# NEWSLETTER


## INDICE:





ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

# BIBLIOGRAFIA ADHD DICEMBRE 2016

Acta Paediatr Int J Paediatr. 2017;106:96-100.

**ADAPTIVE SKILLS ARE USEFUL FOR EVALUATING THE EFFECT OF PHARMACOLOGICAL TREATMENT IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Lindblad I, Nasic S, Landgren M, et al.***

**Aim**: There are few long-term studies of adaptive functions as an outcome measure of pharmacological treatment in attention-deficit/hyperactivity disorder (ADHD). This study assessed the adaptive abilities of children with ADHD before and after several years of pharmacological treatment.

**Method**: We studied 12 children with a mean age of 15 years seven boys and five girls who had continued pharmacological treatment for ADHD for more than four years. The Adaptive Behaviour Assessment Scales Second Edition ratings by their teachers were compared before and after they had received treatment for ADHD.

**Results**: On a group level, the conceptual, practical and general adaptive composite domains improved significantly between the baseline and follow-up study. There were clear individual variations: more than half of the group increased from an adaptive level far below average to average, a minority displayed no major changes, and one individual deteriorated. The girls tended to have better outcomes than the boys.

**Conclusion**: This study was nonrandomised and only analysed within-group changes in a small number of participants. However, the findings suggest that four to five years of stimulant treatment had markedly positive effects on adaptive functioning in more than half of the school-age children with ADHD

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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 Psychiatr Scand. 2016;134:533-45.

**SUBTHRESHOLD AND THRESHOLD ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN CHILDHOOD: PSYCHOSOCIAL OUTCOMES IN ADOLESCENCE IN BOYS AND GIRLS.**

***Norén Selinus E, Molero Y, Lichtenstein P, et al.***

**Objective**: To examine the association between different levels of childhood attention deficit hyperactivity disorder (ADHD) symptoms and sex differences in psychosocial outcomes during adolescence.

**Method**: Swedish children (n = 4635) were screened for neuropsychiatric symptoms at age 9 or 12. ADHD symptoms were divided into three levels: screen-negative, screen-intermediate, and screen-positive. At follow-up (age 15), parents and teenagers filled out questionnaires regarding (i) hyperactivity/inattention, (ii) peer problems, (iii) school problems, (iv) internalizing problems, (v) antisocial behaviour, (vi) alcohol misuse, and (vii) drug misuse. All outcomes were controlled for symptoms of diagnostic categories other than ADHD.

**Results**: Increasing levels of ADHD symptoms in childhood were associated with higher proportions of adolescents who displayed negative psychosocial outcomes. More girls than boys reported internalizing problems (all levels) and risky drug use (screen-intermediate and screen-positive only). More boys reported antisocial behaviour at the screen-negative and screen-intermediate levels, but at the screen-positive level, similar proportions of girls and boys displayed antisocial behaviour.

**Conclusion**: The findings support the view that ADHD symptoms, as well as their negative outcomes, are dimensionally distributed in the population and that adolescent girls and boys display different risk profiles. The findings confirm that ADHD symptoms are associated with higher risk of drug misuse in girls

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Acta Psychiatr Scand. 2016;134:566-68.

**REACTIVE AGGRESSION IN YOUNG PATIENTS WITH ADHD□A CRITICAL ROLE FOR SMALL PROVOCATIONS.**

***Borgs GP, Runions K, Biskup CS, et al.***

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ADHD Atten Deficit Hyperact Disord. 2016;1-19.

**IS THERE A DIFFERENCE BETWEEN CHILD SELF-RATINGS AND PARENT PROXY-RATINGS OF THE QUALITY OF LIFE OF CHILDREN WITH A DIAGNOSIS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)? A SYSTEMATIC REVIEW OF THE LITERATURE.**

***Galloway H, Newman E.***

There are contemporary indicators that parent proxy-ratings and child self-ratings of a childΓÇÖs quality of life (QoL) are not interchangeable. This review examines dual informant studies to assess parentΓÇôchild agreement on the QoL of children with attention-deficit/hyperactivity disorder. A systematic search of four major databases (PsycINFO, MEDLINE, EMBASE and Cochrane databases) was completed, and related peer-reviewed journals were hand-searched. Studies which reported quantitative QoL ratings for matched parent and child dyads were screened in accordance with relevant inclusion and exclusion criteria. Key findings were extracted from thirteen relevant studies, which were rated for conformity to the recommendations of an adapted version of the STROBE statement guidelines for observational studies. In the majority of studies reviewed, children rated their QoL more highly than their parents. There was some evidence for greater agreement on the physical health domain than psychosocial domains

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Am J Med Genet Part B Neuropsychiatr Genet. 2016;171:1099-104.

**GAD1 GENE POLYMORPHISMS ARE ASSOCIATED WITH HYPERACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Bruxel EM, Akutagava-Martins GC, Salatino-Oliveira A, et al.***

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood. Recent studies suggest a role for +¦-aminobutyric acid (GABA) on ADHD hyperactive/impulsive symptoms due to behavioral disinhibition resulting from inappropriate modulation of both glutamatergic and

GABAergic signaling. The glutamic acid decarboxylase (GAD1) gene encodes a key enzyme of GABA biosynthesis. The aim of the present study was to investigate the possible influence of GAD1 SNPs rs3749034 and rs11542313 on ADHD susceptibility. The clinical sample consisted of 547 families with ADHD probands recruited at the ADHD Outpatient Clinics from Hospital de Cl+¡nicas de Porto Alegre. Hyperactive/impulsive symptoms were evaluated based on parent reports from the Swanson, Nolan, and Pelham ScaleΓÇöversion IV (SNAP-IV). The C allele of rs11542313 was significantly overtransmitted from parents to ADHD probands (P = 0.02). Hyperactive/impulsive score was higher in rs3749034G allele (P = 0.005, Cohen's D = 0.19) and rs11542313C allele (P = 0.03; Cohen's D = 0.16) carriers. GAD1 haplotypes were also associated with higher hyperactive/impulsive scores in ADHD youths (global P-value = 0.01). In the specific haplotype test, the GC haplotype was the one with the highest hyperactive/impulsive scores (P = 0.03). Our results suggest that the GAD1 gene is associated with ADHD susceptibility, contributing particularly to the hyperactive/impulsive symptom domain

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Am J Psychiatry. 2016;173:1213-22.

**A DIFFUSION TENSOR IMAGING STUDYIN CHILDREN WITH ADHD, AUTISM SPECTRUM DISORDER, OCD, AND MATCHED CONTROLS: DISTINCT AND NON-DISTINCT WHITE MATTER DISRUPTION AND DIMENSIONAL BRAIN-BEHAVIOR RELATIONSHIPS.**

***Ameis SH, Lerch JP, Taylor MJ, et al.***

**Objective**: Neurodevelopmental disorders (NDDs) (attention deficit hyperactivity disorder [ADHD], autism spectrum disorder [ASD], and obsessive-compulsive disorder [OCD]) share genetic vulnerability and symptom domains. The authors present direct comparison of structural brain circuitry in children and adolescents with NDDs and control subjects and examine brain circuit-behavior relationships across NDDs using dimensional measures related to each disorder.

**Method**: Diffusion imaging and behavioral measures were acquired in 200 children and adolescents (ADHD: N=31; OCD: N=36; ASD: N=71; controls: N=62; mean age range: 10.3-12.6 years). Following Tract-Based Spatial Statistics, multi group comparison of white matter indices was conducted, followed by pairwise comparisons. Relationships of fractional anisotropy with dimensional measures of inattention, social deficits, obsessive-compulsive symptoms, and general adaptive functioning were conducted across the NDD sample.

**Results**: Lower fractional anisotropy within the splenium of the corpus callosum was found in each NDD group, compared with the control group. Lower fractional anisotropy in additional white matter tracts was found in the ASD and ADHD groups, compared with the control group, but not in the OCD group. Fractional anisotropy was lower in the ASD and ADHD groups compared with the OCD group but was not different in ADHD participants compared with ASD participants. A positive relation between fractional anisotropy (across much of the brain) and general adaptive functioning across NDDs was shown.

**Conclusions**: This study identified disruption in interhemispheric circuitry (i.e., fractional anisotropy alterations in the corpus callosum) as a shared feature of ASD, ADHD, and OCD. However, fractional anisotropy alterations may be more widespread and severe in ASD and ADHD than in OCD. Higher fractional anisotropy throughout the brain appears to be related to better adaptive function across NDDs

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Anadolu Psikiyatr Derg. 2016;17:442-50.

**ASSOCIATION BETWEEN THE METABOTROPIC GLUTAMATE RECEPTOR7 RS3749380 POLYMORPHISM AND METHYLPHENIDATE TREATMENT OUTCOME IN CHILDREN WITH ADHD.**

***Choi BS, Kim B.***

**Objective**: Attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental disorder characterized by inattention, disorganization, and/or hyperactivity-impulsivity. This study investigated the association between the metabotropic glutamate receptors (GRM) 7 rs3749380 polymorphism genotypes and subjective/objective treatment responses to methylphenidate (MPH) in Korean children with ADHD.

**Methods**: This study enrolled 86 medication-na+»ve children with ADHD in an open-label 8-week trial of MPH. The subjects were genotyped and then evaluated using the ADHD Rating Scale (ARS), the Continuous Performance Test (CPT) and the Clinical Global Impression Scale (CGI) before and after treatment.
**Results**: After 8-week MPH treatment, children with the GRM7 rs3749380 polymorphism T/T genotype had a different response in terms of visual response times and auditory commission errors on the CPT than C/C or C/T genotype groups.
**Conclusions**: These results suggest that the GRM7 rs3749380 polymorphism is associated with the response of MPH in patients with ADHD. Further studies, including replication of our findings using a control or comparison group and a larger sample, are warranted to evaluate the association between the GRM7 genes and treatment responses to MPH in subjects with ADHD

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Appl Psychophysiol Biofeedback. 2016 Dec;41:375-80.
**ANTICIPATORY ELECTRODERMAL RESPONSE AS A DIFFERENTIATING SOMATIC MARKER BETWEEN CHILDREN WITH ADHD AND CONTROLS.**
***Odle M, Ouellette JA***.
Six children with Attention Deficit Hyperactivity Disorder (ADHD) and five control children between the ages of 9 and 11 years were administered an adapted version of the Iowa Gambling Task while measuring anticipatory electrodermal response (EDR). Anticipatory EDR measures were compared between groups. Results indicate that the ADHD group exhibited significantly lower autonomic reactivity to anticipated consequences, evidencing a neuropsychological profile similar to patients with lesions in the ventromedial prefrontal cortex.

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Assessment. 2016 Dec;23:655-71.
**ITEM RESPONSE THEORY ANALYSIS OF ADHD SYMPTOMS IN CHILDREN WITH AND WITHOUT ADHD.**
***Li JJ, Reise SP, Chronis-Tuscano A, et al***.
Item response theory (IRT) was separately applied to parent- and teacher-rated symptoms of attention-deficit/hyperactivity disorder (ADHD) from a pooled sample of 526 six- to twelve-year-old children with and without ADHD. The dimensional structure ADHD was first examined using confirmatory factor analyses, including the bifactor model. A general ADHD factor and two group factors, representing inattentive and hyperactive/impulsive dimensions, optimally fit the data. Using the graded response model, we estimated discrimination and location parameters and information functions for all 18 symptoms of ADHD. Parent- and teacher-rated symptoms demonstrated adequate discrimination and location values, although these estimates varied substantially. For parent ratings, the test information curve peaked between -2 and +2 SD, suggesting that ADHD symptoms exhibited excellent overall reliability at measuring children in the low to moderate range of the general ADHD factor, but not in the extreme ranges. Similar results emerged for teacher ratings, in which the peak range of measurement precision was from -1.40 to 1.90 SD. Several symptoms were comparatively more informative than others; for example, is often easily distracted ('Distracted') was the most informative parent- and teacher-rated symptom across the latent trait continuum. Clinical implications for the assessment of ADHD as well as relevant considerations for future revisions to diagnostic criteria are discussed.

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Autism Res. 2016.
**MID-CHILDHOOD OUTCOMES OF INFANT SIBLINGS AT FAMILIAL HIGH-RISK OF AUTISM SPECTRUM DISORDER.**
***Shephard E, Milosavljevic B, Pasco G, et al***.
Almost one-in-five infants at high familial risk for autism spectrum disorder (ASD), due to having an older sibling with an ASD diagnosis, develop ASD themselves by age 3 years. Less is known about the longer-term outcomes of high-risk infants. To address this issue, we examined symptoms of ASD and associated

developmental conditions (attention-deficit/hyperactivity disorder (ADHD); anxiety), language, IQ, and adaptive behaviour at age 7 years in high- and low-risk children studied from infancy. We compared outcomes between high-risk children who met criteria for ASD at age 7, high-risk children without ASD, and low-risk control children. Diagnostic stability between 3 and 7 years was moderate. High-risk siblings with ASD showed elevated levels of ADHD and anxiety symptoms and lower adaptive behaviour than low-risk control children. High-risk siblings without ASD had higher repetitive behaviours, lower adaptive functioning, and elevated scores on one anxiety subscale (Separation Anxiety) compared to low-risk controls. The findings indicate that the difficulties experienced by high-risk siblings at school age extend beyond ASD symptoms. Better understanding of these difficulties may improve models of the development of co-occurring problems seen in children with ASD

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BBA Clinical. 2016;6:153-58.

**ATTENTION DEFICIT-HYPERACTIVITY DISORDER SUFFERS FROM MITOCHONDRIAL DYSFUNCTION.**

***Verma P, Singh A, Nthenge-Ngumbau DN, et al.***

**Background** Pathophysiology of attention-deficit hyperactivity disorder (ADHD) is not known, and therefore the present study investigated mitochondrial defects, if any in cybrids created from patients and control population.

**Methods** To investigate mitochondrial pathology in ADHD, cybrids cell lines were created from ADHD probands and controls by fusing their platelets with ¤ü-¦-cells prepared from SH-SY5Y neuroblastoma cell line. Cellular respiration, oxidative stress, mitochondrial membrane potential and morphology were evaluated employing oxygraph, mitochondria-specific fluorescence staining and evaluation by FACS, and immunocytochemistry. HPLC-electrochemical detection, quantitative RT-PCR and Blue Native PAGE were employed respectively for assays of serotonin, mitochondrial ATPase 6/8 subunits levels and complex V activity.

**Results** Significantly low cellular and mitochondrial respiration, ATPase6/8 transcripts levels, mitochondrial complex V activity and loss of mitochondrial membrane potential and elevated oxidative stress were observed in ADHD cybrids. Expression of monoamine oxidizing mitochondrial enzymes, MAO-A and MAO-B levels remained unaffected. Two-fold increase in serotonin level was noted in differentiated cybrid-neurons.

**Conclusions** Since cybrids are shown to replicate mitochondrial defects seen in post-mortem brains, these observed defects in ADHD cybrids strongly suggest mitochondrial pathology in this disorder. General significance Mitochondrial defects are detected in ADHD cybrids created from patients' platelets, implying bioenergetics crisis in the mitochondria could be a contributory factor for ADHD pathology and/or phenotypes

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Biol Psychiatry. 2016;80:923-32.

**ATTENTION-DEFICIT/HYPERACTIVITY DISORDER REMISSION IS LINKED TO BETTER NEUROPHYSIOLOGICAL ERROR DETECTION AND ATTENTION-VIGILANCE PROCESSES.**

***Michelini G, Kitsune GL, Cheung CHM, et al.***

**Background** The processes underlying persistence and remission of attention-deficit/hyperactivity disorder (ADHD) are poorly understood. We examined whether cognitive and neurophysiological impairments on a performance-monitoring task distinguish between ADHD persisters and remitters.

**Methods** On average 6 years after initial assessment, 110 adolescents and young adults with childhood ADHD (87 persisters, 23 remitters) and 169 age-matched control participants were compared on cognitive-performance measures and event-related potentials of conflict monitoring (N2) and error processing (error-related negativity and positivity) from an arrow flanker task with low-conflict and high-conflict conditions. ADHD outcome was examined with parent-reported symptoms and functional impairment measures using a categorical (DSM-IV) and a dimensional approach.

**Results** ADHD persisters were impaired compared with controls on all cognitive-performance and event-related potential measures (all $p < .05$). ADHD remitters differed from persisters and were indistinguishable from control participants on the number of congruent (low-conflict) errors, reaction time variability, error-

related negativity, and error-related positivity (all p .05). Remitters did not differ significantly from the other groups on incongruent (high-conflict) errors, mean reaction time, and N2. In dimensional analyses on all participants with childhood ADHD, ADHD symptoms and functional impairment at follow-up were significantly correlated with congruent errors, reaction time variability, and error-related positivity (r = .19.23, p .05).
**Conclusions** Cognitive and neurophysiological measures of attention-vigilance and error detection distinguished ADHD remitters from persisters. These results extend our previous findings with other tasks and indicate that such measures are markers of remission and candidates for the development of nonpharmacological interventions

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Biol Psychiatry. 2016.

**MATERNAL POLYCYSTIC OVARY SYNDROME AND RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN THE OFFSPRING.**

***Kosidou K, Dalman C, Widman L, et al.***

**Background**: Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder, and boys are two to three times more likely to develop ADHD. Maternal polycystic ovary syndrome (PCOS), a common metabolic disorder associated with excess circulating androgens, has been associated with increased risk for autism spectrum disorder in the offspring. In this study, we aimed to investigate whether maternal PCOS increases the risk for ADHD in the offspring.
**Methods**: We conducted a matched case-control study using health and population data registers for all children born in Sweden from 1984 to 2008. Maternal PCOS was defined by ICD-coded register diagnosis. The outcome of ADHD was defined as an ICD-coded register diagnosis of ADHD and/or registered prescription of medications to treat ADHD. A total of 58,912 ADHD cases (68.8% male) were identified and matched to 499,998 unaffected controls by sex and birth month and year.
**Results**: Maternal PCOS increased the odds of offspring ADHD by 42% after adjustment for confounders (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.26-1.58). Exclusion of ADHD cases with comorbid autism spectrum disorder attenuated but did not explain the relationship (OR, 1.34; 95% CI, 1.18-1.52). The risk was somewhat elevated for ADHD with comorbid autism spectrum disorder (OR, 1.76; 95% CI, 1.37-2.26). The risk for ADHD was higher among obese mothers with PCOS (OR, 1.68; 95% CI, 1.31-2.17) and was highest among obese mothers with PCOS and other features of metabolic syndrome (OR, 2.59; 95% CI, 1.02-6.58).
**Conclusions**: This study provides evidence that maternal PCOS may subtly influence the neurodevelopment of the offspring, resulting in increased risk for neurodevelopmental disorders such as ADHD

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Biol Psychiatry. 2016;80:916-22.

**MEDICATION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND RISK FOR DEPRESSION: A NATIONWIDE LONGITUDINAL COHORT STUDY.**

***Chang Z, D'Onofrio BM, Quinn PD, et al.***

**Background** Attention-deficit/hyperactivity disorder (ADHD) is associated with high rates of psychiatric comorbidity, including depression. However, it is unclear whether ADHD medication increases or decreases the risk for depression.
**Methods** We studied all individuals with a diagnosis of ADHD born between 1960 and 1998 in Sweden (N = 38,752). We obtained data for prescription of ADHD medication, diagnosis of depression and other psychiatric disorders, and sociodemographic factors from population-based registers. The association between ADHD medication and depression was estimated with Cox proportional hazards regression.
**Results** After adjustment for sociodemographic and clinical confounders, ADHD medication was associated with a reduced long-term risk (i.e., 3 years later) for depression (hazard ratio = 0.58; 95% confidence interval, 0.51 0.67). The risk was lower for longer duration of ADHD medication. Also, ADHD medication was associated with reduced rates of concurrent depression; within-individual analysis suggested that occurrence

of depression was 20% less common during periods when patients received ADHD medication compared with periods when they did not (hazard ratio = 0.80; 95% confidence interval, 0.70 0.92).
**Conclusions** Our study suggests that ADHD medication does not increase the risk of later depression; rather, medication was associated with a reduced risk for subsequent and concurrent depression

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Biol Psychiatry. 2017;81:86.
**ERRATUM: ABERRANT CROSS-BRAIN NETWORK INTERACTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ITS RELATION TO ATTENTION DEFICITS: A MULTISITE AND CROSS-SITE REPLICATION STUDY**
***(Biological Psychiatry (2015) (S0006322315009014) (10.1016/j.biopsych.2015.10.017))***.
Withdrawal notice to: Aberrant Cross-Brain Network Interaction in Children With Attention-Deficit/Hyperactivity Disorder and Its Relation to Attention Deficits: A Multisite and Cross-Site Replication Study by Weidong Cai, Tianwen Chen, Luca Szegletes, Kaustubh Supekar, Vinod Menon. Biological Psychiatry 2015; in press, corrected proof. This article has been withdrawn at the request of the editors and authors due to an inadvertent coding error. During the course of analysis of data from a different study, the authors discovered a single coding error in the MATLAB script used in this study that transforms output of FSL independent component analysis to a MATLAB compatible format for subsequent analysis. Specifically, there was an error in the way the MATLAB function reshape was used, which resulted in some parts of the data being incorrectly structured. After the error was discovered, the authors checked the entire code, confirmed the single error, corrected the error and repeated the entire analyses. Although the revised findings are generally consistent with the original findings, the new analyses have altered findings of the paper, including an inability to reproduce the results obtained in one of the three datasets (OHSU) and changes to the classification accuracy results in the other two datasets (NYU and PKU). Due to the extent and nature of the changes to the paper, the editors and authors concluded that, to ensure maximum clarity and transparency, this version of the paper required withdrawal since it had not yet appeared in a print issue of the journal. The revised version of the paper is being treated as a new paper and is undergoing peer review. The authors sincerely apologize for the error

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2016;1:539-47.
**MODIFIABLE AROUSAL IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ITS ETIOLOGICAL ASSOCIATION WITH FLUCTUATING REACTION TIMES.**
***James SN, Cheung CHM, Rijsdijk F, et al***.
**Background** Cognitive theories of attention-deficit/hyperactivity disorder (ADHD) propose that high within-subject fluctuations of cognitive performance in ADHD, particularly reaction time (RT) variability (RTV), may reflect arousal dysregulation. However, direct evidence of arousal dysregulation and how it may account for fluctuating RTs in ADHD is limited. We used skin conductance (SC) as a measure of peripheral arousal and aimed to investigate its phenotypic and familial association with RTV in a large sample of ADHD and control sibling pairs.
**Methods** Adolescents and young adults (N = 292), consisting of 73 participants with ADHD and their 75 siblings, and 72 controls and their 72 siblings, completed the baseline (slow, unrewarded) and fast-incentive conditions of a RT task, while SC was simultaneously recorded.
**Results** A significant group-by-condition interaction emerged for SC level (SCL). Participants with ADHD had decreased SCL, compared with controls, in the baseline condition but not the fast-incentive condition. Baseline SCL was negatively associated with RTV, and multivariate model fitting demonstrated that the covariance of SCL with RTV, and of SCL with ADHD, was mostly explained by shared familial effects.

