic (identical) twins in Australia, the United States, and Scandinavia who were assessed for ADHD in Preschool, Kindergarten, Grade 1, and Grade 2. Differences within each twin pair were used as a direct measure of non-shared environmental effects. The Trait-State-Occasion (TSO) model developed by Cole et al. (Psychological Methods, 10, 3–20, 2005) was used to separate the non-shared environmental effects into stable factors, and transient factors that excluded measurement error. Stable factors explained, on average, 44 % and 39 % of the environmental variance in hyperactive-impulsive and inattentive symptoms, respectively. Transient effects explained the remaining 56 % and 60 % of variance. The proportion of stable variance was higher than expected based on previous research, suggesting promise for targeted interventions if future research identifies these stable risk factors

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J Abnorm Child Psychol. 2016 Nov;44:1455-71.

PRESCHOOL NEUROPSYCHOLOGICAL MEASURES AS PREDICTORS OF LATER ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Breaux RP, Griffith SF, Harvey EA.

The present study examined preschool neuropsychological measures as predictors of school-age attention deficit hyperactivity disorder (ADHD). Participants included 168 children (91 males) who completed neuropsychological measures at ages 3 and 4, and who were evaluated for ADHD and oppositional defiant disorder at age 6. The Conners' Kiddie Continuous Performance Test (K-CPT), NEPSY Statue subtest, and a delay aversion task significantly distinguished at-risk children who later did and did not meet criteria for ADHD, with poor to fair overall predictive power, specificity, and sensitivity. However, only the K-CPT ADHD Confidence Index and battery added incremental predictive validity beyond early ADHD symptoms. This battery approach, which required impairment on at least 2 of the 3 significant measures, yielded fair overall predictive power, specificity, and sensitivity, and correctly classified 67 % of children. In addition, there was some support for the specificity hypothesis, with evidence that cool executive function measures (K-CPT and Statue subtest) tended to predict inattentive symptoms. These findings suggest that neuropsychological deficits are evident by preschool-age in children with ADHD, but neuropsychological tests may still misclassify approximately one-third of children if used alone. Thus, neuropsychological measures may be a useful component of early ADHD assessments, but should be used with caution and in combination with other assessment methods

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J Abnorm Child Psychol. 2016 Nov;44:1473-85.

PRE- AND PERINATAL RISK FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER: DOES NEUROPSYCHOLOGICAL WEAKNESS EXPLAIN THE LINK?

Wiggs K, Elmore AL, Nigg JT, et al.

Etiological investigations of attention-deficit hyperactivity disorder (ADHD) and disruptive behavior problems support multiple causal pathways, including involvement of pre- and perinatal risk factors. Because these risks occur early in life, well before observable ADHD and externalizing symptoms emerge, the relation between risk and symptoms may be mediated by neurodevelopmental effects that manifest later in neuropsychological functioning. However, potential dissociable effects of pre/perinatal risk elements on ADHD and familial confounds must also be considered to test alternative hypotheses. 498 youth aged 6–17 years (55.0 % male) completed a multi-stage, multi-informant assessment including parent and teacher symptom reports of symptoms and parent ratings of pre/perinatal health risk indicators. Youth completed a neuropsychological testing battery. Multiple mediation models examined direct effects of pre- and perinatal health risk on ADHD and other disruptive behavior disorder symptoms and indirect effects via neuropsychological functioning. Parental ADHD symptoms and externalizing status was covaried to control for potential familial effects. Effects of prenatal substance exposure on inattention were mediated by memory span and temporal processing deficits. Further, effects of perinatal health risk on inattention, hyperactivity-impulsivity, and ODD were mediated by deficits in response variability and temporal processing. Further, maternal health risks during pregnancy appeared to exert direct rather than indirect effects on outcomes. Results suggest that after controlling for familial relatedness of ADHD between parent and child, early developmental health risks may influence ADHD via effects on neuropsychological processes underpinning the disorder

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J Adolesc. 2016;53:222-30.

ACUTE EFFECTS OF METHYLPHENIDATE ON IMPULSIVITY AND ATTENTIONAL BEHAVIOR AMONG ADOLESCENTS COMORBID FOR ADHD AND CONDUCT DISORDER.

Dougherty DM, Olvera RL, Acheson A, et al.

Adolescents with Attention Deficit Hyperactivity Disorder (ADHD) and Conduct Disorder (CD) experience deficits in neuropsychological measures of attention, inhibition, and reward processes. Methylphenidate treatment for ADHD and CD has acute effects on these processes. Some of these same aspects of performance are separately described in the Behavioral Model of Impulsivity, which uses a modified approach to measurement. This study characterized the acute effects of methylphenidate attention, initiation, inhibition, and reward processes described in this model of impulsivity. Thirty-one adolescents from the United States of America with comorbid ADHD and CD completed measures of impulsivity (response initiation, response inhibition, and consequence) and attention following placebo, 20-ámg, and 40-ámg of a long-acting dose of methylphenidate. Methylphenidate effects on attentional performance was more robust than on any of the measures of impulsivity. Adolescent performance from this behavioral perspective is interpreted in the context of divergence from previous neuropsychological tests of acute methylphenidate effects

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J Atten Disord. 2016 Nov;20:968-78.

GAMBLING, DELAY, AND PROBABILITY DISCOUNTING IN ADULTS WITH AND WITHOUT ADHD.

Dai Z, Harrow SE, Song X, et al.

Objective: We investigated the relationship between impulsivity, as measured by delay and probability discounting, and gambling-related cognitions and behavior in adults with and without ADHD.

Method: Adults who met Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) diagnostic criteria for ADHD (n = 31) and controls (n = 29) were recruited from the community. All completed an interview that included an assessment of psychiatric disorders, gambling questionnaires, and simulated gambling, delay, and probability discounting tasks.

Results: The ADHD group was more likely to meet the criteria for problem gambling and was more impulsive than controls based on a composite discounting measure. ADHD symptoms were correlated with gambling-related cognitions and behavior. Probability, but not delay discounting, explained significant variance in gambling-related measures after controlling for ADHD symptoms.

Discussion: Results confirm an association between adult ADHD and gambling, and suggest that the facets of impulsivity related to risk proneness may be an independent risk factor for problem gambling in this population

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J Atten Disord. 2016 Nov;20:946-57.

ATTENTION PROBLEMS AND ACADEMIC ACHIEVEMENT: DO PERSISTENT AND EARLIER-EMERGING PROBLEMS HAVE MORE ADVERSE LONG-TERM EFFECTS?

Rabiner DL, Carrig MM, Dodge KA.

Objective: This study examined whether the negative association between children's attention difficulties and their academic functioning is largely confined to children whose attention problems persist across early grades and whether it depends on when attention problems emerge in children's schooling.

Method: Children from the normative sample of the Fast Track study were classified into four attention problem groups based on the presence versus absence of attention problems in first and second grade.

Results: Those with attention problems in both grades showed a decline in reading and math achievement during the K-5 interval relative to children with attention problems in first grade only. Both groups of inattentive first graders also performed worse than comparison children. In contrast, children whose attention problems emerged in second grade did not differ from comparison children on any achievement outcome performed significantly better than inattentive first graders.

Conclusion: The implications of these findings are discussed

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J Atten Disord. 2016 Nov;20:913-24.

NEUROPSYCHOLOGICAL PROFILES ON THE WAIS-IV OF ADULTS WITH ADHD.

Theiling J, Petermann F.

Objective: The aim of the study was to investigate the pattern of neuropsychological profiles on the Wechsler Adult Intelligence Scale–IV (WAIS-IV) for adults With ADHD relative to randomly matched controls and to assess overall intellectual ability discrepancies of the Full Scale Intelligence Quotient (FSIQ) and the General Ability Index (GAI).

Method: In all, 116 adults With ADHD and 116 controls between 16 and 71 years were assessed.

Results: Relative to controls, adults With ADHD show significant decrements in subtests with working memory and processing speed demands with moderate to large effect sizes and a higher GAI in comparison with the FSIQ.

Conclusion: This suggests first that deficits identified with previous WAIS versions are robust in adults With ADHD and remain deficient when assessed with the WAIS-IV; second that the WAIS-IV reliably differentiates between patients and controls; and third that a reduction of the FSIQ is most likely due to a decrement in working memory and processing speed abilities. The findings have essential implications for the diagnostic process

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J Child Adolesc Psychopharmacol. 2016 Sep;26:658-59.

PAINFUL MUSCLE CRAMPS POSSIBLY ASSOCIATED WITH WITHDRAWAL FROM METHYLPHENIDATE.

Coskun M, Kaya I.

Presents a case report of a female subject with attention-deficit/ hyperactivity disorder (ADHD) who developed painful muscle cramps in her legs associated with withdrawal from IR methylphenidate (MPH). A 13-year-old girl with a normal developmental history and intellectual capacity had been followed-up with diagnoses of ADHD, anxiety disorders and obsessive compulsive disorders (OCD) since she was 6 years of age. MPH has been the first line psychopharmacological treatment in children and adolescents with ADHD, and results in significant improvement in 70–80% of affected children. Regardless of the underlying pathophysiological mechanisms, such an unusual side effect may pose significant distress to subjects and parents, and complicate treatment compliance. Clinicians treating children with ADHD should be familiar with rare side effects associated with MPH treatment

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J Child Psychol Psychiatry. 2016 Nov;57:1218-26.

A RANDOMIZED CONTROLLED TRIAL OF COGNITIVE BEHAVIORAL THERAPY FOR ADHD IN MEDICATION-TREATED ADOLESCENTS.

Sprich SE, Safren SA, Finkelstein D, et al.

Objective: To test cognitive behavioral therapy (CBT) for persistent attention-deficit hyperactivity disorder (ADHD) symptoms in a sample of medication-treated adolescents.

Methods: Forty-six adolescents (ages 14–18), with clinically significant ADHD symptoms despite stable medication treatment were randomly assigned to receive CBT for ADHD or wait list control in a cross-over design. Twenty-four were randomized to CBT, 22 to wait list, and 15 crossed-over from wait list to CBT. A blind independent evaluator (IE) rated symptom severity on the ADHD Current Symptom Scale, by adolescent and parent report, and rated each subject using the Clinical Global Impression Severity Scale (CGI), a global measure of distress and impairment. These assessments were performed at baseline, 4-months (post-CBT or post wait list), and 8-months (post-treatment for those originally assigned to the wait list condition and 4-month follow-up for those originally assigned to CBT).

Trial Registration: http://clinicaltrials.gov/show/NCT01019252.

Results: Using all available data, mixed effects modeling, and pooling for the wait list cross-over, participants who received CBT received a mean score 10.93 lower on the IE-rated parent assessment of symptom severity (95% CI: -12.93, -8.93; p < .0001), 5.24 lower on the IE-rated adolescent assessment of symptom severity (95% CI: -7.21, -3.28; p < .0001), and 1.17 lower IE-rated CGI (95% CI: -1.39, -.94; p < .0001). Results were consistent across 100 multiple imputations (all p < .0001). There was a greater proportion of responders after CBT by parent (50% vs. 18%, p = .00) and adolescent (58% vs. 18% p = .02) report.
Conclusions: This study demonstrates initial efficacy of CBT for adolescents with ADHD who continued to exhibit persistent symptoms despite medications

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J Child Psychol Psychiatry. 2016 Nov;57:1268-76.

COMMON INFECTIONS WITH POLYOMAVIRUSES AND HERPESVIRUSES AND NEUROPSYCHOLOGICAL DEVELOPMENT AT 4 YEARS OF AGE, THE RHEA BIRTH COHORT IN CRETE, GREECE.

Karachaliou M, Chatzi L, Roumeliotaki T, et al.

Background: Viral infections of the central nervous system may have detrimental effects for the developing brain, but the effects of less virulent common infections are unclear. We aim to investigate the impact of common viral infections of early childhood on neuropsychological performance of children at age four.
Methods: We used cross-sectional data on 674 children participating at the 4 years of age follow-up of the Rhea birth cohort in Crete, Greece. Blood levels of IgG antibodies to 10 polyomaviruses (BKPyV, JCPyV, KIPyV, WUPyV, HPyV6, HPyV7, TSPyV, MCPyV, HPyV9, and HPyV10) and four herpesviruses [Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), and herpes simplex virus-2 (HSV-2)] were measured using multiplex serology. Child's neuropsychological development at age four was assessed using the McCarthy Scales of Children's Abilities, the Attention-Deficit Hyperactivity Disorder Test (ADHDT), and the Strengths and Difficulties Questionnaire (SDQ). Multiple linear regression models were used to explore the associations.
Results: Seroprevalence to polyomaviruses ranged from 21% for HPyV9 to 82% for HPyV10. Seroprevalence for EBV was 53%, for CMV 26%, for HSV-1 3.6%, and for HSV-2 1.5%. Children seropositive to =8 polyomaviruses had lower score in ADHDT inattention subscale [ß = -1.28 (95% CI: -2.56, -0.001)] and lower score in SDQ hyperactivity–inattention subscale [ß = -.99 (95% CI: -1.60, -0.37)] versus children seropositive to =3 polyomaviruses. Seropositivity to BKPyV, a potential neurotropic virus, was associated with higher score in ADHDT inattention subscale [ß = .87 (95% CI: 0.03, 1.71)].
Conclusions: These findings suggest that acquisition of polyomaviruses during development may influence behavioral outcomes in early childhood

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J Clin Psychiatry. 2016;77:e1270-e1277.

BEHAVIORAL EFFECTS OF NEUROFEEDBACK COMPARED TO STIMULANTS AND PHYSICAL ACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RANDOMIZED CONTROLLED TRIAL.

Geladé K, Janssen TWP, Bink M, et al.

Objective: The efficacy of neurofeedback as a treatment for attention-deficit/hyperactivity disorder (ADHD), and whether neurofeedback is a viable alternative for stimulant medication, is still an intensely debated subject. The current randomized controlled trial compared neurofeedback to (1) optimally titrated methylphenidate and (2) a semi-active control intervention, physical activity, to account for nonspecific effects.
Methods: A multicenter 3-way parallel-group study with balanced randomization was conducted. Children with a DSMIV- TR diagnosis of ADHD, aged 7.13 years, were randomly allocated to receive neurofeedback (n = 39), methylphenidate (n = 36), or physical activity (n = 37) over a period of 10.12 weeks. Neurofeedback comprised theta/beta training on the vertex (Cz). Physical activity consisted of moderate to vigorous intensity exercises. Neurofeedback and physical activity were balanced in terms of number (~30) and duration of sessions. A double-blind pseudorandomized placebo-controlled crossover titration procedure was used to determine an optimal dose in the methylphenidate intervention. Parent and teacher ratings on the Strengths

and Difficulties Questionnaire (SDQ) and Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) were used to assess intervention outcomes. Data collection took place between September 2010 and March 2014.
Results: Intention-to-treat analyses revealed an improvement in parent-reported behavior on the SDQ and the SWAN Hyperactivity/Impulsivity scale, irrespective of received intervention (+¢p2 = 0.21.0.22, P .001), whereas the SWAN Inattention scale revealed more improvement in children who received methylphenidate than neurofeedback and physical activity (+¢p2 = 0.13, P .001). Teachers reported a decrease of ADHD symptoms on all measures for methylphenidate, but not for neurofeedback or physical activity (range of +¢p2 = 0.14.0.29, P < .001).
Conclusions: The current study found that optimally titrated methylphenidate is superior to neurofeedback and physical activity in decreasing ADHD symptoms in children with ADHD. Trial Registration: ClinicalTrials.gov identifier: NCT01363544

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Journal of Learning Disabilities. 2016 Nov;49:597-615.
PERCEIVED CLOSE RELATIONSHIPS WITH PARENTS, TEACHERS, AND PEERS: PREDICTORS OF SOCIAL, EMOTIONAL, AND BEHAVIORAL FEATURES IN ADOLESCENTS WITH LD OR COMORBID LD AND ADHD.
Al-Yagon M.
This study examined the role of adolescents' perceived close relationships with significant others (attachment relationships with mothers/fathers, appraisal of homeroom teacher as secure base, and quality of peer friendship) in explaining differences in their socioemotional and behavioral functioning (peer-network/peer-dyadic loneliness, positive/negative affect, and externalizing/internalizing problems), among adolescents with learning disabilities (LD), with comorbid LD and attention-deficit/hyperactivity disorder (ADHD), or with typical development (TD). Participants were 280 adolescents in Grades 10 through 11 in three groups: LD (n = 90), comorbid LD and ADHD (n = 91), and TD (n = 98). Preliminary analyses yielded significant group differences on most socioemotional and behavioral measures. Structural equation modeling (SEM) analysis indicated high fit between the theoretical model and empirical findings and partially different patterns of relationships among the model's components for the three populations. The discussion focuses on the possible unique value of close relationships with each significant attachment figure for adolescents with LD, comorbid LD–ADHD, and TD

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Journal of Learning Disabilities. 2016 Nov;49:563-66.
SPECIAL ISSUE INTRODUCTION: ADOLESCENTS AND YOUNG ADULTS WITH LD AND/OR ADHD—THEORETICAL, EMPIRICAL, AND PRACTICAL PERSPECTIVES.
Al-Yagon M.
The series of articles presented in this special issue focus on investigating two highly relevant objectives for adolescents and young adults with learning disabilities and/or attention-deficit/hyperactivity disorder: (a) examination of neuropsychological, educational, familial, and socioemotional features among individuals with these disabilities, in the adolescence and young adulthood developmental phases, and (b) exploration of specific dimensions of interventional programs and contextual (e.g., class) environments aiming to enhance these youngsters' academic achievements. Corresponding with these objectives, the six studies in this special issue provide new evidence regarding these two major topics, utilizing mixed qualitative and quantitative data analysis methods

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Journal of Learning Disabilities. 2016 Nov;49:582-96.

ATTENTION FUNCTIONING AMONG ADOLESCENTS WITH MULTIPLE LEARNING, ATTENTIONAL, BEHAVIORAL, AND EMOTIONAL DIFFICULTIES.

Shalev L, Kolodny T, Shalev N, et al.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by high levels of inattention, hyperactivity, and impulsivity; however, these symptoms can result from a variety of reasons. To obtain a comprehensive understanding of the various difficulties of individuals with ADHD, especially when co-occurrence difficulties are present, it is essential to combine neuropsychological and subjective assessment tools. In the present field study the authors investigated a group of adolescents with multiple deficits (MD) using neuropsychological and subjective measures. Teachers' ratings verified extremely high levels of symptoms of oppositional behavior, inattention, hyperactivity-impulsivity, social problems, and emotional problems in this group. As expected, MD group participants showed decreased abilities to maintain attention on task for a long period of time, focus attention and effectively inhibit adjacent distractors, and resist conflicting irrelevant information. Importantly, although significant differences in the attention measures were observed at the group level, not all MD participants displayed deviant performance. Thus, we conclude that the heterogeneous group of adolescents with MD comprises individuals with primary attention deficits as well as those with other nonattentional deficits that show equivalent behavioral symptoms. Using neuropsychological tools can be useful in differentiating between different core deficits and in guiding appropriate interventions.

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Journal of Learning Disabilities. 2016 Nov;49:567-81.

SCHOOL EXPERIENCES OF ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wiener J, Daniels L.

This article reports on a qualitative study of the school experiences of adolescents with attention-deficit/hyperactivity disorder (ADHD) in the context of quantitative research on teacher attitudes and practices, adolescent self-appraisals, and social and family relationships. Twelve adolescents with ADHD participated in in-depth, semistructured interviews addressing major aspects of school life. Using a modified grounded theory framework, researchers coded these interviews. Three themes emerged: (a) support for a performance deficit, (b) academic and social engagement, and (c) moving from dependence to independence. What is most striking is the low level of agency students demonstrated; that is, rather than acting with purpose on their environments, they seemed to react to things that happened to them. These findings suggest that teachers of adolescents with ADHD know about the nature of the disorder, understand that students' difficulties with organization and academic performance are not typically intentional, use evidence-based interventions to support students, and provide the monitoring and scaffolding needed for academic achievement. The students also provide specific suggestions for parents and peers regarding the supports they need to be successful

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J Neural Transm. 2016;1-12.

TRANSCRANIAL DIRECT CURRENT STIMULATION IMPROVES CLINICAL SYMPTOMS IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Soff C, Sotnikova A, Christiansen H, et al.

Anodal transcranial direct current stimulation (tDCS) of the prefrontal cortex has repeatedly been shown to improve working memory. As patients with attention deficit hyperactivity disorder (ADHD) are characterized by both underactivation of the prefrontal cortex and deficits in working memory that correlate with clinical symptoms, it is hypothesized that the modulation of prefrontal activity with tDCS in patients with ADHD increases performance in working memory and reduces symptoms of ADHD. To test this hypothesis, fifteen adolescents with ADHD (12ΓÇô16 years old, three girls and 12 boys) were treated according to the randomized, double-blinded, sham-controlled, crossover design with either 1 mA anodal tDCS over the left dorsolateral prefrontal cortex or with the sham protocol 5 days each with a 2 weeks pause between these conditions. Anodal tDCS caused a significant reduction in clinical symptoms of inattention and impulsivity in

adolescents with ADHD compared to sham stimulation. The clinical effects were supported by a significant reduction in inattention and hyperactivity in a standardized working memory test (QbTest). The described effects were more pronounced 7 days after the end of stimulation, a fact which emphasizes the long-lasting clinical and neuropsychological changes after tDCS. This study provides the first evidence that tDCS may reduce symptoms of ADHD and improve neuropsychological functioning in adolescents and points on the potential of tDCS as a form of treatment for ADHD

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J Pediatr. 2016.

CHEMICAL LEUKODERMA ASSOCIATED WITH METHYLPHENIDATE TRANSDERMAL SYSTEM: DATA FROM THE US FOOD AND DRUG ADMINISTRATION ADVERSE EVENT REPORTING SYSTEM.

Cheng C, La Grenade L, Diak IL, et al.

Objective: To identify and characterize cases of chemical leukoderma, an underrecognized adverse event, associated with the methylphenidate transdermal system (MTS) reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS).

Study design: We searched the Food and Drug Administration Adverse Event Reporting System for reports of chemical leukoderma associated with MTS, received by the Food and Drug Administration from April 6, 2006 to December 23, 2014.

Results: We identified 51 cases of chemical leukoderma reported with the use of MTS. The median age was 11 years; 43 cases reported leukoderma at or near the application site only, and 7 reported leukoderma at other parts of the body in addition to the application site; 1 case did not provide enough information to confirm the affected site. The time to onset ranged from 2 months to 4 years after the initiation of MTS. MTS was discontinued in 31 cases. Thirteen patients were prescribed treatment for repigmentation. Three cases reported continued spread of leukoderma after MTS was discontinued. Nineteen cases were diagnosed as vitiligo, including 5 cases reporting histologic features consistent with vitiligo. Leukoderma was persistent in all cases. The median follow-up interval after the discontinuation of MTS in 23 cases was 14 months.

Conclusions: As outlined in recent changes to the prescribing information for MTS, health care professionals need to be aware of the potential risk of chemical leukoderma caused by MTS, especially given that chemical leukoderma is often misdiagnosed as idiopathic vitiligo. MTS should be discontinued at the earliest sign of pigment loss and other treatment options considered

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J Psychiatr Res. 2016 Nov;82:126-35.

PRE- AND PERINATAL COMPLICATIONS IN RELATION TO TOURETTE SYNDROME AND CO-OCCURRING OBSESSIVE-COMPULSIVE DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Abdulkadir M, Tischfield JA, King RA, et al.

Pre- and perinatal complications have been implicated in the onset and clinical expression of Tourette syndrome albeit with considerable inconsistencies across studies. Also, little is known about their role in co-occurring obsessive-compulsive disorder (OCD) and attention–deficit/hyperactivity disorder (ADHD) in individuals with a tic disorder. Therefore, we aimed to investigate the role of pre- and perinatal complications in relation to the presence and symptom severity of chronic tic disorder and co-occurring OCD and ADHD using data of 1113 participants from the Tourette International Collaborative Genetics study. This study included 586 participants with a chronic tic disorder and 527 unaffected family controls. We controlled for age and sex differences by creating propensity score matched subsamples for both case-control and within-case analyses. We found that premature birth (OR = 1.72) and morning sickness requiring medical attention (OR = 2.57) were associated with the presence of a chronic tic disorder. Also, the total number of pre- and perinatal complications was higher in those with a tic disorder (OR = 1.07). Furthermore, neonatal complications were related to the presence (OR = 1.46) and severity (b = 2.27) of co-occurring OCD and also to ADHD severity (b = 1.09). Delivery complications were only related to co-occurring OCD (OR = 1.49). We conclude that early exposure to adverse situations during pregnancy is related to the presence of chronic

tic disorders. Exposure at a later stage, at birth or during the first weeks of life, appears to be associated with co-occurring OCD and ADHD. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

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Journal of Psychiatry & Neuroscience. 2016 Nov;41:405-12.

COMT AND DAT1 GENES ARE ASSOCIATED WITH HYPERACTIVITY AND INATTENTION TRAITS IN THE 1993 PELOTAS BIRTH COHORT: EVIDENCE OF SEX-SPECIFIC COMBINED EFFECT.

Akutagava-Martins GC, Salatino-Oliveira A, Kieling C, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) symptoms are dimensionally distributed in the population. This study aimed to assess the role of the catechol-O-methyltransferase (COMT) and of the dopamine transporter (DAT1) genes on ADHD symptoms in the general population.

Methods: We investigated 4101 individuals from the 1993 Pelotas Birth Cohort Study using the parent version of the Strengths and Difficulties Questionnaire (SDQ) at ages 11 and 15 years. The SDQ hyperactivity/inattention scores were the main outcomes.

Results: Linear regression analyses demonstrated that the increasing number of COMT¹58Val and DAT1 10R alleles significantly predicted increasing SDQ hyperactivity/inattention scores in boys at both 11 and 15 years of age (ß coefficient = 0.049, t = 2.189, p = 0.029, R^2 = 0.012, and ß coefficient = 0.064, t = 2.832, p = 0.005, R2 = 0.008, respectively). The presence of both COMT¹58Val and DAT1 10R alleles was also associated with full categorical ADHD diagnosis at 18 years of age in boys (?² = 4.561, p = 0.033, odds ratio 2.473, 95% confidence interval 1.048–5.838) from this cohort. We did not observe these associations in girls.

Limitations: Our analyses of SDQ hyperactivity/inattention scores were not corrected for SDQ scores of conduct problems because these variables were highly correlated.

Conclusion: This study demonstrates a role for COMT and DAT1 genes on hyperactivity/inattention symptoms and provides further support for ADHD as the extreme of traits that vary in the population. It also confirms previous evidence for sexual dimorphism on COMT and DAT1 gene expression

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J Shanghai Jiaotong Univ Med Sci. 2016;36:1191-95.

ANALYSIS OF RISK FACTORS FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN PUPILS.

Liu X, Ji YT, Li SH, et al.

Objective: To explore the prevalence of attention-deficit/hyperactivity disorder (ADHD) in different grades of pupils and analyze the risk factors for ADHD in school-aged children.

Methods: The diagnosis history of ADHD and general information of children in nine cities such as Shanghai, Guangzhou, Xi'an, etc. were collected from their parents by questionnaires with the use of cluster-stratified method. Six grades in primary schools were assigned to 3 groups, i.e. the grade 1 and 2 group, grade 3 and 4 group, and grade 5 and 6 group. Prevalence of ADHD in 3 groups and differences in study pressure between children with and without ADHD and in prevalence of ADHD between children with different enrollment ages were calculated. Risk factors related to the prevalence of ADHD were analyzed by Logistic regression model.

Results: The difference in the prevalence of ADHD between three groups were statistically significant (P<0.05). The prevalence of ADHD in the grade 3 and 4 group was the highest (5.2%). Grade 3 and 4, earlier school enrollment, and study pressure were risk factors for the prevalence of ADHD after adjustment of sex, education of parents, delivery method, etc.

Conclusion: Grade 3 and 4, earlier school enrollment (<6 years of age), and study pressure increase the risk of ADH in pupils

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J Am Acad Child Adolesc Psychiatry. 2016 Nov;55:931-36.

CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND HOMELESSNESS: A 33-YEAR FOLLOW-UP STUDY.

García Murillo L, Ramos-Olazagasti MA, Mannuzza S, et al.

Objective: To examine whether childhood attention-deficit/hyperactivity disorder (ADHD) predicts homelessness in adulthood, and whether the persistence of childhood ADHD through adolescence influences the likelihood of homelessness.

Method: A 33-year prospective, controlled, follow-up was performed of clinic-referred, 6- to 12-year-old boys of white ethnicity with ADHD (probands; mean = 8), at a mean age of 41 years (follow-up [FU] = 41). Comparisons, children without ADHD from the same medical center, were matched for age and socioeconomic status (SES). Both groups were evaluated at a mean age of 18 years (FU18). Homelessness was assessed at FU41 in 134 of 207 probands (65%) and 136 of 178 (76%) comparisons. We tested the following: the relationship between childhood ADHD and homelessness; whether adolescent dysfunctions (conduct disorder, non-alcohol substance use disorder, arrests, and school dropout) accounted for this relationship, if found; and whether ADHD that persisted through FU18 elevated probands' homelessness rate.

Results: Probands had significantly higher rates of homelessness than comparisons (23.7% vs. 4.4%; ?²1 = 21.15, df = 1, p < .001). In a multivariate analysis, including childhood ADHD and covariates, the probands' significant elevation of homelessness remained (odds ratio [OR] = 3.60, 95% CI = 1.32–9.76, p = .01). Probands with persistent ADHD through adolescence had significantly more homelessness than remitted probands (?²1 = 12.73, p < .001), but this relationship was no longer significant when conduct disorder at FU18 was controlled (OR = 1.97, 95% CI = 0.89–4.38, p = .09).

Conclusion: Among boys of white ethnicity who were followed into adulthood, childhood ADHD was associated with an elevated rate of homelessness. Findings point to the need for clinical monitoring of childhood ADHD through adolescence, even when ADHD does not persist, in hopes of mitigating a cascade of malfunction that includes homelessness. (PsycINFO Database Record (c) 2016 APA, all rights reserved)

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J Am Acad Child Adolesc Psychiatry. 2016 Nov;55:937-44.

CHILDHOOD FACTORS AFFECTING PERSISTENCE AND DESISTENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN ADULTHOOD: RESULTS FROM THE MTA.

Roy A, Hechtman L, Arnold LE, et al.

Objective: To determine childhood factors that predict attention-deficit/hyperactivity disorder (ADHD) persistence and desistence in adulthood.

Method: Regression analyses were used to determine associations between childhood factors and adult ADHD symptom persistence in 453 participants (mean age, 25 years) from the Multimodal Treatment Study of Children with ADHD (MTA). Childhood IQ, total number of comorbidities, child-perceived parenting practices, child-perceived parent-child relationships, parental mental health problems, marital problems of parents, household income levels, and parental education were assessed at a mean age of 8 years in all participants. Adult ADHD persistence was defined using DSM-5 symptom counts either with or without impairment, as well as mean ADHD symptom scores on the Conners' Adult ADHD Rating Scale (CAARS). Age, sex, MTA site, and childhood ADHD symptoms were covaried.

Results: The most important childhood predictors of adult ADHD symptom persistence were initial ADHD symptom severity (odds ratio [OR] = 1.89, standard error [SE] = 0.28, p = .025), comorbidities (OR = 1.19, SE = 0.07, p = .018), and parental mental health problems (OR = 1.30, SE = 0.09, p = .003). Childhood IQ, socioeconomic status, parental education, and parent-child relationships showed no associations with adult ADHD symptom persistence.

Conclusion: Initial ADHD symptom severity, parental mental health, and childhood comorbidity affect persistence of ADHD symptoms into adulthood. Addressing these areas early may assist in reducing adult ADHD persistence and functioning problems

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J Am Acad Child Adolesc Psychiatry. 2016;55:674-82.

EFFECTS OF D-METHYLPHENIDATE, GUANFACINE, AND THEIR COMBINATION ON ELECTROENCEPHALOGRAM RESTING STATE SPECTRAL POWER IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Loo SK, Bilder RM, Cho AL, et al.

Objective Psychostimulant medications are the gold standard of treatment for attention-deficit/hyperactivity disorder (ADHD); however, a significant minority (Γê+30%) of individuals with ADHD fail to respond favorably. Noradrenergic agents are increasingly used as ADHD monotherapies or adjuncts for suboptimal stimulant response, yet knowledge of their cortical effects is limited. This study is the first to examine comparative effects of guanfacine (an +¦ adrenergic 2A agonist), psychostimulant, and their combination on resting state cortical activity in ADHD.

Method The sample comprised 179 participants aged 7 to 14 years old with ADHD (113 boys, 55 girls). Participants were randomized to 1 of 3 blinded conditions: guanfacine (GUAN), d-methylphenidate (DMPH), or the combination (COMB). Electroencephalography (EEG) was performed pre, mid, and post medication titration, with concomitant assessment of behavioral and cognitive functioning.

Results Analyses of spectral power measures during resting EEG suggested that each medication condition displayed a distinct profile of effects on cortical activity. Significant time effects suggested that GUAN decreased global alpha band (8–12 hertz [Hz]) power, DMPH and COMB increased centro-parietal beta band (13Γê Æ21 Hz) power, and COMB resulted in decreased theta band (4–7 Hz) power. Relative to other medication groups, COMB was associated with significantly lower theta band power and DMPH with higher beta band power compared with those in the GUAN group. Medication-related changes in theta power were correlated with improvements in behavioral and cognitive functioning.

Conclusion These data reveal distinct underlying medication-related effects on neural mechanisms. The COMB condition uniquely exhibited an EEG profile that was associated with improved behavioral and cognitive functioning. Clinical trial registration information' Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder; http://clinicaltrials.gov/; NCT00429273

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J Am Acad Child Adolesc Psychiatry. 2016;55:667-73.

COGNITIVE EFFECTS OF STIMULANT, GUANFACINE, AND COMBINED TREATMENT IN CHILD AND ADOLESCENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Bilder RM, Loo SK, McGough JJ, et al.

OBJECTIVE: Psychostimulants are partially effective in reducing cognitive dysfunction associated with attention-deficit/hyperactivity disorder (ADHD). Cognitive effects of guanfacine, an alternative treatment, are poorly understood. Given its distinct action on α2A receptors, guanfacine may have different or complementary effects relative to stimulants. This study tested stimulant and guanfacine monotherapies relative to combined treatment on cognitive functions important in ADHD.

METHOD: Children with ADHD (n = 182; aged 7-14 years) completed an 8-week, double blind, randomized, controlled trial with 3 arms: d-methylphenidate (DMPH), guanfacine (GUAN), or combination treatment with DMPH and GUAN (COMB). A nonclinical comparison group (n = 93) had baseline testing, and a subset was retested 8 weeks later (n = 38). Analyses examined treatment effects in 4 cognitive domains (working memory, response inhibition, reaction time, and reaction time variability) constructed from 20 variables.

RESULTS: The ADHD group showed impaired working memory relative to the nonclinical comparison group (effect size = -0.53 SD unit). The treatments differed in effects on working memory but not other cognitive domains. Combination treatment improved working memory more than GUAN but was not significantly better than DMPH alone. Treatment did not fully normalize the initial deficit in ADHD relative to the comparison group.

CONCLUSION: Combined treatment with DMPH and GUAN yielded greater improvements in working memory than placebo or GUAN alone, but the combined treatment was not superior to DMPH alone and did not extend to other cognitive domains. Although GUAN may be a useful add-on treatment to psychostimulants, additional strategies appear to be necessary to achieve normalization of cognitive function in ADHD.

CLINICAL TRIAL REGISTRATION INFORMATION: Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder; http://clinicaltrials.gov/; NCT00429273.

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Laryngoscope. 2016.

GRADE REPETITION AND PARENTS' PERCEPTION OF HEARING LOSS: AN ANALYSIS OF DATA FROM CHILDREN IN THE UNITED STATES.

Gilani S, Roditi R, Bhattacharyya N.

Objectives/Hypothesis: To determine whether parent-perceived hearing problems are associated with grade repetition among children in the United States.

Study Design: Retrospective cohort analysis of a contemporary national database.

Methods: The National Survey of Children's Health 2011 to 2012 was analyzed. Hearing loss, as perceived and reported by parents, was categorized as: no hearing problem, history of a hearing problem, or current hearing problem. Children never repeating a grade versus repeating one or more grades (kindergarten-high school) were identified. Univariate statistics and multivariate logistic regression analyzed the association of hearing problems with grade repetition. Patients with mental retardation, autism, and attention-deficit/hyperactivity disorder were excluded from the analysis. After adjusting for race, sex, and poverty level, odds ratios for grade repetition were computed.

Results: Among 66.1 million (average age, 8.3 years, 49.0% male) children, 97.3% never had a hearing problem, 1.7% had a history of a hearing problem, and 1.0% had a current hearing problem. Overall, 7.1% repeated a grade. Grade repetition was reported in 6.9% of children without a hearing problem versus 9.4% with a history of a hearing problem and 19.3% with a current hearing problem ($P < 0.001$). After adjustment for race, poverty level, and sex, a history of a hearing problem demonstrated an odds ratio of 1.9 (95% confidence interval 0.82-4.13) for grade repetition, whereas a current hearing problem demonstrated an odds ratio of 3.0 (1.90-4.80).

Conclusion: Parents' perception of children's hearing problems is strongly associated with grade repetition. This trend is noticed in elementary school more than in high school

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Law Hum Behav. 2015 Apr;39:198-207.

THE DSM-5 WITH LIMITED PROSOCIAL EMOTIONS SPECIFIER FOR CONDUCT DISORDER AMONG DETAINED GIRLS.

Colins OF, Andershed H.

The new DSM-5 specifier 'with Limited Prosocial Emotions' (LPE) is expected to provide greater information about impairment of children and adolescents with conduct disorder (CD). This study examined the clinical utility of the LPE specifier symptom threshold among female adolescents being detained in Belgium (n = 191 girls; ages 12-17). Standardized questionnaires and a structured diagnostic interview were used to assess the LPE specifier, CD, and variables of interest. Approximately 62% (n = 118) of the girls met criteria for CD. Depending on the instrument that was used to assess the LPE specifier criteria, 26% to 37% of the girls with CD met criteria for the LPE specifier symptom threshold (CD + LPE). Overall, CD + LPE girls were not significantly different from CD-only girls regarding psychiatric morbidity (i.e., attention-deficit/hyperactivity disorder, oppositional defiant disorder, substance use disorder, major depression, and anxiety disorders). However, CD + LPE girls were more aggressive, rule-breaking, delinquent, and had higher levels of psychopathic traits than CD-only girls. This study supports the view that the LPE specifier identifies a group of seriously antisocial individuals, but could not replicate previous findings that the LPE specifier symptom threshold identifies CD individuals who exhibit more psychiatric morbidity than CD individuals who are without the specifier symptom threshold. These findings altogether suggest that the clinical usefulness of the DSM-5 specifier for the diagnosis of CD is restricted, at least in detained girls.

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Lupus. 2016 Apr;25:447-48.
SIMPLE SCREENING TOOL FOR ASSESSING ATTENTION DEFICIT IN PEDIATRIC LUPUS.
Nuruzzaman F, Sherman Y, Ostfeld BM, et al.