**Conclusions** ADHD is associated with decreased, but modifiable, tonic peripheral arousal. A shared familial cause underlies the relationship between arousal and RTV and between arousal and ADHD. Given the malleability of SCL, if our findings are replicated, it warrants further exploration as a potential treatment target for ADHD

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BMC Pediatr. 2016;16.

**BLOOD LEAD CONCENTRATIONS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN KOREAN CHILDREN: A HOSPITAL-BASED CASE CONTROL STUDY.**

***Park JH, Seo JH, Hong YS, et al.***

**Background**: Because the developing brain of a child is vulnerable to environmental toxins, even very low concentration of neurotoxin can affect children's neurodevelopment. Lead is a neurotoxic heavy metal which has the harmful effect on the striatal-frontal circuit of brain. This area of the brain is known to be closely related to attention deficit hyperactivity disorder (ADHD) pathophysiology. The primary objective of the present study was to investigate whether elevated blood lead concentration is a risk factor for ADHD. The secondary objective was to examine the association between blood lead concentration and symptom severity.

**Methods**: We conducted a frequency-matched, hospital-based case-control study with 114 medically diagnosed ADHD cases and 114 controls. The participants were matched for age and sex. The diagnoses of ADHD were assessed with semi-structured diagnostic interviews. The participants completed the continuous performance test (CPT), and their parents completed the ADHD-rating scale (ADHD-RS). Blood lead concentrations were measured by using graphite furnace atomic absorption spectrometry featuring Zeeman background correction.

**Results**: Children with ADHD exhibited blood lead concentrations that were significantly higher than those of the controls (1.90 -¦ 086 ++g/dl vs. 1.59 -¦ 0.68 ++g/dl, p = 0.003). The log transformed total blood lead concentration was associated with a higher risk of ADHD (OR: 1.60, 95 % CI: 1.04-2.45, p < 0.05). The analysis also revealed that the children with blood lead concentrations above 2.30 ++g/dl were at a 2.5-fold (95 % CI: 1.09-5.87, p < 0.05) greater risk of having ADHD. After adjusting for covariates, our multivariate regression models indicated that blood lead concentrations were not significantly associated with ADHD-RS or CPT profiles among the ADHD cases.

**Conclusion**: Even low blood lead concentrations are a risk factor for ADHD in children. This study warrants primary prevention policies to reduce the environmental lead burden. Future studies may be required to ascertain the effects of lead on symptom severity in ADHD

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BMC Psychiatry. 2016 Dec;16.

**RECOMMENDATIONS FOR THE TRANSITION OF PATIENTS WITH ADHD FROM CHILD TO ADULT HEALTHCARE SERVICES: A CONSENSUS STATEMENT FROM THE UK ADULT ADHD NETWORK.**

***Young S, Adamou M, Asherson P, et al.***

The aim of this consensus statement was to discuss transition of patients with ADHD from child to adult healthcare services, and formulate recommendations to facilitate successful transition. An expert workshop was convened in June 2012 by the UK Adult ADHD Network (UKAAN), attended by a multidisciplinary team of mental health professionals, allied professionals and patients. It was concluded that transitions must be planned through joint meetings involving referring/receiving services, patients and their families. Negotiation may be required to balance parental desire for continued involvement in their child's care, and the child's growing autonomy. Clear transition protocols can maintain standards of care, detailing relevant timeframes, responsibilities of agencies and preparing contingencies. Transition should be viewed as a process not an event, and should normally occur by the age of 18, however flexibility is required to accommodate individual

needs. Transition is often poorly experienced, and adherence to clear recommendations is necessary to ensure effective transition and prevent drop-out from services

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BMJ Open. 2016;6.

**CAFFEINE CONSUMPTION DURING PREGNANCY AND ADHD AT THE AGE OF 11 YEARS: A BIRTH COHORT STUDY.**

***Del-Ponte B, Santos IS, Tovo-Rodrigues L, et al.***

**Objective**: Studies evaluating caffeine intake during pregnancy and long-term outcomes, such as the child's neurobehaviour, are still scarce and their results are inconsistent. The objective of the present study was to evaluate the association between maternal consumption of caffeine during pregnancy and attention deficit hyperactivity disorder (ADHD) at the age of 11 years.

**Methodology**: All children born in the city of Pelotas, Brazil, during the year 2004, were selected for a cohort study. The mothers were interviewed at birth to obtain information on coffee and yerba mate consumption during pregnancy, among other matters. At the age of 11 years, presence of ADHD was evaluated using the Development and Well-Being Assessment (DAWBA) questionnaire, applied to the mothers. The prevalence of ADHD was calculated, with 95% CIs. The association between caffeine consumption and ADHD was tested by means of logistic regression.

**Results**: 3485 children were included in the analyses. The prevalence of ADHD was 4.1% (95% CI 3.4% to 4.7%): 5.8% (95% CI 4.7% to 6.9%) among boys and 2.3% (95% CI 1.5% to 3.0%) among girls. The prevalence of caffeine consumption during the entire pregnancy and in the first, second and third trimesters was 88.7% (87.7% to 89.7%), 86.5% (85.4% to 87.5%), 83.0% (81.8% to 84.2%) and 92.3% (91.4% to 93.1%), respectively. Caffeine consumption during the entire pregnancy and the first, second and third trimesters were not associated with ADHD in the crude or adjusted analysis.

**Conclusions**: The present study did not show any association between maternal caffeine consumption during pregnancy and ADHD at the age of 11 years

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Brain Behav. 2016;6.

**DOPAMINERGIC MODULATION OF DEFAULT MODE NETWORK BRAIN FUNCTIONAL CONNECTIVITY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.**

***Silberstein RB, Pipingas A, Farrow M, et al.***

**Introduction**: Recent evidence suggests that attention deficit hyperactivity disorder (ADHD) is associated with a range of brain functional connectivity abnormalities, with one of the most prominent being reduced inhibition of the default mode network (DMN) while performing a cognitive task. In this study, we examine the effects of a methylphenidate dose on brain functional connectivity in boys diagnosed with ADHD while they performed a cognitive task.

**Method**: Brain functional connectivity was estimated using steady-state visual evoked potential partial coherence before and 90-ámin after the administration of a methylphenidate dose to 42 stimulant drug-na+»ve boys newly diagnosed with ADHD while they performed the A-X version of the continuous performance task (CPT A-X).

**Results**: Methylphenidate robustly reversed the transient functional connectivity increase in the A-X interval seen premedication to a postmedication decrease during this interval. In addition, methylphenidate-induced reductions in individual reaction time were correlated with corresponding reductions in functional connectivity.

**Conclusion**: These findings suggest that methylphenidate suppresses the increased functional connectivity observed in ADHD and that such suppression is associated with improved performance. Our findings support the suggestion that the increased functional connectivity we have observed in ADHD is associated with abnormal DMN activity. In addition, we comment on the significance of specific frequency channels mediating top-down communication within the cortex and the extent to which our findings are selectively sensitive to top-down intracortical communication

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Brain Behav. 2016;6.

**BRAIN FUNCTIONAL CONNECTIVITY ABNORMALITIES IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER.**

***Silberstein RB, Pipingas A, Farrow M, et al.***

**Introduction**: Recent evidence suggests that attention-deficit hyperactivity disorder (ADHD) is associated with brain functional connectivity (FC) abnormalities.

**Methods**: In this study, we use steady-state visually evoked potential event-related partial coherence as a measure of brain FC to examine functional connectivity differences between a typically developing (TD) group of 25 boys and an age/IQ-matched group of 42 drug naive boys newly diagnosed with ADHD (ADHD group). Functional connectivity was estimated while both groups performed a low-demand reference task and the A-X version of the continuous performance task (CPT A-X).

**Results**: While the TD and ADHD groups exhibited similar prefrontal FC increases prior to the appearance of the target in the reference task, these groups demonstrated significant FC differences in the interval preceding the appearance of the target in the CPT A-X task. Specifically, the ADHD group exhibited robust prefrontal and parieto-frontal FC increases that were not apparent in the TD group.

**Conclusion**: The FC differences observed in the ADHD group are discussed in the context of inadequate suppression of cortical networks that may interfere with task performance

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Brain Dev. 2017;39:130-37.

**ACTH HAS BENEFICIAL EFFECTS ON STUTTERING IN ADHD AND ASD PATIENTS WITH ESES: A RETROSPECTIVE STUDY.**

***Altunel A, Sever A, Altunel E+û.***

**Introduction** Etiology of stuttering remains unknown and no pharmacologic intervention has been approved for treatment. We aimed to evaluate EEG parameters and the effect of adrenocorticotropic hormone (ACTH) therapy in stuttering.

**Methods** In this retrospective study, 25 patients with attention deficit and hyperactivity (ADHD) or autism spectrum disorder (ASD), and comorbid stuttering were followed and treated with ACTH for electrical status epilepticus in sleep (ESES). Sleep EEGs were recorded at referral and follow-up visits and short courses of ACTH were administered when spikeΓÇôwave index (SWI) was 15%. The assessment of treatment effectiveness was based on reduction in SWI, and the clinician-reported improvement in stuttering, and ADHD or ASD. Statistical analyses were conducted in order to investigate the relationship between the clinical and EEG parameters.

**Results** Following treatment with ACTH, a reduction in SWI in all the patients was accompanied by a 72% improvement in ADHD or ASD, and 83.8% improvement in stuttering. Twelve of the 25 patients with stuttering showed complete treatment response. Linear regressions established that SWI at final visit significantly predicted improvement in ADHD or ASD, and in stuttering. If symptoms had recurred, improvement was once again achieved with repeated ACTH therapies. Stuttering always improved prior to, and recurred following ADHD or ASD.

**Conclusion** The underlying etiology leading to ESES may play a significant role in the pathophysiology of stuttering and connect stuttering to other developmental disorders. ACTH therapy has beneficial effects on stuttering and improves EEG parameters

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Brain Dev. 2017;39:101-06.

**BEHAVIORAL OUTCOMES OF SCHOOL-AGED FULL-TERM SMALL-FOR-GESTATIONAL-AGE INFANTS: A NATIONWIDE JAPANESE POPULATION-BASED STUDY.**

***Takeuchi A, Yorifuji T, Takahashi K, et al.***

**Background** Small for gestational age (SGA) birth is linked with neurological deficits among children at pre-school age, but the evidence is still limited on whether such deficits are still observable at school age. We investigated the association between SGA birth and behavioral development at school age among full-term infants.

**Methods** We analyzed data from a large, Japanese, nationwide, population-based longitudinal survey that started in 2001. We restricted the study participants to children born at 37 41-áweeks of gestation with information on birth weight and behavioral outcomes at 8-years of age (n=33,795). Behavioral outcomes including three attentional problems and four aggressive behaviors queried at 8-years of age by survey questions were used as outcome indicators. We then used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between SGA birth and each outcome, adjusting for potential infant- and parent-related confounding factors.
**Results** Among full-term children, SGA children were more likely to interrupt people (OR 1.10, 95% CI 1.01, 1.20), unable to wait his/her turn (OR 1.17, 95% CI 1.00, 1.38), and destroy toys and/or books (OR 1.15, 95% CI 1.00, 1.31).
**Conclusions** This is the largest study ever conducted on this issue. SGA birth is negatively associated with some attentional problems and aggressive behavior at school age among full-term children. Appropriate long-term developmental follow-up and support may be needed for full-term SGA infants

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Brazilian Neurosurgery. 2016;35:239-43.
**ADHD AND CEREBELLAR VERMIS TUMOR: DTI ANALYSIS OF AN INCIDENTAL FINDING.**
***Baldissin MM, De Souza EM.***
The increase in number of magnetic resonance imaging (MRI) scans for investigation of neurological diseases in childhood and adolescence leads to increase of incidental findings of central nervous system (CNS) tumors in these stages of life. Among MRI techniques, diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) have been increasingly used in brain studies. These images are based on random motion of water molecules in the body, which can change depending on constitution and geometry of biological tissues, as well as the existence of pathologies. This paper reports the use of DTI and DWI to evaluation of a CNS tumor incidentally detected in a patient diagnosed previously with Attention Deficit Hyperactivity Disorder (ADHD). He was diagnosed at age 9 and has been treated with medicines and psycho-pedagogical therapies. At age 15 a MRI detected a cerebellar vermis tumor with a volume of 2 cm3. Due to parental decision, the patient did not undergo any surgical intervention. During the follow-up period we did not observe significant changes in tumor size or diffusion directions in the tumor and surrounding brain tissues. The main brain tracts presented normal diffusion patterns, both in terms of size and geometry. The DTI analysis showed that lesion was quite homogeneous and isotropic, with no significant restriction of diffusion. There also were no significant diffusion pattern changes in other regions of the brain which possibly could be related to ADHD. So, given the characteristics of lesion and the patient's clinical symptoms, it cannot be directly related to ADHD

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Child Adolesc Psychiatry Ment Health. 2016 Dec;10.
**A PRELIMINARY STUDY OF MOVEMENT INTENSITY DURING A GO/NO-GO TASK AND ITS ASSOCIATION WITH ADHD OUTCOMES AND SYMPTOM SEVERITY.**
***Li F, Zheng Y, Smith SD, et al.***
**Objective**: At present, there are no well-validated biomarkers for attention-deficit/hyperactivity disorder (ADHD). The present study used an infrared motion tracking system to monitor and record the movement intensity of children and to determine its diagnostic precision for ADHD and its possible associations with ratings of ADHD symptom severity.
**Methods**: A Microsoft motion sensing camera recorded the movement of children during a modified Go/No-Go Task. Movement intensity measures extracted from these data included a composite measure of total movement intensity (TMI measure) and a movement intensity distribution (MID measure) measure across 15 frequency bands (FB measures). In phase 1 of the study, 30 children diagnosed with ADHD or at subthreshold for ADHD and 30 matched healthy controls were compared to determine if measures of movement intensity successfully distinguished children with ADHD from healthy control children. In phase 2, associations between measures of movement intensity and clinician-rated ADHD symptom severity (Clinical

Global Impression Scale [CGI] and the ADHD-Rating Scale IV [ADHD-RS]) were examined in a subset of children with ADHD (n = 14) from the phase I sample.
**Results**: Both measures of movement intensity were able to distinguish children with ADHD from healthy controls. However, only the measures linked to the 15 pre-determined 1 Hz frequency bands were significantly correlated with both the CGI scores and ADHD-RS total scores.
**Conclusions**: Preliminary findings suggest that measures of movement intensity, particularly measures linked to the 10–11 and 12–13 Hz frequency bands, have the potential to become valid biomarkers for ADHD

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Child Adolesc Psychiatry Ment Health. 2016 Dec;10.
**ASSOCIATION OF PERIPHERAL BDNF LEVEL WITH COGNITION, ATTENTION AND BEHAVIOR IN PRESCHOOL CHILDREN.**
***Yeom CW, Park YJ, Choi SW, et al.***
**Background**: Brain-derived neurotrophic factor (BDNF) has been reported to affect development, cognition, attention and behavior. However, few studies have investigated preschool children with regard to these areas. We evaluated the relationship between cognition, attention and peripheral blood concentration of BDNF in preschool children.
**Methods**: Twenty-eight children (mean age: 6.16 ± 0.60 years) were recruited. For all subjects, serum and plasma BDNF levels were assessed; intelligence was assessed using the Korean standardisation of the Wechsler Intelligence Scale for Children (KEDI-WISC); attention was assessed using the computerised continuous performance test (CCPT), the children's color trails test (CCTT), the Stroop color-word test for preschool children, and the attention-deficit/hyperactivity disorder rating scale (K-ARS); and finally emotional and behavioral problems were assessed using the child behavior checklist (K-CBCL). We confirmed the previously reported correlations between the various psychometric properties assessed and serum and plasma levels of BDNF in our sample.
**Results**: Serum BDNF levels were negatively correlated with both KEDI-WISC full scale IQ (FSIQ, r = -0.39, p = 0.04) and verbal IQ (VIQ, r = -0.05, p = 0.01), but not with the performance IQ (PIQ, r = -0.12, p = 0.56). There were no significant relationships between plasma BDNF level and VIQ, PIQ or FSIQ. No correlations were found between either serum or plasma level of BDNF and any of the attentional measures (CCPT, ARS, CCTT or Stroop color word test). The CBCL total behavioral problem and attention problem sections were positively correlated with plasma BDNF level (r = 0.41, p = 0.03), (r = 0.44, p = 0.02), however, no relationship was found between the serum BDNF and any of the composite CBCL measures.
**Conclusions**: Our results suggest that high peripheral BDNF may be negatively correlated with intelligence, behavioral problems and clinical symptoms of neuro-developmental disorders such as intellectual disability in preschool children. A high peripheral BDNF concentration may, if these findings are further replicated, prove to be a useful biomarker for such issues in preschool children

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Child Neuropsychol. 2016;1-16.
**RISKY DECISION-MAKING IN CHILDREN WITH AND WITHOUT ADHD: A PROSPECTIVE STUDY.**
***Humphreys KL, Tottenham N, Lee SS.***
Learning from past decisions can enhance successful decision-making. It is unclear whether difficulties in learning from experience may contribute to risky decision-making, which may be altered among individuals with attention-deficit/hyperactivity disorder (ADHD). This study follows 192 children with and without ADHD aged 5 to 10 years for approximately 2.5-áyears and examines their risky decision-making using the Balloon Emotional Learning Task (BELT), a computerized assessment of sequential risky decision-making in which participants pump up a series of virtual balloons for points. The BELT contains three task conditions: one with a variable explosion point, one with a stable and early explosion point, and one with a stable and late explosion point. These conditions may be learned via experience on the task. Contrary to expectations, ADHD status was not found to be related to greater risk-taking on the BELT, and among younger children ADHD status is in fact associated with reduced risk-taking. In addition, the typically-developing children without ADHD showed significant learning-related gains on both stable task conditions. However, the children

with ADHD demonstrated learning on the condition with a stable and early explosion point, but not on the condition with the stable and late explosion point, in which more pumps are required before learning when the balloon will explode. Learning during decision-making may be more difficult for children with ADHD. Because adapting to changing environmental demands requires the use of feedback to guide future behavior, negative outcomes associated with childhood ADHD may partially reflect difficulties in learning from experience

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Child Psychiatry Hum Dev. 2016 Dec;47:871-82.

**THE MODERATING EFFECT OF PHYSICAL ACTIVITY ON THE ASSOCIATION BETWEEN ADHD SYMPTOMS AND PEER VICTIMIZATION IN MIDDLE CHILDHOOD.**

***Mitchell TB, Cooley JL, Evans SC, et al.***

Previous research has demonstrated that symptoms of attention-deficit/hyperactivity disorder (ADHD) are associated with higher levels of victimization, but little is known about protective factors. The purpose of the study was to examine whether physical activity attenuated the associations among ADHD symptoms and physical and relational victimization 1.5 years later. Participants included 168 s through fourth grade students (M age = 8.43; 52.4 % boys) who completed self-reports of physical activity and victimization; teachers provided ratings of ADHD symptoms. ADHD symptoms predicted subsequent increases in physical, but not relational, victimization among children who reported engaging in moderate/high levels of physical activity, especially out of the school context (moderate: ß = .26, p = .03; high: ß = .55, p < .001). Findings suggest that children with ADHD symptoms may benefit from being taught the skills necessary to appropriately engage in physical activity and from being monitored while engaging in activity in order to limit physical victimization that they might experience

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Child Psychiatry Hum Dev. 2016 Dec;47:857-70.

**THE PROSPECTIVE LINKS BETWEEN HYPERACTIVE/IMPULSIVE, INATTENTIVE, AND OPPOSITIONAL-DEFIANT BEHAVIORS IN CHILDHOOD AND ANTISOCIAL BEHAVIOR IN ADOLESCENCE: THE MODERATING INFLUENCE OF GENDER AND THE PARENT–CHILD RELATIONSHIP QUALITY.**

***Giannotta F, Rydell AM.***

We prospectively investigated the effect of child hyperactive/impulsive, inattentive, and oppositional/defiant behaviors on the development of youth antisocial behaviors, and the moderating influence of gender and the parent–child relationship quality in a normative sample. Participants (N = 673, 50 % girls) were assessed at 10 years of age (parent reports) and at age 15 (parent and adolescent reports). Using latent change models, we found that initial levels of, as well as increases in, hyperactivity/impulsivity and oppositional behaviors and initial levels of inattention behaviors predicted youth antisocial behaviors. The increase in oppositional behaviors was predictive of youth antisocial behaviors in girls only. Child hyperactive/impulsive behaviors predicted youth antisocial behaviors only in children for whom the quality of the parent–child relationship deteriorated from childhood to adolescence. Thus, both initial levels of and increases in disruptive behaviors as well as gender are important for understanding the development of antisocial behaviors in adolescence. We received partial support for the hypothesized, moderating role of a high-quality parent–child relationship

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Child Psychiatry Hum Dev. 2016 Dec;47:966-74.

**THE DIFFERENTIAL RELATIONS BETWEEN EMPATHY AND INTERNALIZING AND EXTERNALIZING SYMPTOMS IN INPATIENT ADOLESCENTS.**

***Gambin M, Sharp C.***

Impaired empathy is associated with a variety of psychiatric conditions; however, little is known about the differential relations between certain forms of psychopathology and cognitive and affective empathy in adolescent girls and boys. The aim of this study was to examine the relations between externalizing and

internalizing disorders and cognitive and affective empathy, respectively, while controlling for covariance among different forms of psychopathology, separately in girls and boys. A total of 507 inpatient adolescents (319 girls and 188 boys) in the age range of 12–17 years completed the Basic Empathy Scale that measures affective and cognitive empathy. The Youth Self-Report Form and Child Behavior Checklist were used to assess the severity of psychopathological symptoms. Results demonstrated that affective and cognitive empathy were negatively associated with conduct problems only in girls, but not in boys. Affective empathy was positively related to internalizing problems observed by parents and youths and self-reported ADHD symptoms in girls and boys. The clinical implications of these differential relationships for externalizing versus internalizing symptoms and empathy are discussed

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Child Psychiatry Hum Dev. 2016 Dec;47:841-56.

**MULTI-DOMAIN PREDICTORS OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN PRESCHOOL CHILDREN: CROSS-INFORMANT DIFFERENCES.**

***Lavigne JV, Gouze KR, Hopkins J, et al.***

Numerous studies indicated that agreement between parent and teacher ratings of symptoms of attention-deficit/hyperactivity disorder in children of all ages is poor, but few studies have examined the factors that may be associated with rater differences. The present study examined the contextual, parent, parenting, and child factors associated with rater differences in a community sample of 4-year-old children. Parents and teachers of 344 4-year-olds recruited from preschools and pediatric practices completed the preschool versions of the Child Symptom Inventory. Measures of socioeconomic status, family stress and conflict, caretaker depression, parental hostility, support-engagement, and scaffolding skills, and child negative affect (NA), sensory regulation (SR), effortful control (EC), inhibitory control, and attachment security were obtained either by parental report or observational measures. ? 2 difference tests indicated that child factors of EC and SR, and contextual factor of stress and conflict, contributed more to parent-ratings of ADHD-I and ADHD-HI than to teacher-ratings of those same types of symptoms. Two factors contributed more to teacher-than to parent-rated ADHD-I, NA and caretaker depression. Results indicate there are differences in factors associated with ADHD symptoms at home and school, and have implications for models of ADHD.

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CNS Drugs. 2016;1-11.

**TARGETING FUNCTIONAL IMPAIRMENTS IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH ADHD.**

***Sasser T, Schoenfelder EN, Stein MA.***

The diagnostic criteria for attention-deficit hyperactivity disorder (ADHD) require both symptoms and impairment to be present. Impairment in functioning is commonly the primary reason for referral, and is also a better predictor of long-term outcomes than ADHD symptoms. And yet, only recently has research begun to examine the impact of ADHD treatments on functional impairment using efficient and psychometrically sound outcome measures. In this article, we identify several noteworthy multidimensional measures of functional impairment (ADHD FX, Barkley Functional Impairment Scale [BFIS], Impairment Rating Scale [IRS], Weiss Functional Impairment Rating Scale [WFIRS]) utilized in recent clinical trials for ADHD, and describe their psychometric properties and clinical utility. We also review existing evidence on the impact of pharmacological and behavioral treatments on different domains of functional impairment in ADHD youth as measured by these specific measures. Further research is needed to evaluate longitudinal effects of ADHD treatments on functional impairment, and the use of these measures in adaptive treatment designs

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CNS Spectr. 2015;20:67-68.

**A STUDY OF METHYLPHENIDATE EXTENDED-RELEASE CAPSULES IN A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PROTOCOL IN CHILDREN AND ADOLESCENTS WITH ADHD.**

***Wigal SB, Adjei AL, Childress A, et al.***

**Objective**: To determine whether MPH-MLR's ratio of immediate/extended-release (IR/ER) content (37%/63%), unique among the available controlled-release MPH products, produces a clinically meaningful rapid initial (morning) postdose effect with a subsequent more prolonged effect across the day.

**METHODS**: A parallel, randomized, double-blind, fixed-dose, placebo-controlled study was conducted at 16 centers to evaluate the safety and efficacy of MPH-MLR (10, 15, 20, 40 mg/day) in the treatment of ADHD in patients aged 6-18 years. There were 4 study phases: 1) 4-week Screening/Baseline; 2) 1-week double-blind treatment; 3) 11-week, open-label, dose-optimization period; and 4) 30-day follow-up call. The primary endpoint was change from Baseline to the end of phase 2 in ADHD Rating Scale, version 4 (ADHD-RS-IV); secondary endpoints included the Clinical Global Impression-Improvement scale (CGI-I), adverse events (AEs), and quality of life (QoL) measures. Differences between treatment groups were analyzed by an analysis of covariance including terms for treatment, investiga-tional site, and baseline ADHD-RS-IV total score as a covariate for the intent-to-treat population.

**RESULTS**: Children (N = 280; mean age, 10.8 a 3.0 years) diagnosed with ADHD (by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria) were screened and 230 entered the double-blind phase and were administered MPH-MLR 10 mg (n = 49), MPH-MLR 15 mg (n = 44), MPH-MLR 20 mg (n = 45), MPH-MLR 40 mg (n = 45), or placebo (n = 47) and 221 completed the 1-week double blind phase. MPH-MLR resulted in significantly greater improvement versus placebo in mean ADHD-RS-IV score (P<0.05) and CGI-I score (P<0.05). Clinical significance was seen at each of the 4 MPH-MLR fixed doses. 200 subjects completed the subsequent 11-week open label phase, during which their MPH-MLR dose was optimized. There was continuing improvement in efficacy over time. QoL measures did not statistically improve during the one-week double-blind period but showed significant improvements by study end. The most common AEs were consistent with known MPH AEs. Most treatment-emergent AEs were mild or moderate in severity, and there were no serious drug-related AEs throughout the study.

**CONCLUSIONS**: Once-daily MPH-MLR significantly reduced mean baseline ADHD-RS-IV total score in this double-blind study compared with placebo in ADHD children aged 6-18 years. The novel drug release profile, unique immediate/extended drug release ratio, and 8 dose strengths provide more options for customized treatment of ADHD

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CNS Spectr. 2015;20:68.

**TIME COURSE OF RESPONSE TO METHYLPHENIDATE EXTENDED-RELEASE CAPSULES IN CHILDREN WITH ADHD: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY.**

***Wigal S, Childress A, Greenhill L, et al.***

**Objective**: To compare an extended-release multilayer bead formulation of methylphenidate (MPH-MLR) to placebo in children with ADHD in an analog classroom setting.

**METHODS**: Children 6-12 years with ADHD were evaluated in a laboratory classroom setting at a single site (CT identifier NCT01269463). After a screening period (up to 4 weeks) and a 2-day washout period, enrolled children were started on MPH-MLR 15 mg daily and entered an open-label, individualized dose optimization treatment period (2-4 weeks). The double-blind crossover period (weeks 5 and 6) included 1 week each of placebo and the optimized MPH-MLR dose given daily. Laboratory time course evaluations were performed at the end of weeks 5 and 6. The primary efficacy endpoint was the mean of the on-treatment/post-dose Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) total scores over time points collected 1 to 12 hours after dosing. A mixed-effects analysis of covariance was used to evaluate the endpoints.

**RESULTS**: The evaluable population included 20 subjects. The least squares (LS) mean postdose SKAMP Total score was higher for placebo (2.18 vs. 1.32, P = 0.0001) indicating greater improvement with treatment. No difference in SKAMP Total score between subjects who initially received MPH-MLR or placebo in the double-blind phase was noted. From hours 1-12, the mean of all LS SKAMP Total Scores was significantly better for MPH-MLR than placebo (P Γëñ0.0261). No new or unexpected safety findings were noted in the study.

**CONCLUSION**: MPH-MLR showed a significant decrease in SKAMP scores compared to placebo in ADHD children aged 6 to 12 years with an estimated onset within 1 hour of dosing and duration measured to 12 hours postdose

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Cogn Behav Pract. 2016.

**COGNITIVE BEHAVIORAL THERAPY FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN COLLEGE STUDENTS: A REVIEW OF THE LITERATURE.**

***He JA, Antshel KM.***

The current review presents a theory-guided review of the existing cognitive behavioral therapy (CBT) interventions for attention-deficit/hyperactivity disorder (ADHD) in college students. Across the eight studies that investigated this topic, moderate reductions were shown in inattentive symptoms but little to no change was reported in hyperactive/impulsive symptoms. Results indicated a moderate treatment effect on self-reported quality of life and school/work functioning, yet less of an impact on GPA, response inhibition, social functioning, and executive functioning. Methodological and statistical problems and inconsistencies were noted. Since college students are emerging adults, it is likely that the optimum CBT intervention for college students with ADHD lies somewhere in between the existing clinic-based adult ADHD CBT interventions as well as the school-based adolescent ADHD psychosocial interventions. Directions for future research and recommendations for clinicians in university settings are provided in an attempt to further develop the existing college students CBT clinical research evidence base

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Complement Ther Med. 2017;30:14-23.

**HERBAL MEDICINES IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A SYSTEMATIC REVIEW.**

***Anheyer D, Lauche R, Schumann D, et al.***

**Objective** The purpose of this review is to identify evidence in herbal therapy in the treatment of ADHD concerning effectiveness and drug tolerability.

**Method** For this Medline/PubMed, Scopus and the Cochrane Central Register of Controlled Trials (Central) were searched from their inception to 15 July 2016. Only randomized controlled trails (RCT) with children (0 18 years) suffering from ADHD were included in this review.

**Results** Nine RCTs with 464 patients comparing herbal pharmaceuticals to placebo or active control were included. Seven different herbs were tested in the treatment of ADHD symptoms. Low evidence could be found for Melissa officinalis, Valeriana officinalis and Passiflora incarnata. Limited evidence could be found for pine bark extract and Gingko biloba. The other herbal preparations showed no efficacy in the treatment of ADHD symptoms.

**Conclusion** While there is still a lack of sufficient numbers of RCTs no concrete recommendations for use can be made so far

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Compr Psychiatry. 2017;73:53-60.

**DYNAMIC THIOL/DISULFIDE HOMEOSTASIS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ITS RELATION WITH DISEASE SUBTYPES.**

***Avcil S, Uysal P, Avcil M, et al.***

**Background** The aim of this study was to evaluate a novel oxidative stress marker (thiol/disulfide homeostasis) in attention deficit hyperactivity disorder (ADHD) children for the first time in literature.

**Methods** Ninety children with ADHD diagnosed according to DSM-V and as control group, 65 healthy children were included to the study. Native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol were compared between the groups.

**Results** Total and native thiol levels were significantly higher whereas the disulfide/native thiol ratios were significantly lower in children with ADHD. ADHD combined type appeared to have higher disulfide, disulfide/native thiol and disulfide/total thiol ratios compared to other subtypes. Disulfide levels of the males with ADHD were significantly higher than those of the females with ADHD.
**Conclusion** This study suggests that thiol/disulfide homeostasis is abnormal in children with ADHD. It may be used as a novel OS marker in ADHD children because it is easy, practical, fully automated and relatively inexpensive

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Egyptian Journal of Radiology and Nuclear Medicine. 2016.

**T2* MAGNETIC RESONANCE IMAGING: A NON-INVASIVE BIOMARKER OF BRAIN IRON CONTENT IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Hasaneen BM, Sarhan M, Samir S, et al.***

**Purpose**: The aims of this study were the followings: First: To compare brain iron content in children with Attention-Deficit/Hyperactivity Disorder (ADHD) and healthy control subjects, estimated by T2* MRI value and its reciprocal R2*. Second: To assess the association between brain iron content and distinct types of ADHD (predominantly inattentive, predominantly hyperactive/impulsive, or combined). Third: To test the ability of T2* MRI to grade the severity of ADHD. Patients and methods: 35 children (17 ADHD patients and 18 healthy non-ADHD controls) underwent T2*-MRI to assess brain iron content. R2* value is calculated for both thalami.
**Results**: ADHD group showed significantly lower R2* (mean 14.9s-1 -¦1.3) value when compared to control group (mean R2* 16.6s-1 -¦0.9) (p =<0.001). Best cutoff value for R2* was 15.65s-1, and R2* less than 15.65s-1 showed good AUC for prediction of ADHD. Combined ADHD type showed significantly lower R2* when compared to inattentive type (p =0.033 respectively). No significant correlations were found between R2* value and severity of ADHD.
**Conclusion**: T2* MRI represents a reliable non-invasive tool for probing brain iron contents. Lower R2* values correlate with ADHD type but not with ADHD severity

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Endocrine Reviews. 2015;36.

**CRITICAL POTENTIAL MISDIAGNOSIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN WITH UNDERLYING PHEOCHROMOCYTOMA/PARAGANGLIOMA.**

***Batsis M, Prodanov T, Zilbermint M, et al.***

Behavioral symptoms related to catecholamine excess in the setting of pheochromocytoma/ paraganglioma (PHEO/PGL) may overlap with those seen in attention deficit hyperactivity disorder (ADHD); however, ADHD should be a diagnosis of exclusion. It is not known how frequently pediatric patients with PHEO/PGL report inability to concentrate, hyperactivity, or poor school performance; thus far only two cases have described PHEO/PGL presenting with ADHD-like symptoms. (1) We performed a retrospective review of patients < 18 year-old at the time of their diagnosis of PHEO/PGL with a documented prior diagnosis of ADHD. The chi-squared test was used to compare the observed prevalence of ADHD in the PHEO/PGL cohort compared to what would be expected given population estimates. Nine out of the 43 pediatric patients (21%) seen at the National Institutes of Health Clinical Center and diagnosed with PHEO/PGL between 2006-2014 had previously been diagnosed with ADHD. According to the National Survey of Children's health, in 2011, 11% of children/adolescents aged 4 to 17 had ever received an ADHD diagnosis (1). Our prevalence of 21% is significantly higher than the expected 11% (p = 0.0356) These 9 individuals initially presented with behavioral symptoms including hyperactivity, difficulty concentrating, and poor school performance, and were diagnosed with ADHD. Four had been treated with amphetamine and dextroamphetamine or methylphenidate. One patient was admitted for a two-week behavior intervention for oppositional/defiant disorder. Median age at the time of diagnosis of PHEO/PGL was 14, range 6.6-15. Four patients were diagnosed with PHEO, 3 with extra adrenal PGL, and 2 with metastatic/multiple PGL. Seven patients were identified to have causative mutations for genetic syndromes associated with PHEO/PGL: SDHB, 5; SDHA, 1; MEN2A, 1; VHL, 1. Plasma

norepinephrine was elevated in 3 out 7 patients, plasma dopamine was elevated in 1 out of 8, plasma metanephrine was elevated in 1 patient out of 8. Hypertension was a presenting symptom in 4 out of the 9 patients. All patients underwent surgical resection of their tumors. In 3 patients, behavioral abnormalities resolved following tumor resection. The misdiagnosis of ADHD in the setting of a PHEO/PGL is concerning for a number of reasons. Medications used in the treatment of ADHD are known to exacerbate hypertension and should be used in caution in individuals at risk for hypertensive crisis as they may potentiate the adrenergic effects of catecholamines. As there may be overlap in the presentation of these two disorders, children with ADHD-like symptoms who have signs and symptoms that could be compatible with PHEO/PGL such as headaches and hypertension and/or a family history of neuroendocrine tumors should be evaluated for the possibility of PHEO/PGL prior to initiating stimulant medications

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Endocrine Reviews. 2016;37.

**CIRCULATING PHTHALATES DURING CRITICAL ILLNESS IN CHILDREN AND THEIR LONG-TERM ATTENTION DEFICIT LEGACY: AN ASSOCIATION STUDY OF A DEVELOPMENT AND A VALIDATION COHORT.**

***Verstraete S, Vanhorebeek I, Covaci A, et al.***

**Background**: The long-term legacy of pediatric critical illness comprises a severe and unexplained attention deficit.1 Phthalates, which may be neurotoxic, are used to soften plastic indwelling medical devices and can leach into the circulation. 2, 3 Hypothesis: We hypothesized that in children treated in the pediatric intensive care unit (PICU), circulating phthalates leaching from indwelling medical devices contribute to their long-term attention deficit.

**Methods**: Circulating plasma concentrations of di (2-ethylhexyl)phthalate (DEHP) metabolites were quantified in 100 healthy children and 449 children who had been treated in PICU and were neurocognitively tested 4 years later. In a development patient cohort (N=228), a multivariable bootstrap study identified stable thresholds of exposure to circulating DEHP metabolites above which there was an independent association with worse neurocognitive outcome. Subsequently, in a second patient cohort (N=221), the observed independent associations were validated.

**Results**: Plasma concentrations of DEHP metabolites, that were virtually undetectable [0.029(0.027-0.031) ++mol/l] in healthy children, were 4.41(3.76-5.06) ++mol/l in critically ill children upon PICU admission (P<0.001). Plasma DEHP metabolite concentrations decreased rapidly but remained 18-times elevated until PICU discharge (P<0.001). After adjusting for baseline risk factors and duration of PICU stay, and further for PICU complications and treatments, exceeding the potentially harmful threshold for exposure to circulating DEHP metabolites was independently associated with the attention deficit (all P 0.008) and impaired motor coordination (all P 0.02). The association with the attention deficit was confirmed in the validation cohort (all P 0.01). This phthalate exposure effect explained half of the attention deficit in post-PICU patients.

**Conclusions and Relevance**: Exposure to phthalates leaching from indwelling medical devices used for intensive medical care in children was independently and robustly associated with their long-term attention deficit. Development of alternative plasticizers for this application may be indicated

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Epidemiol Psychiatr Sci. 2016;25:573-80.

**ASSOCIATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND KAWASAKI DISEASE: A NATIONWIDE POPULATION-BASED COHORT STUDY.**

***Kuo HC, Chang WC, Wang LJ, et al.***

**Aims**. The association between Kawasaki disease (KD) and Attention deficit hyperactivity disorder (ADHD) has rarely been studied. In this study, we investigated the hypothesis that KD may increase the risk of ADHD using a nationwide Taiwanese population-based claims database.

**Methods**. Our study cohort consisted of patients who were diagnosed with KD between January 1997 and December 2005 (N = 651). For a comparison cohort, five age- and gender-matched control patients for every patient in the study cohort were selected using random sampling (N = 3255). The cumulative incidence of ADHD was 3.89/1000 (from 0.05 to 0.85) in this study. All subjects were tracked for 5 years from the date of

cohort entry to identify whether or not they had developed ADHD. Cox proportional hazard regression analysis was performed to evaluate 5-year ADHD-free survival rates.
**Results**. Of all patients, 83 (2.1%) developed ADHD during the 5-year follow-up period, of whom 21 (3.2%) had KD and 62 (1.9%) were in the comparison cohort. The patients with KD seemed to be at an increased risk of developing ADHD (crude hazard ratio (HR): 1.71; 95% confidence interval (CI) = 1.04-2.80; $p < 0.05$). However, after adjusting for gender, age, asthma, allergic rhinitis, atopic dermatitis and meningitis, the adjusted hazard ratios (AHR) of the ADHD in patients with KD showed no association with the controls (AHR: 1.59; 95% CI = 0.96-2.62; $p = 0.07$). We also investigated whether or not KD was a gender-dependent risk factor for ADHD, and found that male patients with KD did not have an increased risk of ADHD (AHR: 1.62; 95% CI = 0.96-2.74; $p = 0.07$) compared with the female patients.
**Conclusions**. The findings of this population-based study suggest that patients with KD may not have an increased risk of ADHD and whether or not there is an association between KD and ADHD remains uncertain

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Eur Child Adolesc Psychiatry. 2016 Dec;25:1307-18.

**ASSOCIATION BETWEEN AUTISM SYMPTOMS AND FAMILY FUNCTIONING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A COMMUNITY-BASED STUDY.**

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

Autism spectrum disorder (ASD) symptoms are elevated in populations of children with attention-deficit/hyperactivity disorder (ADHD). This study examined cross-sectional associations between ASD symptoms and family functioning in children with and without ADHD. Participants were recruited to a longitudinal cohort study, aged 6–10 years (164 ADHD; 198 controls). ADHD cases were ascertained using community-based screening and diagnostic confirmation from a diagnostic interview. ASD symptoms were measured using the Social Communication Questionnaire. Outcome variables were parent mental health, family quality of life (FQoL), couple conflict and support, and parenting behaviours. After adjustment for a range of child and family factors (including other mental health comorbidities), higher ASD symptoms were associated with poorer FQoL across all three domains; emotional impact ($p = 0.008$), family impact ($p = 0.001$) and time impact ($p = 0.003$). In adjusted analyses by subgroup, parents of children with ADHD + ASD had poorer parent self-efficacy ($p = 0.01$), poorer FQoL ($p = 0.05$), with weak evidence of an association for less couple support ($p = 0.06$), compared to parents of children with ADHD only. Inspection of covariates in the adjusted analyses indicated that the association between ASD symptoms and most family functioning measures was accounted forby child internalising and externalising disorders, ADHD severity, and socioeconomic status; however, ASD symptoms appear to be independently associated with poorer FQoL in children with ADHD. The presence of ASD symptoms in children with ADHD may signal the need for enhanced family support.

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Eur Child Adolesc Psychiatry. 2016;1-8.

**WHAT TO EXPECT AND WHEN TO EXPECT IT: AN FMRI STUDY OF EXPECTANCY IN CHILDREN WITH ADHD SYMPTOMS.**

***van Hulst BM, De Zeeuw P, Rijks Y, et al.***

Changes in cognitive control and timing have both been implicated in ADHD. Both are involved in building and monitoring expectations about the environment, and altering behavior if those expectations are violated. In ADHD, problems with expectations about future events have high face validity, as this would be associated with behavior that is inappropriate only given a certain context, similar to symptoms of the disorder. In this fMRI study, we used a timing manipulated go/nogo task to assess brain activity related to expectations about what (cognitive control) and when (timing) events would occur. We hypothesized that problems in building expectations about the environment are a more general, trans-diagnostic characteristic of children with hyperactive, impulsive and inattentive symptoms. To address this, we included children with ASD and symptoms of ADHD, in addition to children with ADHD and typically developing children. We found between-group differences in brain activity related to expectations about when (timing), but not what events will occur (cognitive control). Specifically, we found timing-related hypo-activity that was in part unique to children with

a primary diagnosis of ADHD (left pallidum) and in part shared by children with similar levels of ADHD symptoms and a primary diagnosis of ASD (left subthalamic nucleus). Moreover, we found poorer task performance related to timing, but only in children with ASD and symptoms of ADHD. Ultimately, such neurobiological changes in children with ADHD symptoms may relate to a failure to build or monitor expectations and thereby hinder the efficiency of their interaction with the environment

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Eur Child Adolesc Psychiatry. 2016;1-20.