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Matern Child Health J. 2016 Feb;20:466-76.
OBESITY, PHYSICAL ACTIVITY AND SEDENTARY BEHAVIORS IN CHILDREN WITH AN AUTISM SPECTRUM DISORDER.
Corvey K, Menear KS, Preskitt J, et al.
BACKGROUND AND OBJECTIVES: Previous literature using small sample sizes and limited geographic areas report that overweight/obesity and physical inactivity occur at higher rates among children with autism spectrum disorder (ASD) compared to typically developing peers. The purpose of this study was to examine obesity, overweight, physical activity, and sedentary behavior among children and youth with and without ASD using nationally representative data and controlling for secondary conditions, including intellectual and learning disabilities, ADHD, developmental delay, and other mental, physical, and medical conditions, as well as medication use.
METHODS: Data were collected from the 2011-2012 National Survey of Children's Health, a cross-sectional survey of 65,680 (weighted N = 49,586,134) children aged 6-17 (1385 with ASD, weighted N = 986,352). Logistic regression was used to estimate odds ratios, adjusting for demographics and possible secondary conditions.
RESULTS: Having a diagnosis of ASD was associated with higher odds of obesity (OR 1.76, CI 1.27-2.43; p = <0.001). However, after additional adjustment for possible secondary conditions, ASD diagnosis was no longer associated with obesity. Those with moderate ASD (OR 0.58, CI 0.36-0.93; p = <0.05) reported lower odds of sedentary behavior, but this association failed to achieve significance after adjustment for secondary conditions and medication use. No significant associations between ASD and overweight or physical activity were found.
CONCLUSIONS: These findings suggest that ASD diagnosis is not significantly associated with obesity status after adjustment for possible secondary conditions and medication use. Decision makers, clinicians, and researchers developing interventions for children with ASDs should consider how secondary conditions may impact obesity and related activities

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Matern Child Health J. 2016 Mar;20:665-73.
SHARED DECISION MAKING IN THE CARE OF CHILDREN WITH DEVELOPMENTAL AND BEHAVIORAL DISORDERS.
Lipstein EA, Lindly OJ, Anixt JS, et al.
OBJECTIVE: Shared decision making (SDM) is most needed when there are multiple treatment options and no "right" choice. As with quality and experience of care, frequency of SDM may vary by health condition. The objectives of this study were (1) to compare parent report of SDM between a physical and a behavioral health condition and; (2) to compare parent report of SDM between two different behavioral health conditions.
METHODS: Data on children age 3-17 years with asthma, attention deficit/hyperactivity disorder (ADHD), and/or autism spectrum disorder (ASD) were drawn from the 2009/10 National Survey of Children with Special Health Care Needs. Weighted logistic regression was used to compare a parent-reported, composite measure of SDM. Analyses controlled for sociodemographic factors that may influence experience of SDM.
RESULTS: Compared to parents of children with asthma, parents of children with ADHD were significantly less likely to report experiencing consistent SDM (AOR 0.73). Compared to parents of children with ADHD, those of children with ASD had significantly lower odds of experiencing consistent SDM (AOR 0.59). Those with both ADHD and ASD had the same odds as those with ASD alone of experiencing consistent SDM.

CONCLUSION: Use of SDM is particularly limited in developmental and behavioral conditions, such as ADHD and ASD. These data suggest that challenges to implementing SDM may include disease type, complexity, and use of specialty care. Research to identify specific barriers and facilitators of SDM is needed to inform interventions that will promote SDM in developmental and behavioral conditions

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Mol Psychiatry. 2016;21:1589-98.

SEPARATING THE WHEAT FROM THE CHAFF: SYSTEMATIC IDENTIFICATION OF FUNCTIONALLY RELEVANT NONCODING VARIANTS IN ADHD.

Tong JHS, Hawi Z, Dark C, et al.

Attention deficit hyperactivity disorder (ADHD) is a highly heritable psychiatric condition with negative lifetime outcomes. Uncovering its genetic architecture should yield important insights into the neurobiology of ADHD and assist development of novel treatment strategies. Twenty years of candidate gene investigations and more recently genome-wide association studies have identified an array of potential association signals. In this context, separating the likely true from false associations ('the wheat' from 'the chaff') will be crucial for uncovering the functional biology of ADHD. Here, we defined a set of 2070 DNA variants that showed evidence of association with ADHD (or were in linkage disequilibrium). More than 97% of these variants were noncoding, and were prioritised for further exploration using two tools - genome-wide annotation of variants (GWAVA) and Combined Annotation-Dependent Depletion (CADD) - that were recently developed to rank variants based upon their likely pathogenicity. Capitalising on recent efforts such as the Encyclopaedia of DNA Elements and US National Institutes of Health Roadmap Epigenomics Projects to improve understanding of the noncoding genome, we subsequently identified 65 variants to which we assigned functional annotations, based upon their likely impact on alternative splicing, transcription factor binding and translational regulation. We propose that these 65 variants, which possess not only a high likelihood of pathogenicity but also readily testable functional hypotheses, represent a tractable shortlist for future experimental validation in ADHD. Taken together, this study brings into sharp focus the likely relevance of noncoding variants for the genetic risk associated with ADHD, and more broadly suggests a bioinformatics approach that should be relevant to other psychiatric disorders

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Neuroimage Clin. 2016;11:476-85.

AGE ASSOCIATIONS WITH NEURAL PROCESSING OF REWARD ANTICIPATION IN ADOLESCENTS WITH BIPOLAR DISORDERS.

Urosevic S, Luciana M, Jensen JB, et al.

Reward/behavioral approach system hypersensitivity is implicated in bipolar disorders (BD) and in normative development during adolescence. Pediatric onset of BD is associated with a more severe illness course. However, little is known about neural processing of rewards in adolescents with BD or developmental (i.e., age) associations with activation of these neural systems. The present study aims to address this knowledge gap. The present sample included 21 adolescents with BD and 26 healthy adolescents, ages 13 to 19. Participants completed a functional magnetic resonance imaging (fMRI) protocol using the Monetary Incentive Delay (MID) task. Behavioral performance was similar between groups. Group differences in BOLD activation during target anticipation and feedback anticipation periods of the task were examined using whole-brain analyses, as were group differences in age effects. During both target anticipation and feedback anticipation, adolescents with BD, compared to adolescents without psychopathology, exhibited decreased engagement of frontal regions involved in cognitive control (i.e., dorsolateral prefrontal cortex). Healthy adolescents exhibited age-related decreases, while adolescents with BD exhibited age-related increases, in activity of other cognitive control frontal areas (i.e., right inferior frontal gyrus), suggesting altered development in the BD group. Longitudinal research is needed to examine potentially abnormal development

of cognitive control during reward pursuit in adolescent BD and whether early therapeutic interventions can prevent these potential deviations from normative development

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NeuroImage Clin. 2016;12:796-805.

FUNCTIONAL CONNECTIVITY IN CORTICO-SUBCORTICAL BRAIN NETWORKS UNDERLYING REWARD PROCESSING IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Oldehinkel M, Beckmann CF, Franke B, et al.

BACKGROUND: Many patients with attention-deficit/hyperactivity disorder (ADHD) display aberrant reward-related behavior. Task-based fMRI studies have related atypical reward processing in ADHD to altered BOLD activity in regions underlying reward processing such as ventral striatum and orbitofrontal cortex. However, it remains unclear whether the observed effects are region-specific or related to changes in functional connectivity of networks supporting reward processing. Here we use resting-state fMRI to comprehensively delineate the functional connectivity architecture underlying aberrant reward processing in ADHD.

METHODS: We assessed resting-state functional connectivity of four networks that support reward processing. These networks showed high spatial overlap with the default mode, fronto-parietal, lateral visual, and salience networks, yet only activity within the salience network was effectively sensitive to reward value. We parcelled these networks into their functional cortical and subcortical subregions and obtained functional connectivity matrices by computing Pearson correlations between the regional time series. We compared functional connectivity within each of the four networks between participants with ADHD and controls, and related functional connectivity to dimensional ADHD symptom scores across all participants (N = 444; age range: 8.5-30.5; mean age: 17.7).

RESULTS: We did not observe significant ADHD-related alterations in functional connectivity of the salience network, which included key reward regions. Instead, levels of inattention symptoms modulated functional connectivity of the default-mode and fronto-parietal networks, which supported general task processing.

CONCLUSIONS: The present study does not corroborate previous childhood evidence for functional connectivity alterations between key reward processing regions in adolescents and young adults with ADHD. Our findings could point to developmental normalization or indicate that reward-processing deficits result from functional connectivity alterations in general task-related networks

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Neuropsychiatr Enfance Adolesc. 2016;64:445-54.

SOCIAL SKILLS AND IMPAIRMENT IN CHILDREN WITH ADHD: STATE OF KNOWLEDGE AND PROSPECTS OF INTERVENTIONS.

Verret C, Massé L, Picher MJ.

Background Social skills deficit is a central issue in adaptive functioning of children with attention deficit hyperactivity disorder (ADHD).

Method This article is a narrative summary based on a review of the international literature, French and English, regarding social skills of children with ADHD. The definition of ADHD is derived from DSM-5 terminology.

Results This article provides current state of knowledge of social problems in children with a ADHD and their impact on social status and friendship as well as moderating and mediator factors affecting the developmental trajectory of these difficulties. The efficiency of the social skills training programs are discussed in regard to their modalities and targets.

Conclusion Although some limitations exist in current researches, social skills of children with ADHD could be improved under some conditions. It is notably preferable to offer social skills training programs that take into account the particular nature of their perceived difficulties. Refresher training courses should be developed in accordance with these children's learning needs. In order to optimise children's acquisition of taught social skills, activities should be carried out in their natural environment and in various contexts.

Finally, caregivers are perceived as the main agents of change in these children's behaviour modification and social context transformation

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Neuropsychol Rev. 2016 Mar;26:44-72.

A Systematic Review and Meta-analysis of Neuroimaging in Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) Taking Attention-Deficit Hyperactivity Disorder (ADHD) Into Account.

Noordermeer SD, Luman M, Oosterlaan J.

Oppositional defiant disorder (ODD) and conduct disorder (CD) are common behavioural disorders in childhood and adolescence and are associated with brain abnormalities. This systematic review and meta-analysis investigates structural (sMRI) and functional MRI (fMRI) findings in individuals with ODD/CD with and without attention-deficit hyperactivity disorder (ADHD). Online databases were searched for controlled studies, resulting in 12 sMRI and 17 fMRI studies. In line with current models on ODD/CD, studies were classified in hot and cool executive functioning (EF). Both the meta-analytic and narrative reviews showed evidence of smaller brain structures and lower brain activity in individuals with ODD/CD in mainly hot EF-related areas: bilateral amygdala, bilateral insula, right striatum, left medial/superior frontal gyrus, and left precuneus. Evidence was present in both structural and functional studies, and irrespective of the presence of ADHD comorbidity. There is strong evidence that abnormalities in the amygdala are specific for ODD/CD as compared to ADHD, and correlational studies further support the association between abnormalities in the amygdala and ODD/CD symptoms. Besides the left precuneus, there was no evidence for abnormalities in typical cool EF related structures, such as the cerebellum and dorsolateral prefrontal cortex. Resulting areas are associated with emotion-processing, error-monitoring, problem-solving and self-control; areas associated with neurocognitive and behavioural deficits implicated in ODD/CD. Our findings confirm the involvement of hot, and to a smaller extent cool, EF associated brain areas in ODD/CD, and support an integrated model for ODD/CD (e.g. Blair, Development and Psychopathology, 17(3), 865-891, 2005)

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Neuropsychopharmacology. 2016.

White Matter Microstructural Alterations in Children with ADHD: Categorical and Dimensional Perspectives.

Wu ZM, Bralten J, Cao QJ, et al.

Studies of brain alterations in children with attention-deficit/hyperactivity disorder (ADHD) have shown heterogeneous results. The aims of the current study were to investigate white matter microstructure in children using both categorical and dimensional definitions of ADHD and to determine the functional consequences of observed alterations. In a large single-site sample of children (aged 8ΓÇô15 years) with ADHD (n=83) and healthy controls (n=122), we used tract-based spatial statistics on diffusion tensor imaging data to investigate whole-skeleton differences of fractional anisotropy (FA), mean, axial, and radial diffusivity (MD, AD, RD), and mode of anisotropy related to ADHD status (categorical) and symptom severity (dimensional). For categorical differences observed, we analyzed their association with cognitive functioning in working memory and inhibition. Compared with healthy controls, children with ADHD showed decreased FA and increased RD in widespread, overlapping brain regions, mainly in corpus callosum (CC) and major tracts in the left hemisphere. Decreased FA was associated with inhibition performance in the participants with ADHD. Using dimensional definitions, greater hyperactivity/impulsivity symptom severity was associated with higher FA also in widespread regions, mainly in CC and major tracts in the right hemisphere. Our study showed white matter alterations to be related to ADHD status and symptom severity in patients. The coexistence of decreased FA and increased RD in the absence of alterations in MD or AD might indicate altered myelination as a pathophysiological factor in ADHD.Neuropsychopharmacology advance online publication, 26 October 2016; doi:10.1038/npp.2016.223

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Neurosci Biobehav Rev. 2016;71:529-41.

CHANGING ASD-ADHD SYMPTOM CO-OCCURRENCE ACROSS THE LIFESPAN WITH ADOLESCENCE AS CRUCIAL TIME WINDOW: ILLUSTRATING THE NEED TO GO BEYOND CHILDHOOD.

Hartman CA, Geurts HM, Franke B, et al.

Literature on the co-occurrence between Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) is strongly biased by a focus on childhood age. A review of the adolescent and adult literature was made on core and related symptoms of ADHD and ASD. In addition, an empirical approach was used including 17,173 ASD-ADHD symptom ratings from participants aged 0 to 84 years. Results indicate that ASD/ADHD constellations peak during adolescence and are lower in early childhood and old age. We hypothesize that on the border of the expected transition to independent adulthood, ASD and ADHD co-occur most because social adaptation and EF skills matter most. Lower correlations in childhood and older age may be due to more diffuse symptoms reflecting respectively still differentiating and de-differentiating EF functions. We plea for a strong research focus in adolescence which may -after early childhood- be a second crucial time window for catching-up pattern explaining more optimal outcomes. We discuss obstacles and oppportunities of a full lifespan approach into old age

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Nord J Psychiatry. 2016 Aug;70:436-41.

CHANGES IN THE CLINICAL FEATURES OF CHILD AND ADOLESCENT PSYCHIATRIC INPATIENTS: A NATIONWIDE TIME-TREND STUDY FROM FINLAND.

Kronstrom K, Ellila H, Kuosmanen L, et al.

BACKGROUND: Few studies have focused on the recent trends in clinical features child and adolescent inpatient. AIMS: This study focuses on the change in the characteristics of child and adolescent psychiatric inpatients in Finland.

METHODS: The data collection was carried out on selected study days in 2000 and 2011. Questionnaires were sent to the psychiatrists of all child and adolescent wards in Finland.

RESULTS: By comparing the data obtained in 2000 (n = 504) and 2011 (n = 412), several changes were found: the percentage of girls in adolescent wards grew and the diagnoses of depression, anxiety disorders, attention deficit hyperactivity disorder and eating disorders increased. In contrast, the diagnoses of psychosis and conduct or oppositional disorders decreased. General functioning was evaluated with the Childrens Global Assessment Scale (CGAS). There were no changes in the distribution of CGAS scores among child inpatients, whereas among adolescents the share of inpatients with lowest CGAS scores (1-30) increased significantly. The mean length of stay dropped.

CONCLUSIONS: The growing percentage of girls in adolescent wards is associated with an increase in diagnoses that are more prevalent among girls than boys, namely depression, anxiety, and eating disorders. The changes in the distribution of diagnoses may be due to changes in diagnostic or referral practices, or reflect true changes in the prevalence of disorders among children and adolescents in need of inpatient treatment. The share of adolescent inpatients with the poorest general functioning has increased. The observed shortening in inpatient treatment time seems to be a result of changes in treatment practices

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Osteoporosis International. 2016;1-5.

IMPACT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER THERAPY ON FRACTURE RISK IN CHILDREN TREATED IN GERMAN PEDIATRIC PRACTICES.

Jacob L, Kostev K.

Summary: Two thousand eight hundred ninety-four children and adolescents treated by 243 pediatricians were analyzed. Patients receiving attention deficit hyperactivity disorder (ADHD) medications were at a lower risk of fractures than patients without ADHD medications. The strongest impact was in the age group of 6–9 years. Finally, there was a significant association between therapy duration and fracture risk.

Introduction: The aim of this study was to analyze the impact of ADHD therapy on fracture risk in children treated by German pediatricians.

Methods: Children and adolescents initially diagnosed with ADHD and fractures between 2010 and 2015 were identified by 243 pediatricians. In this nested case-control study, each ADHD case with a fracture was matched (1:1) to an ADHD control without a fracture for age, gender, index year, and physician. In total, 2894 individuals were available for analysis. The main outcome of the study was the risk of fracture as a function of ADHD therapy. Multivariate logistic regression models were created to determine the effect of ADHD therapy on the risk of fracture in the entire population and in three age-specific subgroups.
Results: Patients receiving ADHD medications were at a lower risk of fracture than patients without ADHD medications (OR = 0.61). The impact of ADHD therapy on the risk of fracture was stronger in the age group of 6ΓÇô9 years (OR = 0.41) than in the age groups of 10–13 years (OR = 0.68) and 14–17 years (OR = 0.74). Finally, a significant correlation was found between therapy duration and fracture risk (OR = 0.71 per month).
Conclusion: ADHD therapy was associated with a decrease in the risk of fracture in children and adolescents treated by German pediatricians

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Paediatr Drugs. 2016 Jun;18:197-208.
PHARMACOTHERAPY FOR DRAVET SYNDROME.
Wallace A, Wirrell E, Kenney-Jung DL.
Dravet syndrome (DS) is an intractable pediatric epilepsy syndrome, starting in early childhood. This disorder typically manifests with febrile status epilepticus, and progresses to a multifocal epilepsy with febrile and non-febrile seizures with encephalopathy. Most cases are due to a mutation in the SCN1A gene. This article reviews treatments for DS, with an emphasis on pharmacotherapy. While many medications are used in treating the seizures associated with DS, these patients typically have medically refractory epilepsy, and polytherapy is often required. First-line agents include valproate and clobazam, although there are supportive data for topiramate, levetiracetam, stiripentol and the ketogenic diet. Other agents such as fenfluramine are promising therapies for Dravet syndrome. Sodium channel-blocking anticonvulsants such as carbamazepine and lamotrigine are generally contraindicated in this syndrome. Nonpharmacologic therapies (such as neurostimulation or surgery) are understudied in DS. Because DS is a global encephalopathy, pharmacologic treatment of non-epileptic manifestations of the disease is often necessary. Attention-deficit hyperactivity disorder is often encountered in patients with DS, and psychostimulants can be helpful for this indication. Other psychoactive drugs are less studied in this context. Extrapyramidal and gait disorders are often encountered in DS as well. While DS is a severe epileptic encephalopathy with a high (up to 15 %) mortality rate in childhood, careful pharmacologic management can improve these patients' clinical picture and quality of life

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Patient. 2016;1-12.
A LATENT CLASS ANALYSIS TO IDENTIFY VARIATION IN CAREGIVERS□ÇÖ PREFERENCES FOR THEIR CHILD□ÇÖS ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATMENT: DO STATED PREFERENCES MATCH CURRENT TREATMENT?
Ng X, Bridges JFP, Ross MM, et al.
Objectives: To investigate variation in caregiver preferences for their child's attention-deficit/hyperactivity disorder (ADHD) care and to determine if their stated preferences align with current care management.
Methods: Caregivers of a child aged 4ΓÇô14 years and in care for ADHD were recruited from pediatric outpatient clinics and advocacy groups across the state of Maryland. Participants completed a survey collecting demographics, the childs treatment, and caregiver preferences elicited using a best-worst scaling experiment (case 2). Latent class analysis was used to identify distinct preference segments and bivariate analyses were used to compare the association between segment membership with what the child was currently receiving for their ADHD.
Results: Participants (n = 184) were predominantly White (68%) and the child's mother (84%). Most children had ADHD for 2 or more years (79%). Caregiver preferences were distinguished by two segments:

continuous medication (36%) and minimal medication (64%). The two groups had very different preferences for when medication was administered ($p < 0.001$), but they had similar preferences for provider-oriented and non-medication interventions ($p > 0.05$ for the caregiver behavior training, provider communication, provider specialty, and out-of-pocket costs). One third of the sample did not receive the preferred individualized education program and 42% of the minimal medication group reported using medication 7 days a week all year round.
Conclusions: Although behavior management training and school accommodations aspects of an ADHD care plan are more important to caregivers than evidence-based medication, fewer families had access to educational accommodations. Further research is needed to clarify how stated preferences for care align with treatments used in actual practice settings

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Pediatr Int. 2015 Aug;57:546-51.
ADHD SYMPTOMS, BREAST-FEEDING AND OBESITY IN CHILDREN AND ADOLESCENTS.
Turkoglu S, Bilgic A, Akca OF.
BACKGROUND: Attention-deficit-hyperactivity disorder (ADHD) has been found to be related to overweight/obesity in children and adolescents, but it is a heterogeneous disorder, and the relationships between the dimensions of ADHD and overweight/obesity are not clear. The aim of this study was to explore which dimensions of the disorder are specifically associated with overweight/obesity.
METHODS: The study sample consisted of 300 treatment-naive children with ADHD and 75 healthy controls aged 7-17 years. The ADHD module of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version was used to diagnose ADHD. The severity of ADHD symptoms was assessed via Conners' Parent Rating Scale (CPRS). The weight, height, and breast-feeding duration of the study samples and controls were recorded. Body mass index (BMI) was categorized according to the national age/sex-specific reference values.
RESULTS: The rate of overweight/obese children was higher in the ADHD group. The association between ADHD symptoms and BMI percentile scores was evaluated using structural equation modeling. In that model, it was observed that the Cognitive Problems/Inattentive and Oppositional subscores of the CPRS had a positive predictive effect on the BMI percentile scores, but breast-feeding duration had a negative predictive effect on the BMI percentile scores.
CONCLUSION: Inattention, oppositionality and breast-feeding duration were associated with overweight/obesity in children and adolescents with ADHD. Longitudinal studies are needed to more fully understand this relationship and the mechanisms underlying the association between ADHD and overweight/obesity

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Pediatr Int. 2015 Oct;57:930-35.
ELECTROENCEPHALOGRAM VALID RATE IN SIMPLE REACTION TIME TASK AS AN EASY INDEX OF CHILDREN'S ATTENTION FUNCTIONS.
Liao YC, Guo NW, Lei SH, et al.
BACKGROUND: Electroencephalogram (EEG) signal artifacts occur often in children, but an EEG valid rate (VR), constructed by excluding the artifacts, might be meaningful to evaluate children's neuropsychological functions. The aim of this study was to develop an easy screening index, the EEGVR, and to investigate attention function in children using this index.
METHODS: The EEG was carried out during a 4 min simple reaction time (SRT) task as standard procedure in 50 children, consisting of 26 with attention-deficit-hyperactivity disorder (ADHD; mean age, 9.8 years; range, 8-11.3 years) and 24 without (mean age, 10.1 years; range, 7.8-12 years). An easy index was derived from the valid rate (VR) of EEG using area under the receiver operating characteristic curve. The index was applied to regroup the 50 children into high VR (HVR) and low VR (LVR) groups, while the Comprehensive Non-verbal Attention Test (CNAT) and four behavioral questionnaires were compared between the two groups in order to investigate the validity of this index.

RESULTS: The EEGVR at 75% was optimal to identify HVR and LVR (sensitivity, 0.769; specificity, 0.792). The LVR group had significantly lower scores on both CNAT and the behavioral questionnaires, although the demographic variables and full-scale intelligence quotient (FSIQ) were similar between the two groups.
CONCLUSIONS: The EEGVR in an SRT task might be an easy and effective index to screen the attention function of children, and could consequently contribute to the early diagnosis of ADHD

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Pediatr Neurol. 2016 Apr;57:22-28.

ASPECTS OF ATTENTION IN RETT SYNDROME.

Rose SA, Djukic A, Jankowski JJ, et al.

BACKGROUND: We sought to examine fundamental aspects of attention in children with Rett syndrome, a severely disabling neurodevelopmental disorder caused by spontaneous mutations in the X-linked MECP2 gene. To gauge their attention, we used eye tracking, which bypasses the profound impairments in expressive language and hand use in Rett syndrome. We report two aspects of attention-shifting and sustaining-basic abilities known to drive cognitive growth.
METHODS: Two groups were compared: those with Rett syndrome (N = 20; 3-15 years) and a typically developing comparison group (N = 14; 3-16 years), using a task in which an attractive central stimulus was followed, after a short gap, by a dynamic target presented to one side. Time to shift to the target location (reactive and anticipatory saccades) and time fixating the target were assessed.
RESULTS: Children with Rett syndrome were consistently slower to shift (largely because of fewer anticipations); their reactive saccades were also slower than those of typically developing children, but not significantly so. The Rett syndrome group spent considerable time looking at the target (over 75% of available time), although significantly less so than the typically developing group.
CONCLUSIONS: These findings indicate that children with Rett syndrome could maintain attention on a stimulus and orient relatively quickly to the appearance of a target in the visual field. However, they had difficulty in anticipating predictable events, a difficulty in endogenous attention that is likely to have deleterious implications for executive functioning

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Pediatric Diabetes. 2016.

COMORBIDITY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND TYPE 1 DIABETES IN CHILDREN AND ADOLESCENTS: ANALYSIS BASED ON THE MULTICENTRE DPV REGISTRY.

Hilgard D, Konrad K, Meusers M, et al.

Background: The interaction between type 1 diabetes mellitus (T1DM) and attention deficit hyperactivity disorder (ADHD) in children and adolescents has been studied rarely. We aimed to analyse metabolic control in children and adolescents with both T1DM and ADHD compared to T1DM patients without ADHD.
Patients and methods: Auxological and treatment data from 56.722 paediatric patients (<20 years) with T1DM in the multicentre DPV (Diabetes Prospective Follow-up Initiative) registry were analysed. T1DM patients with comorbid ADHD were compared to T1DM patients without ADHD using multivariable mixed regression models adjusting for demographic confounders.
Results: We identified 1.608 (2.83%) patients with ADHD, 80.8% were male. Patients with comorbid ADHD suffered twice as often from diabetic ketoacidosis compared to patients without ADHD [10.2; 9.7-10.8 vs [5.4; 5.3-5.4] (P < .0001). We also found significant differences in HbA1c [8.6% (7.3-9.4); 66.7 mmol/mol (56.3-79.4) vs 7.8% (7.0-9.0); 62.1 mmol/mol (53.2-74.7)], insulin dose/kg [0.9 IU/kg (0.7-1.1) vs 0.8 IU/kg (0.7-1.0)], body mass index-standard deviation score (BMI-SDS) [0.2 (-0.5 to 0.8) vs 0.3 (-0.3 to 0.9)], body weight-SDS [0.1 (-0.5 to 0.8) vs 0.3 (0.3 - 0.9)]; (all P < 0.0001), and systolic blood pressure after adjustment [mean: 116.3 vs 117.1 mm Hg)]; (P < 0.005).

Conclusion: Paediatric patients with ADHD and T1DM showed poor metabolic control compared to T1DM patients without ADHD. Closer cooperation between specialized paediatric diabetes teams and paediatric psychiatry/psychology seems to be necessary to improve diabetes care and metabolic control in this group of patients

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Pediatric Diabetes. 2016.

ADHD, LEARNING DIFFICULTIES AND SLEEP DISTURBANCES ASSOCIATED WITH KCNJ11-RELATED NEONATAL DIABETES.

Landmeier KA, Lanning M, Carmody D, et al.

Objectives: Mutations in KCNJ11 are the most common cause of permanent neonatal diabetes mellitus (NDM). Approximately 25% of patients have obvious neurological dysfunction, but whether milder related problems might be more common has been unclear. We sought to assess the prevalence of parental concerns about learning, behavior, attention deficit hyperactivity disorder (ADHD), social competency, and sleep in subjects with KCNJ11-related NDM compared to unaffected sibling controls.

Study design: Subjects or their guardians in the University of Chicago Monogenic Diabetes Registry completed a survey examining learning, behavior, ADHD and sleep. Thirty subjects with KCNJ11 -related NDM and 25 unaffected sibling controls were assessed. Data were analyzed using GraphPad Prism 6. Nonparametric analysis was performed using Fisher's exact test for group comparisons.

Results: Thirteen (43%) individuals with KCNJ11 -related NDM had treatment for or a diagnosis of ADHD compared to two (8%) of the sibling controls ($P < 0.05$). Compared to their sibling controls, individuals with KCNJ11 mutations had significant differences in behavior difficulties, social awareness, academic achievement and the need for an Individualized Education Plan (IEP). As seen in other neurodevelopmental disorders, individuals with KCNJ11 mutations also had significantly higher rates of sleep difficulties ($P < 0.01$).

Conclusion: Patients with KCNJ11 -related NDM are at an increased risk for delays in learning, social-emotional and behavioral development, ADHD and sleep difficulties based on parent report. Early identification, along with integrated medical and developmental support, may promote better neurodevelopmental outcomes for this unique population. Further investigation utilizing detailed neuropsychological testing will better define the neurodevelopmental consequences of KATP mutations

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Perm J. 2016;20:65-69.

E-MAILS IN A PSYCHIATRIC PRACTICE: WHY PATIENTS SEND THEM AND HOW PSYCHIATRISTS RESPOND.

Moldawsky RJ, Shah PV.

CONTEXT: Little is known about what prompts patients to use e-mail with their physicians and how physicians respond to these e-mails.

OBJECTIVE: To identify the main reasons why patients e-mail and to learn how psychiatrists manage these e-mails as part of these patients' overall care.

DESIGN: One hundred patient-initiated e-mails to each of two psychiatrists in a group practice were studied retrospectively for primary reason for the e-mail and for psychiatrists' handling of each e-mail. Other data were collected to assess how representative the e-mailing patients were of the psychiatrists' patient panels.

RESULTS: Age, sex, and diagnoses of the e-mailers were similar to our overall panels. The most common reasons for e-mailing were refill requests (19.5%), questions about prescribed medication (16.5%), and worsening of symptoms (11.5%). The modal e-mail was a patient with attention-deficit/hyperactivity disorder requesting a refill. The psychiatrists' most common responses were authorizing a refill (25%), reassurance (22%), and making or moving up a scheduled appointment (16%). For all patients who reported a worsening of symptoms, responses, communicated by e-mail or telephone, included a combination of an earlier appointment and/or change in medication or dose and/or referral for psychotherapy. Both psychiatrists found e-mail to be an efficient enhancement of their practice, and it was inferred that this was also a satisfying mechanism for patients.

CONCLUSION: Physician-patient communication via e-mail is timesaving for both, and the benefits to patient care should reassure physicians who are wary of using e-mail in their practice. Potential risks to patients without face-to-face or telephone contact appear to be minimal

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Physiol Res. 2015;64 Suppl 5:S595-S601.

TESTOSTERONE IN RELATION TO BEHAVIORAL PROBLEMS IN PRE-PUBERTAL BOYS WITH AUTISM SPECTRUM DISORDERS.

Pivovarciova A, Durdiakova J, Hnilicova S, et al.

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by impairment in social communication and presence of stereotyped/restricted behaviors. Children with ASD very often demonstrate co-morbid psychiatric problems, problems known to be affected by testosterone in neurotypical populations. However, there are few reports investigating relationships between testosterone and psychiatric conditions in children with ASD. The aim of this study was to determine the relationship between plasmatic levels of testosterone and behavioral/emotional problems in pre-pubertal boys with ASD. The study sample consisted of 31 pre-pubertal boys (ages 3-10) with ASD. Parents completed the Nisonger Child Behavior Rating Form (NCBRF) to assess specific behavioral/emotional problems as observed in the previous 2 months. Plasmatic testosterone levels were determined in boys according to standardized procedures. It was found that there were positive correlations between testosterone levels and the conduct problems subscale (p=0.034, rs=0.382) of NCBRF and also between testosterone levels and the hyperactive subscale (p=0.025, rs=0.402) of NCBRF. Findings in this study are in line with research conducted in the neurotypical population. This is the first large study investigating testosterone and emotional/behavioral problems in ASD and warrants further research in this field in order to clarify the etiopathogenesis of psychiatric co-morbidities and improve their treatment

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PLoS ONE. 2016;11.

ATTENTION NETWORK DYSFUNCTION IN BULIMIA NERVOSA - AN FMRI STUDY.

Seitz J, Hueck M, Dahmen B, et al.

Objective: Recent evidence has suggested an increased rate of comorbid ADHD and subclinical attentional impairments in bulimia nervosa (BN) patients. However, little is known regarding the underlying neural mechanisms of attentional functions in BN.

Method: Twenty BN patients and twenty age- and weight-matched healthy controls (HC) were investigated using a modified version of the Attention Network Task (ANT) in an fMRI study. This design enabled an investigation of the neural mechanisms associated with the three attention networks involved in alerting, reorienting and executive attention.

Results: The BN patients showed hyperactivation in parieto-occipital regions and reduced deactivation of default-mode-network (DMN) areas during alerting compared with HCs. Posterior cingulate activation during alerting correlated with the severity of eating-disorder symptoms within the patient group. Conversely, BN patients showed hypoactivation during reorienting and executive attention in anterior cingulate regions, the temporo-parietal junction (TPJ) and parahippocampus compared with HCs, which was negatively associated with global ADHD symptoms and impulsivity, respectively.

Discussion: Our findings demonstrate altered brain mechanisms in BN associated with all three attentional networks. Failure to deactivate the DMN and increased parieto-occipital activation required for alerting might be associated with a constant preoccupation with food or body image-related thoughts. Hypoactivation of executive control networks and TPJ might increase the likelihood of inattentive and impulsive behaviors and poor emotion regulation. Thus, dysfunction in the attentional network in BN goes beyond an altered executive attentional domain and needs to be considered in the diagnosis and treatment of BN

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PLoS ONE. 2016;11.

DESIGNING AN IPAD APP TO MONITOR AND IMPROVE CLASSROOM BEHAVIOR FOR CHILDREN WITH ADHD: ISELFCONTROL FEASIBILITY AND PILOT STUDIES.

Schuck S, Emmerson N, Ziv H, et al.

Children with Attention Deficit/Hyperactivity Disorder (ADHD) receive approximately 80% of instruction in the general education classroom, where individualized behavioral management strategies may be difficult for teachers to consistently deliver. Mobile device apps provide promising platforms to manage behavior. This pilot study evaluated the utility of a webbased application (iSelfControl) designed to support classroom behavior management. iSelfControl prompted students every 'Center' (30-minutes) to self-evaluate using a universal token-economy classroom management system focused on compliance, productivity, and positive relationships. Simultaneously, the teacher evaluated each student on a separate iPad. Using Multi Level Modeling, we examined 13 days of data gathered from implementation with 5th grade students (N = 12) at a school for children with ADHD and related executive function difficulties. First, an unconditional growth model evaluated the overall amount of change in aggregated scores over time as well as the degree of systematic variation in scores within and across teacher-student dyads. Second, separate intercepts and slopes were estimated for teacher and student to estimate degree of congruency between trajectories. Finally, differences between teacher and student scores were tested at each time-point in separate models to examine unique 'Center' effects. 51% of the total variance in scores was attributed to differences between dyads. Trajectories of student and teacher scores remained relatively stable across seven time-points each day and did not statistically differ from each other. On any given day, students tended to evaluate their behaviors more positively (entered higher scores for themselves) compared to corresponding teacher scores. In summary, iSelfControl provides a platform for self and teacher evaluation that is an important adjunct to conventional classroom management strategies. The application captured teacher/student discrepancies and significant variations across the day. Future research with a larger, clinically diagnosed sample in multiple classrooms is needed to assess generalizability to a wider variety of classroom settings

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PLoS ONE. 2016;11.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND LIFESTYLE-RELATED BEHAVIORS IN CHILDREN.

Tong L, Xiong X, Tan H.

Attention-deficit/hyperactivity disorder (ADHD) has been associated with obesity in children. Lifestyle-related behaviors (external eating, screen time and physical inactivity) are well known to be associated with increased risk of obesity, but their associations with ADHD are unclear. The objectives of this study were to clarify the associations between ADHD symptoms in children and their associated lifestyle. A cross sectional study was carried out with a total of 785 primary students aged 9 to 13 years old and their parents were recruited by stratified random sampling from primary schools of China. The Cochran-Mantel- Haenszel (CMH) test was used to examine the relationships between ADHD symptoms and health related behaviors. We found that children with ADHD symptoms were likely to spend more time using a computer during school days; they were also more likely to eat while using a computer. These children were also more likely to eat while seated in a car, using a smart phone, using a computer at bedtime, and snacking before going to sleep than children without ADHD symptoms. An increased risk of obesity in children with ADHD symptoms was associated with the overuse of electronic devices, eating while using electronic devices, and delaying bedtimes to snack and use electronic devices

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PLoS ONE. 2016;11.

STATISTICAL EVIDENCE SUGGESTS THAT INATTENTION DRIVES HYPERACTIVITY/IMPULSIVITY IN ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Sokolova E, Groot P, Claassen T, et al.

Background: Numerous factor analytic studies consistently support a distinction between two symptom domains of attention-deficit/hyperactivity disorder (ADHD), inattention and hyperactivity/impulsivity. Both

dimensions show high internal consistency and moderate to strong correlations with each other. However, it is not clear what drives this strong correlation. The aim of this paper is to address this issue.
Method: We applied a sophisticated approach for causal discovery on three independent data sets of scores of the two ADHD dimensions in NeuroIMAGE (total N = 675), ADHD-200 (N = 245), and IMpACT (N = 164), assessed by different raters and instruments, and further used information on gender or a genetic risk haplotype.
Results: In all data sets we found strong statistical evidence for the same pattern: the clear dependence between hyperactivity/impulsivity symptom level and an established genetic factor (either gender or risk haplotype) vanishes when one conditions upon inattention symptom level. Under reasonable assumptions, e.g., that phenotypes do not cause genotypes, a causal model that is consistent with this pattern contains a causal path from inattention to hyperactivity/impulsivity.
Conclusions: The robust dependency cancellation observed in three different data sets suggests that inattention is a driving factor for hyperactivity/impulsivity. This causal hypothesis can be further validated in intervention studies. Our model suggests that interventions that affect inattention will also have an effect on the level of hyperactivity/impulsivity. On the other hand, interventions that affect hyperactivity/impulsivity would not change the level of inattention. This causal model may explain earlier findings on heritable factors causing ADHD reported in the study of twins with learning difficulties

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PM R. 2016;8:S156.

CONCUSSION-LIKE SYMPTOM REPORTING IN HIGH SCHOOL STUDENT ATHLETES WITH ADHD.

Cook NE, Huang D, Silverberg N, et al.

Objective: Symptom reporting in student athletes with attentiondeficit hyperactivity disorder (ADHD) who are slow-to-recover from a sport-related concussion can be difficult to interpret; it can be challenging to differentiate pre-existing symptoms from concussion related symptoms. This study documents preseason symptom reporting in athletes with and without ADHD.
Design: Cross-sectional, case-control, cohort survey study.
Setting: High schools from the state of Maine, USA.
Participants: Participants were 37,510 high school athletes who completed a baseline preseason health survey and symptom questionnaire between 2009 and 2014. None reported suffering a concussion within the past 6 months. A total of 2,409 (6.4%) self-reported having ADHD, and 786 (32.6%) reported taking medication to treat ADHD. Three groups included: (1) controls, (2) ADHD with medication use (Medication), and (3) ADHD but no medication use (No Medication).
Interventions: None. Main Outcome Measures: The Post-Concussion Scale includes 22 symptoms such as headache, dizziness, concentration problems, and forgetfulness. Students rate the severity of each symptom from 0 to 6.
Results: Groups differed significantly on the Post-Concussion Scale [girls: X2(2)=22.6.29, P <.001; boys: X2(2)=267.15, P <.001]. Pairwise comparisons revealed similar results for both sexes; namely, the Medication group (boys: Md=4; girls: Md=9) and No Medication group (boys: Md=3.5; girls: Md=7) did not differ from one another. Both the No Medication group (girls: Mann-Whitney U=2,881,457, P <.001; boys: U=8,170,938, P <.001) and the Medication group differed significantly from Controls (girls: Md=2; U=1,187,040.5, P <.001; boys: Md=1; U=3,836,183.5, P <.001). Girls with ADHD, regardless of medication status, had greater total symptom scores compared to boys with ADHD. Frequencies of endorsing specific symptoms (ie, item score > 1), stratified by group and gender, are presented.
Conclusions: Better understanding of symptom reporting in uninjured student athletes with ADHD can facilitate the clinical interpretation of symptoms in those who are slow to recover following a concussion

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Proc Natl Acad Sci U S A. 2016 Apr;113:3879-84.

NEURAL BASIS OF REWARD ANTICIPATION AND ITS GENETIC DETERMINANTS.

Jia T, Macare C, Desrivieres S, et al.