**THE POTENTIAL RELEVANCE OF DOCOSAHEXAENOIC ACID AND EICOSAPENTAENOIC ACID TO THE ETIOPATHOGENESIS OF CHILDHOOD NEUROPSYCHIATRIC DISORDERS.**

***Tesei A, Crippa A, Ceccarelli SB, et al.***

Over the last 15 years, considerable interest has been given to the potential role of omega-3 polyunsaturated fatty acids (PUFAs) for understanding pathogenesis and treatment of neurodevelopmental and psychiatric disorders. This review aims to systematically investigate the scientific evidence supporting the hypothesis on the omega-3 PUFAs deficit as a risk factor shared by different pediatric neuropsychiatric disorders. Medline PubMed database was searched for studies examining blood docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) status in children with neuropsychiatric disorders. Forty-one published manuscripts were compatible with the search criteria. The majority of studies on attention-deficit/hyperactivity disorder (ADHD) and autism found a significant decrease in DHA levels in patients versus healthy controls. For the other conditions examinedΓÇödepression, juvenile bipolar disorder, intellectual disabilities, learning difficulties, and eating disorders (EDs)ΓÇöthe literature was too limited to draw any stable conclusions. However, except EDs, findings in these conditions were in line with results from ADHD and autism studies. Results about EPA levels were too inconsistent to conclude that EPA could be associated with any of the conditions examined. Finally, correlational data provided, on one hand, evidence for a negative association between DHA and symptomatology, whereas on the other hand, evidence for a positive association between EPA and emotional well-being. Although the present review underlines the potential involvement of omega-3 PUFAs in the predisposition to childhood neuropsychiatric disorders, more observational and intervention studies across different diagnoses are needed, which should integrate the collection of baseline PUFA levels with their potential genetic and environmental influencing factors

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Eur Child Adolesc Psychiatry. 2016;1-9.

**IMPACT OF DEPRESSIVE/ANXIETY SYMPTOMS ON THE QUALITY OF LIFE OF ADOLESCENTS WITH ADHD: A COMMUNITY-BASED 1-YEAR PROSPECTIVE FOLLOW-UP STUDY.**

***Pan PY, Yeh CB.***

Adolescents with attention-deficit/hyperactivity disorder (ADHD) often exhibit functional impairment even those having less visible symptoms. Therefore, it is of great clinical importance to identify ADHD symptoms among adolescents in the community. Furthermore, little is known regarding the role of internalizing symptoms in their quality of life. Thus, this study aimed to screen ADHD in a sample of high school students using the Adult ADHD Self-report Scale (ASRS) and to investigate the impact of internalizing symptoms on their well-being. In the first year, adolescents aged 15ΓÇô17 years old from a senior high school (N = 1947) completed the Adult ADHD Self-rating Scale (ASRS), Wender Utah Rating Scale, Impulsiveness Scale, BeckΓÇÖs Depression Inventory and BeckΓÇÖs Anxiety Inventory. In the second year, the World Health Organization Quality of Life-BREF was applied for the measurement of their psychosocial outcomes. Results showed that adolescents with higher ASRS scores manifested more severe concurrent depressive and anxiety symptoms. ADHD symptoms among these adolescents were significantly associated with poorer quality of life 1 year later ($p < 0.001$). And both depressive and anxiety symptoms were mediators in the relationship between ADHD symptoms and quality of life. The finding of this study supports that the concurrent internalizing symptoms may underlie the negative relations between ADHD symptoms and quality

of life in adolescents in the community. The application of ASRS in adolescents may help clinicians in early intervention for their ADHD problems as well as emotional symptoms

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Europ J Spec Needs Educ. 2016;1-16.

**AN ETHNOGRAPHIC FIELD STUDY OF THE INFLUENCE OF SOCIAL INTERACTIONS DURING THE SCHOOL DAY FOR CHILDREN DIAGNOSED WITH ADHD.**

***Feder KM, Bak CK, Petersen KS, et al.***

The aim of this ethnographic field study was to investigate the influence of school-day social interactions on the well-being and social inclusion of children diagnosed with ADHD. The empirical data consisted of participant observations and informal interviews over a three-month period at a Danish primary school. Two ADHD-diagnosed 11-year-old boys in the fourth and fifth grades were followed on an alternating basis. The field notes were analysed using a qualitative content analysis that incorporated Etienne Wenger's concepts of social identity and participation. The results revealed that the effects of school-day social interactions are complex and situation dependent. Medication, friendships and relationships with teachers and other adults strongly influence how children diagnosed with ADHD participate in social interactions and, consequently, how they thrive. We argue that it is important to emphasise the mediation of these children's participation in the classroom community throughout an entire school day to ensure their social inclusion and well-being

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Front Human Neurosci. 2016 Nov;10.

**FUNCTIONAL CONNECTIVITY OF CHILD AND ADOLESCENT ATTENTION DEFICIT HYPERACTIVITY DISORDER PATIENTS: CORRELATION WITH IQ.**

***Park By, Hong J, Lee SH, et al.***

Attention deficit hyperactivity disorder (ADHD) is a pervasive neuropsychological disorder that affects both children and adolescents. Child and adolescent ADHD patients exhibit different behavioral symptoms such as hyperactivity and impulsivity, but not much connectivity research exists to help explain these differences. We analyzed openly accessible resting-state functional magnetic resonance imaging (rs-fMRI) data on 112 patients (28 child ADHD, 28 adolescent ADHD, 28 child normal control (NC), and 28 adolescent NC). We used group independent component analysis (ICA) and weighted degree values to identify interaction effects of age (child and adolescent) and symptom (ADHD and NC) in brain networks. The frontoparietal network showed significant interaction effects ($p = 0.0068$). The frontoparietal network is known to be related to hyperactive and impulsive behaviors. Intelligence quotient (IQ) is an important factor in ADHD, and we predicted IQ scores using the results of our connectivity analysis. IQ was predicted using degree centrality values of networks with significant interaction effects of age and symptom. Actual and predicted IQ scores demonstrated significant correlation values, with an error of about 10%. Our study might provide imaging biomarkers for future ADHD and intelligence studies

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Hum Brain Mapp. 2016.

**INTEGRATED MULTIMODAL NETWORK APPROACH TO PET AND MRI BASED ON MULTIDIMENSIONAL PERSISTENT HOMOLOGY.**

***Lee H, Kang H, Chung MK, et al.***

Finding underlying relationships among multiple imaging modalities in a coherent fashion is one of the challenging problems in multimodal analysis. In this study, we propose a novel approach based on multidimensional persistence. In the extension of the previous threshold-free method of persistent homology, we visualize and discriminate the topological change of integrated brain networks by varying not only threshold but also mixing ratio between two different imaging modalities. The multidimensional persistence is implemented by a new bimodal integration method called 1D projection. When the mixing ratio is predefined, it constructs an integrated edge weight matrix by projecting two different connectivity information

onto the one dimensional shared space. We applied the proposed methods to PET and MRI data from 23 attention deficit hyperactivity disorder (ADHD) children, 21 autism spectrum disorder (ASD), and 10 pediatric control subjects. From the results, we found that the brain networks of ASD, ADHD children and controls differ, with ASD and ADHD showing asymmetrical changes of connected structures between metabolic and morphological connectivities. The difference of connected structure between ASD and the controls was mainly observed in the metabolic connectivity. However, ADHD showed the maximum difference when two connectivity information were integrated with the ratio 0.6. These results provide a multidimensional homological understanding of disease-related PET and MRI networks that disclose the network association with ASD and ADHD

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Int J Eating Disord. 2016;49:1036-39.

**SEVERE AVOIDANT/RESTRICTIVE FOOD INTAKE DISORDER AND COEXISTING STIMULANT TREATED ATTENTION DEFICIT HYPERACTIVITY DISORDER.**

***Pennell A, Couturier J, Grant C, et al.***

There is a growing body of literature describing the development, clinical course, and treatment of avoidant/restrictive food intake disorder (ARFID), a diagnostic category introduced in the DSM-5. However, information surrounding complex cases of ARFID involving coexisting medical and/or psychiatric disorders remains scarce. Here we report on two cases of young patients diagnosed concurrently with ARFID and attention deficit hyperactivity disorder (ADHD) who both experienced significant growth restriction following initiation of stimulant medication. The appetite suppressant effect of stimulants exacerbated longstanding avoidant and restrictive eating behaviors resulting in growth restriction and admission to an inpatient eating disorders unit. The implications of ARFID exacerbated by stimulant-treated ADHD are explored, as well as the treatment delivered. These cases suggest that further research is needed to explore management options to counteract the appetite suppression effects of stimulants, while simultaneously addressing attention deficit symptoms and oppositional behavior. -® 2016 Wiley Periodicals, Inc. (Int J Eat Disord 2016; 49:1036ΓÇô1039)

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Int J Psychophysiol. 2016.

**THETA/BETA NEUROFEEDBACK IN CHILDREN WITH ADHD: FEASIBILITY OF A SHORT-TERM SETTING AND PLASTICITY EFFECTS.**

***Van Doren J, Heinrich H, Bezold M, et al.***

Neurofeedback (NF) is increasingly used as a therapy for attention-deficit/hyperactivity disorder (ADHD), however behavioral improvements require 20 plus training sessions. More economic evaluation strategies are needed to test methodological optimizations and mechanisms of action. In healthy adults, neuroplastic effects have been demonstrated directly after a single session of NF training. The aim of our study was to test the feasibility of short-term theta/beta NF in children with ADHD and to learn more about the mechanisms underlying this protocol.Children with ADHD conducted two theta/beta NF sessions. In the first half of the sessions, three NF trials (puzzles as feedback animations) were run with pre- and post-reading and picture search tasks. A significant decrease of the theta/beta ratio (TBR), driven by a decrease of theta activity, was found in the NF trials of the second session demonstrating rapid and successful neuroregulation by children with ADHD.For pre-post comparisons, children were split into good vs. poor regulator groups based on the slope of their TBR over the NF trials. For the reading task, significant EEG changes were seen for the theta band from pre- to post-NF depending on individual neuroregulation ability. This neuroplastic effect was not restricted to the feedback electrode Cz, but appeared as a generalized pattern, maximal over midline and right-hemisphere electrodes.Our findings indicate that short-term NF may be a valuable and economical tool to study the neuroplastic mechanisms of targeted NF protocols in clinical disorders, such as theta/beta training in children with ADHD

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Iranian Journal of Psychiatry and Clinical Psychology. 2016;21:317-26.

**PSYCHOMETRIC PROPERTIES OF A PERSIAN SELF-REPORT VERSION OF SWANSON, NOLAN AND PELHAM RATING SCALE (VERSION IV) FOR SCREENING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADOLESCENTS.**

***Kiania B, Hadianfard H.***

**Objectives**: The aim of the current study was to reconstruct develope and evaluate the validity and reliability of a persian Self-Report version of Swanson, Nolan and Pelham Rating Scale (version IV) (SNAP-IV).

**Method**: The study population consisted of all 13 to 15 years female students of Shiraz city. To prepare the persian self-report form of SNAP-IV rating scale, the English text of the scale (parent form) was translated into Farsi. Then some changes were made in the transalted text in line with self-reporting form of the scale. Content, response framework, and expressiveness of Persian form were confirmed by psychologists referrees. Then, 290 students who were selected through convenient sampling method completed the questionnaire. To assess construct validity, the Letter-Number Sequencing subtest was conducted on 30 students. Also, SNAP-IV rating scale (parent form) was given to the parents of these 30 students. Data were analyzed using descriptive statistics (mean, standard deviation and skewness), Pearson's correlation and exploratory factor analysis.

**Results**: The results of the confirmatory factor analysis revealed two distinct factors of inattention and hyperactivity/impulsivity. These two factors explained 38.23% of total variance. Cronbach's alpha coefficient, Spearman- Brown coefficient and Guttman split-half coefficient for inattention dimension were 0.81, 0.81 and 0.80, respectively and for hyperactivity/impulsivity were 0.75, 0.65 and 0.64, respectively.

**Conclusion**: Based on the results the persian Self-Report version of the SNAP-IV can be used for assessing and screening adolescents with attention deficit/hyperactivity disorder.

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J Abnorm Psychol. 2016.

**NARRATIVE PRODUCTION IN CHILDREN WITH AUTISM SPECTRUM DISORDER (ASD) AND CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): SIMILARITIES AND DIFFERENCES.**

***Kuijper SJM, Hartman CA, Bogaerds-Hazenberg STM, et al.***

The present study focuses on the similarities and differences in language production between children with autism spectrum disorder (ASD) and children with attention-deficit/hyperactivity disorder (ADHD). In addition, we investigated whether Theory of Mind (ToM), working memory, and response inhibition are associated with language production. Narratives, produced by 106 Dutch-speaking children (36 with ASD, 34 with ADHD, and 36 typically developing) aged 6 to 12 during ADOS assessment, were examined on several linguistic measures: verbal productivity, speech fluency, syntactic complexity, lexical semantics, and discourse pragmatics. Children were tested on ToM, working memory, and response inhibition and parents filled in the Children's Communication Checklist (CCC-2). Gold-standard diagnostic measures (Autism Diagnostic Observation Schema [ADOS], Autism Diagnostic Interview Revised [ADI-R], and the Parent Interview for Child Symptoms [PICS]) were administered to all children to confirm diagnosis. Regarding similarities, both clinical groups showed impairments in narrative performance relative to typically developing children. These were confirmed by the CCC-2. These impairments were not only present on pragmatic measures, such as the inability to produce a narrative in a coherent and cohesive way, but also on syntactic complexity and their production of repetitions. As for differences, children with ADHD but not children with ASD showed problems in their choice of referring expressions and speech fluency. ToM and working memory performance but not response inhibition were associated with many narrative skills, suggesting that these cognitive mechanisms explain some of the impairments in language production. We conclude that children with ASD and children with ADHD manifest multiple and diverse language production problems, which may partly relate to their problems in ToM and working memory.

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J Abnorm Psychol. 2016.

**SEX MODERATES THE IMPACT OF BIRTH WEIGHT ON CHILD EXTERNALIZING PSYCHOPATHOLOGY.**

***Momany AM, Kamradt JM, Ullsperger JM, et al.***

Low birth weight (LBW) has consistently been associated with childhood attention deficit/hyperactivity disorder (ADHD), and a similar association has been found for childhood externalizing disorders, such as oppositional defiant disorder (ODD) and conduct disorder (CD), albeit to a lesser degree. Although the association between LBW and these disorders has been robustly replicated, few studies have adequately controlled for confounding variables, such as parental age at birth and prenatal tobacco use, examined the specificity of the risk of LBW for ADHD symptoms, or investigated potential nonlinear (i.e., quadratic) effects of birth weight (BW). Additionally, the extent to which LBW confers risk for these disorders depending on childhood sex has rarely been examined. The current study examined associations between BW and ADHD, ODD, and CD symptom dimensions as well as the extent to which such associations are moderated by child sex, while also controlling for confounding variables. Significant interactions between sex and BW emerged across all analyses predicting ADHD and externalizing psychopathology, such that associations were stronger in males relative to females. Results remained when controlling for a number of confounds, including parental age, prenatal tobacco use, comorbid psychopathology, as well as other indicators of maternal and child health during the pre- and perinatal period. Both linear and quadratic associations emerged between BW and both hyperactivity and CD symptoms, whereas BW predicted inattention and ODD symptoms in a linear fashion. Future research should continue to investigate the impact of BW on ADHD and externalizing psychopathology, in particular, the biological mechanisms underlying this association.

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J Affective Disord. 2016.

**EMPIRICALLY DERIVED PATTERNS OF PSYCHIATRIC SYMPTOMS IN YOUTH: A LATENT PROFILE ANALYSIS.**

***Kircanski K, Zhang S, Stringaris A, et al.***

**Background**: By conceptualizing domains of behavior transdiagnostically, the National Institute of Mental Health Research Domain Criteria (NIMH RDoC) initiative facilitates new ways of studying psychiatric symptoms. In this study, latent profile analysis (LPA) was used to empirically derive classes or patterns of psychiatric symptoms in youth that transect traditional nosologic boundaries.

**Methods**: Data were drawn from 509 children and adolescents (ages 7-18 years; mean age =12.9 years; 54% male) who were evaluated in the NIMH Emotion and Development Branch and were heterogeneous with respect to presenting diagnoses and symptoms. Youth and/or their parents completed measures of several core symptom dimensions: irritability, anxiety, depression, and attention deficit hyperactivity disorder (ADHD). LPA was used to parse response patterns into distinct classes, based on the levels of, and interrelations among, scores on the different measures.

**Results**: Five classes emerged: low levels of symptomatology (52% of sample); anxiety and mild depressive symptoms (17%); parent-reported irritability and ADHD (16%); irritability and mixed comorbid symptoms (10%); and high levels of irritability, anxiety, depression, and ADHD (5%). Importantly, these latent classes cut across informants and the clinical conditions for which youth were initially evaluated. Further, the classes characterized by irritability exhibited the poorest overall functioning.

**Limitations**: These data were cross-sectional. Examination of external validators, including neurobiological correlates and symptom course, is warranted.

**Conclusions**: Results inform our understanding of the structure of psychiatric symptoms in youth and suggest new ways to operationalize psychopathology and examine it in relation to neurobiology

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J Behav Educ. 2016 Dec;25:478-97.

**A SINGLE-SUBJECT STUDY OF A TECHNOLOGY-BASED SELF-MONITORING INTERVENTION.**

***Vogelgesang KL, Bruhn AL, Coghill-Behrends WL, et al.***

Students with ADHD often struggle with self-regulation skills. One strategy demonstrating considerable success in helping these students regulate their behavior is self-monitoring. Although there is an abundance

of research on self-monitoring, research on the use of technology for self-monitoring is only beginning to emerge. The primary goal of this single-subject study was to examine the effects of an iPad application (SCORE IT) for self-monitoring on the behavior of three fifth-grade students with or at risk for ADHD who were exhibiting low rates of academic engagement in a general education environment. A secondary goal was to gain an in-depth understanding of the teacher's perceptions of the feasibility and value of the intervention. Overall, the SCORE IT intervention resulted in substantial improvements in academic engagement, and teacher perceptions of the feasibility and worth of the intervention were reported as highly favorable. Limitations and future directions for research are discussed

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J Child Adolesc Psychopharmacol. 2016;26:889-99.

**IMPACT OF STIMULANT MEDICATION USE ON HEART RATE AND SYSTOLIC BLOOD PRESSURE DURING SUBMAXIMAL EXERCISE TREADMILL TESTING IN ADOLESCENTS.**

***Westover AN, Nakonezny PA, Adinoff B, et al.***

**Objectives**: Inappropriately decreased heart rate (HR) during peak exercise and delayed heart rate recovery (HRR) has been observed in adult users of stimulant medications who underwent exercise testing, suggesting autonomic adaptation to chronic stimulant exposure. In the general population, this pattern of hemodynamic changes is associated with increased mortality risk. Whether the same pattern of hemodynamic changes might be observed in adolescent stimulant medication users undergoing exercise testing is unknown.

**Methods**: Among adolescents (aged 12 to 20 years) that underwent submaximal exercise treadmill testing from 1999 to 2004 in the National Health and Nutrition Examination Survey, propensity score matching of stimulant medication users (n = 89) to matched nonusers (n = 267) was conducted. Testing consisted of a 3-minute warm-up period, two 3-minute exercise stages, and three 1-minute recovery periods, with the goal of reaching 75% of the predicted HR maximum. A linear mixed model analysis was used to evaluate the effect of stimulant exposure on each of the exercise outcomes.

**Results**: Stimulant medication users compared to matched nonusers had a lower peak HR in Stage 2 (154.9 vs. 158.3 beats/minute [bpm], p = 0.055) and lower HR at 1-minute recovery (142.2 vs. 146.4 bpm, p = 0.030). However, submaximal HRR at 1 minute did not differ between stimulant users and matched nonusers (13.0 vs. 12.1 bpm, p = 0.38). Duration of stimulant use was not related to these outcomes.

**Conclusion**: Adolescent stimulant medication users compared to matched nonusers demonstrated a trend toward decreased HR during submaximal exercise, which is potential evidence of chronic adaptation with stimulant exposure. There was no evidence for delayed HRR in this study, and thus, no evidence for decreased parasympathetic activity during initial exercise recovery. Exercise testing outcomes may have utility in future research as a method to assess stimulant-associated autonomic nervous system adaptations

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J Child Adolesc Psychopharmacol. 2016;26:882-88.

**ACUTE AND LONG-TERM CARDIOVASCULAR EFFECTS OF STIMULANT, GUANFACINE, AND COMBINATION THERAPY FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Sayer GR, McGough JJ, Levitt J, et al.***

**Objectives**: This study examines cardiovascular (CV) effects of guanfacine immediate-release (GUAN-IR), dexmethylphenidate extended-release (DMPH), and their combination (COMB) during acute and long-term treatment of youth with attention-deficit/hyperactivity disorder.

**Methods**: Two hundred seven participants aged 7-14 years enrolled in an 8-week double-blind randomized trial of GUAN-IR (1-3 milligrams (mg)/day), DMPH (5-20 mg/day), or COMB with fixed-flexible dosing and titrated to optimal behavioral response. Heart rate, systolic blood pressure (BP), diastolic BP, and electrocardiograms were assessed at baseline, end of blinded optimization, and over a 1-year open-label maintenance phase.

**Results**: During acute titration, GUAN-IR decreased heart rate, systolic BP, and diastolic BP; DMPH increased heart rate, systolic BP, diastolic BP, and corrected QT (QTc) interval; COMB increased diastolic

BP, but had no effects on heart rate, systolic BP, or QTc. During maintenance, GUAN-IR-associated decreases in heart rate and DMPH-associated increases in systolic BP returned to baseline values. Other variables across the three groups remained unchanged from the end of blinded titration. There were no discontinuations due to CV adverse events.
**Conclusion**: GUAN-IR, DMPH, and COMB were well tolerated and safe. Expected changes in CV parameters during acute titration were seen in GUAN-IR and DMPH groups, with COMB values falling intermediately between the two other treatment groups. No serious CV events occurred in any participant. GUAN-IR- and DMPH-associated CV changes generally returned to baseline with sustained therapy. These data suggest that COMB treatment might attenuate long-term CV effects of GUAN-IR and stimulant monotherapy, possibly reducing risk of the small but statistically significant changes associated with either single treatment. Clinicaltrials.gov Identifier: NCT00429273

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J Child Adolesc Psychopharmacol. 2016;26:873-81.
**EFFECT OF APTENSIO XR (METHYLPHENIDATE HCL EXTENDED-RELEASE) CAPSULES ON SLEEP IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**
***Owens J, Weiss M, Nordbrock E, et al.***
**Objective**: To evaluate measures of sleep (exploratory endpoints) in two pivotal studies of a multilayer bead extended-release methylphenidate (MPH-MLR) treatment of attention-deficit/hyperactivity disorder in children.
**Methods**: Study 1 evaluated the time course of response to MPH-MLR (n = 26) patients in an analog classroom setting through four phases: screening (Γëñ28 days), open label (OL) dose optimization (4 weeks), double-blind (DB) crossover (2 weeks; placebo vs. optimized dose), and follow-up call. Study 2 was a forced-dose parallel evaluation of MPH-MLR (n = 230) in four phases: screening (Γëñ28 days), DB (1 week; placebo or MPH-MLR 10, 15, 20, or 40 mg/day), OL dose optimization (11 weeks), and follow-up call. Sleep was evaluated by parents using the Children's or Adolescent Sleep Habits Questionnaire (CSHQ or ASHQ) during the DB and OL phases. DB analysis: Study 1 (crossover), analysis of variance; Study 2, analysis of covariance. OL analysis: paired t-test.
**Results**: DB: treatments were significantly different in Study 1 only for CSHQ Sleep Onset Delay (MPH-MLR, 1.90 vs. placebo, 1.34; p = 0.0046, placebo was better), and Study 2 for CSHQ Parasomnias (treatment, p = 0.0295), but no MPH-MLR treatment was different from placebo (pairwise MPH-MLR treatment to placebo, all p ΓëÑ 0.170). OL: CSHQ total and Bedtime Resistance, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, and Sleep-disordered Breathing subscales decreased (improved, Study 1) significant only for CSHQ Night Wakings (p < 0.05); in Study 2 CSHQ total and Bedtime Resistance, Sleep Duration, Night Wakings, Parasomnias, and Daytime Sleepiness, and ASHQ total, Bedtime, Sleep Behavior, and Morning Waking all significantly improved (p < 0.05).
**Conclusions**: In both studies, there was minimal negative impact of MPH-MLR on sleep during the brief DB phase and none during the longer duration OL phase. Some measures of sleep improved with optimized MPH-MLR dose

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J Child Fam Stud. 2016 Dec;25:3716-27.
**EFFECTS OF THE INCREDIBLE YEARS PROGRAM IN FAMILIES OF CHILDREN WITH ADHD.**
***Lessard J, Normandeau S, Robaey P.***
The efficacy of two parent training programs for families of school-age children diagnosed with attention-deficit/hyperactivity disorder was examined as well as comorbidity as a treatment moderator. Seventy-seven families were assigned to either medication plus the Incredible Years parent training program (parents received on average 26 h of interventions), medication plus a telephone support group (parents received on average 4 h of interventions), or a medication group. Parenting practices were assessed pre-intervention and post-intervention through direct observations and parental self-reports. Results showed that parents in the Incredible Years and telephone support groups reported using more praise and incentives compared to

parents in the medication group. Parents in the Incredible Years group also reported using less harsh and inconsistent discipline compared to parents in the other two groups, while parents in the telephone support reported using less harsh and inconsistent discipline compared to the medication group. Findings from the observational measure indicated that parents in the Incredible Years group used less harsh/negative parenting practices and more positive parenting practices following the intervention compared to parents in the telephone support and medication groups. Comorbidity did not moderate treatment effects. This study provides support for the Incredible Years program combined with medication to improve parenting in families of school-age children diagnosed with attention-deficit/hyperactivity disorder with or without the presence of comorbidity

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J Child Fam Stud. 2016 Dec;25:3644-56.

**RELATIONS BETWEEN PARENTING STRESS, PARENTING STYLE, AND CHILD EXECUTIVE FUNCTIONING FOR CHILDREN WITH ADHD OR AUTISM.**

***Hutchison L, Feder M, Abar B, et al.***

Relations among parenting stress, parenting style, and child executive functioning for children with disabilities are not easily teased apart. The current study explored these relations among 82 children and adolescents age 7–18: 21 with attention deficit/hyperactivity disorder, 33 with autism spectrum disorder, and 28 typically developing. Results indicated that children with attention deficit/hyperactivity disorder or autism spectrum disorder had more executive functioning deficits, and their parents reported more parenting stress and a greater use of permissive parenting, compared to typically developing children. In general, increased parenting stress was associated with greater use of authoritarian and permissive parenting styles, as well as more problems with behavior regulation for children. Authoritarian and permissive parenting styles were associated with poorer child executive functioning. Child diagnostic group (attention deficit/hyperactivity disorder, autism spectrum disorder, typically developing) moderated relations between parent stress and child functioning, and between parenting style and child functioning. Implications for intervention with families of children with disabilities are discussed

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J Child Fam Stud. 2016 Dec;25:3451-61.

**PARENTAL PSYCHOPATHOLOGY IN FAMILIES OF CHILDREN WITH ADHD: A META-ANALYSIS.**

***Cheung K, Theule J.***

Research on the strength of the relationship between parental psychopathology and child attention deficit/hyperactivity disorder is mixed. A meta-analysis was conducted to evaluate the association between parental psychopathology and child attention deficit/hyperactivity disorder and to establish the degree and size of the effect. The present study included 85 published and unpublished studies that included a quantitative comparison between parental psychopathology and child attention deficit/hyperactivity disorder. Parents of children with attention deficit/hyperactivity disorder had higher rates of psychopathology symptoms than parents of children without attention deficit/hyperactivity disorder (d = 0.39, 95 % confidence interval [0.31, 0.48], p < .001, k = 32). Approximately 16.90 % of parents of children with attention deficit/hyperactivity disorder had a mental disorder (95 % confidence interval [14.29, 19.89], p < .001, k = 48). Parents of children with attention deficit/hyperactivity disorder had 2.85 times the odds of parents of children without attention deficit/hyperactivity disorder of having a mental disorder (95 % confidence interval [1.77, 4.59], p < .001, k = 18), whereas parents of children with attention deficit/hyperactivity disorder and co-occurring externalizing disorders had 1.99 times the odds of parents of children with attention deficit/hyperactivity disorder alone of having a mental disorder (95 % confidence interval [0.70, 5.66], p = .195, k = 4). Type of manuscript was the only moderator analysis that was statistically significant (Q = 4.30, p = .038, k = 20). Unpublished manuscripts were associated with larger effect sizes in comparison to published journal articles; however, one of the unpublished manuscripts was identified as an outlier.

The results suggest that clinicians may want to incorporate interventions targeted at addressing a parent's psychopathology when working with families of children with attention deficit/hyperactivity disorder

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J Child Neurol. 2016 Dec;31:1607-10.

**REPEAT CONCUSSION AND RECOVERY TIME IN A PRIMARY CARE PEDIATRIC OFFICE.**

***Taubman B, McHugh J, Rosen F, et al.***

The authors enrolled 95 patients in a primary care office who presented with a concussion. Of these patients, 63% were sport concussions. The authors matched 90 of these patients to children in the authors' practice presenting for sports physicals or regular check-ups in the following demographics: age, participating in a particular sport, having attention-deficit disorder/attention-deficit hyperactivity disorder, gender, and grade. The authors found the odds of recurrent concussions, in a primary care pediatric office, to be a ratio of 2.909 (95% confidence interval 1.228-7.287). Recovery time for repeat concussion versus an initial concussion was analyzed. Patients with a recurrent concussion after a year recovered an average of 12.0 days after injury versus 13.4 days for those with no previous concussion (NS). Patients with a recurrent concussion within a year recovered a mean of 6.27 (SD 1.29) days sooner than patients with no previous concussion ($P < .0001$). This unexpected finding is preliminary, and the authors encourage further research

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J Child Psychol Psychiatry. 2016 Dec;57:1414-23.

**RESPONSE TIME VARIABILITY UNDER SLOW AND FAST-INCENTIVE CONDITIONS IN CHILDREN WITH ASD, ADHD AND ASD+ADHD.**

***Tye C, Johnson KA, Kelly SP, et al.***

**Background**: Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) show significant behavioural and genetic overlap. Both ADHD and ASD are characterised by poor performance on a range of cognitive tasks. In particular, increased response time variability (RTV) is a promising indicator of risk for both ADHD and ASD. However, it is not clear whether different indices of RTV and changes to RTV according to task conditions are able to discriminate between the two disorders.

**Methods**: Children with ASD (n = 19), ADHD (n = 18), ASD + ADHD (n = 29) and typically developing controls (TDC; n = 26) performed a four-choice RT task with slow-baseline and fastincentive conditions. Performance was characterised by mean RT (MRT), standard deviation of RT (SD-RT), coefficient of variation (CV) and ex-Gaussian distribution measures of Mu, Sigma and Tau.

**Results**: In the slow-baseline condition, categorical diagnoses and trait measures converged to indicate that children with ADHD-only and ASD + ADHD demonstrated increased MRT, SD-RT, CV and Tau compared to TDC and ASD-only. Importantly, greater improvement in MRT, SD-RT and Tau was demonstrated in ADHD and ASD + ADHD from slow-baseline to fast-incentive conditions compared to TDC and ASD-only.

**Conclusions**: Slower and more variable RTs are markers of ADHD compared to ASD and typically developing controls during slow and less rewarding conditions. Energetic factors and rewards improve task performance to a greater extent in children with ADHD compared to children with ASD. These findings suggest that RTV can be distinguished in ASD, ADHD and ASD + ADHD based on the indices of variability used and the conditions in which they are elicited. Further work identifying neural processes underlying increased RTV is warranted, in order to elucidate disorder-specific and disorder-convergent aetiological pathways

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J Consult Clin Psychol. 2016;84:1078-93.

**EFFICACY OF A FAMILY-FOCUSED INTERVENTION FOR YOUNG DRIVERS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.**

***Fabiano GA, Schatz NK, Morris KL, et al.***

**Objective**: Teenage drivers diagnosed with attention-deficit/hyperactivity disorder (ADHD) are at significant risk for negative driving outcomes related to morbidity and mortality. However, there are few viable psychosocial treatments for teens with ADHD and none focus on the key functional area of driving. The Supporting the Effective Entry to the Roadway (STEER) program was evaluated in a clinical trial to investigate whether it improved family functioning as a proximal outcome and driving behavior as a distal outcome.

**Method**: One hundred seventy-two teenagers with ADHD, combined type, were randomly assigned to STEER or a driver education driver practice program (DEDP).

**Results**: Relative to parents in the DEDP condition, parents in STEER were observed to be less negative at posttreatment and 6-month follow-up but not at 12-month follow-up, and there were no significant differences for observed positive parenting. Relative to teens in the DEDP condition, teens in STEER reported lower levels of risky driving behaviors at posttreatment and 6-month follow-up, but not at 12-month follow-up. Groups did not differ on objective observations of risky driving or citations/accidents.

**Conclusions**: The STEER program for novice drivers with ADHD was effective in reducing observations of negative parenting behavior and teen self-reports of risky driving relative to DEDP; groups did not significantly differ on observations of positive parenting or driving behaviors

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Journal of Head Trauma Rehabilitation. 2016;31:407-18.

**COGNITIVE INTERVENTION FOR ATTENTION AND EXECUTIVE FUNCTION IMPAIRMENTS IN CHILDREN WITH TRAUMATIC BRAIN INJURY: A PILOT STUDY.**

***Treble-Barna A, Sohlberg MM, Harn BE, et al.***

**Objective**: To test the effectiveness of the Attention Improvement and Management (AIM) program, a cognitive intervention for improving impairments in attention and executive functions (EFs) after pediatric traumatic brain injury (TBI).

**Setting**: Tertiary care children's hospital. Participants: A total of 13 children with complicated mildto-severe TBI (average of 5 years postinjury) and 11 healthy comparison children aged 9 to 15 years completed the study.

**Design**: Open-label pilot study with a nontreated control group. Main

**Measures**: Subtests from the Test of Everyday Attention-for Children (TEA-Ch) and the Delis-Kaplan Executive Function System (D-KEFS), the self-and parent-report from the Behavior Rating Inventory of Executive Function (BRIEF), and the Goal Attainment Scale (GAS).

**Results**: Relative to the healthy comparison group, children with TBI demonstrated significant improvement postintervention on a neuropsychological measure of sustained attention, as well as on parent-reported EFs. The majority of families also reported expected or more-than-expected personalized goal attainment.

**Conclusions**: The study provides preliminary evidence for the effectiveness of AIM in improving parent-reported EFs and personalized real-world goal attainment in children with TBI

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Journal of Immunology Research. 2016;2016.

**ATTENTION DEFICIT DISORDER AND ALLERGIC RHINITIS: ARE THEY RELATED?**

***Melamed I, Heffron M.***

The association between ADHD and allergy remains controversial. Our previous findings suggest that nerve growth factor may link the nervous and immune systems. The primary objective of this study was to determine if a combination of cetirizine + methylphenidate is effective in children with comorbid ADHD and allergic rhinitis. We also examined the role of nerve growth factor in these comorbidities. Our randomized, double-blind, placebo-controlled, crossover study enrolled 38 children diagnosed with comorbid ADHD and allergy

using cetirizine (n=12), sustained-release methylphenidate (n=12), or cetirizine + methylphenidate (n=14). Endpoints compared baseline to posttreatment evaluations for allergic rhinitis and ADHD scores. Serum nerve growth factor levels were measured using ELISA. For allergy endpoints, combination therapy produced results superior to individual therapy. For ADHD, similar scores were achieved for individual therapy; however, combination therapy resulted in improved scores. Nerve growth factor levels were downregulated following this trend. We conclude that ADHD and allergic rhinitis may have common mechanism and represent a comorbid condition that links the nervous system to the immune system. Further studies are needed

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Journal of Mazandaran University of Medical Sciences. 2016;26:80-89.

**COMPARING THE EFFECTIVENESS OF BEHAVIORAL MANAGEMENT TRAINING IN PARENTS AND NARRATIVE THERAPY IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER ON QUALITY OF MOTHER-CHILD RELATIONSHIP.**

***Emadian SO, Bahrami H, Hassanzadeh R, et al.***

**Background and purpose**: Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood that is associated with parent-child conflict and parental stress. The aim of this study was to compare the effectiveness of delivering behavioral management training to parents and narrative therapy to children on the quality of mother-child relationship in children with ADHD.

**Materials and methods**: A quasi-experimental study with pretest-posttest and control group was performed. The research population included all children aged 7 to 12 years old with ADHD and their mothers in Sari, Iran. A total of 30 cases were selected and divided into three groups. The mothers in first group attended nine sessions of behavioral management training which were presented according to BarkleyΓÇÖs pattern. Group narrative therapy was done among children in second group for eight sessions, while the third group received no training. Parent-child Stress Index was used for data collection.

**Results**: The results showed that the mean of post-test score for parent-child conflict in first group was 78.11-¦16.78 and in narrative therapy group was 76.9-¦13.92, indicating no significant difference between these two groups, but the score in control group was 96.22-¦22.95 that was significantly higher compared with the experimental groups (P<0.05).

**Conclusion**: The results showed no significant difference between behavioral management training to parents and narrative therapy in improving the quality of mother-child relationship in children with ADHD and compared with the control group, both methods were found to be significantly effective in improving the quality of mother-child relationships

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Journal of Medical Toxicology. 2016;12:402-05.

**AN INFANT WITH A PROLONGED SYMPATHOMIMETIC TOXIDROME AFTER LISDEXAMFETAMINE DIMESYLATE INGESTION.**

***Wood KE, Krasowski MD.***

**Introduction**: Stimulant medications are approved to treat attention deficit hyperactivity disorder (ADHD) in children over the age of 6-áyears. Fatal ingestion of stimulants by children has been reported, although most ingestions do not result in severe toxicity. Lisdexamfetamine dimesylate, a once daily long-acting stimulant, is a prodrug requiring conversion to its active form, dextroamphetamine, in the bloodstream. Based on its unique pharmacokinetics, peak levels of d-amphetamine are delayed. We describe a case of accidental ingestion of lisdexamfetamine dimesylate in an infant.

**Case Report**: A previously healthy 10-month-old infant was admitted to the hospital with a 5-h history of tachycardia, hypertension, dyskinesia, and altered mental status of unknown etiology. Confirmatory urine testing, from a specimen collected approximately 16-h after the onset of symptoms, revealed an urine amphetamine concentration of 22,312-ng/mL (positive cutoff 200-ng/mL). The serum amphetamine concentration, from a specimen collected approximately 37-h after the onset of symptoms, was 68-ng/mL (positive cutoff 20-ng/mL). Urine and serum were both negative for methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA, Ecstasy), and

methylenedioxyethamphetamine (MDEA). During the hospitalization, it was discovered that the infant had access to lisdexamfetamine dimesylate prior to the onset of symptoms.
**Conclusion**: Amphetamine ingestions in young children are uncommon but do occur. Clinicians should be aware of signs and symptoms of amphetamine toxicity and consider ingestion when a pediatric patient presents with symptoms of a sympathetic toxidrome even when ingestion is denied

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J Neural Transm. 2016;1-13.

**STRUCTURAL BRAIN IMAGING CORRELATES OF ASD AND ADHD ACROSS THE LIFESPAN: A HYPOTHESIS-GENERATING REVIEW ON DEVELOPMENTAL ASD□ADHD SUBTYPES.**

***Rommelse N, Buitelaar JK, Hartman CA.***

We hypothesize that it is plausible that biologically distinct developmental ASDΓÇôADHD subtypes are present, each characterized by a distinct time of onset of symptoms, progression and combination of symptoms. The aim of the present narrative review was to explore if structural brain imaging studies may shed light on key brain areas that are linked to both ASD and ADHD symptoms and undergo significant changes during development. These findings may possibly pinpoint to brain mechanisms underlying differential developmental ASDΓÇôADHD subtypes. To this end we brought together the literature on ASD and ADHD structural brain imaging symptoms and particularly highlight the adolescent years and beyond. Findings indicate that the vast majority of existing MRI studies has been cross-sectional and conducted in children, and sometimes did include adolescents as well, but without explicitly documenting on this age group. MRI studies documenting on age effects in adults with ASD and/or ADHD are rare, and if age is taken into account, only linear effects are examined. Data from various studies suggest that a crucial distinctive feature underlying different developmental ASDΓ ÇôADHD subtypes may be the differential developmental thinning patterns of the anterior cingulate cortex and related connections towards other prefrontal regions. These regions are crucial for the development of cognitive/effortful control and socio-emotional functioning, with impairments in these features as key to both ASD and ADHD

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J Neurodevelopmental Disord. 2016 Dec;8.

**INVESTIGATING THE EFFECTS OF COPY NUMBER VARIANTS ON READING AND LANGUAGE PERFORMANCE.**

***Gialluisi A, Visconti A, Willcutt EG, et al.***

**Background**: Reading and language skills have overlapping genetic bases, most of which are still unknown. Part of the missing heritability may be caused by copy number variants (CNVs).
**Methods**: In a dataset of children recruited for a history of reading disability (RD, also known as dyslexia) or attention deficit hyperactivity disorder (ADHD) and their siblings, we investigated the effects of CNVs on reading and language performance. First, we called CNVs with PennCNV using signal intensity data from Illumina OmniExpress arrays (~723,000 probes). Then, we computed the correlation between measures of CNV genomic burden and the first principal component (PC) score derived from several continuous reading and language traits, both before and after adjustment for performance IQ. Finally, we screened the genome, probe-by-probe, for association with the PC scores, through two complementary analyses: we tested a binary CNV state assigned for the location of each probe (i.e., CNV+ or CNV-), and we analyzed continuous probe intensity data using FamCNV.
**Results**: No significant correlation was found between measures of CNV burden and PC scores, and no genome-wide significant associations were detected in probe-by-probe screening. Nominally significant associations were detected (p~10-2–10-3) within CNTN4 (contactin 4) and CTNNA3 (catenin alpha 3). These genes encode cell adhesion molecules with a likely role in neuronal development, and they have been previously implicated in autism and other neurodevelopmental disorders. A further, targeted assessment of candidate CNV regions revealed associations with the PC score (p~0.026–0.045) within CHRNA7 (cholinergic nicotinic receptor alpha 7), which encodes a ligand-gated ion channel and has also been implicated in neurodevelopmental conditions and language impairment. FamCNV analysis detected a region

of association (p~10-2–10-4) within a frequent deletion ~6 kb downstream of ZNF737 (zinc finger protein 737, uncharacterized protein), which was also observed in the association analysis using CNV calls.
**Conclusions**: These data suggest that CNVs do not underlie a substantial proportion of variance in reading and language skills. Analysis of additional, larger datasets is warranted to further assess the potential effects that we found and to increase the power to detect CNV effects on reading and language

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J Obsessive-Compulsive Relat Disord. 2017;12:1-8.

**THE LINK BETWEEN ADHD-LIKE INATTENTION AND OBSESSIONS AND COMPULSIONS DURING TREATMENT OF YOUTH WITH OCD.**

***Guzick AG, McNamara JPH, Reid AM, et al.***

Attention-deficit/hyperactivity disorder (ADHD) has been found to be highly comorbid in children and adolescents with obsessive-compulsive disorder (OCD). Some have proposed, however, that obsessive anxiety may cause inattention and executive dysfunction, leading to inappropriate ADHD diagnoses in those with OCD. If this were the case, these symptoms would be expected to decrease following successful OCD treatment. The present study tested this hypothesis and evaluated whether ADHD symptoms at baseline predicted OCD treatment response. Obsessive-compulsive and ADHD symptoms were assessed in 50 youth enrolled in a randomized controlled trial investigating selective serotonin reuptake inhibitor and cognitive behavioral treatment. Repeated-measures analysis of variance (RMANOVA) revealed that ADHD symptoms at baseline do not significantly predict treatment outcome. A multivariate RMANOVA found that OCD treatment response moderated change in inattention; participants who showed greater reduction in OCD severity experienced greater reduction in ADHD-inattentive symptoms, while those with less substantial reduction in obsessions and compulsions showed less change. These findings suggest that children and adolescents with OCD and inattention may experience meaningful improvements in attention problems following OCD treatment. Thus, in many youth with OCD, inattention may be inherently tied to obsessions and compulsions. Clinicians may consider addressing OCD in treatment before targeting inattentive-type ADHD

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J Pediatr Endocrinol Metab. 2016;29:1293-97.