Dysfunctional reward processing is implicated in various mental disorders, including attention deficit hyperactivity disorder (ADHD) and addictions. Such impairments might involve different components of the reward process, including brain activity during reward anticipation. We examined brain nodes engaged by reward anticipation in 1,544 adolescents and identified a network containing a core striatal node and cortical nodes facilitating outcome prediction and response preparation. Distinct nodes and functional connections were preferentially associated with either adolescent hyperactivity or alcohol consumption, thus conveying specificity of reward processing to clinically relevant behavior. We observed associations between the striatal node, hyperactivity, and the vacuolar protein sorting-associated protein 4A (VPS4A) gene in humans, and the causal role of Vps4 for hyperactivity was validated in Drosophila Our data provide a neurobehavioral model explaining the heterogeneity of reward-related behaviors and generate a hypothesis accounting for their enduring nature

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2017;73:56-63.

ASSOCIATION OF NOREPINEPHRINE TRANSPORTER GENE POLYMORPHISMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN KOREAN POPULATION.

Oh SY, Kim YK.

We investigated the association of three single nucleotide polymorphisms(SNP) of the norepinephrine transporter (NET) gene SLC6A2, T-182C (rs2242446), A-3081T (rs28386840), and G-1287A (rs5569) with the prevalence of attention-deficit/hyperactivity disorder (ADHD), its clinical severity, and other disease-related characteristics in a Korean population. The genotype, allele frequency and haplotype of 103 ADHD patients and 173 controls were analyzed for these three SNPs. All participants completed the Korean version of the ADHD Rating Scale (K-ARS). The ADHD group also completed the Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC) and the Continuous Performance Test (CPT) in a drug-naive state. The ¤ç2 test and logistic regression analysis revealed no significant differences in the genotype distribution or allele frequencies of each SNP between the ADHD group and the control. In the haplotype analysis, the most common T-A-G haplotype was related to an increased risk of ADHD in females (P-á=-á0.002). There was no statistical significance between clinical features of ADHD and any specific allele of each SNP after multiple test correction except lower omission error in non-A girl carriers (GG type) of G-1287A (carrier 76.75-á-¦-á18.74, non-carrier 55.00-á-¦-á9.26, t-á=-á3.026, P-á=-á0.007, Bonferroni-corrected P-á=-á0.042). Some values related A-3081 and G-1287A showed a trend approaching the significance level when analyzed separately by gender. Even though it was not statistically meaningful after multiple test correction, G allele might have some protective effect against development of ADHD symptoms and this finding was consistent with previous studies

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Psicothema. 2014;26:471-76.

INFLUENCE OF THE SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND COMORBID DISORDERS ON FUNCTIONING IN ADULTHOOD.

Miranda A, Berenguer C, Colomer C, et al.

BACKGROUND: ADHD is a chronic disorder that generally has a negative effect on socio-personal adaptation. The objectives of the current study were to examine the adaptive functioning in the daily lives of adults with ADHD compared to adults without the disorder and to test the influence of ADHD symptoms and comorbid problems on different areas of adaptive functioning.

METHOD: Seventy-seven adults between 17 and 24 years old, 40 with a clinical diagnosis of combined-subtype ADHD in childhood and 37 controls, filled out the Weiss Functional Impairment Scale, the Weiss Symptom Record and Conners' Adult ADHD Rating Scale.

RESULTS: Significant differences were found between adults with and without ADHD in family and academic functioning. Moreover, the ADHD symptomatology as a whole predicted significant deficiencies in the family environment and self-concept, whereas inattention specifically predicted worse academic performance and life skills. The comorbidities mainly affected the family and risky activity domains (dangerous driving, illegal behaviors, substance misuse and sexually inappropriate behaviors).
CONCLUSIONS: The results illustrate the importance of developing a multimodal approach to helping ADHD adults cope with associated comorbid disorders, offering them supportive coaching in organizing daily activities, and incorporating the family and/or partner in the treatment plan

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Psicothema. 2014;26:477-82.

PROPRIOCEPTIVE DIAGNOSTICS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Iglesias T, Liutsko L, Tous JM.

BACKGROUND: Previous studies have shown the importance of motor control in children with attention deficit hyperactivity disorder. The objective of our study was to verify any statistically significant differences of fine motor performance in children with attention deficit hyperactivity disorder (ADHD) symptoms compared to the control group in proprioceptive sensory condition.
METHOD: Proprioceptive Diagnostics of Temperament and Character was used for the measurement of fine motor precision (proprioceptive sensory condition). The biases from the linear models (lineograms) and line length were registered for three movement types (frontal, transversal and sagittal) in both hands. Line length variability was obtained from the parallels.
RESULTS: MANOVA with Bonferroni correction for multiple comparisons revealed significant statistically differences between the ADHD and control group in fine motor graphical performance in four variables. Age and sex differences were taken into account and discussed. Discriminant analysis confirmed that both groups can be classified at a statistically significant level.
CONCLUSION: This is the first empirical study to compare differences between children with and without ADHD symptoms in fine motor precision performed in the proprioceptive condition. Discriminant analysis confirmed the capacity of some specific movement type to classify the groups

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Psychiatry Res. 2016 Apr;238:8-13.

COMBINED PHARMACOTHERAPY-MULTIMODAL PSYCHOTHERAPY IN CHILDREN WITH DISRUPTIVE BEHAVIOR DISORDERS.

Masi G, Milone A, Manfredi A, et al.

Although multi-component psychotherapeutic interventions are first-line treatments for Disruptive Behavior Disorders (DBD), pharmacotherapy is often associated for more severe patients. Our aim was to explore effectiveness of an associated pharmacotherapy in referred children with DBD receiving a one-year psychotherapeutic intervention. Aggression, callous unemotional (CU) traits and emotional dysregulation were outcome measures. The sample included 144 children, aged 8-12 years, 41 (29%) with an ADHD comorbidity. Fifty-five (38%) patients received an additional pharmacotherapy with one medication, methylphenidate, a second generation antipsychotic, or a mood stabilizer. Data were collected before and after the one-year treatment. According to the Child Behavior Checklist (CBCL), aggressive behaviors, rule-breaking behaviors and emotional dysregulation improved in the whole group, as well as parent- and child-reported CU traits. The hierarchical regression model showed that additional pharmacotherapy significantly predicted lower scores at the CBCL aggressive behaviors and emotional dysregulation, but not CU traits at the end of the treatment. The interaction between methylphenidate and ADHD comorbidity predicted lower aggressive behaviors after the treatment. In summary, this naturalistic investigation suggest that an additional pharmacotherapy significantly improved aggression and emotional dysregulation, but not CU traits. When

ADHD was comorbid, methylphenidate was more effective than antipsychotics or mood stabilizers in reducing aggression

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Psychiatry Res. 2016;246:275-83.

GLUCOCORTICOID RECEPTOR VARIANTS IN CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND COMORBID PSYCHIATRIC DISORDERS.

Schote AB, Bonenberger M, P+ílmason H, et al.

Stress results in a variety of neuroendocrine, immune and behavioral responses and represents a risk factor for many disorders. Following exposure to stress, glucocorticoids are secreted from the adrenal cortex and act via the ligand-activated glucocorticoid receptor (GR). Several polymorphisms of the GR-encoding gene NR3C1 have been described and functionally investigated. However, the impact of these variants on complex diseases such as Attention-Deficit/Hyperactivity Disorder (ADHD) is still unclear. In this study, 251 children with ADHD, 19 affected and 35 unaffected siblings, and their parents were included in a family-based association study assessing seven common variants of NR3C1 (TthIII_rs10052957; NR3C1-I_rs10482605; ER22/23EK_rs6189/rs6190; N363S_rs56149945; BclI_rs41423247; GR-9beta_rs6198). A four-marker haplotype (TthIII-NR3C1-I-ER22/23EK) was nominally associated with ADHD. In addition, in index children with ADHD, associations with comorbid disorders, inattentive and hyperactive-impulsive symptoms were explored. N363S minor allele carriers were more likely to show comorbid conduct disorder (CD). In our study, NR3C1 variants moderately affected ADHD and had a significant effect on comorbid CD. Therefore, NR3C1 as an important gene of the hypothalamicΓÇôpituitaryΓÇôadrenal axis seems to be particularly relevant for the pathophysiology of ADHD combined with comorbid CD. For a deeper understanding, investigations in larger samples of healthy, ADHD and CD individuals are warranted

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Psychol Assess. 2015 Jun;27:678-88.

RELATIONS BETWEEN RESPONSE TRAJECTORIES ON THE CONTINUOUS PERFORMANCE TEST AND TEACHER-RATED PROBLEM BEHAVIORS IN PRESCHOOLERS.

Allan DM, Lonigan CJ.

Although both the continuous performance test (CPT) and behavior rating scales are used in both practice and research to assess inattentive and hyperactive/impulsive behaviors, the correlations between performance on the CPT and teachers' ratings are typically only small-to-moderate. This study examined trajectories of performance on a low target-frequency visual CPT in a sample of preschool children and how these trajectories were associated with teacher-ratings of problem behaviors (i.e., inattention, hyperactivity/impulsivity [H/I], and oppositional/defiant behavior). Participants included 399 preschool children (mean age = 56 months; 49.4% female; 73.7% White/Caucasian). An attention deficit/hyperactivity disorder (ADHD) rating scale was completed by teachers, and the CPT was completed by the preschoolers. Results showed that children's performance across 4 temporal blocks on the CPT was not stable across the duration of the task, with error rates generally increasing from initial to later blocks. The predictive relations of teacher-rated problem behaviors to performance trajectories on the CPT were examined using growth curve models. Higher rates of teacher-reported inattention and H/I were uniquely associated with higher rates of initial omission errors and initial commission errors, respectively. Higher rates of teacher-reported overall problem behaviors were associated with increasing rates of omission but not commission errors during the CPT; however, the relation was not specific to 1 type of problem behavior. The results of this study indicate that the pattern of errors on the CPT in preschool samples is complex and may be determined by multiple behavioral factors. These findings have implications for the interpretation of CPT performance in young children

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Psychol Assess. 2015 Dec;27:1349-63.

CROSS-CULTURAL VALIDATION OF A BEHAVIORAL SCREENER FOR EXECUTIVE FUNCTIONS: GUIDELINES FOR CLINICAL USE AMONG COLOMBIAN CHILDREN WITH AND WITHOUT ADHD.

Garcia-Barrera MA, Karr JE, Duran V, et al.

Garcia-Barrera, Kamphaus, and Bandalos (2011) derived a 25-item executive functioning screener from the Behavior Assessment System for Children (BASC), measuring 4 latent executive constructs: problem solving, attentional control, behavioral control, and emotional control. The current study included a cross-cultural examination of this screener in Colombian children with and without attention-deficit/hyperactivity disorder (ADHD). BASC teacher ratings were collected for Colombian children ages 6-11 years (848 healthy children [53% boys] and 155 children with ADHD [76% boys]). To examine the psychometric properties of the screener, a multistep procedure was implemented, including (a) confirmatory factor analysis (CFA) and factorial invariance testing across gender, age group (6-8 years, 9-11 years), and ADHD status to replicate and extend the original derivation; (b) item response theory (IRT) analysis to evaluate the information provided by individual items; and (c) given IRT results, a repeated CFA and invariance testing after the exclusion of 1 item from the problem-solving factor. The 24-item 4-factor model fit was adequate for controls and for ADHD participants. Results support the use of the 24-item executive functioning screener in a cross-cultural context. In turn, in supplemental material, normative data for the Colombian sample are reported along with bilingual guidelines (i.e., Spanish/English) for implementing the screener in clinical practice. Even though the screener is useful when examining executive functions, it was not designed as a diagnostic measure for developmental disorders such as ADHD; as such, it should only inform about status of executive functioning

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Psychol Assess. 2015 Jun;27:524-33.

Psychometric properties and adaptation of the ASRS in a Spanish sample of patients with substance use disorders: Application of two IRT Rasch models.

Sanchez-Garcia M, Fernandez-Calderon F, Carmona-Marquez J, et al.

The Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005) is one of the most extensively used scales to detect attention-deficit hyperactivity disorder (ADHD) in adults. The aim of this work is to analyze the psychometric properties of the 18 ASRS items in people with substance use disorders (SUDs). Furthermore, we aimed to (a) confirm or, if necessary, modify the dichotomization criteria of the items proposed by the authors, and (b) identify the most informative items for a screening version or, when applicable, confirm the use of the 6 items that comprise the initially proposed short version. The ASRS was completed for 170 patients with SUD at the Provincial Unit for Drug Dependence of Huelva, Spain, aged 16 to 78 years. Two Rasch models-the dichotomous Rasch model and the Rating Scale Model (RSM) for polytomous items-were used in the psychometric analysis. The ASRS items fitted the RSM adequately, but the locations of the items along the underlying construct led us to propose new criteria of dichotomization. After analyzing the information function of dichotomized items, we identified 6 items that should integrate a new screening scale. Our dichotomization proposal is different from the original one and takes into account the different weights of the items. The selected screening version showed better metric properties than the other analyzed versions. Future research should test our proposal by using external criteria and to obtain evidences for other populations, cultures, or patient profiles

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Psychol Med. 2015 Jul;45:2045-56.

PERSISTENCE AND REMISSION OF ADHD DURING ADULTHOOD: A 7-YEAR CLINICAL FOLLOW-UP STUDY.

Karam RG, Breda V, Picon FA, et al.

BACKGROUND: Course and predictors of persistence of attention deficit hyperactivity disorder (ADHD) in adults are still largely unknown. Neurobiological and clinical differences between child and adult ADHD raise the need for follow-up studies of patients diagnosed during adulthood. This study investigates predictors of ADHD persistence and the possibility of full remission 7 years after baseline assessment.

METHOD: A 7-year follow-up study of adults with ADHD (n = 344, mean age 34.1 years, 49.9% males) was conducted. Variables from different domains (social demographics, co-morbidities, temperament, medication status, ADHD measures) were explored with the aim of finding potential predictors of ADHD persistence.
RESULTS: Retention rate was 66% (n = 227). Approximately a third of the sample (n = 70, 30.2%) did not maintain ADHD criteria and 28 (12.4%) presented full remission (<4 symptoms), independently of changes in co-morbidity or cognitive demand profiles. Baseline predictors of diagnostic persistence were higher number of inattention symptoms [odds ratio (OR) 8.05, 95% confidence interval (CI) 2.54-25.45, p < 0.001], number of hyperactivity/impulsivity symptoms (OR 1.18, 95% CI 1.04-1.34, p = 0.01), oppositional defiant disorder (OR 3.12, 95% CI 1.20-8.11, p = 0.02), and social phobia (OR 3.59, 95% CI 1.12-11.47, p = 0.03).
CONCLUSIONS: Despite the stage of brain maturation in adults suggests stability, approximately one third of the sample did not keep full DSM-IV diagnosis at follow-up, regardless if at early, middle or older adulthood. Although full remission is less common than in childhood, it should be considered as a possible outcome among adults

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Psychol Med. 2016 Apr;46:1103-14.

DISRUPTIVE MOOD DYSREGULATION DISORDER AT THE AGE OF 6 YEARS AND CLINICAL AND FUNCTIONAL OUTCOMES 3 YEARS LATER.

Dougherty LR, Smith VC, Bufferd SJ, et al.

BACKGROUND: Little is known about the predictive validity of disruptive mood dysregulation disorder (DMDD). This longitudinal, community-based study examined associations of DMDD at the age of 6 years with psychiatric disorders, functional impairment, peer functioning and service use at the age of 9 years.
METHOD: A total of 473 children were assessed at the ages of 6 and 9 years. Child psychopathology and functional impairment were assessed at the age of 6 years with the Preschool Age Psychiatric Assessment with parents and at the age of 9 years with the Kiddie-Schedule of Affective Disorders and Schizophrenia (K-SADS) with parents and children. At the age of 9 years, mothers, fathers and youth completed the Child Depression Inventory (CDI) and the Screen for Child Anxiety Related Disorders, and teachers and K-SADS interviewers completed measures of peer functioning. Significant demographic covariates were included in all models.
RESULTS: DMDD at the age of 6 years predicted a current diagnosis of DMDD at the age of 9 years. DMDD at the age of 6 years also predicted current and lifetime depressive disorder and attention-deficit/hyperactivity disorder (ADHD) at the age of 9 years, after controlling for all age 6 years psychiatric disorders. In addition, DMDD predicted depressive, ADHD and disruptive behavior disorder symptoms on the K-SADS, and maternal and paternal reports of depressive symptoms on the CDI, after controlling for the corresponding symptom scale at the age of 6 years. Last, DMDD at the age of 6 years predicted greater functional impairment, peer problems and educational support service use at the age of 9 years, after controlling for all psychiatric disorders at the age of 6 years.
CONCLUSIONS: Children with DMDD are at high risk for impaired functioning across childhood, and this risk is not accounted for by co-morbid conditions

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Psychol Assess. 2015;27:1324-36.

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

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

The factor structure and potential uniform differential item functioning (DIF) among gender and three racial/ethnic groups of adolescents (African American, Latino, White) were evaluated for attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) symptom scores of the DISC Predictive Scales (DPS; Leung et al., 2005; Lucas et al., 2001). Primary caregivers reported on DSM-IV ADHD, CD, and ODD symptoms for a probability sample of 4,491 children

from three geographical regions who took part in the Healthy Passages study (mean age = 12.60 years, SD = 0.66). Confirmatory factor analysis indicated that the expected 3-factor structure was tenable for the data. Multiple indicators multiple causes (MIMIC) modeling revealed uniform DIF for three ADHD and 9 ODD item scores, but not for any of the CD item scores. Uniform DIF was observed predominantly as a function of child race/ethnicity, but minimally as a function of child gender. On the positive side, uniform DIF had little impact on latent mean differences of ADHD, CD, and ODD symptomatology among gender and racial/ethnic groups. Implications of the findings for researchers and practitioners are discussed

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Psychopharmacology. 2016;1-13.

BDNF CONCENTRATIONS AND DAILY FLUCTUATIONS DIFFER AMONG ADHD CHILDREN AND RESPOND DIFFERENTLY TO METHYLPHENIDATE WITH NO RELATIONSHIP WITH DEPRESSIVE SYMPTOMATOLOGY.

Cubero-Mill+ín I, Ruiz-Ramos MJ, Molina-Carballo A, et al.

Rationale: Brain-derived neurotrophic factor (BDNF) enhances the growth and maintenance of several monoamine neuronal systems, serves as a neurotransmitter modulator and participates in the mechanisms of neuronal plasticity. Therefore, BDNF is a good candidate for interventions in the pathogenesis and/or treatment response of attention deficit hyperactivity disorder (ADHD).

Objective: We quantified the basal concentration and daily fluctuation of serum BDNF, as well as changes after methylphenidate treatment.

Method: A total of 148 children, 4ΓÇô5 years old, were classified into groups as follows: ADHD group (n = 107, DSM-IV-TR criteria) and a control group (CG, n = 41). Blood samples were drawn at 2000 and 0900 hours from both groups, and after 4.63 -¦ 2.3 months of treatment, blood was drawn only from the ADHD group for BDNF measurements. Factorial analysis was performed (Stata software, version 12.0).

Results: Morning BDNF (36.36 -¦ 11.62 ng/ml) in the CG was very similar to that in the predominantly inattentive children (PAD), although the evening concentration in the CG was higher (CG 31.78 -¦ 11.92 vs PAD 26.41 -¦ 11.55 ng/ml). The hyperactive impulsive group, including patients with comorbid conduct disorder (PHI/CD), had lower concentrations. Methylphenidate (MPH) did not modify the concentration or the absence of daily BDNF fluctuations in the PHI/CD children; however, MPH induced a significant decrease in BDNF in PAD and basal day/night fluctuations disappeared in this ADHD subtype. This profile was not altered by the presence of depressive symptoms.

Conclusions: Our data support a reduction in BDNF in untreated ADHD due to the lower concentrations in PHI/CD children, which is similar to other psychopathologic and cognitive disorders. MPH decreased BDNF only in the PAD group, which might indicate that BDNF is not directly implicated in the methylphenidate-induced amelioration of the neuropsychological and organic immaturity of ADHD patients

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Redox Rep. 2016;21:248-53.

INCREASED OXIDATIVE STRESS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sezen H, Kandemir H, Savik E, et al.

Objectives: The purpose of this study was to investigate oxidative stress in children with attention deficit hyperactivity disorder (ADHD).

Methods: Total oxidant status (TOS), total antioxidant status (TAS), paraxonase-1 (PON-1) and arylesterase (ARE) activity were measured in 76 children (44 boys, 32 girls) diagnosed with ADHD according to the DSM-IV and 78 healthy children (46 boys, 32 girls).

Results: Age and sex were similar between the groups ($P > 0.05$). TOS and the oxidative stress index (OSI) were higher in the patient group than the control group ($P < 0.001$). PON-1 ($P = 0.002$), ARE ($P = 0.010$) activity and TAS ($P < 0.001$) were lower in the patient group than the control group.

Discussion: We found decreased PON-1, ARE activity and TAS, and increased TOS and OSI in children with ADHD. Our study showed that there is significantly increased oxidative stress in children with ADHD

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Res Dev Disabil. 2016 Apr;51-52:160-72.

META-ANALYSIS OF QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS WITH ADHD: BY BOTH PARENT PROXY-REPORT AND CHILD SELF-REPORT USING PEDSQL.

Lee YC, Yang HJ, Chen VC, et al.

Attention deficit hyperactivity disorder (ADHD) is a prevalent developmental disorder that seriously and negatively impacts a child's health-related quality of life (HRQOL). However, no meta-analysis has been conducted to examine the magnitude of impact, domains affected and factors moderating the impact. This review included nine studies that compared HRQOL of children or adolescents with ADHD with those with typical development using both child self-reports and parent proxy-reports. Seven among nine studies were meta-analytically synthesized to examine the degree of impact of ADHD on children and adolescents, parent-child discrepancy, and the moderators. The results indicate that ADHD impact a child's or adolescent's HRQOL negatively with a moderate effect in physical and a severe effect in psychosocial (i.e., emotional, social, and school) domains. Parental ratings of overall HRQOL in children or adolescents with ADHD were not significantly different from child's ratings when compared with typically developing children and adolescents. Age was negatively associated with all domains of HRQOL in children and adolescents with ADHD both by parent- and child-ratings, and the strongest effect was found in parental ratings of child's emotional HRQOL, with a moderate correlation. This meta-analysis suggests that HRQOL may be assessed in children and adolescents with ADHD both by parent proxy- and child self-reports, and that interventions may be planned accordingly. Future meta-analysis may explore how measures of HRQOL and other factors including child, parental, familiar and school characteristics influence the impact of ADHD and the parent-child agreement in children and adolescents

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Rev Colomb Psiquiatr. 2015 Apr;44:115-20.

SOCIODEMOGRAPHIC CHARACTERISTICS AND MENTAL DISORDERS IN CHILDREN AND ADOLESCENTS PSYCHIATRIC OUTPATIENT CLINIC CHILDREN OF MEDELLIN.

Ricardo-Ramirez C, Alvarez-Gomez M, Rodriguez-Gazquez ML.

INTRODUCTION: Mental disorders in the world affecting 15% to 30% in children and adolescents, altering its function and emotional, cognitive and social. Affect interpersonal relationships, school performance and increased substance use and the risk of suicide.

OBJECTIVE: describe the social-demographic characteristics and mental disorders of children and adolescents of psychiatric consultation.

METHOD: Retrospective descriptive study that analyzed all the histories of children and adolescents of both sexes from 5 to 16 years who attended for the first time outpatient psychiatry university clinic of Medellin, from July 2010 to July 2012.

RESULTS: We studied 197 patients, the average age was 11+/-3.5 years, male sex was the most common 69%, 46.2% belonged to nuclear family. The most prevalent psychiatric disorders were 44.2% ADHD, depressive disorders 9.1% and 8.1% TOC. 61% had psychiatric comorbidity, the most frequent was oppositional defiant disorder with ADHD 35.6%.

CONCLUSIONS: The frequency of mental disorders and comorbidities found in this study were similar to those reported by other researchers

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Rev Colomb Psiquiatr. 2015 Jul;44:150-58.

DESCRIPTION OF CLINICAL AND NEUROCOGNITIVE PROFILES IN OFFSPRING OF BIPOLAR-TYPE-I PARENTS FROM A MULTIMODAL INTERVENTION PROGRAM: PRISMA.

Palacio-Ortiz JD, Uribe-Villa E, Duque-Rios P, et al.

INTRODUCTION: Offspring of bipolar parents are a high risk population for the develop of mental diseases, their study allow determining the genetic risk, early symptoms, prodromes and psychopathology of bipolar disorder.

OBJECTIVE: To describe the psychopathological characteristics and neurocognitives profiles of the offspring of bipolar type I parents. And to identify the presence of sub-syndromal symptoms in all the symptom domains.
METHODS: A descriptive and cross-sectional study was conducted on 110 offspring between 6 and 30 years old. Semi-structured diagnostic interviews were performed. The intelectual coeficient was determined and a neuropsychological assessment was performed on 89 offspring.
RESULTS: The most prevalent disorder in the offspring was ADHD (27.6%), with major depression (15.5%) and separation anxiety (14.1%) also being prevalent. Seven patients of the sample were diagnosed with bipolar disorder. There was a statistically significant difference between the age groups for ADHD prevalence. The most frequent sub-syndromal symptoms were observed in the disruptive group. Alterations in the cognitive domains: attention, verbal fluency, work memory, and speed of information processing, were observed in the group younger than 18 years.
CONCLUSIONS: The offspring of bipolar parents have an elevated rate of psychopathology and cognitive alterations. They are a high risk population for the development of mental disease. These subjects also require close longitudinal observation and early and preventive therapeuthic interventions

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Rev Neurol. 2016 Jan;62:61-67.
THE IMPORTANCE OF SLEEP PROBLEMS IN CHILDREN WITH HEADACHE AND OTHER NEURODEVELOPMENTAL DISORDERS IN NEUROPAEDIATRIC SERVICES.
Perez-Villena A, Soto-Insuga V, Castano-De la Mota C, et al.
INTRODUCTION: Sleep disorders are common in children with neurological disorders. The aim of this study is to know the opinion of neuropediatricians and the prevalence of these disturbances in Spain. **PATIENTS AND METHODS**: Multicenter cross-sectional study (12 Spanish hospitals, 15 researchers). BEARS survey was collected in three groups: A (2-5 years), (6-12 years), and C (> 12 years). The opinion of neuropediatricians was also collected.
RESULTS: 939 questionnaires were filled. The main results in groups B and C were ADHD (32.4% and 30.1% respectively) and headache (25.1% and 27.6% respectively), whereas in group A neurodevelopmental disorders (32.4%) and epilepsy (21.4%) were the main diagnoses. Disturbances in at least one area of sleep were found in 92% of children in group A (n = 209, mean 3 years), 64.2% in group B (n = 534, mean 9.4 years) and 58.2% in group C (n = 196, mean 13.7 years). Sixty-one surveys were answered by neuropediatricians (16.75% of the total sent), estimating that less than a quarter of the patients (24.5%) suffered. Even, up to 23% of doctors claimed that the prevalence of sleep disorders was < 10%.
CONCLUSIONS: 58-92% of parents-patients under follow up at a neuropediatrician office in Spain have some degree of disturbed sleep. Although most neurologists emphasize the importance of an early diagnosis and treatment of sleep disorders in children with neurological disorders, its frequency is often underestimated (risk of underdiagnosis)

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Revista Brasileira de Psiquiatria. 2016;38:348-49.
SLEEP DURATION AND INTENSITY OF ADHD SYMPTOMS.
Gomes-Tiago AP, Costa DS, Alvim-Soares AM, et al.

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Scand J Psychol. 2015 Feb;56:53-61.
ASSOCIATIONS BETWEEN ATTACHMENT-RELATED SYMPTOMS AND LATER PSYCHOLOGICAL PROBLEMS AMONG INTERNATIONAL ADOPTEES: RESULTS FROM THE FINADO STUDY.
Elovainio M, Raaska H, Sinkkonen J, et al.
We examined the associations between attachment-related symptoms (symptoms of reactive attachment disorder (RAD), symptoms of disinhibited social engagement disorder (DSED), and clinging) and later

psychological problems among international adoptees. The study population comprised internationally adopted children (591 boys and 768 girls, 6-15 years) from the ongoing Finnish Adoption (FinAdo) study. Data were gathered with self-administered questionnaires both from adoptive parents and from adoptees aged over 9 years. Attachment-related symptoms were measured using of a short (8-item) questionnaire and later behavioral/emotional problems were assessed using the Child Behavior Checklist (CBCL) and the Five to Fifteen (FTF) scale for attention-deficit/hyperactivity disorder (ADHD) symptoms. RAD and DSED symptom subscales were associated with an increased risk of emotional and behavioral problems and ADHD. Especially the mixed type of attachment-related symptoms was strongly associated with later emotional and behavioral problems

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Scand J Psychol. 2015 Oct;56:489-97.

ANTISOCIAL BEHAVIOR REDUCES THE ASSOCIATION BETWEEN SUBDIMENSIONS OF ADHD SYMPTOMS AND ALCOHOL USE IN A LARGE POPULATION-BASED SAMPLE OF ADOLESCENTS.

Lovenhag S, Larm P, Aslund C, et al.

The aim of this study was to investigate possible effects of antisocial behavior on reducing the association between subdimensions of ADHD symptoms (inattention, hyperactivity and impulsivity) and alcohol use. Boys and girls were analyzed separately using a population-based Swedish adolescent sample. A randomly selected cross-sectional survey was performed in secondary and upper secondary schools in Vastmanland County during 2010. Participants were a population of 2,439 15-16 year-olds and 1,425 17-18 year-olds (1,947 girls and 1,917 boys). Psychosocial adversity, antisocial behaviors, symptoms of ADHD and alcohol use were assessed by questionnaires. Except for girls' inattention, subdimensions of ADHD symptoms were not associated with alcohol use when variance due to antisocial behavior was accounted for. Among boys, instead of an indirect effect of antisocial behavior on the association between impulsivity and alcohol use, a moderating effect was found. Among girls, the inattention component of ADHD was independently associated with alcohol use even when adjusted for antisocial behavior. The reduced associations between symptoms of hyperactivity, impulsivity, and alcohol use for boys and girls after adjusting for antisocial behavior suggest a considerable overlap between hyperactivity, impulsivity, and antisocial behavior. The direct pathway between inattention and alcohol use among girls suggests that girls with inattention symptoms are at risk of alcohol use regardless of antisocial behavior. Special attention should be given to these girls. Accounting for antisocial behavior reduced the relation between subdimensions of ADHD symptoms and alcohol use, and antisocial behaviors should therefore be screened for when symptoms of ADHD are present

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Sci Rep. 2016 Feb;6:21609.

MEDIATING EFFECT OF ANXIETY AND DEPRESSION ON THE RELATIONSHIP BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND SMOKING/DRINKING.

Tong L, Shi HJ, Zhang Z, et al.

Attention-deficit/hyperactivity disorder (ADHD) has been often found to be comorbid with other disorders, including anxiety, depression, and unhealthy behaviors such as drinking alcohol and smoking. These factors were often discussed separately, and the mediating effects of mental health on substance use are unknown. To study the mediating effects of anxiety and depression on the relationship between ADHD and drinking/smoking behaviors, we conducted a cross-sectional study of 1870 college students from Shanghai, China. The Adult ADHD Self-Report Scale (ASRS-v1.1) and Wender Utah Rating Scale (WURS) were used to identify the current and past ADHD. Structural Equation Modeling was carried out to clarify the mediating effect of anxiety and depression on the relationship between core ADHD symptoms and smoking/drinking behaviors. We found that inattention as one of the core symptoms of ADHD was associated with an increased risk of depression as a direct effect, as well as slightly increased risk of smoking/drinking behaviors by an indirect effect of depression. Hyperactivity-impulsivity, as another core symptom of ADHD had a robust impact on smoking and drinking behaviors, while being mediated by anxiety and depression. In conclusion,

anxiety and depression was associated with further increased risk behaviors of smoking/drinking alcohol among those students with ADHD

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Sci Rep. 2016 Jan;6:19664.

EVALUATION OF CHILDREN WITH ADHD ON THE BALL-SEARCH FIELD TASK.

Rosetti MF, Ulloa RE, Vargas-Vargas IL, et al.

Searching, defined for the purpose of the present study as the displacement of an individual to locate resources, is a fundamental behavior of all mobile organisms. In humans this behavior underlies many aspects of everyday life, involving cognitive processes such as sustained attention, memory and inhibition. We explored the performance of 36 treatment-free children diagnosed with attention-deficit hyperactivity disorder (ADHD) and 132 children from a control school sample on the ecologically based ball-search field task (BSFT), which required them to locate and collect golf balls in a large outdoor area. Children of both groups enjoyed the task and were motivated to participate in it. However, performance showed that ADHD-diagnosed subjects were significantly less efficient in their searching. We suggest that the BSFT provides a promising basis for developing more complex ecologically-derived tests that might help to better identify particular cognitive processes and impairments associated with ADHD

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Shiraz E Medical Journal. 2016;17.

EFFECTIVENESS OF METHYLPHENIDATE SUPPLEMENTED BY ZINC,CALCIUM,AND MAGNESIUM FOR TREATMENT OF ADHD PATIENTS IN THE CITY OF ZAHEDAN.

Firouzkouhi Moghaddam M, Rakhshani T, Khosravi M.

Background: This study investigates the therapeutic effect of a combination of methylphenidate and a zinc,calcium,and magnesium supplement for the treatment of attention deficit hyperactivity disorder (ADHD) in a population of children from the city of Zahedan.

Methods: This clinical trial involved 40 patients with ADHD aged 6 to 12. Simple convenience sampling was conducted and the patients were randomly divided into two groups: a case group which received methylphenidate and a zinc,calcium,and magnesium supplement; and a control group which received methylphenidate plus a placebo. Numerical variables were presented as a mean (SD) and nominal and categorized variables were summarized by absolute frequencies and percentages. To compare the baseline measurements between the two groups,a chi-square test,an independent t-test,and a paired test were used. The data analysis was done using the statistical software SPSS,version 18.0.

Results: The mean age of the children in the case group was 9.6 -¦ 1.5 years and that of the children in the control group was 8.9 -¦ 1.6 years (P = 0.235). Of the children,32 were boys (80%) and 8 were girls (20%) (P = 0.429). The mean for symptom severity in the case group was 40.4 -¦ 2.4 before treatment,and 19.5 -¦ 6.1 after 8 weeks of treatment (P < 0.001).

Conclusions: This study shows that a zinc,calcium,and magnesium supplement is effective in the treatment of ADHD

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Sleep Med. 2016 Jan;17:52-56.

SLEEP-PROMOTING MEDICATIONS IN CHILDREN: PHYSICIAN PRESCRIBING HABITS IN SOUTHWESTERN ONTARIO, CANADA.

Bock DE, Roach-Fox E, Seabrook JA, et al.

BACKGROUND: Research indicates that physicians may frequently use pharmacotherapy to treat pediatric insomnia despite minimal safety data and very limited indications. Canadian data on the subject are lacking. This study aimed to determine physicians' views on and prescribing habits for sleep-promoting over-the-counter medication (OTCM) and prescription (RXM) medications for children.

METHODS: A modified 26-item version of the 'Pediatric Sleep Medication Survey', originally developed by Judith Owens and colleagues, was sent to 100 pediatricians and a random sample of 421 family physicians in Southwestern Ontario, Canada.
RESULTS: A total of 67 returned surveys were sufficiently complete for analysis. Sixty-one respondents indicated their specialty (28 pediatricians, 33 family physicians). In a typical 6-month period, 89% and 66% of respondents have recommended OTCM and RXM, respectively, for children with sleep problems. Only 20% have received any formal training on pediatric sleep disorders. The most common circumstances and sleep problems for which OTCM or RXM were recommended were mood disorders, developmental delay and attention deficit hyperactivity disorder (ADHD) (56, 40, and 39%, respectively), and insomnia, bedtime struggles/delayed sleep onset and circadian rhythm disorders (52, 48, and 28%, respectively). A total of 30% recommended OTCM or RXM to otherwise healthy children with sleep problems. Melatonin (73%), OTC antihistamines (41%), antidepressants (37%), and benzodiazepines (29%) were the most commonly recommended OTCM and RXM, respectively.
CONCLUSIONS: Respondents in our sample frequently use pharmacotherapy to treat pediatric sleep problems; few have received any training in this area. Our findings indicate the need for evidence-based guidelines and regular physician training in the management of pediatric sleep disorders

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Sleep Med Rev. 2016.
SOMATIC AND NEUROPSYCHIATRIC COMORBIDITIES IN PEDIATRIC RESTLESS LEGS SYNDROME: A SYSTEMATIC REVIEW OF THE LITERATURE.
Angriman M, Cortese S, Bruni O.
Restless legs syndrome (RLS) is a relatively common neurological disorder in childhood, although it is usually overlooked due to the atypical presentation in children and associated comorbid conditions that may affect its clinical presentation. Here, we aimed to perform, for the first time, a systematic review of studies reporting the association between RLS in children and adolescents (<18 y) and somatic or neuropsychiatric conditions. We searched for peer-reviewed studies in PubMed, Ovid (including PsycINFO, Ovid MEDLINE-«, and Embase), Web of Knowledge (Web of Science, Biological abstracts, BIOSIS, FSTA) through November 2015, with no language restrictions. We found 42 pertinent studies. Based on the retrieved studies, we discuss the association between RLS and a number of conditions, including growing pains, kidney disease, migraine, diabetes, epilepsy, rheumatologic disorders, cardiovascular disease, liver and gastrointestinal disorders, and neuropsychiatric disorders (e.g., attention deficit hyperactivity disorder (ADHD), depression, and conduct disorder). Our systematic review provides empirical evidence supporting the notion that RLS in children is comorbid with a number of somatic and neuropsychiatric conditions. We posit that the awareness on comorbid diseases/disorders is pivotal to improve the diagnosis and management of RLS and might suggest fruitful avenues to elucidate the pathophysiology of RLS in children

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Soc Work Public Health. 2016;31:9-18.
TOWARD EFFECTIVE UTILIZATION OF THE PEDIATRIC EMERGENCY DEPARTMENT: THE CASE OF ADHD.
Lynch S, Bautista M, Freer C, et al.
This project's purpose was to characterize attention-deficit/hyperactivity disorder (ADHD)-related emergency department (ED) visits compared with other psychiatric visits made by children with Medicaid and to determine whether any visits were avoidable. Medicaid claims of children who visited the ED for mental health services were analyzed. Logistic regression was used to examine whether demographic, ED-, and system-level variables increased the odds of an ED visit for children with Medicaid, comparing those with ADHD to other psychiatric diagnoses. Children who were African American, arrived during the daytime, and lived in counties with mental health professional shortages had greater odds of an ED visit for ADHD compared to other psychiatric visits. Approximately 24% of all ED visits were for ADHD and about 30% of

these visits may have been avoidable. ADHD-related ED visits comprise a sizeable proportion of all ED visits. Some visits appeared to be emergent but possibly treatable in primary care

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Subst Use Misuse. 2016;51:508-16.

THE ROLE OF COUNTERFACTUAL THINKING ON ATTITUDES TOWARD ADHD MEDICATION USE.

Ramos AM, Becker B, Biemer JA, et al.

OBJECTIVE: Despite serious health risks, attitudes toward Attention-Deficit Hyperactivity Disorder (ADHD) medication use in college students remain favorable. Given the robust link between attitudes and behavior (e.g., the Theory of Planned Behavior), it is important to understand how these attitudes are developed and maintained. The current study examined the role of counterfactual, or "what if"' thinking as a mechanism for the development of attitudes toward ADHD medications.

METHOD: All participants (n = 190) were asked to read either a positive or negative scenario regarding ADHD medication misuse and rate their attitudes toward the behavior; half of the participants were also asked to generate counterfactuals prior to rating their attitudes.

RESULTS: Results suggest that scenario valence influenced the direction of counterfactual statements. Further, through the generation of upward counterfactuals, the negative scenario elicited more positive attitudes toward ADHD medication misuse.

CONCLUSIONS: Based on limited prior research, it is suggested that upward counterfactuals may allow individuals to explain away the misuse of ADHD medication and avoid negative emotions such as guilt and shame related to current or prior ADHD medication misuse. In sum, additional research is needed to confirm preliminary findings that suggest counterfactual thinking could be a precursor to ADHD medication misuse

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Tokai J Exp Clin Med. 2016 Mar;41:54-56.

AUTISM SPECTRUM DISORDER AND CHIARI 1 MALFORMATION CO-OCCURRING IN A CHILD.

Osuagwu FC, Amalraj B, Noveloso BD, et al.

Very few studies have shown associations between autism spectrum disorder, attention deficit hyperactivity disorder and Chiari 1 malformation. Here, we report an 10-year-old male that presented after having seizures with a history of Chiari 1 malformation, autism spectrum disorder and ADHD with moderate mental retardation and speech delay. This case highlights the fact that autism spectrum disorder as biologically based neurodevelopmental disorder with altered brain growth may be associated with Chiari 1 malformation and ADHD

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Value Health. 2016;19:A841.

A COST-EFFECTIVENESS ANALYSIS OF GUANFACINE EXTENDED-RELEASE TREATMENT IN PEDIATRIC ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Maeda S, Shimozuma K, Takeda Y.

Objectives: Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by hyperkinesia, impulsivity, and impaired attention. At present, only the stimulant methylphenidate (MPH) and the non-stimulant atomoxetine (ATX) are covered under insurance for the treatment of ADHD in Japan. In 2007, the non-stimulant guanfacine extended-release (GXR) was approved for use in the US, and joint development of the drug has also progressed in Japan. However, a cost-effectiveness analysis (CEAs) has yet to be conducted on the use of GXR in Japan. In this study, we performed a CEA of GXR treatment in pediatric patients with ADHD in Japan.

Methods: We constructed a Markov model to describe state transitions in ADHD, and conducted a CEA comparing the administration of GXR alone (0.075-0.12 mg/kg/day) with ATX alone (1.2 mg/kg/day). The analysis was conducted from the perspective of the public healthcare payer; reference cases comprised ADHD patients aged 6-18 years, and the study duration was one year. The quality-adjusted life year (QALY)

was used as the effect measure, and the final result of the CEA was presented as an incremental cost-effectiveness ratio (ICER). Costs (excluding GXR price) were calculated using the medical fee points list, and the drug price for GXR was calculated using the mean price of the US, UK, Germany, and France. The QALY value included in the model was adopted from one reported in a published ADHD study.
Results: When compared with the administration of ATX alone, the administration of GXR alone was associated with both a higher cost (approximately US$67) and effect (0.007 QALY); the ICER was approximately US$9600/QALY.
Conclusions: The results of this study indicate that when considering a willingness-to-pay threshold of US$50,000 per QALY, there is a high possibility that the use of GXR will be cost-effective as an ADHD treatment in Japan

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Value Health. 2016;19:A874.

POTENTIAL FACTORS PREDICTING THE RESPONSE IN THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CHILDREN WITH ATOMOXETINE IN ASIA PACIFIC REGION.

Chen Y, Zhang YL, Zhang X, et al.

Objectives: To assess the potential factors predicting the response in the treatment of attention-deficit/hyperactivity disorder (ADHD) children with atomoxetine in China Mainland, Taiwan, and South Korean.
Methods: A post-hoc analysis was done on a 24-week, prospective, open-label, multi-center, uncontrolled study of atomoxetine treatment. Participants were children aged 8 to 11 years, diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, naiumlve to ADHD medications, and met the symptomatic severity threshold of 1.5 standard deviations above the age and gender norm for the ADHD-IV-Parent:Inv Rating Scale (ADHDRS) total score (ADHDRS-TS). Good treatment response was defined as age;40% improvement in ADHDRS-TS from baseline to week 24. Multiple logistic regression analysis with stepwise effect selection method was used to determine the factors (including baseline characteristics, ADHDRS-TS change at week 4) associated with treatment response at week 24.
Results: Among 228 children, the mean (-¦SD) age was 9.6 (-¦0.96) years and 85.1% were males. Thirty-six percent were from China Mainland, followed by Taiwan (33.3%) and South Korea (30.7%). The mean ADHDRS-TS at baseline was 35.3(-¦7.1) and 61.8% children had the combined ADHD subtype. Four (1.75%) children had historical illness. At week 4, the mean ADHDRS-TS decreased by 34.4 (-¦22.3) from baseline. By week 24, 73.7% children experienced good treatment response. The odds of being good treatment response at week 24 significantly increased by a factor of 1.69 (95% CI: 1.40 to 2.05, < 0.0001) for each additional 10-points improvement in the ADHDRS-TS by week 4. The associations between treatment response and baseline characteristics were not detected.
Conclusions: Most ADHD children exhibited good treatment response to atomoxetine. The participants with ADHDRS-TS improvement by week 4 were more likely to achieve good treatment response at week 24, which indicates that early response to atomoxetine might be considered as a predictor of the ultimate response

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A NETWORK META-ANALYSIS OF ATOMOXETINE, METHYLPHENIDATE, LISDEXAMFETAMINE, AND BUPROPION FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.

Locatelli I, Veniínik K.

Objectives: According to the clinical guidelines, methylphenidate (MPH) and atomoxetine (ATX) are commonly used drug treatment options for attention deficit hyperactivity disorder (ADHD) in children. However, a new drug lisdexamfetamine (LDX) and established antidepressant bupropion (BUP) as off-label medication are possible treatment options. The aim of this study is to systematically review most recent evidence of clinical effects of drug treatments for ADHD in children under 18 years old.

Methods: A comprehensive literature search using MEDLINE and Clinical trials registers up to February 2016 was performed. Selection criteria were restricted to double-blind randomized controlled clinical trials evaluating the effect of ADHD drugs as head-to-head or placebo comparison. Studies shorter than 2 weeks or with crossover design were excluded. The effect of MPH was separately assessed for immediate release (MPH-IR) and modified release (MPH-MR) formulation. Clinical effect was defined as event rates of clinical improvement as assessed by decline in ADHD-RS questionnaire score by at least 25% or by improved CGI-I score. Pooled odds ratio (OR) were calculated using random effect models with Review Manager (Version 5.3.) and OpenBUGS (Release 3.2.3).
Results: In total 34 studies were identified, in the majority of them placebo was used as comparison. In 23 studies (among them 4 head-to-head) the clinical effect was assessed by ADHD-RS score, while in 27 studies (among them 6 head-to-head) CGI-I score was reported. MPH-IR, MPH-MR, ATX, and LDX showed significantly higher effect when compared to placebo. Results of studies with head-to-head comparison together with indirect comparison calculation revealed that MPH-MR is significantly better than MPH-IR (OR: 3.3 95% CI: 1.7-6.4) or ATX (OR: 1.9 95% CI: 1.4-2.4). Similar results were observed for LDX.
Conclusions: MPH-MR and LDX are more effective than MPH-IR and ATX. No firm evidence about the effect of bupropion can be concluded

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HYPERACTIVITY IN MOTOR RESPONSE INHIBITION NETWORKS IN UNMEDICATED CHILDREN WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER.

Massat I, Slama H, Villemonteix T, et al.

Objectives: Hypo/reduced activity in motor response inhibition (RI) cerebral networks was recently proposed as a promising specific neurobiological marker of attention deficit-hyperactivity disorder (ADHD). Before adopting such a pattern as a key diagnosis tool, we aim to replicate in an independent study the mechanisms underlying reduced RI-related activity in ADHD, after controlling for potentially confounding effects.
Methods: In this fMRI study, we investigated the neural networks mediating successful and failed motor RI in children with ADHD and typically developing children (TDC) using the stop-signal task (SST) paradigm.
Results: In contrast to hypofrontality predictions, children with ADHD exhibit increased neural activity during successful response inhibition in an RI-related brain network encompassing the indirect and/or hyperdirect pathways between the basal ganglia and cortex. Voxel-based morphometry analyses have further evidenced reduced grey matter volume in the left caudate in children with ADHD, which paralleled higher functional responses. Finally, connectivity analyses disclosed tighter coupling between a set of cortical regions and the right caudate as well as the right IFG, networks involved in successful RI.
Conclusions: Hypo/reduced activity in RI cerebral networks in children with ADHD cannot at this time be considered as a systematic biomarker for ADHD.

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Cognitive-behavioral therapy for externalizing disorders: A meta-analysis of treatment effectiveness

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ABSTRACT

Externalizing disorders are the most common and persistent forms of maladjustment in childhood. The aim of this study was to conduct a meta-analysis evaluating the effectiveness of Cognitive Behavioral Therapy (CBT) to reduce externalizing symptoms in two disorders: Attention Deficit Hyperactivity Disorder (ADHD) and Oppositive Defiant Disorder (ODD). The efficacy of CBT to improve social competence and positive parenting and reduce internalizing behaviors, parent stress and maternal depression was also explored. The database PsycInfo, PsycARTICLES, Medline and PubMed were searched to identify relevant studies. Twenty-one trials met the inclusion criteria.

Results showed that the biggest improvement, after CBT, was in ODD symptoms (−0.879) followed by parental stress (−0.607), externalizing symptoms (−0.52), parenting skills (−0.381), social competence (−0.390) and ADHD symptoms (−0.343). CBT was also associated with improved attention (−0.378), aggressive behaviors (−0.284), internalizing symptoms (−0.272) and maternal depressive symptoms (−0.231).

Overall, CBT is an effective treatment option for externalizing disorders and is also associated with reduced parental distress and maternal depressive symptoms. Multimodal treatments targeting both children and caregivers' symptoms (e.g. maternal depressive symptoms) appear important to produce sustained and generalized benefits.

1. Introduction

The estimated prevalence of psychiatric disorders in youth ranges between 10% and 20% (Belfer, 2008; Jaffee, Harrington, Cohen, & Moffitt, 2005). Quality of life in children with mental health issues is poorer than quality of life in healthy children and children suffering from chronic physical illness (Bastiaansen, Koot, Ferdinand, & Verhulst, 2004; Sawyer et al., 2002). If not treated early and effectively, these conditions produce significant adverse outcomes in adulthood, including detrimental, longer-term effects on social relationships, health, and economic success (Karantanos, 2012; Loth, Drabick, Leibenluft, & Hulvershorn, 2014).

Externalizing disorders are common disorders in children (American Psychiatric Association, 2000) and include the diagnoses of Attention Deficit Hyperactivity Disorder (ADHD), Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD). The genetic risk for developing these conditions seems to be greater in the context of impaired parent–child relationships (Samek et al., 2014). After illness onset, externalizing symptoms continue disrupting interpersonal relationships. Parents can show controlling and punitive behaviors, are often less responsive to their children's needs (Hechtman et al., 2004) and can develop psychopathological symptoms themselves (Shin & Stein, 2008).

Results from a 24-year longitudinal study showed that externalizing symptoms in childhood predict disruptive behaviors in adulthood, as well as anxiety, mood and substance use disorders (Reef, Diamantopoulou, van Meurs, Verhulst, & van der Ende, 2011) and a recent meta-analysis found that externalizing disorders are associated with the later development of unipolar depression (Loth

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et al., 2014). Due to the detrimental and long term effects of externalizing disorders on the individual and their families, timely and effective treatments appear to be crucial.

A range of psychological strategies are currently employed to target externalizing symptoms. Multimodal and extensive treatments are recommended, including psychoeducation, behavioral and cognitive behavioral therapy (CBT), interpersonal psychotherapy, family therapy, school-based interventions, social skills training and parent management training (PT), (Lochman, Powell, Boxmeyer, & Jimenez-Camargo, 2011; Masi et al., 2014; NICE, 2013). These treatments can involve individual and family psychotherapy, medication and sociotherapy (Steiner & Remsing, 2007). Cognitive and emotional strategies such as emotion awareness, perspective taking, anger management and problem solving are usually employed and homework are used to enhance motivation and generalization of skills to everyday life (Lochman et al., 2011).

Despite the large availability of data showing the efficacy of CBT techniques to reduce externalizing symptoms (Lochman et al., 2011; Steiner & Remsing, 2007), no quantitative syntheses of findings have been published so far. Thus, the aim of this paper was to conduct a meta-analysis of studies investigating the effectiveness of CBT in reducing externalizing symptoms in children and adolescents. Externalizing, ADHD and ODD symptoms were considered as primary outcomes. Secondary outcomes included social competence, internalizing behavior, parent stress, positive parenting and maternal depression.

2. Method

2.1. Search procedure

MC and OIL conducted the literature research independently and screened titles and abstracts to check studies' eligibility; GB and VC examined the full texts of the identified studies and extracted the data for descriptive and statistical purposes.

The electronic databases PUBMED, MEDLINE, PsycINFO and PsycArticles were searched to identify relevant research articles. Date limits were set from January 1980 (i.e. date of publication of the DSM III) to December 2012. The search terms used were: "Cognitive behavioral therapy" OR "CBT" linked to "externalizing" OR "ADHD" OR "ODD" OR "CD" OR "anger control" OR "anger management" OR "anger treatment".

The reference lists of the papers selected were inspected to identify further eligible studies. Data from unpublished studies were not included.

2.2. Selection criteria

Six inclusion criteria were used: 1) the study investigated the effects of CBT in externalizing disorders using a randomized controlled trial (RCT) design; 2) study participants were younger than 18 years old, 3) the treatment tested was cognitive or behavioral or cognitive-behavioral therapy; 4) the study included a control group (participants on a waiting list or a different treatment group); 5) the diagnostic criteria for an externalizing disorder (ADHD, ODD, CD) were met and 6) the outcome measures were evaluated pre- and post-treatment.

Data were obtained through clinical observations, interviews or questionnaires and reported by parents, teachers and children/adolescents.

2.3. Data extraction

Information about: (1) study's authors and year of publication); (2) sample size and demographics (i.e. age, gender, nationality); (3) treatment target (i.e. parents, teachers, children or combined); (4) measures used; (5) participants reporting on outcome measures (i.e. mothers, fathers or both, teachers, children); (6) participants' diagnoses; (7) type of intervention used and control groups; (8) time of follow-up assessments, (9) study design and quality analysis. Means and standard deviations (SDs) of the outcome measures were also extracted. The primary outcome measures considered were: externalizing behaviors and ADHD and ODD symptoms measured using validated standardized questionnaires (see Table 1). Secondary outcomes were: attention, aggressive behavior, social competence, internalizing behavior, parent stress, positive parenting and maternal depression as measured through validated standardized questionnaires (see Table 1 for details).

Conduct disorder's symptoms were not included amongst the outcome measures as a sufficient number of studies to conduct the analyses were not available.

2.4. Meta-analysis

All meta-analytic computations were performed using the software Comprehensive Meta-analysis (version 2; Borenstein, Hedges, Higgins, & Rothstein, 2011). Pre- and post-treatment means and SDs were entered for each outcome measure and the pre–post change was calculated. A separate meta-analysis was performed for each outcome variable. Effect sizes were calculated (Cohen's *d*). Effect sizes ranging between 0.56 and 1.2 were considered large, effect sizes ranging between 0.33 and 0.55 were considered as moderate and effect sizes ranging from 0 to 0.32 were considered negligible (Lipsey & Wilson, 1993).

The treatment effect was considered to be significant (effect size of 0.5) when the mean of the trained group was half standard deviation larger than the mean of the control group. Final effect sizes ±3 SDs above or below the weighted mean effect size estimate in each data set were identified as outliers and the corresponding studies were excluded from the analyses (Hedges, 1985).

A random effects model was used for the meta-analysis due to the differences identified between studies (Higgins, Thompson, Deeks, & Altman, 2003). The Q-statistic was calculated as indicator of homogeneity. A significant Q rejects the null hypothesis of homogeneity and indicates that the variability among the effect sizes is greater than what is likely to result from subject-level sampling error alone.

The I^2-statistic was calculated as an indicator of heterogeneity in percentages. A value of 0% stands for a no observed heterogeneity and larger values indicate increasing heterogeneity (i.e. 25% considered as low, 50% as moderate and 75% as high heterogeneity).

Specific subgroup analyses were conducted to investigate the variability between studies. These analyses included the different diagnostic groups (ADHD, ODD, CD), responders (mother, father, both parents, teachers) and intervention targets (children, parents, teachers).

A meta-analytic calculation was conducted when at least three studies included the variables considered.

2.5. Assessment of quality

The methodological quality of the studies selected for the meta-analysis was assessed independently by the authors using the Critical Appraisal Skills Programme (CASP) for RCTs (Bradley & Hill, 2001). Data from the qualitative assessment are reported in a previous manuscript (Baglioni et al., 2009). Only studies that reached a cut-off quality score of 60% were included in the meta-analysis.

Table 1
Summary table of the characteristics of the sample and description of treatment conditions.

Authors (year)	Sample characteristics N/mean age of children/percentage of female/ethnic composition	Disorder of children	Treatment	Control condition	Measures	Responders	Receivers of the intervention	Outcome
Barkley, Edwards, Laneri, Fletcher, and Metevia (2001)	N = 39/58 Mean age:14.2/15 %F: 13/10 Ethnic composition:86% Caucasian, 9% Hispanic, 2% African American, 3% Asian	ADHD/ODD	Problem Solving Communication Training (PSCT)	Behavioral Management Training (PSCT + BMT)	Rating of ADHD/ODD Symptoms	Mother/ Father/ Children	Children and Parents	ADHD/ODD/ Aggressive Behavior
Drugli, Larsson, Fossum, and Morch (2010)	N = 54/45 Mean age: nr/nr %F:17/25 Ethnic composition: 100% native caucasian	CD/ODD	Parent Training (PT) PT + Child Therapy (CT)	Waiting List Waiting List	PPI-Positive Parenting Index CBCL-Aggressive PSI-Parent Stress Index BDI	Mothers	Parents Children and Parents	Positive Parenting Aggressive Behavior Parent Stress Mother Depression
Drugli and Larsson (2006)	N = 52/28 Mean age:6.6/6.6 %F: 20/20	CD/ODD	Parent Training (PT)	Waiting List	CBCL	Parents	Parents	Attention Aggressive Behavior
	N = 47/28 Mean age:6.6/6.6 %F:20/20 Ethnic composition:99% native. caucasian		PT + Child Therapy (CT)	Waiting List			Children and Parents	Social Competence Internalizing Behavior
Fehlings, Roberts, Humphries, and Dawe (1991)	N = 13/13 Mean age:9.3/9.6 %F:0/0 Ethnic composition: n.r.	ADHD	CBT	Supportive Therapy	Werry Weiss Activity Scale Behavior Problem Checklist-Attention Problems Self Control Rating Scale	Parents Teachers	Children	ADHD Attention Externalizing Behavior
Grasmann and Stadler (2011)	N = 18/18 Mean age:11/10.5 %F:0/0 Ethnic composition: nr	CD	PT + Child Therapy (CT)	Waiting List	Conners Scale Aggression Scale FBB Oppositional-Aggression Scale FBB	Parents	Children and Parents	ADHD Aggressive Behavior ODD
Hemphill and Littlefield (2001)	N = 102/37 Mean age:8.88/8.54 %F:22.26/3.9 Ethnic composition: n.r.	Externalizing problems	PT + Child Therapy (CT)	Waiting List	CBCL TRF	Parents Teachers	Children and Parents	Externalizing Behavior Internalizing Behavior Social Competence
Jones, Daley, Hutchings, Bywater, and Eames (2007)	N = 50/29 Mean age:46.50/45.90 %F:32/32 Ethnic composition: 100% native caucasian	ADHD	Parent Training (PT)	Waiting List	Conners Scale	Parents	Parents	ADHD
Kratochwill, Elliott, Loitz, Sladeczek, and Carlson (2003)	N = 68/21 Mean age:4.4/4.4 %F:30/30 Ethnic composition: 54% minorities (African Americans, Hispanics, Southeast Asians); 46% native USA	Externalizing and Internalizing problems	Child Therapy (CT)	no treatment	SSRS	Parents Teachers	Children	Social Competence
Larsson et al. (2009)	N = 45/28 Mean age:6.40/6.90 %F:	CD-ODD	Parent Training (PT)	Waiting List	PPI PSI CBCL	Mother Father	Parents	Externalizing Behavior Attention
	N = 52/28 Mean age:6.70/6.90 %F:21.2/21.4 Ethnic composition: 100% native caucasian		Parent Training (PT) + Child Therapy (CT)	Waiting List	ECBI		Parents Teachers	Aggressive Behavior Internalizing Behavior Parent Stress Positive Parenting
Lipman et al. (2006)	N = 52/47 Mean age:9.3/9 %F:19.4/14.8 Ethnic composition: n.r.	Externalizing problems	Family/child/home psychoeducational program	Self Help	BCFPI Children's Inventory of Anger Children's Hostility	Children Parents	Children and Parents	Externalizing Behavior Aggressive Behavior Parent Stress

(continued on next page)

Table 1 (*continued*)

Authors (year)	Sample characteristics N/mean age of children/percentage of female/ethnic composition	Disorder of children	Treatment	Control condition	Measures	Responders	Receivers of the intervention	Outcome
					Index PSI- Parent Stress Index			
Matos, Bauermeister, and Bernal (2009)	N = 20/12 Mean age: 4.6/3.5 %F:nr Ethnic composition: 100% native Hispanic	ADHD	Parent–Child Interaction Therapy	Waiting List	ECBI - Intensity DBRS - Inattention BASC - Aggression FEI – Familiar Experience Index PPI- Positive Parenting Index BASC -Hyperactivity DPRS-ODD BDI	Parents Mother	Children and Parents	Externalizing Behavior Attention Aggressive Behavior Parent Stress Positive Parenting ADHD ODD Mother Depression
McGilloway et al. (2012)	N = 103/46 Mean age:4.11/4.7 %F:42.6/33 Ethnic composition: nr	CD	Incredible Years Basic PT	Waiting List	ECBI Social Competence Scale PSI PPI Conners Scale BDI	Parents Mothers	Parents	Externalizing Behavior Social Competence Parent Stress Positive Parenting ADHD Mother Depression
Nitkowski, Petermann, Büttner, Krause-Leipoldt, and Petermann (2009)	N = 12/12 Mean age:10.2/10 %F:0/25 Ethnic composition: n.r.	CD/ODD	Training for Aggressive Children (TAC)	Waiting List	CBCL TRF SDQ	Parents Teacher	Children	Externalizing Behavior Attention Aggressive Behavior Social Competence
Nixon, Sweeney, Erickson, and Touyz (2003)	N = 17/17 Mean age:46.75/46.75 %F: 17.64/35.29 N = 20/17 Mean age:/46.75 %F:33.33/35.29 Ethnic composition: 100% native australian	ODD	Standard treatment (PCIT) Abbreviated Treatment (PCIT videotape)	Waiting List Waiting List	CBCL ODD Sx PSI	Parents	Children and Parents	Externalizing Behavior Parent Stress ODD
Pfiffner et al. (2007)	N = 36/33 Mean age:8.7/8.7 %F:33.33 Ethnic composition: white 51%; Asian 16%; Hispanic 10%; African American 6%; Mixed 17%	ADHD	Child Life and Attention Skills Program	No treatment	DSM-IV inattention symptom count SSRS	Parents	Children	Attention Social Competence
Scott et al. (2010)	N = 51/45 Mean age:5.18/5.24 %F:32/27 Ethnic composition:37.5% minorities; 62.5% caucasian	CD/ODD/ ADHD	Incredible Years	Self-help	CBCL	Parents	Children and Parents	Externalizing Behavior
Webster-Stratton (1984)	N = 11/11 Mean age:5.20/4.92 %F:45.45/27.27 Ethnic composition: n.r. N = 11/11 Mean age:5.20/4.92 %F:45.45/27.27 Ethnic composition: n.r.	CD	Videotape Individual Therapy	Waiting List Waiting List	CBCL Prosocial Behavior	Parents		Externalizing Behavior Social Competence
Webster-Stratton (1994)	N = 64/39 Mean age:4.89/nr %F: 25.5/0 Ethnic composition: n.r.	ODD	Parent Training advance	Parent Training	CBCL PSI BDI	Mother Father	Children and Parents	Social Competence Parent Stress Mother Depression
Webster-Stratton and Hammond (1997)	N = 27/22 Mean age:5.33/5.64 %F:19.2/31.8 Ethnic composition: 84.6% caucasian	CD/ODD	Parent Training (PT)	Waiting List	ECBI PSI	Mother Father	Parents	Externalizing Behavior Parent Stress

Table 1 (*continued*)

Authors (year)	Sample characteristics N/mean age of children/percentage of female/ethnic composition	Disorder of children	Treatment	Control condition	Measures	Responders	Receivers of the intervention	Outcome
	N = 26/22 Mean age:5.95/5.64 %F:25.9/31.8 Ethnic composition: 88.9.% caucasian		Child Therapy (CT)	Waiting List			Children	
	N = 22/22 Mean age:6.06/5.64 %F:27.3/31.8 Ethnic composition: 81.8% caucasian		Parent Training (PT) + Child Therapy (CT)	Waiting List			Children and Parents	
Webster-Stratton, Reid and Hammond (2004)	N = 31/26 Mean age:5.85/5.86 %F: 9.70/11.5 Ethnic composition:: 71.%/84.6% Euro-American	ODD	Parent Training	Waiting List	Conduct Problems Child Social Competence with Peers	Mother Father Teacher	Parents	Externalizing Behavior Social Competence Positive Parenting
	N = 24/26 Mean age:5.63/5.86 %F:8.33/11.5 Ethnic composition: 83.33%/84.6% Euro-American		Parent Training + Teacher Training	Waiting List	Positive Parenting		Parents and Teacher	
	N = 30/26 Mean age:6.12/5.86 %F: 6.7/11.5 Ethnic composition: 83.3%/84.6% Euro-American		Child Therapy	Waiting List			Children	
	N = 23/26 Mean age: 6.21/5.86 %F:8.7/11.5 Ethnic composition: 78.3%/84.6% Euro-American		Child Therapy + Teacher Training	Waiting List			Children and Teacher	
	N = 25/26 Mean age:5.82/5.86 %F:16/11.5 Ethnic composition: 72%/84.6% Euro-American		Child Therapy + Parent Training + Teacher Training	Waiting List			Parents, Children and Teacher	
Webster-Stratton, Reid, and Beauchaine (2011)	N = 49/50 Mean age:5.34/5.37 %F:27/22 Ethnic composition: n.r.	ADHD	Incredible Years (Parent Training + Child Therapy)	Waiting List	CBCL TRF CTRS-R PPI Conners Scale Mother Report Social Competence	Mother Father Teacher	Parents, Children	Externalizing Behavior Attention Aggressive Behavior Social Competence Internalizing Behavior Positive Parenting ADHD ODD

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; ODD = Opposition Defiant Disorder; CD = Conduct Disorder; PCIT = Parent–Child Interaction Therapy; PPI = Positive Parenting Index; CBCL = Child Behavior Checklist; PSI = Parent Stress Index; BDI = Beck Depression Inventory; TRF = Teacher Report Form; SSRS = Social Skills Rating System; ECBI = Eyberg Child Behavior Inventory; BCFPI = Brief Child and Family Phone Interview; DBRS = Disruptive Behavior Scale for Children; BASC = Behavior Assessment System for Children Observation; FEI = Familiar Experience Index; SDQ = Strengths Difficulties Questionnaire; CCTRS = Conners'Rating Scales Revised; nr = non reported.

3. Results

3.1. Study characteristics

The search flow is shown in Fig. 1. A total of 108 abstracts were identified. Titles and abstracts' screening led to select 79 studies. Twenty-four studies were included after reading the full text. It was not possible to calculate the effect size for three studies, thus the final number of studies included in the meta-analysis was 21. Table 1 shows the studies' characteristics in relation to: a) participants' sample; b) participants' diagnosis; c) type of interventions used in experimental and control conditions; d) intervention recipients; e) outcome measures used; f) participants providing the outcome measures.

Six studies evaluated more than one experimental condition. A total of 1960 participants were recruited in the studies. The following variables were calculated for the total sample: mean age of children; percentage of females included; mean age of mothers (data available for 8 studies) and children's mean IQ (data available for 7 studies). Children had a mean age of 7 (SD = 2.7) and a mean IQ of 104.6 (SD = 6.2). The 22.8% of participants included in the study were females. The mean age of mothers was 34.5 (SD = 3.7).

3.2. Meta-analytic calculation

Ten meta-analyses were conducted on: externalizing behavior, ADHD symptoms, ODD symptoms, internalizing behavior, attention, aggressive behavior, social competence, parental stress, positive parenting and maternal depression. Subgroup analyses were conducted for each outcome to investigate heterogeneous results.

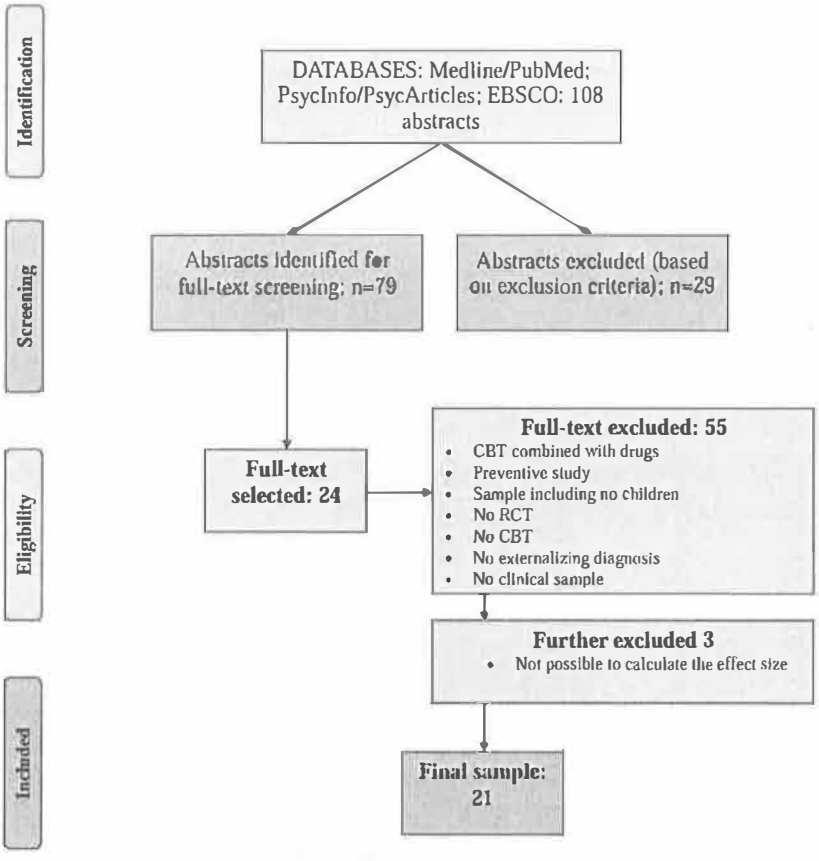


Fig. 1. Flow chart of the literature search and identification of randomized-controlled trials (RCTs) included in this systematic review.

Sources of variability which were evaluated when a sufficient amount of data was available are: diagnoses (including ADHD; ODD and CD); responders (mother, father, both parents, teachers) and intervention targets (children, parents, teachers). Outliers were identified and are listed in the Supplementary Table 1 (S1).

3.3. Efficacy of CBT on primary outcomes

3.3.1. Externalizing symptoms measured through validated standardized questionnaires

Overall, a moderate benefit of CBT on externalizing symptoms was found ($d = -0.52$; 95% CI [−0.68, −0.36]; $z = -6.31$; N = 19; $p < 0.001$; Q-value = 26.91; df(Q) = 18; p = 0.08; and $I^2 = 33.10$) compared to other treatment/control conditions.

The forest plot is shown in Fig. 2.

The subgroup analysis on responders (parents and teachers) showed that parents reported a large improvement in externalizing symptoms following CBT ($d = -0.603$; 95% CI [−0.865, −0.341], N = 10, $p < 0.001$; Q-value = 16.35; df(Q) = 9; p = 0.06; and $I^2 = 44.97$), whereas teachers reported only a moderate improvement ($d = -0.430$; 95% CI [−0.619, −0.240], N = 9, $p < 0.001$; Q-value = 9.135; df(Q) = 8; p = 0.331; and $I^2 = 12.43$).

Subgroup analysis evaluating externalizing symptoms separately depending on the diagnosis (ADHD, ODD, CD) showed the following results. Children with a diagnosis of ADHD showed a moderate symptomatic improvement ($d = -0.404$; 95% CI [−0.710, −0.097], N = 6, $p < 0.01$; Q-value = 10.28; df(Q) = 5; p = 0.06; and $I^2 = 51.38$), whereas greater therapeutic effects were found in children with a diagnosis of ODD ($d = -0.785$; 95% CI [−0.932, −0.638], N = 17, $p < 0.001$; Q-value = 15.64; df(Q) = 16; p = 0.478; and $I^2 = 0$) and CD ($d = -1$; 95% CI [−1.680, −0.320], N = 3, p = 0.004; Q-value = 5.30; df(Q) = 2; p = 0.07; and $I^2 = 62.28$).

Subgroup analysis on intervention targets showed that treatments directed to children only ($d = -0.452$; 95% CI [−0.696, −0.209], N = 9, $p < 0.001$; Q-value = 10.24 df(Q) = 8; p = 0.25; and $I^2 = 21.86$) or delivered to children and parents together produced a moderate effect on symptoms ($d = -0.549$; 95% CI [−0.738, −0.359], N = 15, $p < 0.001$; Q-value = 25.76; df(Q) = 14; p = 0.028; and $I^2 = 45.65$). CBT delivered exclusively to parents ($d = -0.917$; 95% CI [−1.226, −0.609], N = 8, $p < 0.001$; Q-value = 15.24; df(Q) = 7; p = 0.016; and $I^2 = 59.39$), or to children and teachers ($d = -0.871$; 95% CI [−1.226, −0.517], N = 3, $p < 0.001$; Q-value = 0.64; df(Q) = 2; p = 0.726; and $I^2 = 0$) produced greater symptomatic improvement (i.e. large effect sizes).

3.3.2. ADHD symptoms measured through validated standardized questionnaires

Overall, a moderate benefit of CBT on ADHD symptoms was found (d = −0.343; 95% CI [−0.638, −0.049]; z = −2.286; N = 11; p = 0.022; Q-value = 40.00; df(Q) = 10; $p < 0.001$; and I2 = 75.00%) compared to other treatment/control conditions.

The forest plot is shown in Fig. 3.

Parents reported a large improvement in children's ADHD symptoms ($d = -0.677$; 95% CI [−0.912, −0.441], N = 5, $p < 0.001$; Q-value = 2.35; df(Q) = 4; p = 0.671; and I2 = 0). The small numbers of studies reporting teachers (N = 1), children (N = 1), mother (N = 2) or father (N = 2)' ratings only did not allow to

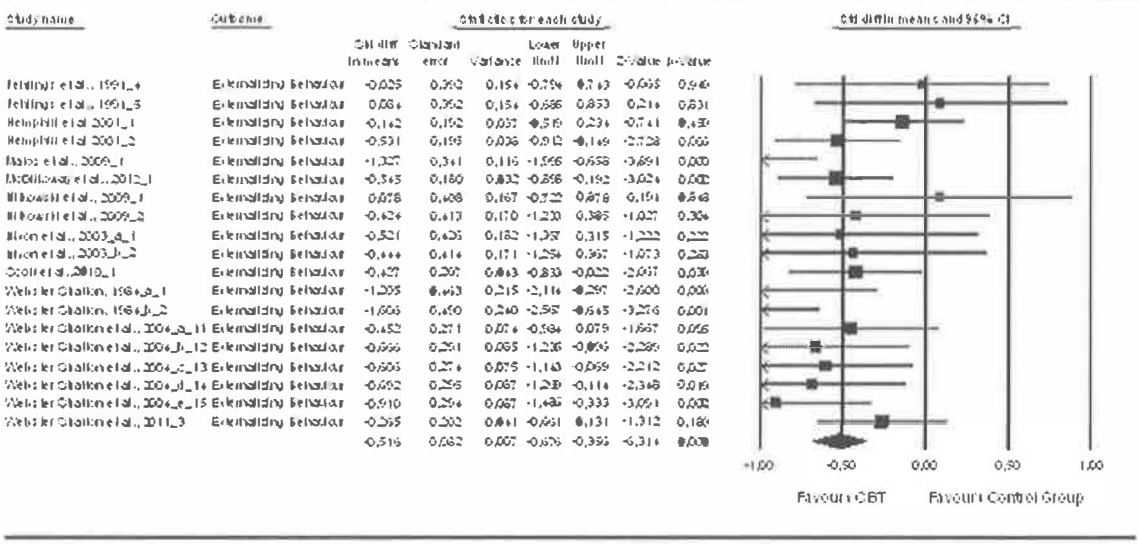


Fig. 2. Forest Plot of meta-analysis of efficacy of CBT on externalizing symptoms.

calculate the mean effect size for these responders.

A medium sized reduction of ADHD symptoms was found in children with a diagnosis of ADHD (d = −0.549; 95% CI [−0.774, −0.324], N = 6, p < 0.001; Q-value = 6.41; df(Q) = 5; p = 0.268; and I2 = 21.98). Analyses for the other diagnostic subgroups were not possible as no studies measured ADHD symptoms in children with a diagnosis of ODD and only two studies included children affected by CD.

A negligible effect of CBT was found when treatment was delivered to children and parent together (d = −0.264; 95% CI [−0.651, −0.124], N = 8, p = 0.182; Q-value = 34.91; df(Q) = 7; p < 0.001; and I2 = 79.95). Analyses on treatment's efficacy when only parents or children were included were not conducted due to an insufficient number of studies.

3.3.3. ODD symptoms measured through validated standardized questionnaires

Overall, a large improvement in ODD symptoms was found when CBT's efficacy was assessed against other treatment/control conditions (d = −0.879; 95% CI [−1.244, −0.513]; z = −4.712; N = 10; p < 0.001; Q-value = 39.18; df(Q) = 9; p < 0.001; and I2 = 77.03%).

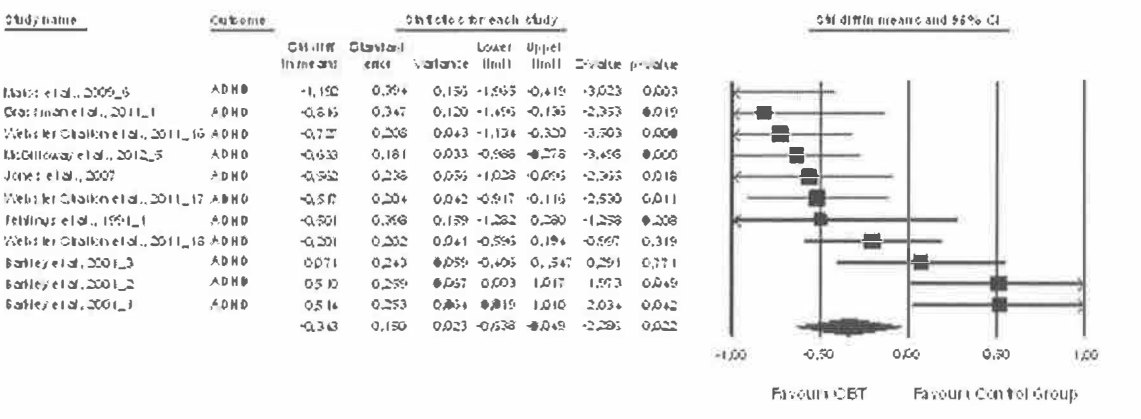
The forest plot is shown in Fig. 4.

Parents reported a large improvement in children's ODD symptoms following CBT (d = −0.809; 95% CI [−1.195, −0.422], N = 4, p < 0.001; Q-value = 3.877; df(Q) = 3; p = 0.275; and I2 = 22.62). The small number of studies reporting teachers, children, mother or father's ratings of ODD symptoms did not allow conducting analyses on these groups.

A moderate reduction of ODD symptoms in children with a diagnosis of ADHD was found (d = −0.494; 95% CI [−0.715, −0.273], N = 4, p < 0.001; Q-value = 7.60; df(Q) = 3; p = 0.055; and I2 = 60.54). Analyses on other diagnostic groups were not possible due to the small number of studies available (ODD = 2 studies and CD = 1 study). The intervention was delivered to both children and parents in all the studies reporting on ODD symptoms reduction.