**PREVALENCE OF MEDICALLY TREATED CHILDREN WITH ADHD AND TYPE 1 DIABETES IN GERMANY - ANALYSIS OF TWO REPRESENTATIVE DATABASES.**

***Kapellen TM, Reimann R, Kiess W, et al.***

**Background**: The aim of this study was to analyze the prevalence of attention deficit hyperactivity disorder (ADHD) in children and adolescents with type 1 diabetes mellitus (T1DM) in Germany.
**Methods**: Two different representative German databases - IMS-«-Disease Analyzer, a database that includes diagnoses as well as other information, and IMS-«-LRx, a database that documents prescriptions - were used to conduct a retrospective analysis. We searched the LRx database for patients who received both insulin and ADHD-specific medication.
**Results**: In 2014, 677,587 children and adolescents aged 0-18 years were treated by a pediatrician and documented in the Disease Analyzer database. Of these patients, 16,833 received the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis of ADHD (2.5%) and 3668 patients were treated for T1DM (0.1%). Of these 3668 patients, a total of 153 children were also diagnosed with ADHD (4.2%; $p<0.05$). In the LRx database, the overall prevalence of children in Germany who received both drugs for the treatment of ADHD and insulin in 2014 amounted to 2.9%. Diagnosis of ADHD is 2.4-3.3 times more frequent in boys than in girls. The highest prevalence was seen in the age group of 12-15 years (3.5%) and the lowest in the age group of 6-11 years (2.5%).
**Conclusions**: Children with diabetes suffer from ADHD significantly more frequently than children without diabetes. The prevalence of medically treated children with ADHD and diabetes is similar to that documented in a recent report by the Barmer GEK health insurance body. However, it is possible that children with T1DM

are much more frequently seen by medical care providers and are thus more likely to be evaluated and receive an appropriate diagnosis

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J Psychiatr Res. 2017;87:30-36.

**PARENTAL WARMTH AND PSYCHIATRIC DISORDERS AMONG PUERTO RICAN CHILDREN IN TWO DIFFERENT SOCIO-CULTURAL CONTEXTS.**

***Santesteban-Echarri O, Ramos-Olazagasti MA, Eisenberg RE, et al.***

**Background** Parental warmth (PW) has a strong influence on child development and may precede the onset of psychiatric disorders in children. PW is interconnected with other family processes (e.g., coercive discipline) that may also influence the development of psychiatric disorders in children. We prospectively examined the association between PW and child psychiatric disorders (anxiety, major depression disorder, ADHD, disruptive behavior disorders) over the course of three years among Puerto Rican youth, above and beyond the influence of other family factors.

**Methods** Boricua Youth Study participants, Puerto Rican children 5 to 13 years of age at Wave 1 living in the South Bronx (New York) (SB) and San Juan and Canguas (PR) (n = 2,491), were followed for three consecutive years. Youth psychiatric disorders were measured by the Diagnostic Interview Schedule for Children-IV (DISC-IV). Generalized Linear Mixed models tested the association between PW (Wave 1) and psychiatric disorders in the next two years adjusting for demographic characteristics and family processes.

**Results** Higher levels of PW were related to lower odds of child anxiety and major depressive disorder over time (OR = 0.69[0.60; 0.79]; 0.49[0.41; 0.58], respectively). The strength of the association between PW and ADHD and disruptive behavior disorder declined over time, although it was still significant in the last assessment (OR = 0.44[0.37; 0.52]; 0.46[0.39; 0.54], respectively). PW had a unique influence on psychiatric disorders beyond the influence of other parenting and family processes. Stronger associations were observed among girls for depression and ADHD.

**Conclusions** Incorporating PW behaviors such as acceptance, support, and comforting into interventions focused on parenting skills may help prevent child psychiatric disorders

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J Psychiatr Res. 2017;85:49-55.

**EXAMINING THE ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SUBSTANCE USE DISORDERS: A FAMILIAL RISK ANALYSIS.**

***Yule AM, Martelon M, Faraone SV, et al.***

**Objective** The main aim of this study was to use familial risk analysis to examine the association between attention deficit hyperactivity disorder (ADHD) and substance use disorders (SUDs) attending to sex effects and the specificity of alcohol and drug use disorder risks.

**Methods** Subjects were derived from two longitudinal case-control family studies of probands aged 6 ΓÇô17 years with and without DSM-III-R ADHD of both sexes and their first degree relatives followed from childhood onto young adult years. Cox proportional hazard models were used to estimate rates of ADHD and SUDs (any SUD, alcohol dependence, and drug dependence). Logistic regression was used to test both co-segregation and assortative mating.

**Results** Our sample included 404 probands (ADHD: 112 boys and 96 girls; Control: 105 boys and 91 girls) and their 1336 relatives. SUDs in probands increased the risk for SUDs in relatives irrespective of ADHD status. The risk for dependence to drug or alcohol in relatives was non-specific. There was evidence that even in the absence of a SUD in the proband, ADHD by itself increased the risk of SUDs in relatives. Proband sex did not moderate the familial relationship between ADHD and SUDs. There was evidence of co-segregation between ADHD and SUD.

**Conclusions** Findings indicate that various independent pathways are involved in the transmission of SUD in ADHD and that these risks were not moderated by proband sex. ADHD children and siblings should benefit from preventive and early intervention strategies to decrease their elevated risk for developing a SUD

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Journal of Psychologists and Counsellors in Schools. 2016 Dec;26:155-65.

**THE MENTAL EFFORT-REWARD IMBALANCES MODEL AND ITS IMPLICATIONS FOR BEHAVIOUR MANAGEMENT.**

***Poulton A, Whale S, Robinson J.***

Attention deficit hyperactivity disorder (ADHD) is frequently associated with oppositional defiant disorder (ODD). The Mental Effort Reward Imbalances Model (MERIM) explains this observational association as follows: in ADHD a disproportionate level of mental effort is required for sustaining concentration for achievement; in ODD the subjective experience of reward for achievement is less than normal. In combination, these mechanisms predispose to reductions in motivation and achievement, and to low mood, oppositional behaviour, and reward seeking. Self-regulation has been used as a management strategy in ADHD, with interventions directed towards encouraging individuals to evaluate and reinforce positive behaviour. Using the logic of the MERIM, self-management strategies would be directed towards encouraging the individual to attribute value to a task or activity with the goal of obtaining the emotional outcome of feeling good about themselves through their achievement. We describe the use of two such strategies: positive rumination and positive reappraisal. These could potentially lead to improvements in functioning, enhancing the quality of life of affected individuals and resulting in fewer incidents of destructive, reward-seeking behaviour in relation to those around them

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J Am Acad Child Adolesc Psychiatry. 2016;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, Roy A, 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 parentchild 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-á= 0.09, p-á=.003). Childhood IQ, socioeconomic status, parental education, and parentchild 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;55:1027-37.

**COMPARING BRAIN MORPHOMETRY ACROSS MULTIPLE CHILDHOOD PSYCHIATRIC DISORDERS.**

***Gold AL, Brotman MA, Adleman NE, et al.***

**Objective** In both children and adults, psychiatric illness-is associated with structural brain alterations, particularly in the prefrontal cortex (PFC). However, most-studies compare gray matter volume (GMV) in healthy volunteers (HVs) to one psychiatric group. We compared GMV among youth with anxiety disorders, bipolar-ádisorder (BD), disruptive mood dysregulation disorder (DMDD), attention-deficit/hyperactivity disorder (ADHD), and HVs.

**Method** 3-Tesla T1-weighted magnetic resonance imaging scans were acquired in 184 youths (39 anxious, 20 BD, 52 DMDD, 20 ADHD, and 53 HV). Voxel-based morphometry analyses were conducted. One-way analysis of variance tested GMV differences with whole-brain familywise error (p-<.05) correction; secondary, exploratory whole-brain analyses used a threshold of p-<-.001,-áΓëÑ200 voxels. Given recent frameworks advocating dimensional approaches in psychopathology research, we also tested GMV associations with continuous anxiety, irritability, and inattention symptoms.

**Results** Specificity emerged in the left dorsolateral PFC (dlPFC), which differed among youth with BD, anxiety, and HVs; GMV was increased in youth with anxiety, but decreased in BD, relative to HVs. Secondary analyses revealed BD-specific GMV decreases in the right lateral PFC, right dlPFC, and dorsomedial PFC, and also anxiety-specific GMV increases in the left dlPFC, right ventrolateral PFC, frontal pole, and right parahippocampal gyrus/lingual gyrus. Both BD and DMDD showed decreased GMV relative to HVs in the right dlPFC/superior frontal gyrus. GMV was not associated with dimensional measures of anxiety, irritability, or ADHD symptoms.

**Conclusion** Both disorder-specific and shared GMV differences manifest in pediatric psychopathology. Some differences were specific to anxiety disorders, others specific to BD, and others shared between BD and DMDD. Further developmental research might map commonalities and differences of structure and function in diverse pediatric psychopathologies

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J Can Acad Child Adolesc Psychiatry. 2016;25:136-37.

**STIMULANTS USE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) KIDS TRIUMPH OR TRIBULATION?**

***Naguy A.***

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J Can Acad Child Adolesc Psychiatry. 2016;25:185-95.

**DIFFERENCES IN REAL WORLD EXECUTIVE FUNCTION BETWEEN CHILDREN WITH PEDIATRIC BIPOLAR DISORDER AND CHILDREN WITH ADHD.**

***Passarotti AM, Trivedi N, Dominguez-Colman L, et al.***

**Background**: Recent research evidence suggests that executive function (EF) is impaired in both pediatric bipolar disorder (PBD) and attention deficit-hyperactivity disorder (ADHD), although the underlying cognitive mechanisms are still unclear. In this study we examined EF, including cognitive and emotional control, in three pediatric groups with overlapping symptoms.

**Methods**: Sixteen children and adolescents with PBD, 17 children and adolescents with ADHD, Type Combined, and 13 children and adolescents with PBD and comorbid ADHD (PBD+ADHD) (mean age=12.70, SD=2.21) were assessed using the Behavioral Rating Inventory of Executive Function ΓÇô Parental Report (BRIEF-PR), clinical scales and neuropsychological tests of attention, working memory and executive function.

**Results**: All groups showed impairment on the Trails A and B tests. However, there were no significant group differences. On the BRIEF-PR while all three groups were impaired in General Executive Functioning and Metacognition only the two PBD groups revealed more extensive EF dysfunction, in both cognitive and emotional control domains, relative to the ADHD group. Conversely, the ADHD group exhibited selective deficits in cognitive domains such as working memory, planning/organization, monitoring, and metacognition. The two PBD groups showed greater impairment than the ADHD group in the domains of Inhibition, Shifting,

Monitoring and Emotional Control. Furthermore, results from regression analyses suggest cognitive predictors of EF impairment in ADHD and mood predictors for inhibition in PBD.
**Conclusions**: The current results contribute new knowledge on domain-specific similarities and differences in executive dysfunction between PBD, ADHD, and the comorbid phenotype, which may inform the diagnostic process and cognitive intervention

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J Can Acad Child Adolesc Psychiatry. 2016;25:145-51.
**SLEEP DISTURBANCES IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD): COMPARATIVE STUDY WITH HEALTHY SIBLINGS.**
***Vaidyanathan S, Shah H, Gayal T.***
**Objectives**: Sleep disturbances in children with ADHD impact their functioning and overall Quality of Life. This paperΓÇÖs purpose is to study the occurrence of sleep disturbances in children with ADHD, in comparison to their healthy siblings and further, within the ADHD group, to look for correlation between sleep disturbances and age, severity of symptoms, presentations of ADHD and illness parameters.
**Methods**: The parents of 120 children of age group between 5-16 years, (60 children diagnosed with ADHD as per DSM-5 criteria and 60 of their healthy siblings) consecutively enrolled from a hospitalΓÇÖs Child Psychiatry Outpatient services were interviewed using Child Sleep Habits Questionnaire (CSHQ) and severity of ADHD symptoms was rated using ADHD RS.
**Results**: Sleep disturbances are more prevalent in pharmacologically treated children with ADHD than their healthy siblings, reduce with increasing age and are found more in the Predominantly Hyperactive/impulsive presentation of ADHD.
**Conclusion**: Sleep disturbances are more prevalent in pharmacologically treated ADHD, making it an important aspect of ADHD management

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Klin Psikofarmakol Bul. 2016;26:426-28.
**TOPIRAMATE IN THE ADJUNCT-¦VE TREATMENT OF TOURETTE SYNDROME: A CASE REPORT.**
***Onen O, Ozek Erkuran H.***
Tourette Syndrome (TS) is an inherited neuropsychiatric disorder with onset in childhood, characterized by multiple motor tics and at least one vocal tic. In many of the cases, Attention Deficit Hyperactivity Disorder (ADHD) is a frequent comorbid disorder. Many treatment options have been suggested for TS and ADHD comorbidity. In this article, we present a case diagnosed with TS and ADHD whose tics were refractory to many other suggested treatment options for Tic Disorders (TD) and worsened during the use of recommended first-line treatment agents for ADHD, that were significantly reduced by using topiramate. New therapeutic options that would be easily used and with less side effects are needed in the treatment of TD. Topiramate treatment seems like an appropriate option raising hope for the future to be used as monotherapy or in adjuvant treatment for TD. Larger trials with longer follow up are required in this field

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Med Sommeil. 2016;13:150-56.
**DIAGNOSING THE HYPERACTIVE CHILD WHO SNORES.**
***Bioulac S, Chalumeau F, Lode-Kolz K.***
Attention deficit hyperactivity disorder (ADHD) is a common disorder, often associated with sleep disorders. Patients with primary sleep disorders often present hyperactivity and/or attention deficit symptoms. Indeed, obstructive sleep disorder breathing (snoring, hypoventilation disorder, and obstructive sleep apnea syndrome) with poor sleep quality can mimic ADHD in children. In this case, inattention and hyperactivity behavior are induced by sleep disorders but do not constitute a clinical diagnosis of ADHD. Therefore, it can sometimes be difficult for the clinician to distinguish between a diagnosis of ADHD with comorbid sleep disorder and a sleep disorder that mimics ADHD symptoms. The objective of this article is to review the

relations between ADHD and obstructive sleep disorder breathing and propose a decision tree to help diagnosis

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Monogr Soc Res Child Dev. 2016 Dec;81:96-110.

**THE CHANGING NATURE OF EXECUTIVE CONTROL IN PRESCHOOL: V. ELUCIDATING NEW PATHWAYS TO DIMENSIONS OF ADHD SYMPTOMS IN PRESCHOOL BY JOINTLY MODELING EXECUTIVE CONTROL AND FOUNDATIONAL COGNITIVE ABILITIES.**

***Nelson JM, James TD, Espy KA.***

In the current study, we aimed to take a further step beyond utilizing traditional latent models of executive control (EC) and employ the bifactor modeling approach described earlier in this volume. Using the bifactor to parse the contributions of latent EC and foundational cognitive abilities to executive task performance allowed us to evaluate the more unique relation of EC to dysregulated behavior in the latter preschool period

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NeuroImage Clin. 2017;13:16-23.

**FRONTO-STRIATAL GLUTAMATE IN CHILDREN WITH TOURETTE'S DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Naaijen J, Forde NJ, Lythgoe DJ, et al.***

**Objective** Both Tourette's disorder (TD) and attention-deficit/hyperactivity disorder (ADHD) have been related to abnormalities in glutamatergic neurochemistry in the fronto-striatal circuitry. TD and ADHD often co-occur and the neural underpinnings of this co-occurrence have been insufficiently investigated in prior studies.

**Method** We used proton magnetic resonance spectroscopy (1H-MRS) in children between 8 and 12 years of age (TD n = 15, ADHD n = 39, TD + ADHD n = 29, and healthy controls n = 53) as an in vivo method of evaluating glutamate concentrations in the fronto-striatal circuit. Spectra were collected on a 3 Tesla Siemens scanner from two voxels in each participant: the anterior cingulate cortex (ACC) and the left dorsal striatum. LC-model was used to process spectra and generate glutamate concentrations in institutional units. A one-way analysis of variance was performed to determine significant effects of diagnostic group on glutamate concentrations.

**Results** We did not find any group differences in glutamate concentrations in either the ACC ($F(3132) = 0.97$, $p = 0.41$) or striatum ($F(3121) = 0.59$, $p = 0.62$). Furthermore, variation in glutamate concentration in these regions was unrelated to age, sex, medication use, IQ, tic, or ADHD severity. Obsessive compulsive (OC) symptoms were positively correlated with ACC glutamate concentration within the participants with TD (rho = 0.35, puncorrected = 0.02).

**Conclusion** We found no evidence for glutamatergic neuropathology in TD or ADHD within the fronto-striatal circuits. However, the correlation of OC-symptoms with ACC glutamate concentrations suggests that altered glutamatergic transmission is involved in OC-symptoms within TD, but this needs further investigation

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NeuroImage Clin. 2017;13:188-200.

**DISTINCT EFFECTS OF CHILDHOOD ADHD AND CANNABIS USE ON BRAIN FUNCTIONAL ARCHITECTURE IN YOUNG ADULTS.**

***Kelly C, Castellanos FX, Tomaselli O, et al.***

One of the most salient long-term implications of a childhood diagnosis of ADHD is an increased risk for substance use, abuse, or dependence in adolescence and adulthood. The extent to which cannabis use affects ADHD-related alterations in brain functional organization is unknown, however. To address this research gap, we recruited a sample of 75 individuals aged 21 25-years with and without a childhood diagnosis of ADHD Combined Type, who were either frequent users or non-users of cannabis. These participants have been followed longitudinally since age 7 9.9-years as part of a large multi-site longitudinal

study of ADHD, the Multimodal Treatment Study of Children with ADHD (MTA). We examined task-independent intrinsic functional connectivity (iFC) within 9 functional networks using a 2-+ù-2 design, which compared four groups of participants: (1) individuals with a childhood diagnosis of ADHD who currently use cannabis (n-=-23); (2) individuals with ADHD who do not currently use cannabis (n-=-22); (3) comparisons who currently use cannabis (n-á=-á15); and (4) comparisons who do not currently use cannabis (n-=-15). The main effects of childhood ADHD were primarily weakened iFC in networks supporting executive function and somatomotor control. Contrary to expectations, effects of cannabis use were distinct from those of diagnostic group and no interactions were observed. Exploratory brain-behavior analyses suggested that ADHD-related effects were primarily linked with poorer neurocognitive performance. Deficits in the integrity of functional networks supporting executive function and somatomotor control are consistent with the phenotypic and neurocognitive features of ADHD. Our data suggest that cannabis use does not exacerbate ADHD-related alterations, but this finding awaits replication in a larger sample. Longitudinal neuroimaging studies are urgently required to delineate the neurodevelopmental cascade that culminates in positive and negative outcomes for those diagnosed with ADHD in childhood

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Neuropsychiatr Dis Treat. 2016;12:3183-90.

**ASSOCIATIONS BETWEEN THE MISMATCH-NEGATIVITY COMPONENT AND SYMPTOM SEVERITY IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.**

***Yamamuro K, Ota T, Iida J, et al***.

**Aim**: Cognitive impairment is an important predictor of functional outcome in patients with attention deficit/hyperactivity disorder (ADHD). However, the neurophysiology of ADHD-related cognitive impairments remains unclear. Event-related potentials (ERPs) represent the noninvasive measurement of neural correlates of cognitive function. Mismatch negativity (MMN) is an ERP component that is presumed to index the preattentive monitoring of changes in the auditory environment.

**Materials and methods**: Previous studies have shown altered MMN amplitude and latency in patients with ADHD. However, little is known about the relationship between MMN and ADHD-symptom severity. To address this, we measured the amplitude and latency of MMN in ERPs and assessed correlations with the clinical severity of ADHD, as measured by the ADHD Rating Scale IV Japanese version. Participants were 51 treatment-na+»ve children and adolescents with ADHD (mean age 10.42-¦3.35 years) and 15 normally developing age- and sex-matched children (mean age 11.8-¦3.36 years).

**Results**: In the ADHD group, MMN amplitudes were attenuated at the central electrode and MMN latencies prolonged at the parietal electrode (Pz) relative to those in the control group. Furthermore, MMN amplitudes at Pz were negatively correlated with ADHD full-scale and hyperactivity impulsivity and inattention subscale scores, and MMN latency at Pz was positively correlated with ADHD hyperactivity impulsivity subscale scores.

**Conclusion**: Our data suggest that MMN reflects the severity of ADHD symptoms in children and adolescents, and provides support for the use of ERPs in evaluating ADHD symptoms in patients

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Neuropsychology. 2016.

**EVALUATION OF RELATIONAL REASONING BY A TRANSITIVE INFERENCE TASK IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Brunamonti E, Costanzo F, Mamm+¼ A, et al***.

Here we explored whether children with ADHD have a deficit in relational reasoning, a skill subtending the acquisition of many cognitive abilities and social rules. Method: We analyzed the performance of a group of children with ADHD during a transitive inference task, a task requiring first to learn the reciprocal relationship between adjacent items of a rank ordered series (e.g., A>B; B>C; C>D; D>E; E>F), and second, to deduct the relationship between novel pairs of items never matched during the learning (e.g., B>D; C>E). Results: As a main result, we observed that children with ADHD were impaired in performing inferential reasoning problems. The deficit in relational reasoning was found to be related to the difficulty in managing a unified

representation of ordered items. Conclusion: The present finding documented a novel deficit in ADHD, contributing to improving the understanding of the disorder

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Neuropsychology. 2016.

**SUBOPTIMAL DECISION MAKING BY CHILDREN WITH ADHD IN THE FACE OF RISK: POOR RISK ADJUSTMENT AND DELAY AVERSION RATHER THAN GENERAL PRONENESS TO TAKING RISKS.**

***Sørensen L, Sonuga-Barke E, Eichele H, et al.***

**Objective**: Suboptimal decision making in the face of risk (DMR) in children with attention-deficit hyperactivity disorder (ADHD) may be mediated by deficits in a number of different neuropsychological processes. We investigated DMR in children with ADHD using the Cambridge Gambling Task (CGT) to distinguish difficulties in adjusting to changing probabilities of choice outcomes (so-called risk adjustment) from general risk proneness, and to distinguish these 2 processes from delay aversion (the tendency to choose the least delayed option) and impairments in the ability to reflect on choice options. Based on previous research, we predicted that suboptimal performance on this task in children with ADHD would be primarily relate to problems with risk adjustment and delay aversion rather than general risk proneness.

**Method**: Drug na+»ve children with ADHD (n = 36), 8 to 12 years, and an age-matched group of typically developing children (n = 34) performed the CGT.

**Results**: As predicted, children with ADHD were not more prone to making risky choices (i.e., risk proneness). However, they had difficulty adjusting to changing risk levels and were more delay aversive-with these 2 effects being correlated.