3.4. Efficacy of CBT on secondary outcomes

Compared to other treatment/control conditions, CBT was associated with:



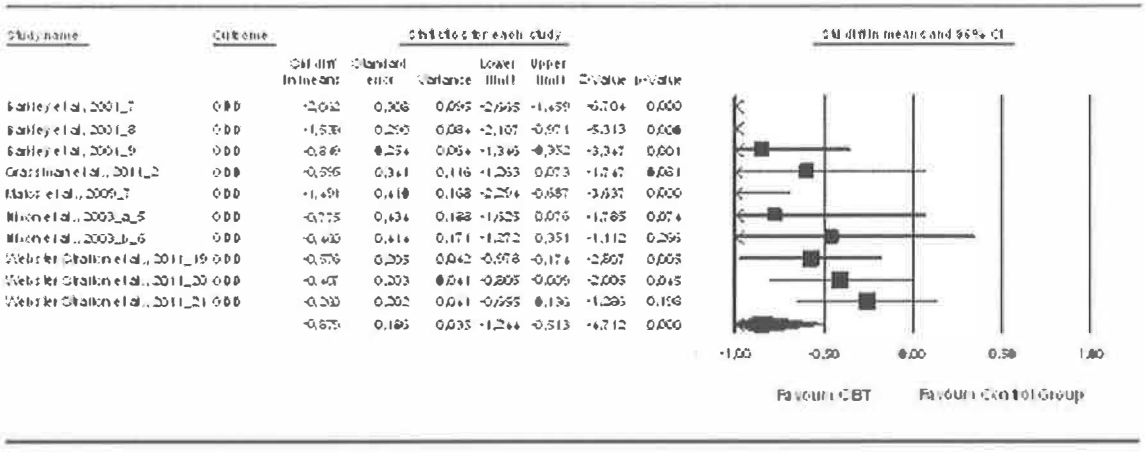


Fig. 4. Forest Plots of meta-analysis of efficacy of CBT on ODD symptoms.

- A small reduction in children's internalizing behaviors ($d = -0.272$; 95% CI [−0.414, −0.131]; z = −3.773; N = 11; p < 0.001; Q-value = 5.98; df(Q) = 10; p = 0.817; and I^2 = 0%; Forest Plot shown in Figure S1).
- A moderate reduction in children's attention deficits ($d = -0.378$; 95% CI [−0.522, −0.234]; z = −5.143; N = 15; p < 0.001; Q-value = 10.01; df(Q) = 14; p = 0.762; and I^2 = 0%; Forest Plot in Figure S2);
- and a small decrease in aggressive behavior ($d = -0.284$; 95% CI [−0.464, −0.104]; z = −3.088; N = 18; p = 0.002; Q-value = 34.87; df(Q) = 17; p = 0.006; and I^2 = 51.24%: Forest Plot in Figure S3).
- A moderate increase in children's social competence (d = 0.390; 95% CI [0.258, 0.522]; z = 5.800; N = 22; p < 0.001; Q-value = 27.42; df(Q) = 21; p = 0.157; and I^2 = 23.41%; Forest Plot in Figure S4).
- A large parental stress reduction ($d = -0.607$; 95% CI [−0.803, −0.412]; z = −6.085; N = 17; p < 0.001; Q-value = 35.18; df(Q) = 16; p = 0.004; and I^2 = 54.51; Forest Plot shown in Figure S5).
- The use of more effective parenting strategies (d = 0.381; 95% CI [0.098, 0.665]; z = 2.634; N = 19; p = 0.008; Q-value = 61.70; df(Q) = 18; p < 0.001; and I^2 = 70.83%; Forest Plot shown in Figure S6).
- Improved depressive symptoms in mothers ($d = -0.231$; 95% CI [−0.441, −0.021]; z = −2.155; N = 4; p = 0.031; Q-value = 2.141; df(Q) = 3; p = 0.544; and I^2 = 0%; Forest Plot shown in Figure S7).

3.4.1. Source of variability on secondary outcomes: responders

Of note, not enough studies were available for children as responders. Mothers reported a significant reduction in children's internalizing behavior ($d = -0.394$; 95% CI [−0.685, −0.103], N = 3, p = 0.008; Q-value = 1.64; df(Q) = 2; p = 0.441; and I^2 = 0), whereas father reported only a negligible change ($d = -0.111$; 95% CI [−0.398, −0.176], N = 3, p = 0.449; Q-value = 0.705; df(Q) = 2; p = 0.703; and I^2 = 0). Mothers and fathers reported a similar, significant reduction of attention deficits after treatment (Mothers: $d = -0.422$; 95% CI [−0.714, −0.131], N = 3, p = 0.005; Q-value = 0.094; df(Q) = 2; p = 0.954; and I^2 = 0; Fathers: $d = -0.315$; 95% CI [−0.602, −0.027], N = 3, p = 0.032; Q-value = 0.185; df(Q) = 2; p = 0.911; and I^2 = 0).

Teachers' reported small, non significant changes in inattention symptoms ($d = -0.147$; 95% CI [−0.469, −0.175], N = 3, p = 0.371; Q-value = 0.675; df(Q) = 2; p = 0.714; and I^2 = 0). Similarly, whilst parents reported significant changes in children's social competence after treatment (d = 0.499; 95% CI [0.325, 0.674], N = 10, p < 0.001; Q-value = 8.160; df(Q) = 9; p = 0.518; and I^2 = 0%), teachers reported smaller changes (d = 0.264; 95% CI [0.010, −.519], N = 8, p = 0.042; Q-value = 9.79; df(Q) = 7; p = 0.201; and I^2 = 28.50).

3.4.2. Source of variability on secondary outcomes: diagnosis

Moderate changes in social competence were found in children with a diagnosis of ADHD (d = 0.469; 95% CI [0.075, 0.864], N = 3, p = 0.020; Q-value = 5.14; df(Q) = 2; p = 0.077; and I2 = 61.05) or ODD (d = 0.361; 95% CI [0.176, 0.547], N = 7, p < 0.001; Q-value = 4.28; df(Q) = 6; p = 0.639; and I2 = 0) after receiving CBT, whereas non-significant changes were observed in children with a diagnosis of CD (d = 0.390; 95% CI [−0.011, 0.790], N = 3, p = 0.060; Q-value = 2.62; df(Q) = 2; p = 0.270; and I2 = 23.66).

Non significant changes in positive parenting were found in the children with a diagnosis of ADHD (d = 0.421; 95% CI [−0.352, 1.195], N = 3, p = 0.286; Q-value = 14.76; df(Q) = 2; p = 0.001; and I2 = 86.45), and children with a diagnosis of ODD (d = 0.274; 95% CI [−0.031, 0.578], N = 10, p = 0.078; Q-value = 3.70; df(Q) = 9; p = 0.930; and I2 = 0).

It was not possible to conduct analyses on the other outcome variables due to the low number of studies available.

3.4.3. Source of variability on secondary outcomes: intervention targets

Improvements in internalizing behaviors were observed only when the treatment was delivered to children and parents together ($d = -0.262$; 95% CI [−0.417, −0.107], N = 8, p = 0.001; Q-value = 3.195; df(Q) = 7; p = 0.866; and I^2 = 0). No significant changes were found for interventions directed exclusively to parents ($d = -0.329$; 95% CI [−0.730, −0.072], N = 3, p = 0.108; Q-value = 2.676 df(Q) = 22; p = 0.262; and I^2 = 25.27). A reduction in symptoms of inattention was observed for interventions directed to children only ($d = -0.671$; 95% CI [−1.038, −0.303], N = 3, p < 0.001; Q-value = 1.501 df(Q) = 2; p = 0.472; and I^2 = 0). Smaller changes were obtained when both children and parents were involved ($d = -0.290$; 95% CI [−0.537, −0.044], N = 4, p = 0.021; Q-value = 3.687, df(Q) = 3; p = 0.297; and I^2 = 18.62). Greater changes in aggressive symptoms were found when the interventions were offered to both parents and children ($d = -0.298$; 95% CI [−0.524, −0.072], N = 13, p = 0.010; Q-value = 32.467, df(Q) = 12; p = 0.001; and I^2 = 63.039) than when they were offered to parents

only (d = −0.325; 95% CI [−0.671, −0.021], N = 3, p = 0.066; Q-value = 1.114 df(Q) = 2; p = 0.573; and I^2 = 0). Parent stress improved with interventions directed to parents (d = −0.699; 95% CI [−1.157, −0.241], N = 5, p = 0.003; Q-value = 14.22; df(Q) = 4; p = 0.007; and I^2 = 71.87) and with interventions directed to parents and children together (d = −0.560; 95% CI [−0.790, −0.330], N = 11, p < 0.001; Q-value = 19.50 df(Q) = 10; p = 0.034 and I^2 = 48.73). Finally, benefits for positive parenting were found for therapies directed exclusively to parents (d = 0.832; 95% CI [0.381, 1.284], N = 5, p < 0.001; Q-value = 9.60 df(Q) = 4; p = 0.048 and I^2 = 58.34) and not for interventions including both parents and children (d = 0.274; 95% CI [−0.295, 0.788], N = 6, p = 0.372; Q-value = 35.19 df(Q) = 5; p < 0.001 and I^2 = 85.79).

4. Discussion

The present meta-analysis of 21 RCTs included a total of 1960 participants and found that CBT is effective to reduce ODD symptoms (−0.879), parental stress (−0.607), externalizing symptoms (−0.52), and ADHD symptoms (−0.343). Moreover, the Cognitive Behavioral Treatment improve parenting skills (−0.381), social competence (−0.390), attention (−0.378), aggressive behaviors (−0.284), internalizing symptoms (−0.272) and maternal depressive symptoms (−0.231).

4.1. Externalizing behavior

Cognitive-behavioral therapy was associated with a significant reduction of externalizing symptoms in children affected by ODD and ADHD. Parents reported a larger benefit than teachers. According to previous data, the intervention appeared more beneficial when an adult caregiver was involved in the treatment of the child (Furlong et al., 2013; Lochman et al., 2011; Masi et al., 2014; Perrin, Sheldrick, McMenamy, Henson, & Carter, 2014; Wolraich et al., 2011).

4.2. ADHD symptoms

A moderate effect of CBT was found on the reduction of ADHD symptoms. Parents reported a larger reduction of symptoms than teachers. This might be due to teachers' lower sensitivity to symptoms change and to their limited involvement in the intervention.

Scholastic difficulties might be due to the large variety of stimuli available in the classroom. These stimuli might have a negative impact on the performance of children in cognitive tasks (Lineweaver et al., 2012; Pelham et al., 2011). Also, impulsivity - a core deficit of ADHD - has been associated with academic underachievement (Neef et al., 2005). ADHD children's choices might be affected more by the quality and immediacy of the reinforcers than by their long term benefits. This is particularly relevant at school, where reinforcers are not always positive and often demonstrate their benefits in the longer term (Neef et al., 2005).

4.3. ODD symptoms

A large reduction of ODD symptoms was found following CBT and parents reported greater changes than teachers. A moderate reduction of oppositive and defiant symptoms was found also in children affected by ADHD. This might be due to the high comorbidity between ODD and ADHD (Biederman et al., 2008; Burns & Walsh, 2002; Harvey, Metcalfe, Herbert, & Fanton, 2011).

4.4. Attention deficit

CBT produces a significant medium effect on inattention symptoms. This result is particularly relevant due to the deficits in the attention supervisor system that characterizes the illness (Bayliss & Roodenrys, 2000; Gozal & Molfese, 2007; Sagvolden, Johansen, Aase, & Russell, 2005). In fact, ADHD symptoms are caused by neuropsychological deficits in the attentional supervisor system (AAS) (Barkley, 2013; Sagvolden et al., 2005) and determined by the interaction between individual factors (e.g. dopaminergic system) and environmental and social factors (Arnsten & Dudley, 2005; Killeen, Tannock, & Sagvolden, 2012; Sagvolden et al., 2005). It is important to underlie that inattention symptoms in ADHD seems to remain stable over time (Colomer-Diago, Miranda-Casas, Herdoiza-Arroyo, & Presentación-Herrero, 2012) and that the use of psycho stimulants, intensive behavioral treatments, executive function and attention trainings show limited efficacy and do not improve academic, behavioral, or cognitive functioning (Rapport, Orban, Kofler, & Friedman, 2013).

Fathers reported smaller reductions of attention deficit symptoms than mothers. This might be due to spending less time communicating with their children (Wood, 2010). Recent studies showed that mothers of children with externalizing disorders were more likely than fathers to search for help and were more likely to perceive children's difficulties when these difficulties were moderate (Mason, 2007). When the externalizing symptoms were severe, fathers were more likely to perceive the problematic behaviors (Mason, 2007).

Teachers reported non-significant changes in inattention problems. This might be due to the impact of attention deficits on scholastic performance and to the greater attentional efforts required at school (Lineweaver et al., 2012; Neef et al., 2005; Pelham et al., 2011).

Treatments directed to children only had a larger impact on inattention problems than treatments delivered to children and parents together. A possible explanation for this finding is that attention and executive function trainings are individual therapies (Chacko, Kofler, & Jarrett, 2014). Treatments involving both children and carers are typically focused on reducing the behavioral symptomatology and the psychiatric symptoms, however the long term effects of evidence-based pharmacological and psychosocial treatments for ADHD are poor and do not target key areas of functional impairment (i.e., family, social, and academic functioning) and executive functioning effectively (Chacko et al., 2014).

4.5. Aggressive behavior

Cognitive Behavioral Treatment showed small effects on aggressive behavior. Fathers perceived greater benefits than mothers. A greater reduction of aggressive behaviors was observed in children affected by ADHD. This might be due to the more favorable prognosis of this condition compared to ODD and CD (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013).

Children with a diagnosis of ADHD are at high risk for developing other types of behavior disorders, including Oppositional Defiant Disorder and Conduct Disorder. This is important because the long-term outcomes of children suffering from these comorbidities are likely to be more unfavorable than the long term outcomes of children suffering from ADHD only (Hofvander, Ossowski, Lundström, & Anckarsäter, 2009; Karantanos, 2012).

The presence of aggressive behaviors is one of the criteria to diagnose ODD or CD (APA, 2013). Children suffering from these disorders often have little empathy or concern for the feelings and wishes of others and are prone to misperceive others' intentions towards them. Guilt and remorse over clear misdeeds are often

absent, whereas poor frustration tolerance and irritability are often expressed. Self-esteem is poor although an image of "toughness" is presented. The small reduction found in aggressive behaviors following CBTcould be due to the severity of the conduct disorders. These are considered one of the most difficult and intractable mental health problems in children and adolescents and treatments for this condition can be complex and challenging, due to the child's uncooperative attitude, fear and distrust of adults (AACAP, 2013).

Interestingly, CBT showed its efficacy on aggressive behaviors only when delivered to parents and children together. This can be explained by the crucial role of parenting strategies in the development and maintenance of externalizing problems (Buonanno, Capo, Romano, Di Giunta, & Isola, 2010). Several studies have found an association between harsh parenting and children externalizing behaviors (Erath, El-Sheikh, & Cummings, 2009; Erath, El-Sheikh, Hinnant, & Cummings, 2011; Mackenbach et al., 2014; Reid, Patterson, & Snyder, 2002). This relation is likely to be reciprocal.

4.6. Internalizing behavior

CBT was associated with a small reduction of internalizing behaviors, particularly in children with a diagnosis of ADHD and when delivered to both children and parents. Mothers reported a greater change. The small effect found on internalizing behaviors could be due to the main focus of the treatments used in the studies analyzed, which was on overt or behavioral symptoms rather than emotional problems (Lochman et al., 2011).

4.7. Social competence

A significant effect of CBT on social competence was found. This improvement was perceived mostly by parents and was greater in children with ADHD or ODD than children with CD. Children affected by CD are more compromised in this area due to the greater severity of the condition and the presence of callous-unemotional (CU) traits with limited prosocial emotions (APA, 2013).

4.8. Parental stress

A large reduction in parental distress was observed following CBT, when treatment was delivered to parents only or to parents and children together. This corroborates findings from other studies which indicate that CBT is effective in reducing parental distress and psychiatric symptoms when treatment is multimodal and involves parents too (Lochman et al., 2011).

4.9. Positive parenting

A moderate improvement in the use of positive parenting strategies was associated with CBT. A large effect was found when the intervention was delivered to parents only. This might be explained by the parent training sessions provided as part of CBT. Parent training is aimed at teaching parents alternative ways to identify and conceptualize child problem behaviors. Parents are encouraged to use positive parenting practices and role-playing and feedback are used to learn stress management and build family cohesion and communication (Lochman et al., 2011; Masi et al., 2014). Evidence-based behavioral parent training programs for children with externalizing problems focus on teaching parents to reinforce positive behaviors, ignore minor misbehaviors, and punish serious misbehavior through time out and response cost procedures (Eyberg, Nelson, & Boggs, 2008; Pelham & Fabiano, 2008).

Therapist-led parent training has been found to improve parent–child communication, increase parenting self-esteem, alleviate maternal depression and parenting stress and reduce child behavioral problems (Reyno & McGrath, 2006).

4.10. Maternal depression

A small improvement in maternal depressive symptoms was observed following CBT. Many studies suggest that children of depressed mothers are at high risk for the development of psychopathology. In particular, maternal depressive symptoms might predict internalizing and externalizing behavior problems (Betts, Williams, Najman, & Alati, 2014; Lee et al., 2013; Thomas, O'Brien, Clarke, Liu, & Chronis-Tuscano, 2014). Recent studies indicate that this association might be explained by the difficulties experienced by depressed mothers in using positive parenting strategies (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Sellers et al., 2014). This provides support for targeting maternal depression in the cognitive-behavioral treatments of externalizing symptoms (Chronis, Gamble, Roberts, & Pelham, 2006; Margari et al. 2013).

5. Conclusion

This meta-analysis assessed the impact of CBT on externalizing problems and comorbid difficulties. The results indicate that CBT is associated with a moderate reduction of externalizing symptoms, ADHD and oppositional defiant symptoms, and inattention problems. CBT is also associated with improved social competence and reduced parental distress. A small reduction of internalizing problems, aggressive behaviors and maternal depressive symptoms are found following CBT.

The magnitude of the effects obtained on parental distress and psychopathology and on educative practices confirms the key role of parenting styles in the maintenance of externalizing problems. However, only few studies investigated the reduction of maternal symptomatology after CBT. Future work will be able to clarify whether introducing specific screening and intervention sessions for mothers can improve treatment's efficacy.

Overall, this meta-analysis suggests that CBT is effective in targeting externalizing disorders. The use of CBT protocols in clinical health services could improve the wide dissemination of evidence-based treatments for these conditions.

The results of this meta-analysis support the hypothesis that multimodal treatments involving children, parents and caregivers (e.g. teachers) are particularly beneficial to reduce externalizing symptoms (Hutchings, Martin-Forbes, Daley, & Williams, 2013; Lochman et al., 2011; Lochman & Wells, 2004; Muratori et al., 2014; Webster-Stratton, Jamila Reid, & Stoolmiller, 2008). However, the strength of this study is that it focuses not only on externalizing symptoms, but also on parental distress and psychopathology. This represents an innovative approach to analyze the key role of maternal depression and dysfunctional parenting strategies in the vulnerability to and maintenance of disruptive behaviors.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brat.2015.10.008.

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Review article

A comparative meta-analysis of TEMPS scores across mood disorder patients, their first-degree relatives, healthy controls, and other psychiatric disorders

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ABSTRACT

Background: The Temperament Evaluation Memphis, Pisa, Paris and San Diego Auto-questionnaire (TEMPS) is validated to assess temperament in clinical and non-clinical samples. Scores vary across bipolar disorder (BD), major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), borderline personality disorder (BPD) and healthy controls (HCs), but a meta-analysis is missing.
Methods: Meta-analysis of studies comparing TEMPS scores in patients with mood disorders or their first-degree relatives to each other, or to a psychiatric control group or HCs.
Results: Twenty-six studies were meta-analyzed with patients with BD (n= 2025), MDD (n=1283), ADHD (n=56) and BPD (n=43), relatives of BD (n=436), and HCs (n=1757). Cyclothymic ($p < 0.001$) and irritable TEMPS scores ($p < 0.001$) were higher in BD than MDD (studies=12), and in MDD vs HCs (studies=8). Cyclothymic ($p < 0.001$), irritable ($p < 0.001$) and anxious ($p=0.03$) scores were higher in BD than their relatives, who, had higher scores than HCs. No significant differences emerged between ADHD and BD (studies=3);
Conclusion: Affective temperaments are on a continuum, with increasing scores ranging from HCs through MDD to BD regarding cyclothymic and irritable temperament, from MDD through BD to HC regarding hyperthymic temperament, and from HC through BD relatives to BD regarding cyclothymic, irritable and anxious temperament. Depressive and anxious temperaments did not differ between BD and MDD, being nonetheless the lowest in HCs. BD did not differ from ADHD in any investigated TEMPS domain.
Limitations: Different TEMPS versions, few studies comparing BD with ADHD or BPD, no correlation with other questionnaires.

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1. Introduction

The “Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego” (TEMPS) has been extensively validated to evaluate sub-affective trait expressions as they were conceptualized in Ancient Greek psychological medicine and, in more recent times, by Nineteenth Century German psychiatry (Akiskal and Akiskal, 2007; Rihmer et al., 2010).

The TEMPS has been developed based on the “Interview” version (TEMPS-I) released in the late 1990s (Akiskal et al., 1998; Placidi et al., 1998), which was subsequently extended to include 84 items (Akiskal and Akiskal, 2005), and ultimately leading to the current 110-item version of the TEMPS-A (Akiskal and Akiskal, 2005; Akiskal et al., 2005). The TEMPS-A includes five domains and items, which serve as criteria for the cyclothymic, dysthymic, irritable, hyperthymic and anxious temperaments (Akiskal and Mallya, 1987; Cassano et al., 1992). The TEMPS-A characterizes the dominant temperament of a subject, which results in a frequency of each temperament within a given population (e.g., about 10% of BP-II patients have cyclothymic temperament vs 1% of healthy individuals (Mechri et al., 2011)).

The TEMPS-A has been validated for use in both healthy people and those with a psychiatric diagnosis, in several languages and different settings, and has consistently demonstrated acceptable psychometric properties (Akiskal and Mallya, 1987; Akiskal et al., 1998). The theoretical construct of the TEMPS-A refers to a constitutional, genetically-determined, biological personality substrate of the individual reflecting an “endophenotype” trait that is stable across the lifespan (Nuttin, 1985). Though void of any intrinsic psychopathological predictive value (Rutter, 1987), the predominant affective temperament holds a place in the multifactorial model of mood disorders, mapping onto the subclinical extreme of the continuum that encompasses bipolar disorder type I (BD-I), type-II BD (BD-II), and major depressive disorder (MDD) on the opposite pole, including also other mood disorders not yet officially accepted (BD-III, IV) (Akiskal et al., 2006) or, possibly, the affective core of distinct diagnostic entities, such as borderline personality disorder (BDP) (Perugi et al., 2011) or, even, attention-deficit/hyperactivity disorder (ADHD) (Landaas et al., 2012; Ekinci et al., 2013).

From this perspective, varying combinations of affective temperamental domains could represent vulnerability markers to different disorders, especially cyclothymic temperament for BD-II or hyperthymic temperament for euphoric mania BD-I (Perugi et al., 2001), and could help differential diagnosis among mood disorders (Perugi et al., 2012). Nonetheless, although stable across the lifespan (Kawamura et al., 2010) and highly genetically-determined (Gonda et al., 2006) even in “affected or unaffected” first-degree relatives (Vazquez et al., 2008), it is unclear whether the actual continuum proposed for affective temperaments across varying psychopathological and non-psychopathological conditions might be actually reflected by a progressive severity of scores.

To the best of our knowledge, no meta-analysis exists evaluating the TEMPS scores across patients with BD or MDD, patients with different psychiatric diagnoses, BD relatives and HCs. The present paper aimed to address this gap and provide the first quantitate report investigating the existence of a metric continuum of the different scores of the five essential domains of the TEMPS.

2. Methods

The present meta-analysis adhered to the MOOSE guidelines (Stroup et al., 2000) and PRISMA statement (Moher et al., 2015), following a predetermined, but unpublished protocol.

2.1. Search strategy and study selection

Two authors (MS, LZ) independently searched Scopus and PubMed from inception until August 1st, 2015 using the search terms (“temperament”[All Fields] OR “character”[All Fields]) AND (“depression” OR “major depression” OR “depressive disorder” OR “affective disorder” OR “bipolar disorder” OR “bipolar” OR mania OR “mood disorder”). The reference list of included articles and of recent reviews were checked for potentially eligible studies. Studies eligible for inclusion provided the following: i) administration of the TEMPS (any validated version) to patients with either BD or MDD or their first-degree relatives compared to each other or compared to ii) healthy controls (HCs); iii) other psychiatric disorders.

2.2. Data extraction

Two authors (MS, LZ) independently extracted data using a data extraction form, including: author, publication year, country, setting, demographic characteristics for BD and control groups (age, number of males, sample size), mean and SD of TEMPS scores in each group. When we identified an article that was eligible but did not contain sufficient data to enable inclusion in the meta-analysis, we contacted the corresponding authors up to three times over a month to request the data.

2.3. Outcome measures and quality assessment

The primary outcome measure was the study-based standardized mean difference (SMD) of each TEMPS score between patients with BD, MDD or their first-degree relative and each available control group. The study quality was independently assessed by two authors (LZ and MS) using a modified version of the Newcastle Ottawa Scale (NOS) (Wells et al., 2000). Our version of the scale was modified (NOS-M) (see Supplementary Material 1) to produce a score ranging from 0 (lowest quality) to 18 (highest quality), which was determined for each study by consensus between the two investigators.

2.4. Meta-analytic method

The meta-analysis was conducted in the following steps. First, we calculated the SMD statistic together with 95% confidence interval (CI) to establish the difference in each TEMPS affective temperament domain score, between patients with BD or MDD or their first-degree relatives and control groups, with RevMan (Review Manager, v5.2) (RevMan, 2012). Second, we conducted meta-regression analyses with Comprehensive meta-analysis (CMA, version 3, http://www.meta-analysis.com) (CMA, 2014) to investigate the following moderators: sex, phase of the disease in both BD and MDD, country of origin. Heterogeneity was assessed with I^2 statistics for each analysis, with a value of $\geq 50\%$ indicating high heterogeneity (Higgins et al., 2003). Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (Begg and Mazumdar, 1994) and Egger bias test (Egger et al., 1997). In case of significant findings indicating publication bias, we calculated the trim and fill adjusted analysis (Duval and Tweedie, 2000) in order to evaluate if the results changed after imputing potentially missing studies.

3. Results

3.1. Selection of studies and retrieved sample

The study selection process is shown in Fig. 1. Characteristics of included studies and patients are reported in Table 1. We included 26 studies in the meta-analysis (Evans et al., 2005, Kesebir et al., 2005, Matsumoto et al., 2005, Benazzi, 2006, Karam et al., 2010, Ekinci et al., 2013, Fornaro et al., 2013b, Greenwood et al., 2013,

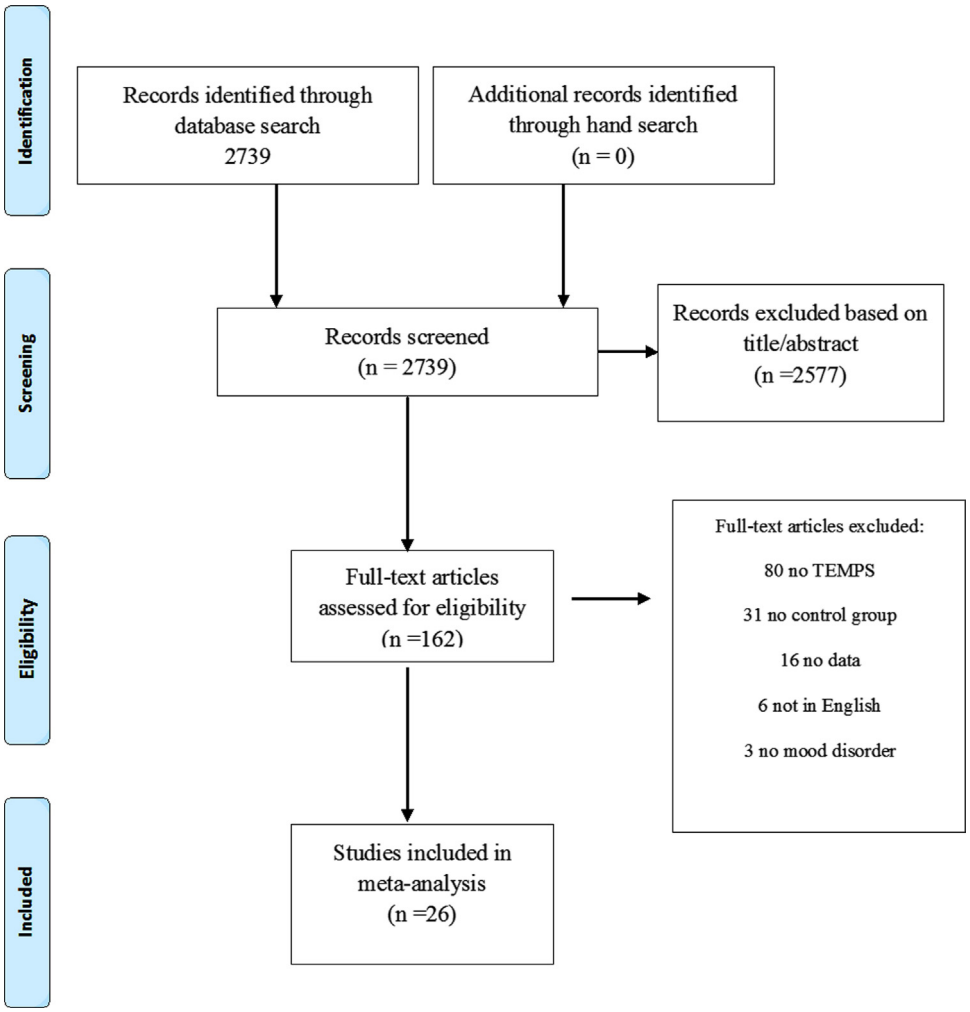

Fig. 1. PRISMA flow diagram of study selection process.

Kesebir et al., 2013, Mahon et al., 2013, de Aguiar Ferreira et al., 2014, Eich et al., 2014, Harnic et al., 2014, Kesebir et al., 2014, Dolenc et al., 2015, Innamorati et al., 2015; Mendlowicz et al., 2005a, Mendlowicz et al., 2005b, Nowakowska et al., 2005, Vazquez et al., 2008, Mazzarini et al., 2009, Nilsson et al., 2010, Pompili et al., 2014, Russo et al., 2014, Rybakowski et al., 2014, Xu et al., 2014). The included studies contained 5628 subjects, including 2025 with BD, 43 with BPD, 56 with ADHD, 1283 with MDD, 28 with ED, 1757 HC, 436 relatives of patients with BD.

Seven studies were carried out in the US or Canada, 6 studies in Italy, 4 in Turkey, and 1 each in Brazil, Slovenia, Switzerland, Lebanon, Japan, Denmark, Poland, Argentina, and China. Most of the included studies included only outpatients (22/26, 84.6%). Twelve studies compared BD vs MDD, 3 studies provided also data about BD-I compared to BD II, 14 studies compared BD vs HC, 8 studies compared MDD vs HC, 16 studies investigated TEMPS scores in BD compared to ADHD, BPD, or ED, 4 studies compared patients with BD vs their relatives, and 4 studies compared relatives of patients with BD vs HC (see Table 2 for all references).

TEMPS-A-110, a self-administered version of TEMPS (or no further specified version of the TEMPS-A) questionnaire was used in 14 studies (Evans et al., 2005; Nowakowska et al., 2005; Benazzi, 2006; Ekinci et al., 2013; Fornaro et al., 2013b; Greenwood et al., 2013; Mahon et al., 2013; Eich et al., 2014; Harnic et al., 2014; Pompili et al., 2014; Russo et al., 2014; Rybakowski et al., 2014; Dolenc et al., 2015; Innamorati et al., 2015). The other 9 studies used the TEMPS – Rio de Janeiro in 1 study (de Aguiar Ferreira et al., 2014); TEMPS-A Rome in 1 study (Fornaro et al., 2013b); Lebanese-Arabic TEMPS-A in 1 study (Karam et al., 2010); Turkish version of TEMPS-A in 3 studies (Kesebir et al., 2005, 2013, 2014); Japanese version of TEMPS-A in 1 study (Matsumoto et al., 2005); Italian version of TEMPS-A in 1 study (Mazzarini et al., 2009); short version of TEMPS-A in 3 studies (Mendlowicz et al., 2005a, 2005b; Nilsson et al., 2010); TEMPS-A Buenos Aires in 1 study (Vazquez et al., 2008); and the Chinese version of TEMPS-A in 1 study (Xu et al., 2014).

Detailed information about the study quality is provided in Supplementary e-Table 2.

3.2. Comparison of affective temperament scores across diagnostic groups

All results are reported in detail in Table 2 and those of particular interest are summarized below.

3.2.1. Bipolar disorder vs major depressive disorder

The meta-analysis pooled data from 12 studies (n=2204), except for the anxious TEMPS scores, for which only 10 studies provided data (n=1660). Patients with BD had significantly higher cyclothymic (SMD=0.54 [0.38, 0.71], $P<0.00001$; $I^2=65\%$, P=0.0009), hyperthymic (SMD=0.39 [0.18, 0.60], P=0.0002; $I^2=78\%$, $P<0.00001$), and irritable (SMD=0.41 [0.22, 0.60], $P<0.0001$; $I^2=73\%$, $p<0.0001$) TEMPS scores compared to patients with MDD. Depressive (P=0.29) and anxious (P=0.54) TEMPS scores were not different between the two groups.

3.2.2. Bipolar disorder type I vs bipolar disorder type II

The meta-analysis pooled data from 3 studies (n=671), except for anxious TEMPS scores for which only 2 studies provided data (n=443). Depressive TEMPS scores were significantly lower in BD-I compared to BD-II (SMD=−0.25 [−0.41,−0.09], P=0.002; $I^2=0\%$, P=0.61). Cyclothymic (P=0.29), hyperthymic (P=0.12), irritable (P=0.84), anxious (P=0.72) TEMPS scores were not different between BD-I and BD-II.

3.2.3. Bipolar disorder vs healthy controls

The meta-analysis pooled data from 14 studies (n=2452), except for anxious TEMPS scores, for which only 12 studies provided data (n=1928). Cyclothymic (SMD=2.22 [1.61, 2.84], $P<0.00001$; $I^2=97\%$, $P<0.00001$), depressive (SMD=1.19 [0.55, 1.82], P=0.0002; $I^2=97\%$, $P<0.00001$), irritable (SMD=1.29 [0.86, 1.72], $P<0.00001$; $I^2=95\%$, $P<0.00001$), and anxious (SMD=1.38 [0.66, 2.09], P=0.0002; $I^2=97\%$, $P<0.00001$) TEMPS scores were significantly higher in the BD group than in HCs. Conversely, hyperthymic TEMPS scores were significantly lower in the BD group compared to HCs (SMD=−0.44 [−0.74,−0.15], P=0.004; $I^2=90\%$; $P<0.00001$).

3.2.4. Major depressive disorder vs healthy controls

The meta-analysis pooled data from 8 studies (n=1901), except for anxious TEMPS score, for which only 6 studies provided data (n=1344).

Cyclothymic (SMD=0.90 [0.60, 1.20], $P<0.00001$; $I^2=87\%$, $P<0.00001$), depressive (SMD=1.29 [0.87, 1.71], $P<0.00001$; I=93%, $P<0.00001$), irritable (SMD=0.52 [0.04, 1.00], P=0.03; $I^2=95\%$, $P<0.00001$), and anxious (SMD=1.01 [0.53, 1.48], $P<0.0001$; $I^2=93\%$, $P<0.00001$) TEMPS scores were significantly higher in the MDD group than in HCs. Conversely, hyperthymic TEMPS scores were significantly lower in the MDD group compared to HCs (SMD=−0.68 [−0.85,−0.50], $P<0.00001$; $I^2=61\%$; P=0.01).

3.2.5. BD vs psychiatric disorders other than MDD

The meta-analysis pooled data from 6 studies (n=262), with 3 studies comparing BD vs ADHD (n=126), 2 studies comparing BD vs BPD (n=80), 1 study comparing BD vs ED (n=56).

Compared to ADHD, the BD group did not differ regarding cyclothymic (p=0.43), hyperthymic (p=0.86), depressive (p=0.79), irritable (p=0.07), or anxious (p=0.40) TEMPS scores.

Compared to BPD, the BD group had significantly higher hyperthymic (SMD=0.69 [0.23, 1.14], P=0.003; $I^2=0\%$, P=0.81) TEMPS scores, and significantly lower depressive (SMD=−1.24 [−1.73,−0.76], $P<0.00001$; $I^2=0\%$; p=0.67), irritable (SMD=−0.91 [−1.38,−0.45], P=0.0001; $I^2=0\%$, p=0.46), and anxious (SMD=−1.42 [−1.91,−0.92], $P<0.00001$; $I^2=\%$, P=0.43) TEMPS scores. Conversely, cyclothymic TEMPS scores did not differ between BPD and BD (P=0.19).

Only one study reported data about TEMPS scores in ED, so a subgroup MA was not meaningful.

Finally, subgroup difference analyses showed that MDD, ADHD, BPD and ED differed significantly from BD regarding cyclothymic (p=0.01), hyperthymic ($P<0.00001$), depressive (P=0.0002), irritable ($P<0.00001$), and anxious ($P<0.0001$) TEMPS scores.

3.2.6. BD vs first-degree BD relatives

Meta-analysis pooled data from 4 studies (n=795). Cyclothymic (SMD=2.89 [1.48–4.29], $P<0.0001$; $I^2=98\%$, $P<0.00001$), irritable (SMD=1.90 [0.77, 3.04], P=0.001; $I^2=98\%$, $P<0.00001$), and anxious (SMD=2.71 [0.23, 5.18], P=0.03; $I^2=99\%$, $P<0.00001$) TEMPS scores were significantly higher in the BD group compared to BD relatives. Hyperthymic (P=0.97) and depressive (not significant after the trim and fill procedure; P=0.09 TEMPS scores did not differ between BD and BD relatives.

3.2.7. First-degree BD relatives vs healthy controls

The meta-analysis pooled data from 4 studies (n=1018). Cyclothymic (SMD=1.54 [0.43, 2.65], P=0.007; $I^2=98\%$, $P<0.00001$), irritable (SMD=[0.48, 1.47], P=0.0001 after the trim and fill procedure) and anxious (SMD=2.11 [0.50, 3.72] P=0.01 after the trim and fill procedure) TEMPS scores were significantly higher in BD relatives than in HCs. Hyperthymic (P=0.12) and

Table 1
Main characteristics of included studies reporting TEMPS data in patients with mood disorders.