**Conclusions**: Our findings add to the growing body of evidence that children with ADHD do not favor risk taking per se when performing gambling tasks, but rather may lack the cognitive skills or motivational style to appraise changing patterns of risk effectively. (PsycINFO Database Record

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NeuroRegulation. 2016;3:55-77.

**NEUROFEEDBACK AS AN INTERVENTION TO IMPROVE READING ACHIEVEMENT IN STUDENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, INATTENTIVE SUBTYPE.**

***La Marca JP, O'Connor RE.***

Research consistently demonstrates that attention deficits have a deleterious effect on academic achievement. Impairments in attention, and not hyperactivity/impulsivity, are associated with learning difficulties and academic problems in students with attention-deficit/hyperactivity disorder (ADHD). To date, most studies have focused on symptoms of hyperactivity/impulsivity, with little research being conducted on interventions for students with ADHD, inattentive subtype. This study examines the use of neurofeedback as an intervention to improve reading achievement in a public school setting. A multiple-baseline-across-participants single-case model was used to assess five fourth-grade students who received 40 daily sessions of neurofeedback. Following the intervention, improvements were observed on objective measures of attention: a continuous performance test (Integrated Visual and Auditory Continuous Performance Test [IVA+Plus]) and/or a test of shifting attention (CNS Vital Signs, Shifting Attention Test [CNS-VS, SAT]). Results on tests of reading fluency revealed little change, although participants demonstrated gains on a measure of reading comprehension (Gray Oral Reading Tests-Fifth Edition [GORT-5]). Results suggest that neurofeedback helped participants to become more accurately engaged with the text with more focused attention to content. Thus, neurofeedback may be a viable option to assist children with attention deficits for improving both attention and reading achievement

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Neuroscience. 2016.

**NEUROFEEDBACK TRAINING EFFECTS ON INHIBITORY BRAIN ACTIVATION IN ADHD: A MATTER OF LEARNING?**

***Baumeister S, Wolf I, Holz N, et al.***

Neurofeedback training (NF) is a promising non-pharmacological treatment for ADHD that has been associated with improvement of attention-deficit/hyperactivity disorder (ADHD)-related symptoms as well as changes in electrophysiological measures. However, the functional localization of neural changes following NF compared to an active control condition, and of successful learning during training (considered to be the critical mechanism for improvement), remains largely unstudied. Children with ADHD (N=16, mean age: 11.81, . SD: 1.47) were randomly assigned to either slow cortical potential (SCP, . n=8) based NF or biofeedback control training (electromyogram feedback, . n=8) and performed a combined Flanker/NoGo task pre- and post-training. Effects of NF, compared to the active control, and of learning in transfer trials (approximating successful transfer to everyday life) were examined with respect to clinical outcome and functional magnetic resonance imaging (fMRI) changes during inhibitory control. After 20 sessions of training, children in the NF group presented reduced ADHD symptoms and increased activation in areas associated with inhibitory control compared to baseline. Subjects who were successful learners (n=9) also showed increased activation in an extensive inhibitory network irrespective of the type of training. Activation increased in an extensive inhibitory network following NF training, and following successful learning through NF and control biofeedback. Although this study was only powered to detect large effects and clearly requires replication in larger samples, the results suggest a crucial role for learning effects in biofeedback trainings

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Neurosci Biobehav Rev. 2016.

**UNDERSTANDING HETEROGENEITY IN CONDUCT DISORDER: A REVIEW OF PSYCHOPHYSIOLOGICAL STUDIES.**

***Fanti KA.***

The present review is concerned with the role of different physiological systems (e.g., skin conductance, heart rate, electromyography, and the eye-bling startle reflex) in understanding heterogeneity in conduct disorder (CD). Four subtyping approaches are considered: age of onset, comorbid psychopathology, callous-unemotional traits, and proactive/reactive aggression. Empirical findings are discussed in terms of distinct theoretical perspectives that aim to explain CD behaviors based on physiological over-arousal, under-arousal, and empathy deficits. According to the studies reviewed, the callous-unemotional (CD + CU) and internalizing (CD + Internalizing) sub-types can best inform CD heterogeneity. Findings indicated that children in the CD + CU and CD + Internalizing subtypes score on opposite extremes on heart rate, skin conductance and startle reactivity measures. Heart rate variability and respiratory sinus arrhythmia dysfunctions, associated with emotional dysregulation, were more evident among children in the CD + Internalizing group, while dysfunctional facial electromyography activity, which has been linked with reduced empathy, with the CD + CU group. In conclusion, it might be important to redefine CD diagnostic criteria based on physiological heterogeneity to enable the identification of distinct subtypes of CD

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Noropsikiyatr Ars. 2016;53:291-95.

**RELATIONSHIP BETWEEN IMPULSIVITY AND SERUM OXYTOCIN IN MALE CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER: A PRELIMINARY STUDY.**

***Demirci E, et al.***

**Introduction**: Here we aimed to determine the relationship between oxytocin levels and impulsivity, which is an important aspect at Attention Deficit Hyperactivity Disorder (ADHD) clinics.

**Methods**: The study population comprised 40 ADHD patients diagnosed based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version, without other psychiatric disorders and chronic diseases aged between 8 and 15 years. The control group comprised 40 healthy, age-matched, male children and adolescents who voluntarily participated in the study. Patients and controls filled the Barratt impulsivity scale-11 (BIS-11). Ten cubic centimeters of blood was collected at 8 am for

determining serum oxytocin levels. ELISA kits were used to measure serum oxytocin levels in a biochemistry laboratory. The obtained data were evaluated using appropriate statistical methods.
**Results**: In this study, compared with the control group, the impulsivity scores were significantly higher and serum oxytocin levels were lower in the ADHD group (52.5-¦18.1 and 37.62-¦9.0, respectively, p<0.001). Serum oxytocin levels showed a negative correlation with impulsivity and attention subscale scores of BIS-11 in the ADHD group.
**Conclusion**: ADHD and impulsivity, which comprise an aspect of ADHD, may be associated with oxytocin. Serum oxytocin levels may contribute to inattention subtypes of impulsivity observed in ADHD

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Noropsikiyatr Ars. 2016;53:348-52.

**EVALUATION OF THE RELATIONSHIP BETWEEN BRAIN-DERIVED NEUROTROPIC FACTOR LEVELS AND THE STROOP INTERFERENCE EFFECT IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.**

***ŞİMŞEK Ş, et al.***

**Introduction**: Brain-derived neurotropic factor (BDNF) has been suggested to play a role in the pathogenesis of attention-deficit hyperactivity disorder (ADHD). In addition, impairment in executive functions has been reported in children with ADHD. This study investigated the presence of a relationship between Stroop test scores and BDNF levels in children with ADHD.
**Methods**: The study was conducted in the Department of Child Psychiatry at Dicle University. The study included 49 children between 6 and 15 years of age (M/F: 42/7), who were diagnosed with ADHD according to DSM-IV, and who did not receive previous therapy. Similar in terms of age and gender to the ADHD group, 40 children were selected in the control group. The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version was administered to all participants. Parents and teachers were administered Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale to measure symptom severity in children with ADHD. Children with ADHD underwent the Stroop test. BDNF levels were evaluated in serum by ELISA.
**Results**: The ADHD and control groups did not differ in terms of BDNF levels. BDNF levels did not differ between ADHD subtypes. There was also no relationship between the Stroop test interference scores and BDNF levels.
**Conclusion**: The findings of the present study are in line with those in studies that demonstrated no significant role of BDNF in the pathogenesis of ADHD

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Noropsikiyatr Ars. 2016;53:321-27.

**POSSIBLE EFFECTS OF COPPER AND CERULOPLASMIN LEVELS ON AUDITORY EVENT POTENTIALS IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.**

***Yorbik Ö, Mutlu C, et al.***

**Introduction**: The aims of the present study were to investigate the relationship between levels of plasma copper (Cu) and ceruloplasmin (Cp) and amplitudes and latencies of P1, N2, and P3 in the parietal and frontal areas of children with attention deficit hyperactivity disorder (ADHD) as well as to compare these Cu levels and event-related potentials (ERPs) indices in controls.
**Methods**: Boys (n=41) with ADHD were divided into two subgroups according to a median split of plasma Cu and Cp levels, separately. ERP indices from the parietal and frontal regions were recorded in children with ADHD and 24 normal boys (control group) using an auditory oddball paradigm.
**Results**: Parietal P3 latency was significantly longer, and parietal P3 amplitude, frontal P3 amplitude, and frontal N2 amplitudes were smaller in children with ADHD than in controls (all p values <0.017). Parietal P1 and frontal P1 latencies were significantly shorter in the higher Cu group than in the lower Cu group (both p values <0.017). Decreased latency of parietal P1 was dependent on plasma levels of Cu (p<0.05). Frontal N2 and parietal N2 amplitudes were significantly lower in the ADHD group with lower Cp levels than in the ADHD group with higher Cp levels (both p values <0.017). Decreased frontal N2 and parietal N2 amplitudes were dependent on plasma levels of Cp (both p values <0.05).

**Conclusion**: Plasma Cu and Cp levels may have an effect on ERPs in ADHD, thus indicating the existence of effects on information processing. Cu levels may have a negative effect on the neuronal encoding of sound, whereas Cp levels may have a positive effect on the processes of cognitive control, conflict monitoring, and stimulus discrimination in children with ADHD

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Nutrients. 2016;8.

**THE INFLUENCE OF HEALTH BEHAVIOURS IN CHILDHOOD ON ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN ADOLESCENCE.**

***Wu X, Ohinmaa A, Veugelers PJ.***

Attention-deficit and hyperactivity disorder (ADHD) in children and adolescents is a global public health burden. Identification of health-related behavioral risk factors including diet quality and physical and sedentary activities for ADHD is important for prioritizing behavioral intervention strategies to improve mental health. This study aimed to examine the association of diet quality, physical activity, and sedentary behaviours in childhood with ADHD throughout adolescence. We linked data from grade five students aged primarily 10 and 11 years old who participated in a population-based lifestyle survey in the Canadian province of Nova Scotia with their administrative health care data. We applied negative binomial regression methods to examine the associations between health behaviours and ADHD. Of the 4875 students, 9.7% had one or more diagnoses of ADHD between the ages of 10/11 and 18 years. The number of primary diagnoses with ADHD was statistically significantly lower among students with better diet quality, higher levels of physical activity, and those that spent less time playing computers and video games ($p < 0.05$). These findings suggest that health promotion programs aiming to improve childrenΓÇÖs diets and active lifestyles may also reduce the public health burden of ADHD

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Nutritional Neuroscience. 2016;1-8.

**EFFECT OF VITAMIN D SUPPLEMENTATION AS ADJUNCTIVE THERAPY TO METHYLPHENIDATE ON ADHD SYMPTOMS: A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL.**

***Mohammadpour N, Jazayeri S, Tehrani-Doost M, et al.***

**Objectives**: Previous studies have shown that serum levels of vitamin D were lower in attention deficit hyperactivity disorder (ADHD) children compared to healthy controls. The aim of the study was to determine the effect of vitamin D supplementation as adjunctive therapy to methylphenidate on symptoms of children with ADHD.

**Methods**: Sixty-two children aged 5Γ Çô12 years with a diagnosis of ADHD based on DSM-IV criteria were randomly assigned into two groups to receive either 2000IU vitamin D or placebo in addition to methylphenidate for 8 weeks. Symptoms severity was assessed by Conner's Parent Rating Scale-Revised[S] (CPRS), ADHD rating scale-IV (ADHD-RS), and Weekly Parent Ratings of Evening and Morning Behavior (WPREMB) at weeks 0, 4, and 8. Serum levels of 25(OH)D were measured at baseline and after 8 weeks. Anthropometric variables, dietary intake, physical activity, sun exposure, and side effects were assessed.

**Results**: Fifty-four participants completed the trial. After 8 weeks of supplementation, serum levels of 25(OH)D significantly increased in the vitamin D group. ADHD symptoms decreased significantly in both groups ($P<0.05$). Evening symptoms and total score of WPREMB scale were significantly different at weeks 4 and 8 between the two groups (P 0.013, 0.016, respectively), but no differences were found in symptoms by CPRS and ADHD-RS scales.

**Discussion**: Vitamin D supplementation as adjunctive therapy to methylphenidate improved ADHD evening symptoms. Future research is needed to clarify vitamin D effects as monotherapy in ADHD and its mechanism.

The trial was registered in www.irct.ir is (IRCT201404222394N10)

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Patient Educ Couns. 2016.

**ADOLESCENT PATIENT EDUCATION REGARDING ADHD STIMULANT DIVERSION AND MISUSE.**

***Colaneri N, Keim S, Adesman A.***

**Objectives**: Recent studies report that adolescents misuse and divert ADHD stimulants. This study evaluates the extent to which physicians educate adolescents with ADHD about stimulant misuse and diversion (M/D).
**Methods**: Child/adolescent psychiatrists (CAP), child neurologists (CN), and developmental-behavioral pediatricians (DBP) in the US completed a questionnaire. Descriptive statistics were performed on the final sample (n = 826); multivariate regressions were performed to identify education practice differences.
**Results**: Only 46% and 44% of physicians educate patients "often" or "very often" on health risks and legal consequences, respectively, of stimulant M/D. CAP are more likely to educate on health and legal consequences than CN, and more likely to educate on legal consequences than DBP. Compared to physicians who prescribe stimulants to 1-10 patients (low prescribers), medium prescribers (11-30 patients) and high prescribers (30+ patients) are more likely to educate about M/D. 60% of physicians counsel patients at least "often" about M/D in a pre-college appointment; 8% have written materials regarding M/D available.
**Conclusions**: Many physcians currently don't educate adolescent patients with ADHD often enough about M/D. CN and DBP, and low prescribers, are less likely to educate about M/D. Practice implications: Physicians who prescribe stimulants must educate patients more often to prevent stimulant M/D

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Pediatr Allergy Immunol. 2016.

**ASSOCIATION BETWEEN PRESCHOOL ECZEMA AND MEDICATION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SCHOOL AGE.**

***Johansson EK, Ballardini N, Kull I, et al.***

**Background**: Several studies show an association between eczema and attention-deficit/hyperactivity disorder (ADHD) in childhood, but the mechanisms and time sequence remain unclear. Information on the association between eczema and other disorders involving the central nervous system (CNS) is limited. The aim was to explore whether preschool eczema was associated with ADHD or other CNS-associated disorders requiring pharmacotherapy at school age and to analyze whether eczema at other ages of childhood was associated with medication for ADHD.
**Methods**: From a Swedish birth cohort, 3606 children were included in the analyses. At 1, 2, 4, 8, 12, and 16 years of age, their parents answered questionnaires regarding eczema the last year. Information on prescribed medications during school age (10-18 years of age) was derived by record linkage to the Swedish Prescribed Drug Register.
**Results**: A total of 1178 (32.7%) of the children had preschool eczema (eczema at 1, 2, and/or 4 years), and 162 (4.5%) of the children had dispensed ADHD medication at school age. Preschool eczema was not associated with ADHD medication at school age (crude odds ratio 1.16; 95% Confidence Intervals: 0.83-1.61). There was no significant association between preschool eczema and use of antidepressants, migraine drugs, or anti-epileptics at school age. Infantile eczema, school-age eczema, and eczema ever up to 16 years of age were not associated with ADHD medication at school age.
**Conclusions**: In this large birth cohort, there were no significant associations between preschool eczema and medications for ADHD, depression/anxiety/phobia, migraine, or epilepsy at school age

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Pediatr Dermatol. 2016.

**EVALUATION OF CUTANEOUS FINDINGS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A PRELIMINARY STUDY.**

***Kaya Erdogan H, Fidan ST, Bulur I, et al.***

Attention deficit hyperactivity disorder (ADHD) is characterized by attention, concentration, mobility, and impulse control problems and is among the most frequently seen psychiatric disorders during childhood. Our aim was to evaluate cutaneous findings in children and adolescents with ADHD. In our study we found that onychophagy, traumatic skin changes, atopy and related symptoms, certain birthmarks, and acne were

frequent cutaneous findings in children with ADHD. Although a limitation is the lack of a control group, ADHD is very common, and our study suggests that further studies of cutaneous findings and ADHD are warranted

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Pharmacoepidemiol Drug Saf. 2016;25:299.

**ANTIDEPRESSANT USE IN PREGNANCY AND THE RISK OF ATTENTION DEFICIT WITH OR WITHOUT HYPERACTIVITY DISORDER IN CHILDREN.**

***Boukhris T, Sheehy O, Berard A.***

**Background**: The association between antidepressant (AD) use during pregnancy and the risk of attention deficit with or without hyperactivity disorder (ADHD) in children is controversial.

**Objectives**: We sought to evaluate the risk of ADHD associated with overall and class-specific antidepressant exposure in-utero.

**Methods**: We performed a register-population based cohort study, using an ongoing population-based cohort, the Quebec Pregnancy/Children Cohort (QPC), which includes data on all pregnancies and children in Quebec from 1998-2009. Antidepressant exposure during pregnancy was defined according to trimester, and specific antidepressant classes. Children with ADHD were defined as those with at least one diagnosis of ADHD or prescription filled for ADHD medications between birth and the end of follow-up. Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios (HRs) with 95% confidence intervals.

**Results**: During 542,897.28 person-years of followup, 4564 infants (3.16%) were diagnosed with ADHD. The mean age at first ADHD diagnosis was 6.35 -¦ 2.33 years (median, 7.00 years) and the mean age at first ADHD medication was 7.00 -¦ 1.54 years (median, 7.03 years). AD use during the 2nd or 3rd trimester of pregnancy was significantly associated with an increased risk of ADHD (aHR= 1.28; 95% CI 1.03- 1.59; 134 exposed cases)) event after adjusting for potential confounders, including maternal history of depression and ADHD; tricyclic ADs use was significantly associated with an increased risk of ADHD (aHR=1.76; 95% CI 1.01-3.06; 16 exposed cases); SSRI and SNRI use were increasing the risk of ADHD but estimates were non-statistically significant.

**Conclusions**: Our findings suggest that use of ADs during the 2nd or 3rd trimester of pregnancy, specifically tricyclic antidepressants, is an independent risk factor for ADHD in children above and beyond the risk associated with maternal depression or ADHD. Our results are suggesting that medications with serotonergic effect during pregnancy have an impact on the risk of ADHD

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Pharmacoepidemiol Drug Saf. 2016;25:97.

**ASSOCIATION BETWEEN ATOPIC DISEASES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SYSTEMATIC REVIEW AND META-ANALYSES.**

***van der Schans J, Cicek R, De Vries TW, et al.***

**Background**: A review by Schmitt and colleagues showed an association between eczema and attention-deficit/hyperactivity disorder (ADHD). Though such an association was not observed for asthma and allergic rhinitis more recent studies indicated also an association with these atopic diseases.

**Objectives**: We aimed to systematically review the available evidence on the association between atopic diseases and ADHD in children and adolescents and to estimate the strength of the association in a metaanalysis.

**Methods**: We performed a systematic review of observational cross-sectional and longitudinal studies with a time-component that assessed the association between atopic disorders and ADHD, including asthma, atopic eczema, and allergic rhinitis in children and adolescents. For longitudinal studies, we estimated a weighted Mantel-Haenszel odds ratio of these associations using a meta-analysis of crude data.

**Results**: The majority of cross-sectional and longitudinal studies reported a statistically significant positive association between one or more atopic diseases and ADHD. The meta-analysis among longitudinal studies revealed an overall weighted odds ratio for asthma of 1.34 (95% confidence interval [CI] 1.24-1.44), 1.32 (95% CI 1.20-1.45) for atopic eczema, and 1.52 (95% CI 1.43-1.63) for allergic rhinitis. Heterogeneity of

study data was low (I2: 0%, p=.46 and p=.64, respectively) for both studies examining asthma and eczema, but substantial for rhinitis studies (I2: 82%, p=.004).
**Conclusions**: Our systematic review provides firm evidence that ADHD is associated with atopic diseases with an average of 30% to 50% higher odds of developing ADHD compared with persons without these diseases

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Pharmacoepidemiol Drug Saf. 2016;25:240.

**PRESCRIBING TRENDS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) MEDICATIONS IN UK PRIMARY CARE, 1995-2015.**

***Renoux C, Shin JY, Dell'Aniello S, et al.***

**Background**: In the past decades, an increased prevalence of Attention-Deficit Hyperactivity Disorder (ADHD) and use of ADHD medications has been observed in several countries, raising concerns about a possible over-diagnosis and inappropriate prescription of ADHD medications. However, longitudinal trends of ADHD medications have not been updated recently. Also, despite a growing interest in adults with ADHD, most studies have been restricted to children and little is known about the prescribing patterns of ADHD medication in adults.
**Objectives**: To describe the prescription of medications for Attention-Deficit Hyperactivity Disorder (ADHD) in the UK between 1995 and 2015.
**Methods**: Using the Clinical Practice Research Datalink (CPRD), we defined a cohort of all patients aged 6 to 45 years, registered with a general practitioner between January 1995 and September 2015. All prescriptions of methylphenidate, dexamphetamine/ lisdexamphetamine, and atomoxetine were identified and annual prescription rates of ADHD were estimated using Poisson regression.
**Results**: Within a cohort of 7,432,735 patients, we identified 698,148 prescriptions of ADHD medications during 41,171,528 person-years of follow-up. Usage was relatively low until the year 2000 during which the prescription rate was 42.7 (95% confidence interval (CI) 20.9 to 87.2) prescriptions per 10,000 persons, increasing to 394.4 (95% CI 296.7 to 524.2) in 2015, corresponding to an almost 800% increase (rate ratio 8.87; 95% CI 7.10 to 11.09). The increase was seen in all age groups and in both sexes but was steepest in boys aged 10 to 14 years. The prescription rate in males was almost 5 times that of females. Methylphenidate remained the most prescribed drug during the 20-year study period, representing 88.9% of all prescriptions in the 6-24 years old, and 63.5% of all prescriptions in adults (25-45 years old).
**Conclusions**: Prescription rates of ADHD medications have increased dramatically in the past two decades. This may be due to both an increase in the number of patients diagnosed with ADHD over time and a higher percentage of those patients treated with medication

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Pharmacoepidemiol Drug Saf. 2016;25:239-40.