Study/country	Design	Inclusion criteria for primary mood disorder patients	Inclusion criteria for control group	Exclusion criteria	Illness phase BD	Illness phase MDD	NOS-M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N relatives
Benazzi (2006) *Italy*	CS outpatients	BD-II, GAF > 80	MDD	–	Euthymic	Euthymic	11.00	138..00	–	–	71..00	–	–	–
De Aguiar (2014) *Brazil*	CS outpatients	BD, HAMD > 17 and YMRS < 8, at least Dep episode with antidepressants for at least 8 weeks	MDD	–	Euthymic	Euthymic	13.00	90..00	–	–	88..00	–	–	–
Dolenc (2015) *Slovenia*	CS outpatients	EuthymicBD	Euthymic, MDD	Not stable, not remission for at least 6 months, psychiatric comorbidity, pregnant women.	Euthymic	Euthymic	13.00	64..00	–	–	36..00	–	–	–
Ecinki (2013) *Turkey*	CS outpatients	> 17yo, BD I euthymic HAMD < 7 YMRS < 5, ADHD, DSM-IV,	ADHD	–	Euthymic	–	16	40	–	40	–	–	40	–
Eich (2014) *Switzerland*	CS out-+inpatients	Euthymic BD, DSM-IV, ICD10, Utah	BPD, ADHD	–	Euthymic	–	10	24 (pure12)	27 (pure12)	23 (pure10)	–	–	–	–
Evans (2005) *US, Canada*	CS outpatients	Families with BD I, BD II	HC: no mood disorder, No relatives with mood disorder	–	NA	–	9.00	155..00	–	–	–	–	–	–
Fornaro (2013) *Italy*	CS outpatients	MDD DSMIV, 18-65yo, HAMD > 18	HC: no lifetime mood disorder, HAMD < 7	Lifetime BD, cyclothymia, schizophrenia, psychosis, Axis II or III comorbidity,		Depressed	13	–	–	–	HCL 32 - 182	–	87	–
Greenwood (2013) *US, Canada*	CS outpatients	BD,	MDD, or relatives of patients with BD, or relatives with MDD. HC: SCID ascertained absence of disease	–	NA	–	10.00	177..00	–	–	118..00			
Harnic (2014) *Italy*	CS-outpatients	BD I, II, DSM.IV, Euthymic HDRS < 8 YMRS < 7, 18–65,	HC	IQ < 70, lifetime neurological disease, suicidal ideation, unstable medical condition, blood exam alterations, substance abuse.	Euthymic	–	15.00	90..00	–	–	–	–	86..00	–
Innamorati (2015) *Italy*	CS-inpatients	BD-I or II DSM-IV,	MDD	Dementia, delirium	NA	NA	12	206			46	–	–	–
Karam (2010) *Lebanon*	CS outpatients	Non institutionalized	-MDD, ADHD, HC	–	NA	–	9	18	–	6	64	–	384	–

		adults, meeting CIDI criteria for BD												
Kesebir (2005) *Turkey*	CS outpatients	BD I with OR without family history for BD	All matched for age, education, gender from a previous study (Vahip et al., 2005) 100 HC matched with patients with BD, 219 first degree relative, and 219 matched with relatives+	–	Euthymic	–	11.00	100..00	–	–	–	–	100 for BD, 219 for relatives	219
Kesebir (2013) *Turkey*	CS outpatients	MDD DSM-IV, remission,	HC	Anxiety, somatoform, alcohol and substance abuse DSM-IV	–	Euthymic	13	–	–	–	100	–	100	–
Kesebir (2014) *Turkey*	CS-outpatients	BD I DSM-IV, remission euthymic HDRS < 8, YMRS < 5	MDD, HC	Unstable medical condition, condition influencing uric acid, psychiatric comorbidity	Euthymic	Euthymic	14.00	41..00	–	–	30..00	–	43..00	–
Mahon (2013) *US*	CS outpatients	BD I, II, NOS, clinically stable	HC. Unaffected sibling: > 2 years older than bipolar onset age of patients and at least 25 -	–	Euthymic	–	15.00	55..00	–	–	–	–	109..00	51.00
Matsumoto (2005) *Japan*	CS outpatients	MDD, BD I, BD II, HRSD < 10, MRS < 12	HC: no psychiatric illness influencing working function, CES-D < 15	Psychotic or organic disorder,	Euthymic	Euthymic	16.00	30..00	–	–	29..00	–	59..00	–
Mazzarini (2009) *Italy*	CS inpatients	BD I, II	MDD	–	NA-	NA	8.00	69..00	–	–	19..00	–	–	–
Mendlowicz (2005) *US*	CS outpatients	Recovered BD I or II (no symptoms or signs 2 months),	HC: normal controls+relatives of bipolar Bropands, at least w 2 relatives w BD or BD+either schizoaffective or MDD.	–	Euthymic	–	12.00	23..00	–	–	–	–	102..00	52.00
Mendlowicz (2005b) *US*	CS outpatients	Depressed BD I, BD II	MDD	–	Depressed	Depressed	12.00	57..00	–	–	94..00	–	–	–
Nilsson (2010) *Denmark*	CS outpatients	BD, female, remission bipolar (< 6 Bech Rafaelsen mania scale and < 6 Bech Rafaelsen Melancholia scale)	Only female BPD	Male	Euthymic	–	13	25	31	–	–	–	29	–
Nowakowska (2005) *US*	CS outpatients	BD, euthymic.	MDD euthymic. HC: no history or family history of psychiatric illness, No drugs or	Psychiatric comorbidity, active substance abuse, axis II personality, or	Euthymic	Euthymic	13.00	49..00	–	–	25..00	–	47..00	–

Table 1 (*continued*)

Study/country	Design	Inclusion criteria for primary mood disorder patients	Inclusion criteria for control group	Exclusion criteria	Illness phase BD	Illness phase MDD	NOS-M	N BD	N BPD	N ADHD	N MDD	N Bulimia or ANBP	N HC	N relatives
			Primmedical problems, employed, stable residency	eating disorders										
Pompili (2014) *Italy*	CS-inpatients	BD, DSM-IV, > 18 yo	MDD, DSM-IV -	Neurological disease,	NA	NA	9.00	288(BDII 202.. BDII 86)	–	–	96..00	–	–	–
Russo (2014) *US*	CS outpatient	BD SCID, Euthymic HDRS < 15 CARS-M < 8, 18-65	HC: SCID NP negative also for 1 degree relatives, 18-65	Neurological disorder, ADHD, substance abuse 3 months, active medical problem, ECT 12 months	Euthymic	–	14	64	–	–	–	–	109	–
Rybakovsky (2014) *Poland*	CS-outpatients	BD I, BD II, DSM-IV	HC, Bulimia or ANBP	–	NA	–	8.00	28..00	–	–	–	28.00	28..00	–
Vazquez (2008) *Argentina*	CS outpatients	First degree relatives of BD patients	HC: healthy, with no family history of BD	BD, < 18 yo		–	15	–	–	–	–	–	115	114
Xu (2014) *China*	PR 2 phases	BD DSM-IV	MDD, and SCL-90, HCL < 8, HAM-D < 6, HC	Pregnancy, serious general medical illness, history of seizure disorder, DSMIV-TR defined organic mental disorders, dementia, schizophrenia, delusional disorder, schizoaffective disorder, active substance use disorder, and history of mental retardation.	NA	NA	9	228	–	–	285	–	200	–
7 US/Canada, 6 Italy, 4 Turkey, 1 Brazil, 1 Slovenia, 1 Switzerland, 1 Lebanon, 1 Japan, 1 Denmark, 1 Poland, 1 Argentina, 1 China.	3 included inpatients, 22 outpatients, 1 in- and outpatients	23 BD, 1 BD relatives, 2 MDD	13 MDD, 17 HC, 1 ED, 2 BPD, 4 BD relatives, 3 ADHD.	–	BD: 13 euthymic, 1 depressed, others not declared.	MDD: 7 euthymic, 2 depressed, others not declared.	Mean NOS-M = 11.46	N BD = 2025	N BPD = 43	N ADHD = 56	N MDD = 1283	N ED = 28	N HC = 1757	N healthy Relatives = 436

Legend: ADHD: Attention Deficit Hyperactivity Disorder; ANBP: anorexia nervosa bulimic purgative; BD: bipolar disorder; BPD: borderline personality disorder; BPRS: brief psychiatric rating scale; CARS-M: clinician-administered rating scale for mania; CS: cross-sectional; DSM-IV: diagnostic and statistical manual, version IV; GAF: global assessment of functioning; HC: healthy control; HCL: hypomania check-list; HDRS: Hamilton depression rating scale; MDD: major depressive disorder; NOS: New Castle- Ottawa scale-Modified; PR: prospective; SCL-90: symptom check-list 90; YMRS: Young mania rating scale.

Table 2
Comparative meta-analysis of TEMPS score among bipolar disorder, major depressive disorder, attention deficit and hyperactivity disorder, borderline personality disorders, bipolar patients relatives, and healthy controls.

Outcome or subgroup	Studies	Participants	Heterogeneity	Effect estimate* (p)	Studies
BD vs MDD					
1.1 Cyclothymic	12	2204	(P=0.0009); I^2=65%	**0.54 [0.38, 0.71] (P < 0.00001)**	Benazzi et al. (2006), DeAguiar et al. (2014), Dolenc et al. (2015), Greenwood et al. (2013), Karam et al. (2010), Kesebir et al. (2014), Matsumoto et al. (2005), Mazzarani et al. (2009), Mendlowicz et al. (2005b), Nowakowska et al. (2005), Pompili et al. (2014) and Xu et al. (2014).
1.2 Hyperthymic	12	2247	(P < 0.00001);I^2=78%	**0.39 [0.18, 0.60] (P=0.0002)**	
1.3 Depressive	12	2247	(P < 0.00001);I^2=78%	−0.11 [−0.31, 0.09] (P=0.29)	
1.4 Irritable	12	2247	(P < 0.0001); I^2=73%	**0.41 [0.22, 0.60] (P < 0.0001)**	
1.5 Anxious	10	1660	(P < 0.0001); I^2=79%	−0.08 [−0.32, 0.17] (P=0.54)	
BD I vs BD II					
Outcome or subgroup	**Studies**	**Participants**	**Heterogeneity**	**Effect estimate**	Evans et al. (2005), Pompili et al. (2014) and Xu et al. (2014)
2.1 Cyclothymic	3	671	(P=0.21); I^2=36%	−0.11 [−0.31, 0.09] (p=0.29)	
2.2 Hyperthymic	3	671	(P=0.49); I^2=0%	0.12 [−0.03, 0.28] (P=0.12)	
2.3 Depressive	3	671	(P=0.61); I^2=0%	**−0.25 [−0.41, −0.09] (P=0.002)**	
2.4 Irritable	3	671	(P=0.34); I^2=7%	0.02 [−0.15, 0.18] (p=0.84)	
2.5 Anxious	2	443	(P=0.40); I^2=0%	−0.04 [−0.23, 0.16] (p=0.72)	
BD vs HC					
Outcome or subgroup	**Studies**	**Participants**	**Eterogeneity**	**Effect estimate**	Ecinki et al. (2013), Greenwood et al. (2013), Harnic et al. (2014), Karam et al. (2010), Kesebir et al. (2005), Kesebir et al. (2014), Mahon et al. (2013), Matsumoto et al. (2005), Mendlowicz et al. (2005), Nilsson et al. (2010), Nowakowska et al. (2005), Russo et al. (2014), Rybakowski et al. (2014) and Xu et al. (2014).
3.1 Cyclothymic	14	2452	(P < 0.00001); I^2=97%	**2.22 [1.61, 2.84] (P < 0.00001)**	
3.2 Hyperthymic	14	2452	(P < 0.00001); I^2=90%	**−0.44 [−0.74, −0.15] (P=0.004)**	
3.3 Depressive	14	2452	(P < 0.00001); I^2=97%	**1.19 [0.55, 1.82] (P=0.0002)**	
3.4 Irritable	14	2452	(P < 0.00001); I^2=95%	**1.29 [0.86, 1.72] (P < 0.00001)**	
3.5 Anxious	12	1928	(P < 0.00001); I^2=97%	**1.38 [0.66, 2.09] (P=0.0002)**	
MDD vs HC					
Outcome or subgroup	**Studies**	**Participants**	**Heterogeneity**	**Effect estimate**	Fornaro et al. (2013), Greenwood et al. (2013), Karam et al. (2010), Kesebir et al. (2013), Kesebir et al. (2014), Matsumoto et al. (2005), Nowakowska et al. (2005) and Xu et al. (2014).
4.1 Cyclothymic	8	1901	(P < 0.00001); I^2=87%	**0.90 [0.60, 1.20] (P < 0.00001)**	
4.2 Hyperthymic	8	1901	(P=0.01); I^2=61%	**−0.68 [−0.85, −0.50] (P < 0.00001)**	
4.3 Depressive	8	1901	(P < 0.00001); I^2=93%	**1.29 [0.87, 1.71] (P < 0.00001)**	
4.4 Irritable	8	1901	(P < 0.00001); I^2=95%	**0.52 [0.04, 1.00] (P=0.03)**	
4.5 Anxious	6	1344	(P < 0.00001); I^2=93%	**1.01 [0.53, 1.48] (P < 0.0001)**	
BD vs OTHERS					
Outcome or subgroup	**Studies**	**Participants**	**Eterogeneity**	**Effect estimate**	Benazzi et al. (2006), DeAguiar et al. (2014), Dolenc et al. (2015), Greenwood et al. (2013); Karam et al. (2010), Kesebir et al. (2014), Matsumoto et al. (2005), Mazzarani et al. (2009), Mendlowicz et al. (2005a, 2005b), Nowakowska et al. (2005); Pompili et al. (2014), Xu et al. (2014), Ecinki et al. (2013), Eich et al. (2014), Nilsson et al., 2010 and Rybakowski et al. (2014).
5.1 Cyclothymic	16	2466	(P=0.01), I^2=71.6%	**0.31 [0.09, 0.53] (P=0.006) Subgroup differences (P=0.01)**	
5.1.1 BD vs MDD	12	2204	(P=0.0009); I^2=65%	**0.54 [0.38, 0.71] (P < 0.00001)**	
5.1.2 BD vs ADHD	3	126	(P=0.63); I^2=0%	0.14 [−0.22, 0.50] (P=0.43)	
5.1.3 BD vs Borderline	2	80	(P=0.001); I^2=90%	−1.09 [−2.73, 0.55] (P=0.19)	
5.1.4 BD vs ED	1	56	NA	−0.04 [−0.56, 0.48] (p=0.88)	
5.2 Hyperthymic	16	2509	(P < 0.00001), I^2=88.7%	**0.30 [0.10, 0.50] (P=0.004); Subgroup differences (P < 0.00001)**	
5.2.1 BD vs MDD	12	2247	(P < 0.00001); I^2=78%	**0.39 [0.18, 0.60] (P=0.0002)**	
5.2.2 BD vs ADHD	3	126	(P=0.91); I^2=0%	−0.03 [−0.39, 0.33] (P=0.86)	
5.2.3 BD vs Borderline	2	80	(P=0.81); I^2=0%	**0.69 [0.23, 1.14] (P=0.003)**	
5.2.4 BD vs ED	1	56	NA	**−0.99 [−1.54, −0.43] (P=0.0005)**	
5.3 Depressive	16	2509	(P=0.0002), I^2=84.8%	−0.18 [−0.37, 0.02] (P=0.08); **Subgroup differences (P=0.0002)**	
5.3.1 BD vs MDD	12	2247	(P < 0.00001); I^2=77%	**−0.11 [−0.31, 0.09] (p=0.03)**	
5.3.2 BD vs ADHD	3	126	(P=0.12); I^2=53%	0.08 [−0.53, 0.69] (p=0.79)	
5.3.3 BD vs Borderline	2	80	(P=0.67); I^2=0%	**−1.24 [−1.73, −0.76] (P < 0.00001)**	
5.3.4 BD vs ED	1	56	NA	−0.04 [−0.57, 0.48] (p=0.88)	
5.4 Irritable	16	2509	(P < 0.00001), I^2=91.3%	0.16 [−0.05, 0.37] (P=0.14); **Subgroup**	

Table 2 (*continued*)

Outcome or subgroup	Studies	Participants	Heterogeneity	Effect estimate* (p)	Studies
				differences (P < 0.00001)	
5.4.1 BD vs MDD	12	2247	(P < 0.0001); I^2=73%	**0.41 [0.23, 0.60] (P < 0.0001)**	
5.4.2 BD vs ADHD	3	126	(P=0.21); I^2=35%	−0.48 [−1.00, 0.03] (p=0.07)	
5.4.3 BD vs Borderline	2	80	(P=0.46); I^2=0%	**−0.91 [−1.38, −0.45] (P=0.0001)**	
5.4.4 BD vs ED	1	56	NA	−0.14 [−0.67, 0.38] (p=0.59)	
5.5 Anxious	14	1922	(P < 0.0001), I^2=87.0%	−0.24 [−0.48, 0.01] (P=0.06); **Subgroup differences (P < 0.0001)**	
5.5.1 BD vs MDD	10	1660	(P < 0.00001); I^2=80%	−0.08 [−0.32, 0.17] (P=0.54)	
5.5.2 BD vs ADHD	3	126	(P=0.12); I^2=53%	−0.26 [−0.88, 0.35] (P=0.40)	
5.5.3 BD vs Borderline	2	80	(P=0.43); I^2=0%	**−1.42 [−1.91, −0.92] (P < 0.00001)**	
5.5.4 BD vs ED	1	56	NA	−0.09 [−0.61, 0.44] (P=0.74)	
BD vs RELATIVES					
Outcome or subgroup	**Studies**	**Participants**	**Heterogeneity**	**Effect estimate**	Greenwood et al. (2013), Kesebir et al. (2005), Mahon et al. (2013), and Mendlowicz et al. (2005)
6.1 Cyclothymic	4	795	(P < 0.00001); I^2=98%	**2.89 [1.48, 4.29] (P < 0.0001)**	
6.2 Hyperthymic	4	795	(P < 0.00001); I^2=94%	0.01 [−0.65, 0.68] (P=0.97)	
6.3 Depressive	4	795	(P < 0.00001); I^2=97%	1.16 [0.11, 2.21] (P=0.03) Not significant after trim and fill.	
6.4 Irritable	4	795	(P < 0.00001); I^2=98%	**1.90 [0.77, 3.04] (P=0.001)**	
6.5 Anxious	4	795	(P < 0.00001); I^2=99%	**2.71 [0.23, 5.18] (P=0.03)**	
BD RELATIVES vs HC					
Outcome or subgroup	**Studies**	**Participants**	**Heterogeneity**	**Effect estimate**	Greenwood et al. (2013); Kesebir et al. (2005); Mahon et al. (2013) and Mendlowicz et al. (2005)
7.1 Cyclothymic	4	1018	(P < 0.00001); I^2=98%	**1.54 [0.43, 2.65] (P=0.007)**	
7.2 Hyperthymic	4	1018	(P < 0.00001); I^2=97%	−0.61 [−1.36, 0.15] (P=0.12)	
7.3 Depressive	4	1018	(P < 0.00001); I^2=99%	−0.03 [−1.41, 1.35] (P=0.97)	
7.4 Irritable	4	1018	(P < 0.00001); I^2=97%	**0.67 [−0.10, 1.43] (P=0.09); 0.98 [0.48, 1.47] p=0.0001 after trim and fill**	
7.5 Anxious	4	1018	(P < 0.00001); I^2=99%	**1.30 [−0.57, 3.17] (P=0.17); 2.11 [0.50, 3.72] p=0.01 after trim and fill**	

* Positive effect size indicates higher scores in the former group compared to the latter.

depressive (P=0.97) TEMPS scores did not differ between BD relatives and HCs.

3.3. Heterogeneity and publication bias

No comparison between BD-I and BD-II had an $I^2 > 50\%$. All comparisons between BD and MDD, BD and HC, MDD and HC, BD vs relatives, and BD relatives vs HC had an $I^2 > 50\%$.

Begg-Mazumdar Kendall's tau (Begg and Mazumdar, 1994), Egger's bias test (Egger et al., 1997) and the trim and fill method (Duval and Tweedie, 2000) did not substantially change the direction and significance of the results in any comparison.

3.3.1. Moderator variables

Results of the meta-regression analyses are reported in Table 3. Briefly, in BD vs MDD non-European study origin moderated lower hyperthymic TEMPS scores (N=12, β=−0.44 [−0.82−0.06], R^2=0.28, P=0.02). The moderator effect was confirmed by *t*-test comparison between the SMD in the BD and MDD groups, according to meta-regression strata (P=0.04) (e-Table 3).

In BD vs HC comparisons, male sex in HCs (N=10, β=0.05 [0.01–0.08], R^2=0.00, P=0.01) moderated higher cyclothymic TEMPS scores, but the R^2=0.00 indicated that results were quantitatively irrelevant. Non-European study origin (N=14, β=1.29 [0.12–2.46] R^2=0.18, P=0.03), and male sex in HCs (N=10, β=0.03 [0.005–0.06], R^2=0.16, P=0.02) moderated higher depressive TEMPS scores. Furthermore, non-European study origin moderated higher irritable (N=14, β=1.00 [0.201.81], R^2=0.18, P=0.01) and anxious (N=12, β=1.87 [0.75−3.00], R^2=0.40, P=0.001) TEMPS scores. Higher anxious TEMPS scores were also significantly moderated by male sex in HCs (N=8, β=0.05 [0.01−0.08], R^2=0.24, p=0.009). The moderator effect of non-European study origin was not confirmed by *t*-test comparison between SMD in BD and HCs regarding depressive scores (P=0.07), while it was confirmed with irritable (P=0.005) and anxious (P=0.001) TEMPS scores according to meta-regression strata (Supplementary table 3).

In MDD vs HC comparisons, non-European study origin moderated higher cyclothymic (N=8, β=0.56 [0.03−1.14] R^2=0.24, P=0.04) and anxious (n=6, β=0.82 [0.14−1.50], R^2=0.55, P=0.02) TEMPS scores. In MDD vs HC comparisons, active depression compared to euthymia moderated lower irritable (N=5, β=−1.44 [−2.3 to −0.6], R^2=0.76, p=0.001), and anxious (N=4, β=−1.03 [−2.02 to −0.04], R^2=0.43, p=0.04) TEMPS scores. Also, male sex in HCs (N=4, β=0.05 [0.02−0.07], R^2=0.78, p=0.003) moderated higher anxious scores. The moderator effect of non-European study origin was confirmed by *t*-test comparison between SMD in MDD and HCs, according to meta-regression strata in cyclothymic (P=0.008) and anxious (P=0.02) scores (Supplementary table 3).

In BD patients vs relatives comparisons, non-European study origin moderated higher anxious TEMPS scores (N=4, β=6.27 [4.74−7.81], R^2=0.94, P<0.001), and the effect was confirmed by *t*-test comparison between SMD in BD patients and relatives according to meta-regression strata (P<0.001) (Supplementary table 3).

In BD relatives vs HC comparisons, non-European study origin moderated lower depressive scores (N=4, β=−2.08 [−3.86 to −0.29], R^2=0.69, p=0.02), and the effect was confirmed by *t*-test comparison between SMD in BD relatives and HCs according to meta-regression strata (P<0.001) (Supplementary table 3).

4. Discussion

The results of the first meta-analysis of TEMPS affective scores across mood disorders and pertinent control groups suggest a continuum model of affective temperament domains spanning from HCs through MDD to BD. Cyclothymic and irritable domain score severities appear to progressively increase according the above mentioned pattern. The same continuum trajectory was observed for cyclothymic, irritable and anxious temperament that each ranged from HCs, through BD relatives, to patients affected by BD, further strengthening the genetic and heritable component as one of the underlying factors that contribute to the multifactorial pathogenesis of BD (Greenwood et al., 2012, 2013). Nonetheless, the above mentioned trend was not replicated with respect to depressive and anxious temperament domains. Conversely, the depressive and anxious domains appear cluster across mood disorders as a group, with similar scores in BD and MDD, which were both significantly higher compared to HCs. A possible interpretation of this finding may be a selection bias, i.e., the inclusion of moderate to severe clinical cases of BD and MDD, rather than of milder presentations. In fact, it has been proposed that higher scores in the cyclothymic, irritable and hyperthymic TEMPS domains correlate significantly with more severe BD presentations (Perugi et al., 2012), suggesting the possibility of some degree of state dependent effects in the upper severity range in addition to underlying, more stable, trait-dependent temperament ratings.

The finding of higher hyperthymic temperament scores n BD than MDD follow the mood polarity of disorder. However, we also found that HCs had even higher hyperthymic ratings than BD patients. This seeming disconnect is likely due to the fact that BD patients were not always euthymic and that BD more frequent presents with depressive or mixed features than with pure (hypo) mania (Judd et al., 2002, 2003, 2005),s, previously described as the "dark side of hypomania" (Hantouche et al., 2003; Cassano et al., 2009). Moreover, patients with atypical depression or BD-II depression appear to have a strong relationship with cyclothymic temperament, whereas BD-I and manic patients have more consistently been related to higher hyperthymic scores. This latter relationship could explain the lower hyperthymic scores in the included BD group compared to HCs, considering that only 4 studies reported separate scores for BD I and BD II.

Pertaining to the continuum model, our results confirm previously hypotheses of increasing temperamental features across diseases and from diseases through relatives to healthy populations, which is a core feature of an endophenotype (Di Florio et al., 2010). Also, since noncompliance has been recognized as a frequent and core problem in BD management (Levin et al., 2015; Sajatovic et al., 2015), and since cyclothymic temperament has been associated with poor treatment adherence (Fornaro et al., 2013a), the cyclothymic TEMPS subscale could possibly be a useful tool in everyday practice, warning about the risk of non-adherence, prompting more careful monitoring, supervision or medication switches from oral to long-acting formulations where available. Even more importantly, cyclothymic temperament is a recognized risk factor for suicidal behavior, being associated with hopelessness beyond polarity in BD. Again, here the cyclothymic TEMPSS subscore could be helpful clinically in increasing surveillance or influencing treatment choice, including lithium (Koek et al., 2012).

Furthermore, the observed temperamental patterns can at least partially explain similarities and differences within the mood disorder group. Both BD and MDD spend major parts of the illness in the depressive phase (Judd et al., 2002, 2003, 2005), likely relating to the similar depressive temperament ratings. Conversely, our results confirm that, as previously suggested (de Aguiar Ferreira et al., 2014) temperament measures are useful in the differential diagnosis between BD and MDD; with significantly higher TEMPS hyperthymic, cyclothymic and irritable domain sores in BD than MDD. Rating these temperamental domains could be useful in particular clinical situations, such as presentation with

Table 3
Meta-regression of moderators of TEMPS score in mood disorders.

Moderator	Number comparisons	B	95% CI		P value	R^2
1 BD vs MDD						
1.1 Cyclothymic						
Country (Europe [ref] vs other continents)	12	0.10	−0.24	0.44	0.57	0.00
BD Phase: (Euthymic [ref] vs depressed)	7	0.13	−0.54	0.80	0.70	0.00
MDD Phase (Euthymic [ref] vs depressed)	7	0.13	−0.54	0.80	0.70	0.00
Males BD %	10	0.0003	−0.01	0.01	0.96	0.00
Males MDD %	9	−0.010	−0.02	0.005	0.19	0.01
1.2 Hyperthymic						
Country (Europe [ref] vs other continents)	**12**	**−0.44**	**−0.82**	**−0.06**	**0.02**	**0.28**
BD Phase: (Euthymic [ref] vs depressed)	7	−0.41	−1.27	0.44	0.35	0.00
MDD Phase (Euthymic [ref] vs depressed)	7	−0.41	1.27	0.44	0.35	0.00
Males BD %	10	−0.001	−0.02	0.03	0.91	0.00
Males MDD %	9	−0.009	−0.03	0.01	0.41	0.00
1.3 Depressive						
Country (Europe [ref] vs other continents)	12	0.33	−0.08	0.74	0.12	0.03
BD Phase: (Euthymic [ref] vs depressed)	7	0.15	−0.63	0.94	0.70	0.00
MDD Phase (Euthymic [ref] vs depressed)	7	0.15	−0.63	0.94	0.70	0.00
Males BD %	11	−0.02	−0.04	0.01	0.06	0.04
Males MDD %	10	−0.003	−0.02	0.02	0.75	0.00
1.4 Irritable						
Country (Europe [ref] vs other continents)	12	−0.73	−2.07	0.68	0.28	0.00
BD Phase: (Euthymic [ref] vs depressed)	6	−0.01	−2.60	2.58	0.99	0.00
MDD Phase (Euthymic [ref] vs depressed)	6	−0.01	−2.60	2.58	0.99	0.00
Males BD %	10	0.06	−0.01	0.12	0.11	0.00
Males MDD %	9	0.04	−0.06	0.07	0.91	0.00
1.5 Anxious						
Country (Europe [ref] vs other continents)	10	−0.96	−2.00	0.09	0.07	0.00
BD Phase: (Euthymic [ref] vs depressed)	5	−0.74	−2.67	1.20	0.46	0.00
MDD Phase (Euthymic [ref] vs depressed)	5	−0.74	−2.67	1.20	0.46	0.00
Males BD %	8	0.03	−0.03	0.08	0.33	0.00
Males MDD %	7	−0.01	−0.06	0.04	0.64	0.00
Males HS	0 studies available					
Males Sib	0 studies available					
Males HC %	2 studies available					
Males BD-I	2 studies available					
Males BD-II	1 studies available					
2. BD vs HC						
2.1 Cyclothymic						
Country (Europe [ref] vs other continents)	14	1.00	−0.30	2.32	0.13	0.00
BD Phase: (Euthymic [ref] vs depressed)	All 11 studies euthymic phase					
Males BD %	12	0.03	−0.02	0.07	0.32	0.00
Males HC %	**10**	**0.05**	**0.01**	**0.08**	**0.01**	**0.00**
2.2 Hyperthymic						
Country (Europe [ref] vs other continents)	14	−0.33	−0.96	0.31	0.32	0.00
BD Phase: (Euthymic [ref] vs depressed)	14	0.09	−0.72	0.89	0.84	0.00
Males BD %	12	−0.008	−0.03	0.01	0.52	0.00
Males HC %	10	−0.02	−0.04	0.008	0.20	0.00
2.3 Depressive						
Country (Europe [ref] vs other continents)	**14**	**1.29**	**0.12**	**2.46**	**0.03**	**0.18**
BD Phase: (Euthymic [ref] vs depressed)	11	−0.32	−2.02	1.38	0.71	0.00
Males BD %	12	0.02	−0.03	0.07	0.42	0.00
Males HC %	**10**	**0.03**	**0.005**	**0.06**	**0.02**	**0.16**
2.4 Irritable						
Country (Europe [ref] vs other continents)	**14**	**1.00**	**0.20**	**1.81**	**0.01**	**0.18**
BD Phase: (Euthymic [ref] vs depressed)	11	−0.48	−1.62	0.65	0.40	0.00
Males BD %	12	0.02	−0.02	0.05	0.35	0.00
Males HC %	10	0.31	−0.002	0.06	0.07	0.00
2.5 Anxious						
Country (Europe [ref] vs other continents)	**12**	**1.87**	**0.75**	**3.00**	**0.001**	**0.40**
BD Phase: (Euthymic [ref] vs depressed)	All 8 studies euthymic					
Males BD %	10	0.03	−0.02	0.08	0.23	0.00
Males HC %	**8**	**0.05**	**0.01**	**0.08**	**0.009**	**0.24**
3. MDD vs HC						
3.1 Cyclothymic						
Country (Europe [ref] vs other continents)	**8**	**0.56**	**0.03**	**1.14**	**0.04**	**0.24**
MDD Phase (Euthymic [ref] vs depressed)	5	−0.62	−1.59	0.35	0.21	0.00
Males MDD %	5	−0.003	−0.04	0.03	0.99	0.00
Males HC %	6	0.01	−0.02	0.04	0.41	0.12
3.2 Hyperthymic						
Country (Europe [ref] vs other continents)	8	0.24	−0.08	0.57	0.15	0.28
MDD Phase (Euthymic [ref] vs depressed)	5	−0.18	−0.59	0.23	0.39	0.05

Table 3 (*continued*)

Moderator	Number comparisons	B	95% CI		P value	R^2
Males MDD %	5	−0.002	−0.02	0.02	0.83	0.00
Males HC %	6	0.003	−0.02	0.03	0.76	0.00
3.3 Depressive						
Country (Europe [ref] vs other continents)	8	−0.71	−1.51	0.10	0.08	0.18
MDD Phase (Euthymic [ref] vs depressed)	**5**	**1.65**	**0.82**	**2.47**	**0.0001**	**0.75**
Males BD %	5	0.001	−0.001	0.03	0.32	0.00
Males MDD %	5	0.0003	−0.06	0.06	1.00	0.00
Males HC %	6	−0.01	−0.06	0.04	0.58	0.01
3.4 Irritable						
Country (Europe [ref] vs other continents)	8	0.74	−0.04	1.52	0.06	0.41
MDD Phase (Euthymic [ref] vs depressed)	**5**	**−1.44**	**−2.30**	**−0.60**	**0.001**	**0.76**
Males MDD %	5	−0.010	−0.08	0.06	0.79	0.00
Males HC %	6	0.007	−0.06	0.07	0.82	0.03
3.5 Anxious						
Country (Europe [ref] vs other continents)	**6**	**0.82**	**0.14**	**1.50**	**0.02**	**0.55**
MDD Phase (Euthymic [ref] vs depressed)	**4**	**−1.03**	**−2.02**	**−0.04**	**0.04**	**0.43**
Males MDD %	3 studies available					
Males HC %	**4**	**0.05**	**0.02**	**0.07**	**0.003**	**0.78**
4. BD vs Relatives						
4.1 Cyclothymic						
Country (Europe [ref] vs other continents)	4	−0.17	−3.8	3.48	0.93	0.00
BD Phase: (Euthymic [ref] vs depressed)	4	−2.7	−6.36	0.97	0.15	0.00
Males BD %	3					
Males HS	2 studies available					
Males Sib	1 study available					
4.2 Hyperthymic						
Country (Europe [ref] vs other continents)	4	−0.64	−1.96	0.68	0.34	0.25
BD Phase: (Euthymic [ref] vs depressed)	**4**	**0.98**	**0.09**	**1.87**	**0.03**	**0.68**
Males BD %	3 studies available					
Males HS	2 studies available					
Males Sib	1 study available					
4.3 Depressive						
Country (Europe [ref] vs other continents)	4	−2.08	−5.02	0.87	0.17	0.00
BD Phase: (Euthymic [ref] vs depressed)	4	−1.17	−4.94	2.6	0.54	0.00
Males BD %	3 studies available					
Males HS	2 studies available					
Males Sib	1 study available					
4.4 Irritable						
Country (Europe [ref] vs other continents)	4	0.34	−2.51	3.19	0.82	0.00
BD Phase: (Euthymic [ref] vs depressed)	4	−1.65	−4.9	1.59	0.32	0.00
Males BD %	3 studies available					
Males HS	2 studies available					
Males Sib	1 study available					
4.5 Anxious						
Country (Europe [ref] vs other continents)	**4**	**6.27**	**4.74**	**7.81**	**P < 0.0001**	**0.94**
BD Phase: (Euthymic [ref] vs depressed)	4	−2.89	−10.37	4.59	0.45	0.00
Males BD %	3 studies available					
Males HS	2 studies available					
Males Sib	1 study available					
5. BD relatives vs Healthy Controls						
5.1 Cyclothymic						
Country (Europe [ref] vs other continents)	4	−1.47	−4.85	1.9	0.39	0.00
Males HS	2 studies available					
Males Sib	1 study available					
Males HC %	2 studies available					
5.2 Hyperthymic						
Country (Europe [ref] vs other continents)	4	0.94	0.57	2.45	0.22	0.25
Males HS	2 studies available					
Males Sib	1 study available					
Males HC %	2 studies available					
5.3 Depressive						
Country (Europe [ref] vs other continents)	**4**	**−2.08**	**−3.86**	**−0.29**	**0.02**	**0.69**
Males HS	2 studies available					
Males Sib	1 study available					
Males HC %	2 studies available					
5.4 Irritable						
Country (Europe [ref] vs other continents)	3 studies available					
Males HS	3 studies available					
Males Sib	3 studies available					
Males HC %	3 studies available					
5.5 Anxious						
Country (Europe [ref] vs other continents)	3 studies available					

Table 3 (*continued*)

Moderator	Number comparisons	B	95% CI	P value	R^2
Males HS	3 studies available				
Males Sib	3 studies available				
Males HC %	3 studies available				

depressed mood, where distinguishing unipolar from bipolar disorder is key decision factor for treatment decisions, yet, this differentiation can be quite challenging (Hirschfeld, 2014).

Regarding the BD vs ADHD comparisons, our results strongly suggest common temperamental features, as indicated before (Landaas et al., 2012), suggesting some shared biological background between the two conditions that are also not infrequently comorbid, especially in youth (Ashcroft et al., 2015; Chen et al., 2015; Lan et al., 2015). Moreover, although only two studies reported data about TEMPS-A in BD vs BPD, our preliminary results suggest that temperament assessments could be helpful in helping to distinguish these two conditions, in addition to taking into consideration a history of childhood sexual abuse, childhood depersonalization, personality variables relating to interpersonal difficulties and sensitivity to criticism, BD family history, and interpersonal features (Bayes et al., 2015).

5. Limitations

Results of this study need to be interpreted within its limitations. First, we only investigated TEMPS affective domains, excluding other potentially interesting questionnaires, such as the Tridimensional Cloninger Inventory (Cloninger et al., 1993). However affective domains as measured by TEMPS have consistent biological and genetic correlates (Gonda et al., 2006; Greenwood et al., 2012, 2013), being a fundamental instrument to “look into brain through the mind's lens”. Second, included studies did not all use all the same TEMPS version. However, former studies have shown consistent reliability of different TEMPS versions (Vahip et al., 2005; Akiskal et al., 2005; Krebs et al., 2006; Vazquez et al., 2007; Figueira et al., 2008; Borkowska et al., 2010; Preti et al., 2010; Lin et al., 2013), supporting our choice to pool the results across these different TEMPS versions. Moreover, we accounted for heterogeneity of measurement instruments using random effect model in meta-analysis, and our publication bias and trim and fill analyses confirmed the results. Third, comparisons between BD and ADHD, and between BD and BPD only included 3 and 2 studies, respectively, limiting the validity and generalizability of these results. This sample size limitation is accentuated by the fact that BD, BPD and ADHD have overlapping features and that controversy exists about the appropriate nosological boundaries (Bayes et al., 2015). Fourth, a deeper insight into the affective temperament can be gained from combining data from different structured questionnaires, such as the TEMPS and TCI. Such analyses have already shown significant correlations between novelty seeking and harm avoidance, on the one hand, and anxious, depressive and cyclothymic temperament domains, on the other (Rozsa et al., 2008). However, such analyses are beyond the aims and scope of this meta-analysis. Fifth, the vast majority of studies included outpatients, possibly introducing a bias, which, however, was not apparent in our subgroup and moderator analyses. Sixth, not all included studies specified inclusion criteria for first degree-relatives, with two studies (Kesebir et al., 2005; Mahon et al., 2013) including first degree relatives and siblings, whereas the other two studies did not provide further details about the nature of the familial relationship. We attempted to contact authors, but were unable to obtain clarification, assuming for the purposes of the analyses that the studies included first degree-relatives, in line with the aims of investigating temperament as an endophenotype and as stable trait across families. Finally, while it would be of great interest to assess TEMPS scores in patients with and without a family history of bipolar disorder, this level of detail was unavailable in the meta-analyzed studies, precluding such subgroup analyses.

Despite these limitations, several strengths of this study are also noteworthy. First, to the authors' knowledge, this is the first meta-analysis of studies comparing TEMPS ratings in within and across mood disorders and in comparison to psychiatric controls and HCs. Second, this study identified different patterns of TEMPS scores in different diseases and in comparison to HC. Third, this metaanalysis confirms the continuum pattern of cyclothymic, irritable and anxious temperament, ranging from the lowest scores in HCs, through relatives of patients with BD, to patients affected by MDD and to patients with BD. Fourth, the sample size and the number of studies included in the analyses were robust for most of the analyses and comparisons, at least vs HCs and comparing BD with MDD.

6. Conclusions

In conclusion, affective temperament as measured by TEMPS has a continuum pattern increasing in severity from HC, through MDD to BD regarding cyclothymic and irritable temperament, from MDD through BD to HC regarding hyperthymic temperament, and from HC through BD relatives to BD regarding cyclothymic, irritable and anxious domains. BD did not differ from MDD regarding depressive and anxious temperament, but these two affective domains separated both mood disorder from HCs who scored far lower than both MDD and BD. BD did not differ from ADHD in any of the investigated TEMPS domains, suggesting a common biological background, although more data are needed to confirm this. Finally, BPD was associated with higher depressive, anxious, and irritable temperament scores compared to BD, lower hyperthymic scores, but similar cyclothymic scores. However only two studies compared these two populations, underscoring the need for further studies investigating the overlap and differentiating features across severe mental disorders and, especially, BPD and BD.

Conflict of interest

Veronese, Solmi, Stubbs, Zaninotto, Toffanin and Lin declare no potential conflict of interest. Dr. Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Actavis, Actelion, Alexza, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, GersonLehrman Group, IntraCellular Therapis, Lundbeck, Medavante, Medscape, Merck, National Institute of Mental Health, Janssen/J & J, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Takeda, Teva, and Vanda. He has received grant support from BMS, Feinstein Institute for Medical Research, Janssen/J & J, National Institute of Mental Health (NIMH), National Alliance for Research in Schizophrenia and Depression (NARSAD), Otsuka and Takeda.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi:10.1016/j.jad.2016.02.013.

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Combined pharmacotherapy-multimodal psychotherapy in children with Disruptive Behavior Disorders

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ABSTRACT

Although multi-component psychotherapeutic interventions are first-line treatments for Disruptive Behavior Disorders (DBD), pharmacotherapy is often associated for more severe patients. Our aim was to explore effectiveness of an associated pharmacotherapy in referred children with DBD receiving a one-year psychotherapeutic intervention. Aggression, callous unemotional (CU) traits and emotional dysregulation were outcome measures. The sample included 144 children, aged 8 – 12 years, 41 (29%) with an ADHD comorbidity. Fifty-five (38%) patients received an additional pharmacotherapy with one medication, methylphenidate, a second generation antipsychotic, or a mood stabilizer. Data were collected before and after the one-year treatment. According to the Child Behavior Checklist (CBCL), aggressive behaviors, rule-breaking behaviors and emotional dysregulation improved in the whole group, as well as parent- and child-reported CU traits. The hierarchical regression model showed that additional pharmacotherapy significantly predicted lower scores at the CBCL aggressive behaviors and emotional dysregulation, but not CU traits at the end of the treatment. The interaction between methylphenidate and ADHD comorbidity predicted lower aggressive behaviors after the treatment. In summary, this naturalistic investigation suggest that an additional pharmacotherapy significantly improved aggression and emotional dysregulation, but not CU traits. When ADHD was comorbid, methylphenidate was more effective than antipsychotics or mood stabilizers in reducing aggression.

1. Introduction

Disruptive Behavior Disorders (DBD), including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), are among the most represented clinical conditions in child and adolescent mental health settings. There is a long and extensive history of research on DBD, namely regarding the best treatment strategies and the predictors of treatment response (American Psychiatric Association, 2000; Moffitt et al., 2008). Major goals in clinical research of DBD are to develop effective treatment models for improving aggressive and rule breaking behaviors, as well as for defining possible risk factors of poor outcomes or relapses. Consistent findings from clinical studies and meta-analyses indicate that a multi-component intervention, usually including child-oriented sessions, family sessions, interventions at school, and based on cognitive behavioral principles and practices, are usually the first-line treatment option for DBD (Mc Cart et al., 2006; Eyberg et al., 2008). Evidence from studies on pharmacological treatments in patients with DBD is still poorly informative, although some limited data support efficacy of second generation antipsychotics (SGA), mood stabilizers (MS), and stimulants (Ipser and Stein, 2007; Turgay, 2009; Loy et al., 2012; Gorman et al., 2015). However, considering that in the clinical practice a co-treatment with psychotherapeutic interventions and pharmacotherapy is a frequent strategy, namely in the more severe patients with DBD, there is a dearth of studies exploring the clinical implications of this association. Recent studies suggest that a combination of both psychotherapeutic and pharmacological approaches can improve the outcome of aggressive children and adolescents with DBD (Aman et al., 2014; Gadow et al., 2014).

A critical issue in evaluating the effectiveness of DBD treatments is patient heterogeneity within the same diagnostic category (Klahr and Burt, 2014). Disentangling this diagnostic domain in meaningful clinical subgroups may have significant clinical and treatment implications. At least two subtypes of DBD can be described, one associated with Callous Unemotional (CU) traits and predatory aggressiveness, and another associated with impulsive

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and reactive aggression, often co-occurring with mood and anxiety disorders (Vitiello and Stoff, 1997; Blair, 2013). Compared to patients with impulsive/reactive aggression, children and/or adolescents with CU traits and predatory aggression have been found to be more resistant both to medications (Masi et al., 2006; Masi et al., 2009), and to multi-component interventions (Masi et al. 2011, 2013; Hawes et al., 2014). However, previous studies have suggested that CU traits can decrease during multi-component treatments, including parenting intervention, individual psychotherapy and pharmacotherapy (Kolko and Pardini, 2010; Muratori et al., 2015).

Another important clinical specifier for a DBD subtyping is the co-occurrence of emotional dysregulation, including mood instability, severe irritability, aggression, temper outburst, and hyper-arousal (Masi et al., 2015a, 2015b). The Child Behavior Check List Dysregulation Profile (CBCL-DP), with simultaneous high values (above two Standard Deviations) in three CBCL syndrome scales (Anxious/Depressed, Attention Problems, and Aggressive Behavior), has been proposed as a possible diagnostic tool for identifying children with Emotional Dysregulation (Faraone et al., 2005; Youngstrom et al., 2005; Volk and Todd, 2007; Holtmann et al., 2011; Mbekou et al., 2014). Previous studies investigated CBCL-DP in DBD (Volk and Todd, 2007; Masi et al., 2015a, 2015b), and found that the CBCL-DP score may be associated with an increased risk of persisting ADHD or superimposed mood disorders. However, to date, implications of this conceptualization on treatment outcome are poorly explored.

Our aim was to address the topic of effectiveness of a combined pharmacotherapy-psychotherapy in children with DBD referred in a clinical setting and treated with a multi-component intervention. This naturalistic investigation compared children receiving the combined treatment and children those receiving the same psychotherapeutic intervention, but not medications. Although it is not possible to draw firm information on the efficacy of the treatments from a naturalistic observation, significant information may stem on effectiveness and course under a specific treatment. In order to explore the specific impact of the two treatment strategies, not only aggressive behavior, but also callous-unemotional traits and emotional dysregulation we selected as outcome measure. In order to explore more specific pharmacological strategies, efficacy of *methylphenidate* was compared with *second generation antipsychotics or mood stabilizers.*

2. Method

2.1. Participants and procedures

In this naturalistic study, a consecutive sample of children initially referred for behavioral problems received a systematic evaluation at the Child and Adolescent Psychiatry and Psychopharmacology Department of our Hospital. At the baseline, trained child psychiatrists administered separately to parents and children a clinical interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Patients also received an assessment of functional impairment, according to the Children Global Assessment Scale (C-GAS) (Shaffer et al., 1983), an evaluation of cognitive abilities with the Wechsler Intelligence Scales for Children – 3rd Ed (WISC-III) (Wechsler, 1991), while parents completed the Child Behavior Checklist (Achenbach and Rescorla, 2001).

The inclusion criteria of the current study were: 1) DSM-IV-TR diagnosis of ODD or CD according to K-SADS-PL; 2) a Full Scale IQ above 85; 3) a CBCL externalizing score above 63. A total of 164 children and families met the inclusion criteria, completed pre-treatment assessments, and started intervention. Twenty participants (14%) discontinued the treatment (i.e., they stopped treatment without mutual consent, and they did not receive further treatment before the second assessment), and they were not included in the analyses. The final sample included 144 children, age range 8 – 12 years, 129 (90%) male and 15 (10%) female, 124 (86%) Caucasians and 20 (14%) African. Forty-one (29%) presented a CD diagnosis and 103 (71%) an ODD diagnosis, 41 (29%) had an ADHD comorbidity, and 30 (23%) had a Mood Disorder (MD) comorbidity (including Depressive Disorders and Bipolar Disorders). Regarding socio-economic status (SES), 42 families (29%) presented a low SES according to Hollingshead and Redlich scale (1958).

All the participants were treated with a multi-component intervention (including a child psychotherapy and parent training intervention) based on cognitive behavioral practices and principles (for further details see Masi et al., 2014). The children and parents received the full dosage of the treatment program, with an average child and parent attendance rate of 83%. The integrity of this model was monitored and measured in the following ways: (a) Therapists attended official training in cognitive behavioral psychotherapy; (b) Therapists attended supervision meetings with a certified cognitive behavioral psychotherapy supervisor; (c) During a weekly staff meeting based on case reviews, therapists completed a checklist of objectives delivered within sessions.

One month before the beginning of the multi-component treatment, all the patients were assessed by child psychiatrists, and, when necessary, they received a medication, based on the severity of the clinical picture and the categorical diagnosis. Fifty-five patients (38%) received a pharmacotherapy: methylphenidate was prescribed to 19 patients with ADHD, while 25 patients received a second generation antipsychotic (risperidone or quetiapine), and 11 a mood stabilizer (lithium carbonate or valproic acid). No patients received more than one medication, and each medication was continued during the 12-month multimodal treatment, with possible dosing adjustments, based on efficacy and tolerability.

Data were collected before the multi-component treatment, and at the end of the treatment. Consent was obtained from parents at initial enrollment and at each of the following assessment points. The Ethical Committee of our Hospital approved the study.

2.2. Measures

- *Categorical diagnosis:* at the baseline, trained child psychiatrists with specific experience in child and adolescent psychiatric disorders administered separately to the parents and children the clinical interview K-SADS-PL (Kaufman et al., 1997), which explores the presence or absence of each symptom according to DSM-IV. The K-SADS-was double-rated, and the interviewer agreement was 89%.
- *Family socioeconomic status* (SES) was assessed with the Hollingshead and Redlich scale (Hollingshead and Redlich, 1958).
- *Intellectual functioning* was assessed with the Wechsler Intelligence Scales for Children – 3rd Ed (WISC-III) (Wechsler, 1991).
- *Behavior Problems* were explored with the CBCL (Achenbach and Rescorla, 2001) at each time point. The CBCL is a 118 item standardized format, completed by parents for recording behavioral problems and skills in children and adolescents from 6 to 18 years of age. The 118 behavior problem items are aggregated in eight different subscales. Each item is scored on a 3-step response scale. Two subscales (Aggressive behavior and Rule-Breaking behavior) are related to the externalizing domain and were used as measure of behavior problems. Reliability across the time points was .78 for the Aggressive behavior and .85 for

the Rule-Breaking behavior (Cronbach's Alpha).
- *Emotional dysregulation* was assessed using the sum of *t*-scores of the following CBCL subscales, Anxious/depression, Attention problems and Aggressive behaviors. The reliability coefficients were .85, .82 and .78, respectively (Cronbach's Alpha).
- *Callous Unemotional Traits* (CU) were assessed at each time point using the CU subscale of Antisocial Process Screening Device (APSD), a 20-item inventory, parent-report version (Frick and Hare, 2001), and the total score of Inventory of Callous Unemotional traits (ICU), a 24-item inventory, self-report version (Frick, 2004). A factorial analysis of APSD using a non-clinical sample of 1120 children and adolescents identified three main dimensions: Callous-Unemotional (6 items), Narcissistic (7 items), and Impulsivity (5 items). The APSD presented good reliability and validity in previous studies (Kotler and Mc Mahon, 2010). In the current sample, the mean Cronbach Alpha across the time points was.75 for the APSD-CU. The ICU includes 12 positively worded (e.g., "I express my feelings openly") and 12 negatively worded items (e.g., "What I think is "right" and "wrong" is different from what other people think"), which are rated on a 4-point Likert-scale, ranging from 0 (not at all true) to 3 (definitely true). Support for the validity of the ICU was obtained in clinical and normative samples (Ciucci et al., 2015; Kimonis et al., 2008). ICU Item scores were combined to form a total score, with adequate internal consistency in the present study (mean Cronbach's Alpha.68 across the time points).
- Outcome measures were the pre- and post-treatment scores at the CBCL Aggressive behaviors and Rule-breaking behaviors scores, CBCL-DP score, and APSD and ICU scores.
- At the end of the treatment all the patients were also evaluated by two independent clinicians with the Global Impression-Improvement (CGI-I) (Guy, 1976), and the rate of concordance between raters was.85.

2.3. Data analysis

A paired *t*-test was performed for testing the Aggressive and Rule breaking behaviors, Dysregulation Profile scores and CU traits during the intervention. A hierarchical regression model examined the contribution of the additional pharmacotherapy treatment to the levels of several outcome measures. In particular, in the regression models, gender, age, SES, CD or ODD diagnosis, ADHD comorbidity and baseline level of the outcome measures were entered at Step 1, and pharmacotherapy (absent or present) was entered at Step 2. In addition, a Repeated Measure Anova examined the effects of a specific drug (MPH, SGA, MS) on outcome measures. In this analysis the between subjects factor was the use of a specific drug (MPH) compared with the two others combined together. All statistical analyses were performed using SPSS v. 21.0.

3. Results

T-test analysis showed that according to the CBCL, in the whole group the aggressive behaviors decreased from 71.72 to 67.56 ($t=6.15$, $p<.001$), rule-breaking behaviors from 66.16 to 63.36 ($t=4.47$, $p<.001$), CBCL-DP score from 204.70 to 195.95 ($t=6.48$, $p<.001$). Furthermore, parent-reported CU traits evaluated by APSD decreased from 5.72 to 4.74 ($t=3.54$, $p<.001$), and self-reported CU traits evaluated by ICU from 27.86 to 24.46 ($t=8.83$, $p<.001$).

When the 55 patients receiving the medication were compared with the 89 without medications (Table 1), age, gender ratio, CD/ODD ratio did not differ between groups. Patients receiving medication presented a higher rate of ADHD (41.8% vs. 20.2%, $p=.008$), mood disorders (34.5% vs. 19.1%, $p=.048$), and a higher

Table 1
Comparison between patients receiving psychotherapy only (n=89) and patients receiving a combined treatment (pharmacotherapy plus psychotherapy, n=55).

Baseline variables	Psychotherapy only (n=89)	Combined (n=55)	*p*
Age, years (SD)	9.6 (1.3)	9.6 (1.4)	Ns
Male, n (%)	77 (86.5)	52 (94.5)	Ns
ODD/CD, n (%)	69/20 (77.5/22.5)	34/21 (61.8/38.2)	Ns
ADHD, n (%)	18 (20.2)	23 (41.8)	.008
Mood Disord., n (%)	17 (19.1)	19 (34.5)	.048
CBCL-aggressive behavior, score (SD)	70.03 (6.30)	74.31 (8.10)	.001
CBCL-rule breaking, score (SD)	65.70 (6.41)	67.11 (6.60)	Ns
CBCL-DP, score (SD)	202.10 (14.90)	208.41 (15.75)	Ns
ICU TOTAL, score (SD)	27.11 (5.71)	29.00 (8.21)	Ns
APSD-CU, score (SD)	5.66 (1.82)	5.69 (2.28)	Ns

Note: CD: Conduct Disorder; ODD: Oppositional Defiant Disorder; CBCL: Child Behavior Checklist; CBCL-DP: Child Behavior Checklist Dysregulation Profile; ICU=Inventory of Callous Unemotional traits; APSD-CU: Antisocial Process Screening Device, Callous Unemotional subscale.

Table 2a
Effect of additional pharmacotherapy: results of three steps multiple regression (n=144). In the first step, age, gender, ODD/CD diagnosis, ADHD/MD comorbidity and SES status were entered in the model; in the second step, the baseline level of the outcome variable; in the third step, the presence/absence of pharmacological treatment. impact of additional pharmacotherapy on outcomes. beta estimates of the last step of hierarchical regression model are reported.

Outcome variables	Baseline level of the outcome variable	Additional pharmacotherapy
CGI-I	.295**	.034
CBCL Aggressive	.348**	−.343**
CBCL Rule-breaking	.444***	.074
CBCL DP	.443***	−.223*
ICU-Y total score	.772***	.009
APSD-P CU score	.519***	−.101

Note: CGI-I: Clinical Global Impression-Improvement score; CBCL: Child Behavior Checklist; CBCL-DP: Child Behavior Checklist Dysregulation Profile; ICU-Y: Inventory of Callous Unemotional traits- Youth version; APSD-P CU: Antisocial Process Screening Device, Parent-report version, Callous Unemotional subscale.

* = p ≪ .05.
** = p ≪ .01.
*** = p ≪ .001.

Table 2b
Comparison between patients receiving methylphenidate (MPH) and patients receiving Second generation antipsychotics (SGA) and/or mood stabilizers (MS).

Baseline	MPH (n=19)	SGA and/or MS (n=36)	p
Males, n (%)	18 (94.7)	34 (94.4)	Ns
Low SES, n (%)	10 (52.6)	15 (41.7)	Ns
ODD/CD, n (%)	12/7 (63.2/36.8)	24/12 (66.7/33.3)	Ns
ADHD, n (%)	19 (100)	9 (25)	≪.0001
Mood disorders, n (%)	2 (10.5)	18 (50)	.004
CBCL Aggressive behavior, mean (sd)	75.03 (8.00)	73.97 (8.10)	Ns
CBCL Rule-Breaking, mean (sd)	68.13 (6.90)	68.10 (6.50)	Ns
CBCL DP, mean (sd)	211.25 (19.24)	210.10 (14.84)	Ns
ICU-Y total score, mean (sd)	28.00 (5.90)	29.80 (8.90)	Ns
APSD-P CU score, mean (sd)	5.73 (1.83)	5.67 (2.43)	Ns

Legenda: ODD/CD: Oppositional Defiant Disorder/Conduct Disorder; ADHD: Attention Deficit Hyperactivity Disorder; CBCL: Child Behavior Checklist; ICU-Y: Inventory of Callous Unemotional traits- Youth version; APSD-P CU: Antisocial Process Screening Device, Parent-report version, Callous Unemotional subscale; Ns=Not significant ($p<.05$).

Table 3
Comparison between patients receiving methylphenidate (MPH) and patients receiving second generation antipsychotics (SGA) and/or mood stabilizers (MS).

Baseline	MPH (n=19)	SGA and/or MS (n=36)	*p*
Males, n (%)	18 (94.7)	34 (94.4)	Ns
ODD/CD, n (%)	12/7 (63.2/36.8)	24/12 (66.7/33.3)	Ns
ADHD, n (%)	19 (100)	9 (25)	.0001
Mood disorders, n (%)	2 (10.5)	18 (50)	.004
CBCL Aggressive behavior, mean (SD)	75.03 (8.00)	73.97 (8.10)	Ns
CBCL Rule-Breaking, mean (SD)	68.13 (6.90)	68.10 (6.50)	Ns
CBCL DP, mean (SD)	211.25 (19.24)	210.10 (14.84)	Ns
ICU-Y total score, mean (SD)	28.00 (5.90)	29.80 (8.90)	Ns
APSD-P CU score, mean (SD)	5.73 (1.83)	5.67 (2.43)	Ns

Note: ODD/CD: Oppositional Defiant Disorder/Conduct Disorder; ADHD: Attention Deficit Hyperactivity Disorder; CBCL: Child Behavior Checklist; ICU-Y: Inventory of Callous Unemotional traits- Youth version; APSD-P CU: Antisocial Process Screening Device, Parent-report version, Callous Unemotional subscale; Ns=Not significant ($p < .05$).

score at the CBCL-aggressive score (74.31 ± 8.10 vs 70.03 ± 6.30, $p=.001$), while CBCL- rule breaking, CBCL-DP, and CU traits (according to both APSD and ICU) did not differ between groups.

Table 2a and 2b shows that according to the hierarchical regression model, in addition to the contribution of gender, age, SES, CD or ODD diagnosis, ADHD comorbidity, and baseline level of the outcome measures, an additional pharmacotherapy significantly predicted the levels of children's aggressive behavior and DP score (24% of explained variance). Namely, the additional pharmacotherapy was associated with lower scores at the CBCL Aggressive behaviors and DP, while it did not predict CBCL Rule-breaking behavior and levels of CU traits at the end of the treatment (Table 3).

When the effect of MPH was compared with the effect of SGA and/or MS, data indicated that aggressive behaviors significantly decreased from 75.03 to 68.73 in children taking MPH, and from 73.97 to 73.00 in children taking SGA/MS ($F=4.880$; $p < .05$). No significant differences resulted from all other Anovas. Furthermore, in children assuming medications, a hierarchical regression model showed that the interaction between MPH and ADHD comorbidity predicted the levels of children's aggressive behaviors after the treatment. This interaction predicted lower levels of aggressive behaviors ($R^2=.290$; $p < .05$) controlled for gender, age, SES, CD or ODD diagnosis, and the baseline level of this outcome measure.

4. Discussion

Considering that multi-component treatment programs are the first option in DBDs, are there further specific treatment protocols targeted for specific distinct DBD subtypes? The aim of this study was to verify if a combined pharmacotherapy improved the response to treatment in a large sample of children with DBD during a multi-component cognitive-behavioral intervention.

Patients receiving and not receiving additional pharmacotherapy were not randomized, but the medication was naturalistically prescribed on the basis of the clinical judgment few weeks before starting the psychotherapeutic intervention, and continued during the psychotherapy, with possible dosing adjustments, according to procedure routinely followed in the clinical practice. This design limits the conclusions about the real efficacy of the treatments.

The patients receiving medications presented higher rates of ADHD and mood disorders, and a higher score at the CBCL-aggressive behavior, while age, gender, CD/ODD ratio, as well as CBCL-DP and CU traits (both parent- and self-reported) did not differ between groups.

A strength of this study was to consider as outcome measures not only behavior problems, but also Callous Unemotional traits and Emotional Dysregulation. Furthermore, different medications were compared, in order to explore more specific treatment protocols, addressing the practical challenges often faced by clinicians in mental health care units (Aarons et al., 2011).

Our findings indicate that, consistently with our previous findings, all the children who received the multimodal treatment showed a significant reduction in all of the outcome measures, including CU traits (Muratori et al., 2015). In the patients receiving an additional pharmacotherapy, a greater improvement of aggressive behavior and CBCL-DP scores was found at the end of the treatment; on the contrary, rule-breaking behavior and CU traits presented a similar improvement in patients with or without medications.

A greater improvement in aggression in patients receiving medication was expected, as it usually represents a primary target for a pharmacological intervention. This finding may be affected by the more severe baseline aggression in patients with medication. However, it is clinically relevant, even from a prevention perspective, as childhood aggression represents a meaningful risk marker for a variety of negative adolescent outcomes, such as delinquency, substance use and poor school adjustment (Lochman and Wells, 2002). Our findings further suggest that a combined treatment may represent the gold standard care for particularly aggressive children. Recently, Lochman and colleagues (Lochman et al., 2015) found that children's baseline level of inhibitory control moderated the effects of an evidence-based multi-component intervention, showing that children with lower initial levels of inhibitory control tend to respond poorly to the psychosocial intervention. An additional pharmacotherapy might promote a better inhibitory control and, consequently, bring the child to benefit more from the psychosocial intervention.

Regarding the Emotional Dysregulation, which did not differ in the two treatment groups at the baseline, we found an incremental effect of a combined treatment, compared to psychotherapy only, in ameliorating CBCL-DP outcome. To our knowledge, no previous studies have used CBCL-DP as a treatment outcome, although dysregulation is a clinical feature common in DBD (Masi et al., 2015a, 2015b). The CBCL-DP score may represent a reliable measure of a broad Emotional Dysregulation dimension (Deutz et al., 2015), e.g. including symptoms of anxiety/depression and inattention, consistent with Blair's conceptualization of some forms of CD (Blair, 2013). The CBCL-DP profile may represent an early marker of severity, associated with an increased risk of poorer outcome. For this reason, this evaluation should be included in a comprehensive child psychiatric assessment of DBD. Although this dimension lacks specificity, its assessment and timely detection in clinical populations may help to disentangle specific high-risk subgroups needing more intense interventions, to target specific treatment strategies, and to contrast negative development. Our results suggest that these features may represent a possible predictor of a greater effectiveness of a combined treatment, as Emotional Dysregulation improves incrementally with a pharmacotherapy.

Regarding the Callous Unemotional traits, evaluated both with self- and parent- measures, they were similar in the two treatment groups at the baseline, and no effect of an additional pharmacotherapy was found. It is well known that CU traits and predatory aggression are predictors of worse outcome after pharmacological treatments (Masi et al., 2006, 2009). Although a possible combination of medication and behavior therapy has been suggested for children with ADHD/Conduct Disorder plus CU traits (Waschbusch

et al., 2007), in our study the additional pharmacotherapy failed to affect the CU traits.

Regarding the effect of specific category of medications, we compared DBD patients with ADHD patients receiving methylphenidate, and DBD patients without ADHD, receiving a second generation antipsychotic (risperidone or quetiapine) or a mood stabilizer (valproic acid or lithium). Our data suggest that when ADHD is comorbid with a DBD, MPH may be more effective than SGA or MS in reducing aggression. However, patients receiving SGA or MS were included in a single group, excluding the possible exploration of the specific effect each class of medications may have (i.e., a greater efficacy of SGAs on aggression). Although the efficacy of stimulants in patients with ADHD and severe behavior problems is supported by previous studies and guidelines (Gorman et al., 2015), in the daily practice, aggression often leads to SGA or MS as the first treatment option, even in ADHD patients. Our findings suggest that when ADHD is comorbid with DBD, MPH should be the first treatment option to improve aggression, even considering its more positive side effect profile, compared to both SGA and MS.

Several limitations restrict the findings of the present study. First of all, the two treatment groups were not randomized, as the medication was prescribed according to clinical considerations (categorical diagnosis, severity). The report is limited by the naturalistic nature of the follow-up, which cannot control for self-selection and prevents drawing strong conclusions about treatment efficacy. In this way it is not possible to draw firm conclusions about the efficacy of the treatments. However, the pharmacological treatment was started only few weeks before the psychotherapy, patients received only one medication, and the same medication was maintained during all the period of the psychotherapeutic treatment, with dosing adjustments. The patients on pharmacotherapy are a minority of the total sample, so patients receiving second generation antipsychotics or mood stabilizers were included in a single group, excluding the possible exploration of the specific effect of each medication. A large, randomized trial is needed to achieve this purpose. Part of the outcome measures were based on parents' reports. Given that parents participated in the treatment program, this issue may determine a bias in favor of reporting positive changes in their children.

However, a major strength of the study is that our findings described a sample of consecutive children with DBDs as a primary diagnosis, treated and followed-up in an ordinary clinical setting. Furthermore, the follow-up was longer than in previous studies, and the attrition rate was very low. Information from naturalistic studies is important to ascertain the effectiveness of the treatments and the course of the disorder (including its dimensions) in a routinary clinical setting, given that information available in the field is still scant.

Our preliminary findings suggest that in referred patients with DBD presenting aggressive behaviors and/or Emotional Dysregulation, a combined psychosocial and psychopharmacological treatment may be considered. On the contrary, CU traits seem less sensitive to a combined pharmacotherapy. Furthermore, when ADHD is comorbid with ODD/CD, MPH should be the first line drug in view of his greater effect on aggressive behavior and a more favorable side effect profile. These data may allow new information and broader inferences on the effectiveness of treatments over extended periods of time in the real world under ordinary clinical conditions.

Conflict of interest

Dr. Masi was in the advisory boards for Eli Lilly, Shire and Angelini, has received research grants from Eli Lilly and Shire, and has been speaker for Eli Lilly, Shire, Lundbeck, and Otsuka. All the other authors do not have conflicts of interest to declare.

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CLINICAL REVIEW

Somatic and neuropsychiatric comorbidities in pediatric restless legs syndrome: A systematic review of the literature

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SUMMARY

Restless legs syndrome (RLS) is a relatively common neurological disorder in childhood, although it is usually overlooked due to the atypical presentation in children and associated comorbid conditions that may affect its clinical presentation. Here, we aimed to perform, for the first time, a systematic review of studies reporting the association between RLS in children and adolescents (<18 y) and somatic or neuropsychiatric conditions. We searched for peer-reviewed studies in PubMed, Ovid (including PsycINFO, Ovid MEDLINE®, and Embase), Web of Knowledge (Web of Science, Biological abstracts, BIOSIS, FSTA) through November 2015, with no language restrictions. We found 42 pertinent studies. Based on the retrieved studies, we discuss the association between RLS and a number of conditions, including growing pains, kidney disease, migraine, diabetes, epilepsy, rheumatologic disorders, cardiovascular disease, liver and gastrointestinal disorders, and neuropsychiatric disorders (e.g., attention deficit hyperactivity disorder (ADHD), depression, and conduct disorder). Our systematic review provides empirical evidence supporting the notion that RLS in children is comorbid with a number of somatic and neuropsychiatric conditions. We posit that the awareness on comorbid diseases/disorders is pivotal to improve the diagnosis and management of RLS and might suggest fruitful avenues to elucidate the pathophysiology of RLS in children.

Introduction

Restless legs syndrome (RLS), also known as Willis Ekbom disease (WED), is a relatively common pediatric disease with an estimated worldwide prevalence of 2–4% in school-aged children and adolescents [1].

Empirical evidence shows that 25% of adults with RLS present an onset of RLS symptoms during childhood or adolescence [2]. However, despite the awareness that RLS does occur in childhood, the pediatric form of RLS is often misdiagnosed and overlooked by many clinicians with limited expertise in pediatric sleep medicine. Possible causes of under-recognition include the mild and intermittent nature of RLS symptoms in childhood, its atypical presentation, and frequent comorbidities and mimics, which may mask the clinical picture. However, the classical presentation of a compelling urge to move the legs, often accompanied by uncomfortable dysesthesias, is present also in children. To make a diagnosis of RLS, this core of sensory-motor symptoms must be present at rest, be at least temporarily relieved by movement, and be more pronounced at night, although this could lack in children [3].

In adults, adolescents and children, RLS may lead to significant morbidity because of the associated sleep disturbance, which impacts on attention, working memory and other higher-level cognitive functions, academic achievement, mood, behavior, quality of life, and family well-being [3,4].

To guide the clinician in the diagnosis of RLS in children/adolescents, in 2003 the National Institutes of Health workshop and the International RLS Study Group (IRLSSG) first proposed the pediatric RLS diagnostic criteria [3]. These criteria defined three

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Glossary of terms

ADHD	attention deficit hyperactivity disorder
ADHD-RS-IV	attention deficit/hyperactivity disorder rating scale-IV
CD	celiac disease
CDI	children depression inventory
CKD	chronic kidney disease
CLD	chronic liver disease
CPI	conduct problem index
D3R	dopamine D3 receptor
DPS	dopaminergic premonitory symptoms
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
GP	growing pains
HRQoL	health-related quality of life
ID	iron deficiency
IDA	iron deficiency anemia
IRLSSG	International restless legs syndrome study group
LTR	liver transplant recipients
NDDs	neurodevelopmental disabilities
OCS	obsessive compulsive symptoms
ODD	oppositional defiant disorder
PANDAS	pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
PLMS	periodic leg movements during sleep
PSQ	pediatric sleep questionnaire
RAP	recurrent abdominal pain
RLS	restless legs syndrome
SDSC	sleep disturbance scale for children
SRBD	sleep related breathing disorder
SSRIs	selective serotonin reuptake inhibitors
TS	Tourette syndrome
WED	Willis-Ekbom disease

possible forms of pediatric RLS: 1) definite (i.e., fulfilling the adult criteria for RLS and relates a description in his or her own words that is consistent with leg discomfort); 2) probable (the child meets all essential adult criteria for RLS, except criterion #4 (the urge to move or sensations are worse in the evening or at night than during the day) and has a biologic parent or sibling with definite RLS; for younger or cognitively impaired children who do not have sufficient language to describe the sensory component of RLS, the child is observed to have behavior manifestations of lower-extremity discomfort); 3) possible (the child has PLMD and a biologic parent or sibling with definite RLS). The empirical evidence based on this first set of criteria, published after 2003, lead in 2010 a group of researchers in the field of pediatric RLS to revise the criteria for pediatric RLS. The pediatric RLS committee agreed that adult and pediatric diagnostic criteria should be combined, but pointed out the need for pediatric specifiers to take into account the peculiar nature of symptoms in childhood and the need to use age-appropriate terms when interviewing children [5]. Pediatric Committee highlighted that:

- the child must describe the RLS symptoms in his/her own words and the clinician needs to be familiar with this language;
- cognitive development determines the applicability of the RLS diagnostic criteria, rather than age;
- for RLS to be diagnosed in childhood, a significant impact on sleep, mood, cognition, and function on behavioral and educational domains should be present;
- the clinical course criteria do not apply for pediatric cases; there is no evidence that “at least twice weekly” can be considered the best determinant of chronicity in pediatric cases.

In the daily clinical practice, it is important to accurately investigate in children the symptoms related to the urge and discomfort components. These can be often missed in a regular visit but are easily discovered when given the opportunity and the correct instruments to the child [6]. Furthermore, it is extremely important to evaluate family history of RLS: indeed, it is not uncommon, while taking the history of the child, to find that a member of the family is affected by RLS without being aware of it.

In the past years, there has been an increasing awareness that RLS is associated not only to cognitive and emotional dysfunction, but also to a series of somatic conditions [7]. Recently, Trenkwalder et al. [8] performed a systematic review of the literature and examined the available studies on RLS and comorbidities in adults, focusing in particular on neurologic and medical disorders and their association with RLS. The authors identified an increased prevalence of RLS only in iron deficiency and kidney disease. As for cardiovascular disease, arterial hypertension, diabetes, migraine, and Parkinson disease, the methodology of studies was too poor to reliably support their association with RLS, although such association could not be excluded. An insufficient evidence was found for conditions such as anemia (without iron deficiency), chronic obstructive pulmonary disease, multiple sclerosis, headache, stroke, narcolepsy, and ataxias.

To our knowledge, there are no published comprehensive reviews examining somatic or neuropsychiatric conditions possibly associated with RLS in children/adolescents. The present work aimed to systematically review empirical evidence on somatic and neuropsychiatric conditions associated with pediatric RLS and discuss the implications of this association for the clinical practice.

Methods

We searched for peer-reviewed papers reporting empirical studies including data on somatic or neuropsychiatric conditions associated with RLS in children and adolescents. We included the following medical conditions, based on the model proposed by Becker and Novak [7]: anxiety, attention-deficit/hyperactivity disorder (ADHD) and related neurodevelopmental conditions, cardiovascular diseases, depression, diabetes, kidney disease, fibromyalgia, insomnia, liver/gastrointestinal disease, migraine, narcolepsy obesity, polyneuropathy, rheumatological disorders (including rheumatoid arthritis) and somatoform pain disorder.

We did not include conditions, mentioned by Becker and Novak [7], not relevant for children (e.g., Parkinson's disease, multiple sclerosis, pregnancy or erectile dysfunction). We also considered “epilepsy” based on previous reports pointing to a possible association between RLS symptoms and epilepsy [9]. Finally, given the body of literature on the relationship between growing pains and RLS, we also addressed this possible association [10].

Due to the restricted number of studies conducted in the pediatric population, to avoid missing data from small sample studies, we did not establish a threshold for the number of subjects included in the studies.

To ensure high levels of methodological adequacy as recommended by the Cochrane group [11] and avoid the inevitable bias caused by dependence on investigators agreeing to provide data from unpublished studies, we did not search for unpublished data.

We excluded non peer-reviewed references (e.g., conference proceedings) since we considered peer-review process as essential to the quality of the publication. We retained all types of study designs, including case reports/case series.

We searched the following electronic databases: PubMed, Ovid (including PsycINFO, Ovid MEDLINE®, and Embase), Web of Knowledge (Web of Science, Biological abstracts, BIOSIS, FSTA). The specific search terms and syntax for each database are reported in the Supplemental Material. The search was finalized on November 22nd, 2015. No language limitations were applied, to avoid biases due to language restrictions. Reference lists of pertinent reviews/systematic reviews were screened to reduce the likelihood of missing any relevant publication. Two authors (MA and SC) independently and blindly performed the search and screening of papers against eligibility criteria. Any disagreement between the two authors was resolved by consensus.

Results

From an initial pool of 1180 potentially eligible references, we retained a total of 42 references for inclusion on the present systematic review. Fig. 1 shows the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart [7,12] reporting study selection.

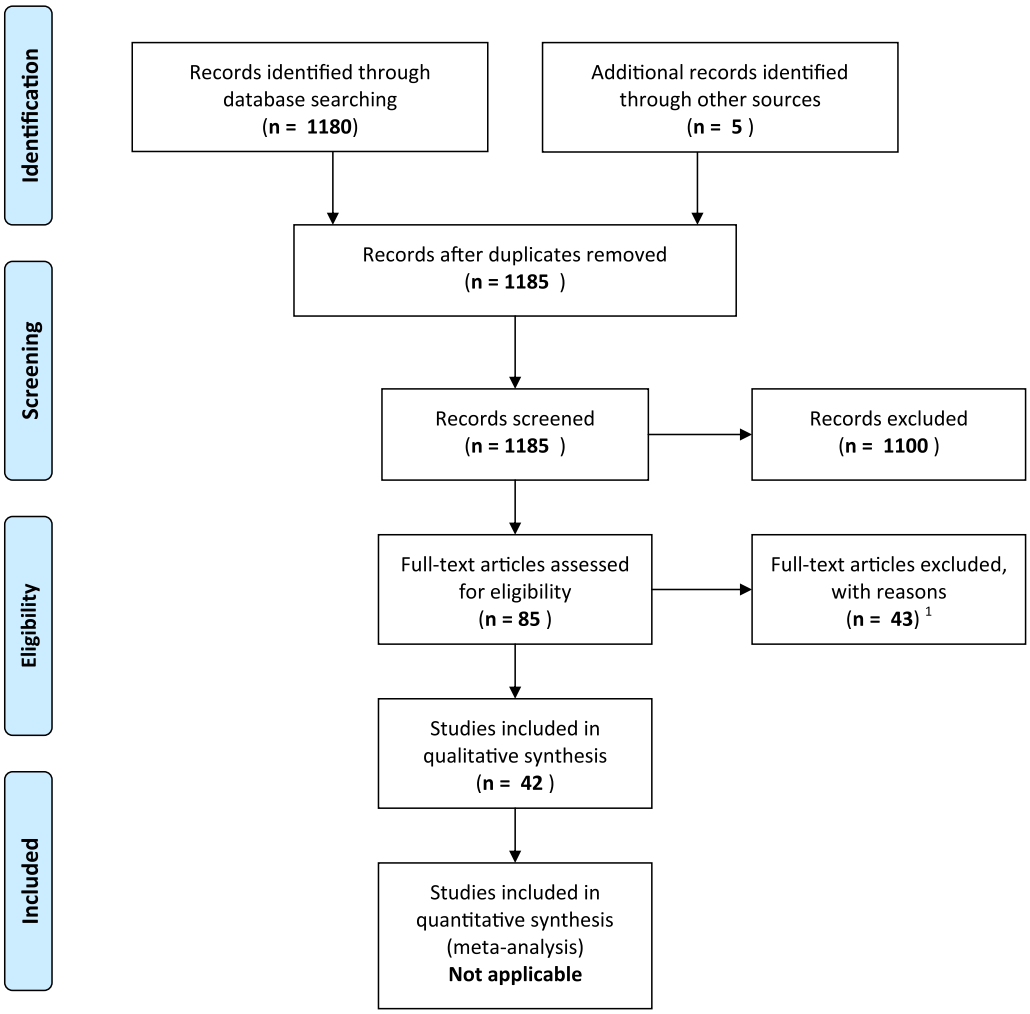
In the following sections, we discuss in turn each condition associated with RLS in children/adolescents based on the retrieved papers. We will first focus on the association between RLS and somatic diseases, and then turn to the link between RLS and neuropsychiatric (neurological and/or psychiatric) conditions (Table 1). We will report studies in adults (not counted in the PRISMA flowchart) when they provide useful etiopathophysiological insights not specifically explored in children/adolescents.

RLS and somatic disorders

Kidney diseases

The prevalence of sleep-related disturbances (including RLS) in patients with end-stage renal failure and/or on dialysis has been examined in adults and, to a lesser extent, in children [13,14].

Indeed, in adults there is evidence suggesting that RLS and PLMD are significantly more common in individuals on dialysis than in the general population [15]. Interestingly, empirical evidence points to an improvement of RLS symptoms in patients with



[1] n = 31: Conference proceedings; n = 12: Literature reviews

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

Table 1
Comorbidities of RLS in children

Authors	Type of study	N. of subjects	Age (mean, SD or age range)	Key findings
Kidney diseases				
Davis et al., 2005 [17]	Clinical study	21	6-20 y	86% of the children undergoing dialysis showed sleep disturbance symptoms: SDB (46%), RLS/PLMS (29%), and EDS (60%).
Applebee et al., 2009 [18]	Clinical study	26	12.1 ± 5 (6–18) y	RLS more prevalent in CKD patients vs. normal children (15.3% vs. 5.9%). No significant association between RLS and CKD stage, CKD etiology, CKD duration, and dialysis or transplant status.
Sinha et al., 2009 [14]	Clinical study	49	6-18 y	37% of CKD patients had a sleep disorder; type RLS/PLM was the most common (32% in the transplant CKD vs. 27% in the non-transplant CKD group)
Riar et al., 2013 [19]	Case-control study	124	13.4 ± 3.1 y	35% of CKD patients met criteria for RLS, the majority being in CKD stages 1–4
Gastrointestinal and liver diseases				
Franco et al., 2008 [26]	Survey-based epidemiologic study	141	Adults (heterogeneous population)	A survey on patients with chronic liver disease in hepatology clinic yielded a 62% prevalence of RLS. No correlation was found between the severity of liver dysfunction and RLS symptoms
Weinstock et al., 2010 [23]	Prospective and retrospective clinical study	85	50 ± 16 y	The incidence of RLS among 85 patients with celiac disease was 35%, with a prevalence of 25% compared with 10% of spouses.
Weinstock et al.,2010 [24]	Prospective clinical study	93	47 ± 13 y	The incidence of RLS in patients with Crohn's disease was 42.7%, with a prevalence of 30.2% compared with 9% of spouses.
Fredericks et al., 2012 [27]	Clinical cross-sectional study	47	10.9 ± 4.6 y	Based on parent report, pediatric transplant recipients had symptoms of SDB, excessive daytime sleepiness, daytime behavior problems, and RLS. Nearly a third of them exceeded clinical cut-off scores on the PLMS/RLS Index.
Andersen et al. 2014 [28]	Follow-up study	47	10.9 ± 4.6 y	Parents of children and adolescents with liver transplants reported higher rates of SDB and RLS/PLMS and lower quality of life even at 3-years follow-up. About 30% of the parent ratings exceeded the cutoff for the RLS/PLMS subscale.
Psychiatric disorders				
Chervin et al., 2003 [36]	Clinical study (conduct disorders)	872	2-14 y	Bullying and other aggressive behaviors were generally 2-3 times more frequent among 114 children at high risk for SDB. Conduct problems were also associated with symptoms of RLS and PLMS
Picchietti et al., 2008 [57]	Clinical study (ADHD, ODD, anxiety and depression)	18	6.1-16.8 y	Clinical sleep disturbance preceded a diagnosis of definite RLS by an average of 11.6 y.
Cortese et al., 2009 [60]	Case report (dystimic disorder)	1	11 y	Ropinirole supplementation 0.50mg/d remarkably improved RLS as well as depressive symptoms,
Pullen et al., 2011 [61]	Clinical study (Psychiatric disorders)	374	10.6 y	64% of the patients with RLS had one or more comorbid psychiatric disorders: ADHD in 25%, mood disturbances in 29.1%, anxiety disorders in 11.5% and behavioral disturbances in 10.9%.
ADHD				
Konofal et al., 2007 [41]	Clinical study	32	5-8 y	Lower ferritin levels in ADHD+RLS subjects versus ADHD only. Positive family history of RLS and previous iron supplementation in infancy were associated with more severe ADHD scores
Silvestri et al., 2009 [51]	Clinical study	55	8.9 y	Major sleep complaints were motor restlessness (50%), sleep walking (47.6%), night terrors (38%), confusional arousals (28.5%), snoring (21.4%), and leg discomfort at night associated with RLS (11.9%). The presence of RLS worsen ADHD symptoms
England et al., 2011 [57]	Double-blind placebo-L-DOPA	29	7-12 y	L-DOPA improved RLS/PLMS in all patients vs. placebo; ADHD was more severe in children without RLS/PLMS than in those with and L- DOPA had no effect on Conners' scales or psychometric tests
Furudate et al., 2013 [52]	Prospective clinical study	25	12.3 y	50% of 16 RLS children responded to iron supplementation. Of them, 50% showed a complete remission of RLS symptoms at 3 mo follow-up.
Kwon et al., 2014 [42]	Clinical study	56	10.7 y	42.9% of patients with ADHD presented with RLS symptoms and 7.1% of these were diagnosed with RLS
Tics/Tourette's syndrome				
Lesperance et al., 2004 [71]	Clinical Study (Tourette's syndrome)	144	6-31 y	RLS was present in 10% of probands and 23% of parents with no gender differences. RLS in probands was linked significantly to maternal RLS but not paternal RLS, suggesting that a maternal RLS factor may contribute to the variable expression of TS
Romano et al., 2004 [70]	Clinical study (tics)	49	3.8 -13.9 y	Parents of children with tics reported restless legs symptoms in 40.5% of cases vs. 5.9% of controls. Sleep-wake transition disorders and insomnia were the most frequent sleep disturbances and were highly correlated with the severity of tics.

Table 1 (*continued*)

Authors	Type of study	N. of subjects	Age (mean, SD or age range)	Key findings
Pain disorders				
Coenders et al., 2014 [21]	Clinical study (chronic pain disorders)	101	10-18 y	Migraine, non-migraine headaches, recurrent abdominal pain and RLS were reported more frequently in patients with chronic pain disorders than controls. RLS was reported in 22.2% vs. 5.4%
Bruni et al., 1997 [87]	Clinical study (migraine)	283	5-14.3 y	A high frequency of sleep disturbances involving motor restlessness and nocturnal hyperactivity in children with migraine and tension-type headache
Larner, 2007 [89]	Family study (migraine)	5	9-65 y	A 65- y-old woman who developed MA in her teenage y from the age of 30 developed RLS. Of her five children, all three girls had developed both MA and RLS. One female grandchild had features of RLS at the age of 9.
Seidel et al., 2012 [88]	Clinical study (migraine)	184	13 ± 3 y	The frequency of RLS in migraine children was significantly higher than in controls (22% vs. 5%)
Growing pains				
Brenning, 1960 [92]	Clinical study	112	0-18 y	Some children with growing pains (GPs) had creeping sensations or cramps suggestive of RLS
Bassetti et al., 2001 [93]	Case control study	55	62 ± 16 y	GPs were more frequent in RLS patients with onset <20 y of age (27%) than in those with onset >20 y of age (3%)
Rajaram et al., 2004 [94]	Case series	11	0-18 y	GPs was a misdiagnosis for RLS in 10 cases
Picchietti et al., 2008 [59]	Retrospective Chart review	18	10.3 y	55.5% of children with RLS had a history of GPs
Turkdogan et al., 2011 [95]	Population study	4346	6-18 y	GPs were reported in 54.5% of the subjects with definite RLS.
Champion et al., 2012 [96]	Twin study	1843	3-16 y	18% of twins with concordant GPs met criteria for RLS as opposed to only 2% of twins with discordant GPs
Wong et al., 2014 [97]	Retrospective study	213	3–16 y	GPs were recorded in 43 of the eligible 230 children referred for PSG of whom 25.6% had a PLMS index ≥5/h, significantly higher than in the children without GPs (10.2%). Children with GPs were three times more likely to have a PLMS index ≥5/h than children without GPs
Various				
Matsuo et al., 2004 [76]	Case report (Infectious disease)	3	6-12 y	Three children with transient RLS-like symptoms possibly associated with group A beta-hemolytic streptococcal infection or mycoplasma pneumoniae infection
Happe et al., 2005 [30]	Clinical study (diabetes mellitus)	46	12.3± 5.5 y	No association of diabetes mellitus type 1 with RLS in children and adolescents but significant association of higher HbA1c values with sleep initiating problems; the parents of children with diabetes mellitus type 1 showed a relatively high prevalence of RLS (18.7%).

Legend: ADHD = attention deficit hyperactivity disorder; CKD = chronic kidney disease; EDS = excessive daytime sleepiness; GP = growing pains; MA= migraine with aura; PLMS = periodic leg movements during sleep; RLS = restless legs syndrome; SDB= sleep disordered breathing; TS= Tourette's syndrome.

end-stage renal failure after renal transplantation, suggesting a potentially overlapping pathophysiological factors between RLS and chronic renal disease [16]. In youth, Davis et al. [17] were the first to assess the prevalence of sleep disturbance symptoms in a population of 21 children and adolescents, aged 6–20 y, on dialysis. The authors conducted a telephone- or clinic-based interview of children and their parents to assess four symptom domains of sleep disorders: 1) sleep disordered breathing (SDB), 2) RLS/PLMs, 3) excessive daytime sleepiness (EDS), and 4) inadequate sleep time. The presence of a "sleep disturbance" was defined by a positive response in any of the four symptom domains. Eighty-six percent of the children undergoing dialysis reported sleep disturbance symptoms: SDB (46%), RLS/PLMs (29%), and EDS (60%), thus showing that RLS symptoms prevalence is higher in pediatric dialysis patients compared to the general pediatric population.

Using a similar methodology, Applebee et al. [18] evaluated the prevalence of RLS in a sample of 26 children (aged 6–8 y) with chronic kidney disease (CKD) in different stages, and its impact on sleep and daytime functioning. They used a telephone survey aimed at assessing RLS, sleep schedule, and daytime sleepiness. Thirty-five percent of children met criteria for RLS (once again, higher than the prevalence in the general population), the majority being in CKD stages 1–4. There were no significant differences in sleep schedule and daytime sleepiness between children with or without RLS. Iron and ferritin levels, available in a subsample of children, were not significantly reduced in the RLS group in comparison with the group without RLS. This suggests that iron deficiency alone is unlikely to be a major etio-pathophysiological factor for RLS symptoms in these patients (see below for a discussion on iron deficiency in RLS).

Subsequently, Riar et al. [19] performed a prospective, cross-sectional study to examine RLS prevalence in 124 pediatric patients with CKD and 85 healthy children, aged 8–18 y. RLS was assessed via a questionnaire that ruled out medical mimics of RLS. Sleep characteristics and health-related quality of life (HRQoL) were also assessed. RLS resulted significantly more prevalent in CKD patients than in normal children (15.3% vs. 5.9%; $p = 0.04$). There was no significant association between RLS and CKD stage, CKD etiology, CKD duration, and dialysis or transplant status. Children with RLS were more likely than controls to rate their sleep quality as fairly bad or very bad (41.2% vs. 8.8%; $p = 0.003$) and report using sleep medications (42.1% vs. 14.7%; $p = 0.01$). Moreover, RLS was associated with lower HRQoL by parent report ($p = 0.03$). Interestingly, only 26.3% of the patients with CKD and RLS had discussed RLS symptoms with a healthcare provider, and only one of these patients had been diagnosed with RLS prior to the study.

The reviewed studies support the notion that RLS is more commonly seen in children with CKD than in the general population. Given that RLS and its related sleep disruption may further

impact on the quality of life of young patients with CKD, this growing body of research suggests that children with all stages of CKD should be routinely screened for RLS symptoms.

Although the pathophysiology underlying the association is unknown, the contribution of end-stage renal disease to sleep disorders is likely multifactorial [20] and there is no evidence so far to suggest that iron deficiency plays a major role.

Gastrointestinal and liver diseases

Although no report specifically and directly assessing a possible association between RLS and gastrointestinal disorders is available in children, the study by Coenders et al. [21] provides indirect evidence of a possible link. This case-control study involved 45 patients of a local chronic pain clinic and 56 controls (age range: 10–18 y) assessed with questionnaires about pain and RLS. RLS, migraine, non-migraine headaches and recurrent abdominal pain (RAP), resulted significantly more frequent in cases than controls.

The mechanism underlying the possible association between RLS and gastrointestinal diseases remains unknown, but it has been suggested that disruption of biochemical pathways connecting enteric and central nervous system, due to alterations in inflammatory mediators and neurotransmitters triggered by small intestinal bacterial overgrowth, may play a role [22]. Indeed, IBS, is often comorbid with other sensitivity disorders, including fibromyalgia and interstitial cystitis, suggesting a role of inflammatory processes in these diseases [22].

The fact that several of the conditions frequently associated with RLS are also linked to inflammatory/immune changes suggests the possibility that inflammatory mechanisms are involved in RLS as well. Inflammation can be responsible for iron deficiency and hypothetically could cause central nervous system iron deficiency-induced RLS. In patients with celiac disease (CD) RLS was found to be a common comorbid condition with an incidence of 35% and a prevalence of 25% compared with 10% of spouses. This condition was probably linked to a dysfunctional iron metabolism; as suggested from Weinstock et al. [23] inflammatory state in CD may increase hepcidin levels and produce iron deficiency that could lead to RLS.

Alternatively, an immune reaction to gastrointestinal bacteria or other antigens may hypothetically contribute to RLS by a direct immunological dysfunction in the central or peripheral nervous system. This explanation could be also account for the increased incidence (42.7%) of RLS in patients with Chron's disease; the prevalence was 30.2% compared with 9% of spouses [24].

Anecdotal reports from adult patients suggest that RLS may be more commonly experienced by patients with chronic liver disease than previously thought [25]. Of clinical interest is suggested that the unpleasant dysaesthesias experienced by patients might be mistakenly attributed to night-time itching or polyneuropathy.

There is some evidence suggesting that patients with chronic liver disease (CLD) may carry additional risk of RLS [26]. In a study conducted as part of a larger investigation of HRQoL and sleep in 47 children (mean age 10.9 y ± 4.6) with liver transplants, parents filled out the pediatric sleep questionnaire (PSQ) and reported symptoms of sleep disordered breathing, excessive daytime sleepiness, daytime behavior problems, and restless legs. Forty percent of parents and 43.8% of children reported significantly lower total HRQoL for the liver transplants recipients (LTRs). A score suggestive of sleep related breathing disorder (SRBD) was found in 11 (23.4%) of children. The mean PLMS/RLS index was 0.23 ± 0.21, with 14 (29.8%) participants exceeding the clinical cut-off score. The mean EDS subscale score was 0.28 ± 0.30, with 19 (40.4%) participants exceeding the clinical cut-off score of 0.33. Sleep problems were common in this cohort of pediatric LTRs and predicted significant variance in HRQoL [27].

Subsequently, Andersen et al. [28] assessed the presence of sleep disturbances and parent and family HRQoL in the same sample of 47 children with liver transplants; 45 and 40% of the parents rated their child above the cutoff score for SRBD and sleepiness symptoms, respectively. Nearly 30% of the parent ratings exceeded the cutoff for the RLS/PLMS subscale. Parents of children and adolescents with scores above the cutoff on the RLS/PLMS and behavior scales on the PSQ endorsed significantly lower HRQoL scores compared with parents whose children had scores below the cutoff on the PSQ scales (64.98 vs. 76.02, $p < 0.01$ for RLS and 69.36 vs. 82.92, $p < 0.01$ for Behavior). The authors suggested that the high rates of inattention, hyperactivity, and executive functioning difficulties in children and adolescents with liver transplants might be linked to the associated sleep problems, mainly RLS and SRBD.

The pathophysiological underpinnings in RLS children and adolescents with liver transplants is poorly understood. A significant number of CLD patients have undiagnosed neuropathy and RLS symptoms may be a reflection of peripheral nervous system dysfunction [26].

Diabetes

The only study on RLS in pediatric patients with diabetes was carried out by Happe et al. [29]. The authors interviewed children with type 1 diabetes mellitus as well as their parents and siblings about RLS according to a standardized questionnaire; 46 patients (25 females, 12.0 ± 3.7 y), 50 siblings (29 females, 12.3 ± 5.5 y) and 75 parents (41 mothers, 40.4 ± 5.1 y; 34 fathers, 42.5 ± 5.3 y; 1.3% with diabetes mellitus) were included. One patient (2.2%), one sibling (2.0%), and 14 parents (18.7%) were diagnosed as having RLS and the authors concluded that there is no significant association of diabetes mellitus type 1 with RLS in children and adolescents. However, HbA1c values were significantly higher in patients reporting problems of sleep initiating ($p = 0.023$) than in patients without problems in sleep initiation, suggesting that the link between RLS and diabetes in children deserves further attention.

RLS and neuropsychiatric disorders

Attention deficit hyperactivity disorder (ADHD)

A significant association between ADHD symptoms and RLS symptoms started being reported in the 90s, leading to an increasing body of research that was first systematically reviewed by Cortese et al. [30]. They reviewed two studies [31,32] examining the prevalence of RLS subjects, three studies [33–35] assessing the prevalence of RLS symptoms in subjects with ADHD, two studies [36,37] exploring the prevalence of ADHD symptoms in subjects with RLS, and one study (the only one conducted in adults at that time) estimating the prevalence of ADHD in RLS subjects with RLS [38]. The authors concluded that up to 44% of subjects with ADHD have been found to have RLS or RLS symptoms, and up to 26% of subjects with RLS have been found to have ADHD or ADHD symptoms. In terms of possible mechanisms underlying the association, Cortese et al. posited that: 1) sleep disruption associated with RLS might lead to inattentiveness, impulsiveness/moodiness, and paradoxical overactivity (as a mechanism to counteract low arousal) that are the core features of ADHD; 2) diurnal manifestations of RLS, such as restlessness and inattention, might mimic ADHD symptoms (so that the relationship would actually be accounted for by a differential diagnosis); 3) RLS and ADHD might both share a common dopamine dysfunction.

Cortese et al. also discussed the limited amount of evidence available at that time (case reports by Walters et al. 29 [39] and Konofal et al. [40]) suggesting that dopaminergic agents (levodopa/

carbidopa in Walters et al. 29 [39] and ropinirole in Konofal et al. [40]) might be an option for both ADHD and RLS symptoms in children with ADHD not responsive to first line ADHD pharmacological treatment (i.e., psychostimulants). The main limitation of the review by Cortese et al. was the inclusion of both studies with a categorical diagnosis of ADHD/RLS and reports in which participants had only symptoms of ADHD or RLS.

Several studies providing additional insights into the prevalence of RLS in individuals with ADHD, as well as into possible underlying mechanisms and treatment implications, have been published after the review by Cortese et al. [30].

With regards to prevalence studies, Kwon et al. [41] assessed the rates of RLS in a sample of 56 Korean children with ADHD (mean age: 10.7 y). Whilst 42.9% of the participants presented with RLS symptoms, which is higher than the reported prevalence of about 22% in children/adolescents in the general population, 3.6% were diagnosed with "definite RLS" and another 3.6% were diagnosed with "probable RLS". Another study in 30 adults with ADHD found a prevalence of RLS of 20%, which is higher than the reported prevalence of 5–15% in adults in the general population [2]. Therefore, these recent studies confirmed that, when considering the prevalence of RLS diagnosed as a categorical disorder, rather than just symptoms of RLS, there is still a significant association between ADHD and RLS.

In terms of pathophysiology, there have been advances on the possible role of iron deficiency. We will report recent insights on the relationship between iron deficiency and RLS before turning more specifically to recent evidence on this link in children. Trenkwalder et al. [8] identified an increased prevalence of RLS in adults with iron deficiency (ID). Interestingly, ID is frequent in the pediatric age, especially in the late infancy/toddler period and there is mounting evidence that ID affects motor activity [42].

Typically, iron stores increase slowly with supplemental iron over weeks to months, and build up is delayed by physical growth. The level of iron stores in humans is easily measured by serum ferritin that is the best indicator of early iron deficiency, but can be a challenging marker to interpret: cut-off values differ across centres and literature sources, and as an acute-phase reactant, false elevations can occur from infection or inflammation [43].

The dopaminergic theory of RLS further supports the ID hypothesis since iron is fundamental for the biosynthesis of dopamine and it is necessary for tyrosine hydroxylation, which is a rate-limiting step for dopamine production. Iron deficiency has been well documented from brain autopsy, magnetic resonance imaging and cerebrospinal fluid studies of adults with RLS [44,45].

There is evidence for decreased spinal dopamine D3 receptor (D3R) signaling in RLS [46] and experimental data suggest that iron deficiency enhances response to acute and persistent pain stimuli, mediated by the influence of D3R upon pain regulation at the spinal level [47].

Some authors have postulated that increased leg activity during the period of IDA might indicate a shared underlying mechanism with RLS [48]. Peirano et al. [49] found that 10-y-old children who experienced IDA in infancy showed a mild but significant increase of tibialis anterior EMG activity during sleep when compared to age-matched normal controls. The activity is characterized by a slightly but significantly higher periodicity due to a selective increase of muscle activations separated by an interval ranging approximately 10–50 s. In another study aimed at gaining insight into the role of iron deficiency in RLS and ADHD, Konofal et al. [40] assessed a sample of 12 children with ADHD + RLS, 10 children with ADHD and 10 controls. They found a trend for lower ferritin levels in ADHD + RLS subjects versus ADHD. Both a positive family history of RLS and previous iron supplementation in infancy were associated with more severe ADHD scores. This lends support to the notion that iron deficiency might aggravate ADHD ad RLS symptoms pointing to possible common pathophysiological links [40]. A subsequent polysomnographic study in 55 ADHD children corroborated this preliminary finding showing that ADHD children reported motor restlessness (50%), sleep walking (47.6%), night terrors (38%), confusional arousals (28.5%), snoring (21.4%), and leg discomfort at night associated with RLS (11.9%). The diagnosis of RLS was found in 14 children (25.4%) of the ADHD sample and PLMS were recorded in 40%. The presence of RLS worsens ADHD symptoms and strong significant correlations emerged for ADHD hyperactive subtype and RLS scoring, PLMS and PLMW indexes, opposition scores [50].

More recently, Furudate et al. [51] investigated the daytime dysfunction in 25 children with RLS and the effects of treatment with iron supplements on RLS symptoms and daytime functioning. RLS children had ADHD scores before treatment significantly higher in comparison with the control group, and only one RLS participant showed a pathologically high ADHD-RS-IV score. Thus, the authors stated that pathological ADHD symptoms secondary to RLS were relatively rare among Japanese children with RLS. Overall, RLS children responded well to small doses of the therapeutic drugs including iron, clonazepam, or pramipexole, or some combination of these drugs. In particular, 50% of participants with initial serum ferritin levels less than 40 ng/mL became 50% responders after iron treatment alone, and a complete remission of symptoms was observed in four RLS children even after discontinuing the iron treatment. Therefore, iron supplementation treatment should be given priority as a therapeutic option for childhood RLS, especially for patients with ADHD and low serum ferritin levels.

A possible interpretation for the observed association between ADHD and RLS is that these two conditions share common genetic determinants. In this respect, BTBD9 gene, which has been identified by two recent genome-wide association studies to be associated with risk of RLS, could be a potential candidate [52]. Interestingly, the RLS risk allele of BTBD9 is associated with decreased serum ferritin concentration [53].

The hypothesis of iron deficiency is compatible with the hypothesis of dopaminergic hypoactivity, since iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Children with ADHD are more likely to have iron deficiency and treatment with supplemental iron has been reported to improve sleep quality and subsequently decrease ADHD symptoms [30].

The only placebo-controlled trial assessing the effects of iron supplementation in children with RLS and ADHD [54] included 23 children with ADHD and serum ferritin levels <30 ng/mL, randomized with a 3:1 ratio to oral iron (ferrous sulfate: 80 mg/d; $n = 18$) or placebo ($n = 5$). After 12 wk, although the reduction on the ADHD symptom severity scores failed to reach significance ($p = 0.055$ and $p = 0.076$, respectively), the authors found a significant decrease in the clinical global impression severity scale ($p < 0.01$). This preliminary evidence suggests that iron supplementation treatment should be given priority as a therapeutic option for childhood RLS, especially for patients with ADHD and low serum ferritin levels.

With regards to other advances in the treatment of patients with RLS and ADHD, low doses of dopaminergic agents (levodopa, pergolide, and ropinirole) have been reported as effective in children diagnosed with both RLS and ADHD, previously unsuccessfully treated with psychostimulants, [30]; this patient profile has also been found to benefit from the concurrent administration of iron supplementation [53]. Additionally, a double −blind randomized controlled trial including 29 children with ADHD (with or without RLS), aged 7–12 y, assigned to L-Dopa or placebo for 8–13 wk, showed that, whilst L-Dopa was efficacious on RLS symptoms, it did not have any significant effect on ADHD core symptoms, polysomnographic parameters, or neuropsychometric tests [55].

Therefore, this study failed to replicate initial insights from case series suggesting that L-Dopa may be effective for both ADHD and RLS symptoms. The England et al. [55] finding is further supported by another study showing that in children with ADHD L-DOPA had little effect on the polysomnographic measures, regardless of RLS status [56].

Depression

Picchietti et al. were among the first to report an association between RLS and psychiatric disorders, including depression [57]. In their retrospective study on 18 children (10 girls and 8 boys) and adolescents with RLS, these authors found that the most commonly reported comorbid psychiatric conditions were ADHD, oppositional defiant disorder (ODD), anxiety disorders and depression [57].

The association between RLS and depression has been also reported in a case report of an 11-y-old girl diagnosed with definite RLS according to 2003 NIH criteria with a score = 31 (i.e., very severe) at the severity scores on the International restless legs syndrome study group (IRLSSG) scale. The girl presented with dysthymic disorder according to DSM-IV criteria, and confirmed by the semi-structured interview Kiddie-SADS-PL. The score on the children depression inventory (CDI) was in the clinical range (score: 21). The total score on the sleep disturbance scale for children (SDSC) was pathological. A standard PSG showed a periodic limb movement index of 16.5. After 3 mo of treatment with ropinirole (a D2/D3 dopamine agonist) RLS, as well as depressive symptoms, remarkably improved, and the total score on the SDSC also improved while PLM index did not remarkably change [58].

Besides this case report, a subsequent study examined the prevalence and nature of psychiatric disorders in 374 children with RLS and the use of psychotropic medications; the mean age of the subjects was 10.6 y and the male to female ratio was approximately 1:1. Sixty-four percent of the patients had one or more comorbid psychiatric disorders: ADHD was found in 25% of patients, mood disturbances in 29.1%, anxiety disorders in 11.5% and behavioral disturbances in 10.9% [59]. The most significant finding of this study was that nearly two-thirds of children who were diagnosed with RLS also had one or more psychiatric diagnoses, and that ADHD was commonly diagnosed in children with RLS, consistent with what has been previously documented. Additionally, high prevalence of other psychiatric disorders was also identified. Interestingly, mood disorders were diagnosed even more frequently than ADHD, although this group also included patients with transient mood disturbances such as adjustment disorders. Mood disorders were more prevalent in females and ADHD was encountered more often in males. Of note, psychotropic medications had been started in a majority of subjects prior to formal diagnosis of RLS.

Adults' and children's studies acknowledged that depression is a very important comorbid psychiatric condition in RLS and is probably mediated by the sleep disruption as well as by the underlying neurotransmitters alterations. To further support this association data suggest that treating RLS improves also depression [60].

A bidirectional relationship between RLS and depression has been posited. Whereas sleep disturbance exacerbates mood and attention problems, the use of psychotropic medications, including antidepressants, potentially exacerbates sleep disturbance in some children with a personal diathesis. Several anecdotal reports and case series suggested that different antidepressant medications and neuroleptics are associated with RLS symptoms [61], possibly due to dopamine antagonism: the use of these medications may be prompted by mood or behavioral disturbances and effects on RLS poorly recognized. Identifying patients at risk for RLS before initiation of antidepressant treatment is challenging; in this regard increased susceptibility to toxic accumulation of drug mediated by P450 hepatic microsomal enzyme polymorphism should be taken into account [56]. Furthermore, a careful baseline assessment of pre-existing RLS symptomatology and familiar predisposition should be performed and an accurate review of RLS symptoms during follow-up should be undertaken.

In the case of neuroleptic treatment, akathisia should be distinguished from emerging RLS symptoms: akathisia-related restlessness is usually generalized and patients do not complain of limb paresthesia or other unpleasant sensations in the limbs. Moreover, relief from voluntary movement and circadian rhythmicity are rarely reported.

The high comorbidity between psychiatric disorders, including depression, and RLS needs a comprehensive multidisciplinary approach that involves sleep specialists, child psychiatrists, and psychologists. Available evidence underscores the need for the child psychiatrist to assess for a patient and family history of RLS, as well as being mindful of the role of psychotropic medications in precipitating or exacerbating RLS.

It is important for the sleep specialist to look for depression and other psychiatric comorbidities; conversely, it is equally important for the child psychiatrists and psychologists to be more aware of RLS as a possible comorbidity in their patients.

Conduct disorder

A survey study on 872 parents of children aged 2–14 y conducted at two general pediatrics clinics showed a significant association between parent-reported conduct problems and symptoms of two childhood sleep disorders, namely sleep disordered breathing (SDB) and RLS [35]. In the study, children with high conduct problems index (CPI) score were significantly more likely than other children to have high PLMS scores, restless legs, and growing pains ($p < 0.0001$). Among children with restless legs, 24% had high CPI score, whereas among children without restless legs, only 12% had high CPI score. The authors concluded that conduct problems were associated with symptoms of SDB, RLS, and PLMS, suggesting new treatment opportunities for these children. This possible association needs to be further explored using rigorous assessment of conduct disorder diagnosis.

Other neurodevelopmental disabilities

Parents of children affected from neurodevelopmental disabilities (NDDs) often report children having difficulties initiating and maintaining sleep because of restlessness and arousals [62] This prompted interest in exploring RLS in this population. We discuss here in detail tics/Tourette syndrome.

RLS can be observed in Tourette syndrome (TS) [63–65] and RLS phenomenology bears some similarity to the tics and compulsions of TS, which are also often preceded by urges or unpleasant sensations. Dysfunction in fronto-striatal systems might be the common pathophysiological substrate for TS, other neuropsychiatric disorders and RLS [28,66,67]. Despite these similarities, the links between RLS and TS in children have received little attention.

A study on sleep disturbances and tics showed that children with tics reported restless legs symptoms during sleep in 40.5% of cases vs. 5.9% of controls ($p = 0.013$) [68]. In another study, Lesperance et al. [69] examined RLS (among other comorbidities) in 144 probands with TS or chronic tics and their parents. RLS was present in 10% of probands and 23% of parents with no gender differences. Additionally, RLS in probands was significantly linked to maternal RLS but not paternal RLS, suggesting that a maternal

RLS factor may contribute to the variable expression of TS. Of note, RLS may be confused with compulsions or complex tics because all these symptoms involve relatively stereotyped movements often preceded by urges or sensations. In the study by Lesperance and colleagues, the presence of RLS was not correlated with the presence of obsessive-compulsive symptoms (OCS), and unlike tics, RLS affected both genders equally.

RLS thus seems to be a significant comorbidity in TS. RLS and OCS tend to worsen with age, whereas tics decrease with age after childhood. Moreover, selective serotonin reuptake inhibitors (SSRIs), which reduce OCS, can aggravate RLS [70]: further studies on the links between RLS and Tourette syndrome may help shed some light on the pathophysiology of these disorders.

A possible role of Group A streptococcal infection in the link RLS-TS has been recently discussed. Indeed, Group A streptococcal infection has been hypothesized to contribute to the exacerbation of tics, or obsessive-compulsive disorder (termed pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection [PANDAS]) and attention-deficit hyperactivity disorder [71–73]. Interestingly, Matsuo et al. [74] speculated that streptococcal or *Mycoplasma* infection, or both, led to the production of transient RLS–like symptoms in three children with serologic evidence for either a group A streptococcal or *Mycoplasma* infection. Only one subject had a well-defined preceding illness with group A streptococcal and *Mycoplasma* infection closely related to the development of RLS–like symptoms and had persistently elevated enzyme-linked immunosorbent optical density values against human caudate and putamen. The other two patients were initially evaluated 3–4 mo after the onset of symptoms and antibasal ganglia antibodies measures did not differ from that of control patients. Therefore, there is no definite evidence that the RLS–like symptoms are associated with antineuronal antibodies but this line of research deserves further exploration.

Migraine

In recent years, several studies identified a higher prevalence of RLS in patients with migraine compared to the general population [75]. Both conditions share common clinical and pathophysiological features being chronic diseases with periodic exacerbations, involving more women and having an important impact on quality of life and quality of sleep. From a pathophysiological point of view, evidence suggests that these conditions may involve dysfunction of the A11 hypothalamic dopaminergic nucleus, considered as the neuroanatomical substrate linking migraine and RLS [76].

Whether RLS is also associated with other primary headache disorders is uncertain and the interrelationship among comorbid RLS, sleep disturbance and headache clinical profiles in patients with migraine has not been fully investigated.

Several studies highlighted the correlations between RLS and migraine in adult patients showing that the presence of migraine was associated with higher RLS severity [77,78]. On the contrary, no associations of RLS with cluster headache and migraine with aura patients was found [79,80]. A recent systematic review reports that RLS prevalence in migraine ranged from 8.7% to 39.0% and that migraine prevalence in RLS ranged from 15.1% to 62.6%. Pooled analyses showed substantially higher effect estimates in case-control studies (pooled OR = 4.19) than in cohort studies (pooled OR = 1.22) [75].

Furthermore, dopaminergic premonitory symptoms (DPS) were present in 47.6% migraine patients with RLS vs. 13.1% in those without RLS [81] and the risk of having RLS is increased in migraine patients (O.R. 1.20) [82] and was >5 times higher in patients with DPS [83].

With regards to children. in a groundbreaking study on sleep disturbances in headache children, Bruni et al. [84] found an increase of symptoms of motor hyperactivity during sleep in children with migraine. Although no symptoms of RLS have been investigated, nocturnal hyperkinesia, unusual movements during sleep and pains during sleep were significantly more prevalent in children with migraine. This study suggested that a possible link between RLS and migraine deserved more attention.

Indeed, this was subsequently assessed more specifically by Seidel et al. [85]. They investigated the prevalence of RLS in pediatric patients, comparing 111 children and adolescents with migraine to 73 headache-free controls using a semi-structured interview and the Epworth sleepiness scale (ESS). The prevalence of RLS in migraine patients resulted significantly higher than in controls (22% vs. 5%; $p < 0.001$), suggesting an association between RLS and migraine in the pediatric population. Mean ESS total scores of migraine patients and controls did not differ significantly. Interestingly, although a fourfold-higher RLS frequency in migraine patients compared to headache-free controls was found, only a single RLS case in the patient group resulted to be familial.

Subsequently, Larner [86] described a family with comorbid migraine with aura (MA) and RLS: The proband was a 65-y-old woman who developed MA in her teenage years and family history revealed that her three girls had developed both MA and RLS during adolescence and that one female grandchild also had features of RLS at the age of 9 y.

To summarize, available evidence suggests higher rates of RLS in migraine patients when compared with the general population, in adults as well as in children, and the presence of migraine has been associated with higher severity of RLS.

Growing pains

We conclude this review with a discussion on the relationship between RLS and growing pains, a common benign condition in childhood characterized by intermittent bilateral leg pain that occurs in the late afternoon or evening. This link can be interpreted as a comorbidity or as a differential diagnosis. Indeed, recent studies focused on the similarities and the differences between pediatric RLS and growing pains (GP), There is a considerable overlap in the diagnostic criteria and the sharing of clinical symptoms [10].

RLS and GPs are common disorders: whereas, as reported above, the prevalence for RLS is about 2% [2], GPs affect approximately 4.7% of the childhood population [87].

Family histories of RLS and GPs often are overlapping and they show similar clinical pictures: leg rubbing to obtain relief from leg discomfort is common to both disorders, though relief by leg movements seems unique to RLS; on the other hand, childhood RLS has been reported to be painful in up to 45% of cases. Typically, children may awaken in the middle of the night complaining of a “throbbing” pain in the legs. Onset usually occurs during early to late childhood, and the location of the pain is prominent in the front of the thighs, calves, or behind the knees [88]. Few studies have been published on the potential links between GPs and RLS. An early study [89] reported that on 112 GPs children with leg discomfort, only 12 had exclusively daytime symptoms. The other 100 children had leg troubles during the night and/or while sitting still in the evening, creeping sensations and cramps suggestive of RLS. Forty seven percent of one or both parents had adult symptoms of RLS if they had a child with GPs. Leg discomfort was found in 45.4% of

children who had parents with adult RLS compared to only 16.7% of children who had parents without adult RLS.

Subsequently, Bassetti et al. [90] in 55 RLS adult patients, found that a history of GPs was more frequent in those with onset of RLS <20 y (27%) as opposed to those with age of onset >20 y (3%).

Building on this evidence, in 2004 Rajaram et al. [91] conducted a clinical study in eleven children (mean age 10.4 y) from a pediatric neurology clinic with a diagnosis of GPs. An interview with parent and children was performed to determine if their symptoms of GPs met criteria for definite RLS; those who met clinical criteria for RLS underwent polysomnography. Ten of the 11 children with GPs met clinical criteria for RLS. There were no differences in the polysomnographic findings between the growing-pain and control groups, and none of the children with RLS had a clinically significant number of PLMS. There were no differences in the polysomnographic findings between the "growing-pain with ADHD" and "growing-pain non-ADHD" subgroups.

Other data from larger studies are available. In a large epidemiological study by Picchietti et al. [2], a significantly high prevalence of GPs in children with RLS vs. those without RLS (80.6% vs 63.2%). was found. In another study [57] on 18 children, with RLS and clinical sleep disturbance about 55% reported a history of GPs.

In a recent cross sectional study [92] of RLS in 4346 Turkish children and adolescents (10–19 y) performed with a seven items questionnaire based on pediatric diagnostic criteria proposed by the IRLSSG, definite RLS was present in 2.74% of the subjects with female predominance ($p = 0.007$) and GPs were reported in 54.5% of the subjects with definite RLS.

Champion et al. [93] applied a twin family design to search for evidence of genetic susceptibility to GPs, and for a genetic relationship between GPs and RLS. The parents of 1843 twin pairs aged 3–16 y were administered a questionnaire, which identified 88 pairs with at least one twin individual fulfilling criteria for GPs. Standard questionnaires for history of GP and RLS were completed for these twin pairs, their siblings and parents. Twenty-three percent of twin individuals with GPs met RLS criteria compared with 8% of twin individuals without GPs ($p = 0.03$). Among twins with GPs concordance, 19% met RLS criteria compared with 2% of twins with GPs discordance ($p = 0.01$). Interestingly, when at least one twin had GPs, 40% of mothers, 24% of fathers, and 18% of siblings had a history of RLS.

In a more recent study by the same group, Wong et al. [94] examined retrospectively records of 230 children aged 3–16 y, who underwent PSG. GPs were recorded in 43 of the eligible 230 children referred for PSG of whom 25.6% had a PLMS index $\geq$5/h, significantly higher than in the children without GPs (10.2%) (Odds ratio 3.04, $\chi^2 = 6.0$, $p = 0.014$). The adjusted odds ratio for the association between GPs and PLMS remained significant at 2.53 (95% CI 1.1–6.1, $p < 0.05$). A PLMS index $\geq$5/h was recorded in 30 of the 230 participants.

In summary, children with GPs were three times more likely to have a PLMS index $\geq$5/h than children without GPs on PSG, giving greater support for the hypothesis that GPs might lie on the phenotypic spectrum of restless legs syndrome.

Conclusions

Pediatric RLS has specific features that make it difficult to correctly recognize: 1) the description of RLS symptoms depends on child's language skills and cognitive development; 2) the quantification of the impact on sleep, mood, cognition, and behavior is difficult; 3) the variability of the presentation of symptoms and the presence of numerous mimics can be challenging for the clinician. All these features could explain why RLS is frequently unrecognized in pediatric practice.

In this review, we showed that pediatric RLS can be comorbid with several diseases and presentation symptoms may overlap.

Here, we performed a systematic review on somatic and neuropsychiatric comorbidities building on and extending a recent systematic review by Trenkwalder et al. focused on adults [8]. Our search methodology included several databases, had no language limitations and included comorbidity with psychiatric disorders as well as with diseases from internal medicine.

We found evidence suggesting a significant association between RLS and several major disorders, such as chronic kidney disease, gastrointestinal disorders, growing pains and a spectrum of neuropsychiatric disorders. Although there are mixed results on the relationship between RLS and some comorbidities that we have explored in this review, likely due to different study methodology, based on the reviewed evidence we suggest that the boundaries of RLS comorbidities should be expanded.

Based on emerging association data, a dichotomous classification of primary and secondary RLS may be misleading, suggesting causality rather than the more complex RLS genetic and environmental interaction [8].

From a clinical standpoint, when approaching a child with RLS symptoms the physicians/pediatricians should be aware of the mimics but also that dysfunctions of several organs (i.e., kidney, liver, bowel, etc.) or psychiatric or neurologic disorders may underlie symptoms of RLS. The correct diagnosis of RLS should take into account that treating those comorbid disorders may greatly help the management of RLS.

Practice points

1. Pediatric RLS can be comorbid with several diseases and presentation symptoms may overlap;
2. When examining a child with RLS symptoms the pediatricians should be aware of the mimics but also that dysfunctions of several organs (i.e., kidney, liver, bowel, etc.) or psychiatric or neurologic or rheumatologic disorders may be associated with symptoms of RLS;
3. Clinicians should take into consideration these comorbid disorders to provide a tailored diagnostic and therapeutic approach that can significantly improve medical care for children and families.

Research agenda

1. Although the underlying pathophysiology is unknown, the association between RLS, somatic and neuropsychiatric disorders is likely multifactorial and there is need to better elucidate these factors;
2. Empirical studies are needed to evaluate the impact of RLS-treatment on quality of life of patients affected from somatic or neuropsychiatric diseases;
3. Treatment of some comorbid conditions may reduce RLS symptoms, and identification of these (treatable) medical conditions is needed for clinical trials and should be optimized. With expansion of scientific and medical knowledge, some non treatable conditions such as neuropsychiatric disorders may become focus of clinical studies.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2016.06.008.

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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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