**GLOBAL UTILIZATION OF ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATIONS - PRELIMINARY RESULTS.**

***Raman SR, Man KKC, Berard A, et al.***

**Background**: The global epidemiology of attention deficit hyperactivity disorder (ADHD) medication use varies by region and measurement methods. Increasing ADHD medication prevalence is evident in North America and Europe but has not been assessed in Asia.
**Objectives**: To determine overall and subgroup-specific prevalence of ADHD medication use in children 3-18 years of age in 4 countries, with particular focus on relative trends in prevalence of medication use over time.
**Methods**: We conducted an observational study using population-based electronic health databases from Hong Kong (HK, 2001-2015), Taiwan (TW, 2000- 2013), Japan (JP, 2010-2015) and the province of Quebec, Canada (QC, 2001-2009), using a common protocol approach to estimate use of licensed ADHD prescribed/dispensed medication (identified by ATC classification codes). Annual prevalence (/1000 children) with 95% confidence intervals (CI) of ADHD medications were calculated within available years in each country between 2000-2015, stratified by age group (3-5, 6-11, 12-18 years) and gender over time.

**Results**: Prevalence of any ADHD medication (/1000 children age 3-18(95%CI)) varied between 0.5 (0.5-0.6) to 21.5 (21.2-21.8) in HK, 3.0 (2.8-3.3) to 12.4 (11.8-12.9) in TW, 2.9 (2.7-3.1) to 5.4 (5.2-5.6) in JP and 0.2 (0.1-0.4) to 17.6 (17.0-18.3) in QC. ADHD medication prevalence increased over available study period in all countries: increased 41 times in HK, 4.1 times in TW, 1.9 times in JP and 73 times in QC. Similar trends were observed in males and females. The male/female ratios in prevalence were 5.0 (HK, 2015), 3.5 (TW, 2013), 2.9 (JP, 2015) and 2.2 (QC, 2009). The age group with highest ADHD medication prevalence was age 6-11 compared to other available age groups: 39 (HK, 2015), 30 (TW, 2013), 6.4 (JP, 2015) and 19.6 (QC, 2009). Methylphenidate was the most commonly used ADHD medication in all countries: 94.9% (HK, 2015), 96.1% (TW, 2013), 55.6% (JP, 2015) and 62% (QC, 2009). Results from 13 additional countries, including adult estimates, are in progress.
**Conclusions**: Use of a common protocol and standard medication measurements indicate large increases in ADHD medication use over time in these 4 countries

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Pharmacoepidemiol Drug Saf. 2016;25:33-34.

**ADHD TREATMENT AND DIAGNOSIS - IMPORTANCE OF RELATIVE AGE IN GRADE IN NORWAY.**

***Karlstad, Furu K, et al.***

**Background**: Studies from several countries have reported that the youngest children in a grade are at higher risk of being diagnosed with ADHD or to receive ADHD drugs than their older-for-grade peers. The school start age cut-off follows the calendar year in Norway, i.e. the youngest-for-grade children are born in December.
**Objectives**: To investigate whether birth month is associated with the risk of receiving ADHD drugs (primary endpoint) or an ADHD diagnosis (secondary endpoint) in primary or specialist healthcare in Norway. Methods: The study population included all children born in Norway during 2000-2008 (31 December 2014, N=507,292). Information was retrieved from three nationwide databases: the Norwegian Prescription Database (dispensed ADHD drugs), the Norwegian Patient Register (ADHD diagnoses in specialist healthcare), and reimbursement data (ADHD diagnoses in primary healthcare). Children were followed from birth and until the first endpoint, death, emigration or end of the study period using Kaplan-Meier (KM) estimators by birth month and separately for boys and girls. Cox proportional hazard analyses were subsequently performed separately for boys and girls with number of days since birth as the time metric, birth month as exposure, and adjusting for calendar year of birth and parental education.
**Results**: 11,003 children (2.17%) had received ADHD drugs. By the end of follow-up, 2.54% of boys born in January, 3.08% of boys born in June, and 3.93% of boys born in December had received ADHD drugs. Corresponding proportions for girls were 0.81%, 1.02%, and 1.68%. The adjusted hazard ratio was 1.57 (95% CI: 1.41-1.75) for boys born in December (ref.: boys born in January), and 2.11 (1.75-2.55) for girls born in December (ref.: girls born in January). The same pattern of higher risk for children born later in the year compared to children born early in the year was also observed for ADHD diagnoses.
**Conclusions**: Children born later in the year are at higher risk of receiving ADHD drugs and of receiving an ADHD diagnosis than children born early in the year

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PLoS ONE. 2016;11.

**DECREASED LEFT CAUDATE VOLUME IS ASSOCIATED WITH INCREASED SEVERITY OF AUTISTIC-LIKE SYMPTOMS IN A COHORT OF ADHD PATIENTS AND THEIR UNAFFECTED SIBLINGS.**

***O'Dwyer L, Tanner C, Van Dongen EV, et al.***

Autism spectrum disorder (ASD) symptoms frequently occur in individuals with attentiondeficit/hyperactivity disorder (ADHD). While there is evidence that both ADHD and ASD have differential structural brain correlates, knowledge of the structural brain profile of individuals with ADHD with raised ASD symptoms is limited. The presence of ASD-like symptoms was measured by the Children's Social Behavior Questionnaire (CSBQ) in a sample of typically developing controls (n = 154), participants with ADHD (n = 239), and their unaffected siblings (n = 144) between the ages of 8 and 29. Structural magnetic resonance imaging (MRI)

correlates of ASD ratings were analysed by studying the relationship between ASD ratings and grey matter volumes using mixed effects models which controlled for ADHD symptom count and total brain volume. ASD ratings were significantly elevated in participants with ADHD relative to controls and unaffected siblings. For the entire group (participants with ADHD, unaffected siblings and TD controls), mixed effect models revealed that the left caudate nucleus volume was negatively correlated with ASD ratings (t = 2.83; P = 0.005). The current findings are consistent with the role of the caudate nucleus in executive function, including the selection of goals based on the evaluation of action outcomes and the use of social reward to update reward representations. There is a specific volumetric profile associated with subclinical ASD-like symptoms in participants with ADHD, unaffected siblings and controls with the caudate nucleus and globus pallidus being of critical importance in predicting the level of ASD-like symptoms in all three groups

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PLoS ONE. 2016;11.

**PROBLEMATIC PEER FUNCTIONING IN GIRLS WITH ADHD: A SYSTEMATIC LITERATURE REVIEW.**

***Kok FM, Groen Y, Fuermaier ABM, et al.***

**Objective** Children with attention deficit hyperactivity disorder (ADHD) experience many peer interaction problems and are at risk of peer rejection and victimisation. Although many studies have investigated problematic peer functioning in children with ADHD, this research has predominantly focused on boys and studies investigating girls are scant. Those studies that did examine girls, often used a male comparison sample, disregarding the inherent gender differences between girls and boys. Previous studies have highlighted this limitation and recommended the need for comparisons between ADHD females and typical females, in order to elucidate the picture of female ADHD with regards to problematic peer functioning. The aim of this literature review was to gain insight into peer functioning difficulties in schoolaged girls with ADHD.
**Methods** PsychINFO, PubMed, and Web of Knowledge were searched for relevant literature comparing school-aged girls with ADHD to typically developing girls (TDs) in relation to peer functioning. The peer relationship domains were grouped into 'friendship', 'peer status', 'social skills/competence', and 'peer victimisation and bullying'. In total, thirteen studies were included in the review.
**Results** All of the thirteen studies included reported that girls with ADHD, compared to TD girls, demonstrated increased difficulties in the domains of friendship, peer interaction, social skills and functioning, peer victimization and externalising behaviour. Studies consistently showed small to medium effects for lower rates of friendship participation and stability in girls with ADHD relative to TD girls. Higher levels of peer rejection with small to large effect sizes were reported in all studies, which were predicted by girls' conduct problems. Peer rejection in turn predicted poor social adjustment and a host of problem behaviours. Very high levels of peer victimisation were present in girls with ADHD with large effect sizes. Further, very high levels of social impairment and social skills deficits, with large effect sizes, were found across all studies. Levels of pro-social behaviour varied across studies, but were mostly lower in girls with ADHD, with small to large effect sizes. Overall, social disability was significantly higher among girls with ADHD than among TD girls.
**Conclusion** Congruous evidence was found for peer functioning difficulties in the peer relationship domains of friendship, peer status, social skills/competence, and peer victimisation and bullying in girls with ADHD

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Psychiatry Res Neuroimaging. 2016;258:30-36.

**DISTINCT DIFFERENCES IN STRIATAL DYSMORPHOLOGY BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER BOYS WITH AND WITHOUT A COMORBID READING DISABILITY.**

***Goradia DD, Vogel S, Mohl B, et al.***

There is evidence of greater cognitive deficits in attention deficit hyperactivity disorder with a comorbid reading disability (ADHD/+RD) compared to ADHD alone (ADHD/−RD). Additionally, the striatum has been consistently implicated in ADHD. However, the extent of morphological alterations in the striatum of ADHD/+RD is poorly understood, which is the main purpose of this study. Based on structural MRI images, the surface deformation of the caudate and putamen was assessed in 59 boys matching in age and IQ [19

ADHD/−RD, 15 ADHD/+RD and 25 typically developing controls (TDC)]. A vertex based analysis with multiple comparison correction was conducted to compare ADHD/−RD and ADHD/+RD to TDC. Compared to TDC, ADHD/+RD showed multiple bilateral significant clusters of surface compression. In contrast, ADHD/−RD showed fewer significant clusters of surface compression and restricted to the left side. Regarding the putamen, only ADHD/−RD showed significant clusters of surface compression. Results demonstrate for the first time a greater extent of morphological alterations in the caudate of ADHD/+RD than ADHD/−RD compared to TDC, which may suggest greater implicated cortical areas projecting to the caudate that are associated with the greater neuropsychological impairments observed in ADHD/+RD

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Psychiatry Res. 2016;246:656-62.

**ADDICTION SEVERITY PATTERN ASSOCIATED WITH ADULT AND CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN PATIENTS WITH ADDICTIONS.**

***Fatséas M, Hurmic H, Serre F, et al.***

Attention Deficit Hyperactivity Disorder (ADHD) is highly prevalent among adults with addictive disorders, but little is known about addiction patterns associated with ADHD diagnosis. This study examined addiction severity in patients with co-occurring addictive disorders and ADHD controlling for the potential influence of associated psychiatric comorbidity. Data were collected in French outpatient addiction treatment centers. A total of 217 patients seeking treatment for substance or gambling addiction were included. At treatment entry, participants were interviewed with the Addiction Severity Index, the Conners Adult ADHD Diagnosis Interview for the DSM-IV (CAADID), the Mini International Neuropsychiatric Interview (MINI) and the Structured Clinical Interview for DSM-IV Axis II for borderline personality disorder (SCID II). History of ADHD was associated with an earlier onset of addiction, poly-dependence (defined by presence of at least two current substance dependence diagnoses in addition to tobacco dependence if present) and borderline personality disorder. Persistence of ADHD during adulthood was associated with a higher prevalence of poly-dependence. This study highlights the need for early implementation of preventive interventions for substance use or behavioral addiction in children/adolescents with ADHD and the need to consider ADHD in the treatment of addictive disorders

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Psychiatry Res. 2016.

**TEMPORAL DISCOUNTING AND EMOTIONAL SELF-REGULATION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.**

***Utsumi DA, Miranda MC, Muszkat M.***

Temporal Discounting (TD) reflects a tendency to discount a reward more deeply the longer its delivery is delayed. TD tasks and behavioral scales have been used to investigate 'hot' executive functions in ADHD. The present study analyzed TD task performance shown by ADHD and control groups for correlations with emotional self-regulation metrics from two scales, the Behavior Rating Inventory of Executive Functions (BRIEF) and the Child Behavior Checklist (CBCL). Children (ages 8-12) with ADHD (n=25) and controls (n=24) were assessed using material rewards (toys) for three types of task: Hypothetical (H); Hypothetical with temporal expectation (HTE); and Real (R). Between-group differences were found for the HTE task, on which the ADHD group showed a higher rate of discounting their favorite toy over time, especially at 10. s and 20. s. This was the only task on which performance significantly correlated with BRIEF metrics, thus suggesting associations between impulsivity and low emotional self-regulation, but no task was correlated with CBCL score. The conclusion is that tasks involving toys and HTE in particular may be used to investigate TD in children with ADHD and as a means of evaluating the interface between the reward system and emotional self-regulation

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Psychiatry Res. 2017;247:222-24.

**BEHAVIORS ASSOCIATED WITH NEGATIVE AFFECT IN THE FRIENDSHIPS OF CHILDREN WITH ADHD: AN EXPLORATORY STUDY.**

***Normand S, Ambrosoli J, Guiet J, et al.***

Our objective was to identify behaviors and contextual situations associated with negative affect observed in the interactions of children with and without ADHD and their real-life friends. We expected negative affect to be linked to rule violations and disagreements about the choice of games. Loss of game was associated with episodes of negative affect in a structured game. Negative appraisal of friend's ability was most frequently associated with negative affect during unstructured free play. Comparison children expressed greater frustration regarding their own abilities, whereas children with ADHD commented more frequently about the inabilities of their friends

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Psychol Assess. 2016.

**SLUGGISH COGNITIVE TEMPO AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) INATTENTION IN THE HOME AND SCHOOL CONTEXTS: PARENT AND TEACHER INVARIANCE AND CROSS-SETTING VALIDITY.**

***Burns GL, Becker SP, Servera M, et al.***

This study examined whether sluggish cognitive tempo (SCT) and attention-deficit/hyperactivity disorder (ADHD) inattention (IN) symptoms demonstrated cross-setting invariance and unique associations with symptom and impairment dimensions across settings (i.e., home SCT and ADHD-IN uniquely predicting school symptom and impairment dimensions, and vice versa). Mothers, fathers, primary teachers, and secondary teachers rated SCT, ADHD-IN, ADHD-hyperactivity/impulsivity (HI), oppositional defiant disorder (ODD), anxiety, depression, academic impairment, social impairment, and peer rejection dimensions for 585 Spanish 3rd-grade children (53% boys). Within-setting (i.e., mothers, fathers; primary, secondary teachers) and cross-settings (i.e., home, school) invariance was found for both SCT and ADHD-IN. From home to school, higher levels of home SCT predicted lower levels of school ADHD-HI and higher levels of school academic impairment after controlling for home ADHD-IN, whereas higher levels of home ADHD-IN predicted higher levels of school ADHD-HI, ODD, anxiety, depression, academic impairment, and peer rejection after controlling for home SCT. From school to home, higher levels of school SCT predicted lower levels of home ADHD-HI and ODD and higher levels of home anxiety, depression, academic impairment, and social impairment after controlling for school ADHD-IN, whereas higher levels of school ADHD-IN predicted higher levels of home ADHD-HI, ODD, and academic impairment after controlling for school SCT. Although SCT at home and school was able to uniquely predict symptom and impairment dimensions in the other setting, SCT at school was a better predictor than ADHD-IN at school of psychopathology and impairment at home. Findings provide additional support for SCT's validity relative to ADHD-IN

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Reproductive Toxicology. 2012;33:619-20.

**EXPOSURE TO POLYFLUOROALKYL CHEMICALS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN U.S. CHILDREN AGED 12-15 YEARS.**

***Hoffman K, Webster TF, Weisskopf MG, et al.***

**Introduction**: Polyfluoroalkyl chemicals (PFCs) have been widely used in consumer products. Exposures in the US and world populations are widespread. PFC exposures have been linked previously to various health impacts, and data in animals suggest that PFCs may be potential developmental neurotoxicants.

**Objectives**: We evaluated the associations between exposures to four PFCs and parental report of diagnosis of attention deficit hyperactivity disorder (ADHD).

**Methods**: Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2003-2004 for children aged 12-15 years. Parental report of a previous diagnosis by a doctor or healthcare professional of ADHD in the child was the primary outcome measure. Perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) levels were measured in serum samples from each child.

**Results**: Of the 586 children in the sample, 51 had a prior diagnosis of ADHD. When PFOS was treated as a continuous predictor, a 1.03 fold increased odds was observed for each ++;g/L increase in serum PFOS after adjustment for confounding (95% CI 1.01-1.05). There were also significant dose response relationships between PFOA and PFHxS levels and ADHD (OR = 1.12; 95% CI 1.01-1.23 and OR= 1.06; 95% CI 1.02-1.11, respectively). Similarly, children with higher PFNA levels were more likely to have ADHD (OR = 1.32; 95% CI 0.86-2.02).
**Conclusions**: Our results, using cross-sectional data, are consistent with increased odds of ADHD in children with higher serum PFC levels. Given the extremely prevalent exposure to PFCs, followup of these analyses with cohort studies is needed

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Res Autism Spectr Disord. 2017;35:1-12.

**INATTENTION AND HYPERACTIVITY IN ASSOCIATION WITH AUTISM SPECTRUM DISORDERS IN THE CHARGE STUDY.**

***Lyall K, Schweitzer JB, Schmidt RJ, et al.***

**Background** Attention deficits in young children with autism spectrum disorder (ASD) are not well understood. This study sought to determine: 1) the prevalence of ADHD symptoms in young children with ASD, typical development (TD), and developmental delay (DD) and 2) the association between ADHD symptoms and cognitive and behavioral functioning in children with ASD.
**Method** ADHD symptoms, defined according to Aberrant Behavior Checklist (ABC) hyperactivity subscale scores, were compared across children aged 2ΓÇô5 from a large case-control study with ASD (n = 548), TD (n = 423), and DD (n = 180). Inattention and hyperactivity items within this subscale were also explored. Within the ASD group, linear and logistic regression were used to examine how ADHD symptoms were associated with cognition as assessed by the Mullen Scales of Early Learning and adaptive functioning as assessed by the Vineland Adaptive Behavior Scales.
**Results** Mean hyperactivity subscale scores were lowest in children with TD (mean = 3.19), higher in children with DD (12.3), and highest in children with ASD (18.2; between-group $p < 0.001$). Among children with ASD, significant associations were observed with higher ADHD symptoms and poorer adaptive and cognitive functioning (adjusted beta for hyperactivity score in association with: Vineland composite = ΓêÆ5.63, p = 0.0005; Mullen visual reception scale = 2.94, p = 0.02; for the highest vs. lowest quartile of hyperactivity score, odds of lowest quintile of these scores was approximately doubled). Exploratory analyses highlighted associations with inattention-related items specifically.
**Conclusion** These results suggest ADHD symptoms may play a key role in the functioning of young children with ASD

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Res Dev Disabil. 2016.

**A CONNECTIVE TISSUE DISORDER MAY UNDERLIE ESSENCE PROBLEMS IN CHILDHOOD.**

***Baeza-Velasco C, Grahame R, Bravo JF.***

**Background**: Ehlers-Danlos syndrome hypermobility type, also known as Joint Hypermobility Syndrome (EDS-HT/JHS), is the most common hereditary disorder of the connective tissue (HDCT). It is characterized by tissue fragility, joint hypermobility and a wide range of articular and non-articular manifestations, which often appear in infancy. The clinical picture of EDS-HT/JHS is poorly known by the medical community, as is the presence of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) problems in affected children.
**Aim**: The present work reviews the clinical and empirical evidence for ESSENCE difficulties in children with EDS-HT/JHS.
**Method**: A narrative review of the literature was undertaken following a comprehensive search of scientific online databases and reference lists. This included publications of quantitative and qualitative research.
**Results**: Motor abnormality, hyperactivity/hypoactivity, inattention, speech/language, social interaction, behavioral, sleep, feeding and emotional problems are ESSENCE difficulties for which there is some evidence of an association with EDS-HT/JHS.

**Conclusion**: Children with EDS-HT/JHS present ESSENCE problems that often coexist and tend to be recognized before the HDCT. Clinicians encountering children with ESSENCE problems should consider the possibility of an underlying HDCT such as EDS-HT/JHS, probably influencing neurodevelopmental attributes in a subgroup of children. Awareness of these interconnected clinical problems might help improve early referral, diagnosis and treatment of EDS-HT/JHS

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Res Dev Disabil. 2017;60:52-64.

**ADHD SEVERITY AS IT RELATES TO COMORBID PSYCHIATRIC SYMPTOMATOLOGY IN CHILDREN WITH AUTISM SPECTRUM DISORDERS (ASD).**

***Mansour R, Dovi AT, Lane DM, et al.***

Comorbid diagnoses identified in pediatric samples have been correlated with a range of outcomes, including greater levels of emotional, behavioral, and educational impairment and the need for more intensive treatment. Given that previous research has documented high levels of comorbid Attention-Deficit/Hyperactivity Disorder (ADHD) in children with Autism Spectrum Disorders (ASD), this study closely examines the relationship between parent-reported ADHD symptoms (i.e., ConnersΓÇÖ Parent Rating Scale, Revised [CPRS-R]) and the prevalence of additional comorbid psychiatric diagnoses in a pediatric ASD sample (n-á=-á99). Regression analyses revealed that greater severity of ADHD symptomatology was significantly related to a greater number of comorbid psychiatric diagnoses, as identified using the Diagnostic Interview for Children and adolescents, 4th Edition (DICA-IV). Additionally, more severe ADHD symptoms were also associated with higher levels of symptom severity on Child Behavior Checklist (CBCL) syndrome subscales. Interestingly, increasing severity of ASD symptomatology, as measured by the Autism Diagnostic Interview, Revised (ADI-R), was not associated with a higher prevalence of comorbid psychiatric diagnoses or CBCL syndrome severity. Our study concluded that higher levels of ADHD severityΓÇönot ASD severityΓÇöwere associated with a higher prevalence of comorbid psychiatric symptomatology in school-age children with ASD. These findings may encourage clinicians to thoroughly assess ADHD symptomatology in ASD children to better inform treatment planning

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School Ment Health. 2016 Dec;8:452-60.

**PREDICTORS OF INFORMANT DISCREPANCIES BETWEEN MOTHER AND MIDDLE SCHOOL TEACHER ADHD RATINGS.**

***Yeguez CE, Sibley MH.***

A diagnosis of attention-deficit/hyperactivity disorder (ADHD) according to the Diagnostic and Statistical Manual, 5th Edition (DSM-5) is assessed in youth using ratings from both a parent and a teacher. However, individual and contextual differences between informants may lead to discrepancies in these ratings (De Los Reyes and Kazdin in Psychol Bull 131(4):483, 2005). The purpose of this study was to examine predictors of discrepancies between mother and middle school teacher reports of ADHD symptoms and related impairment. In an ethnically diverse sample of middle school students with well-diagnosed DSM-IV-TR ADHD (N = 112), we examined a range of mother and school setting characteristics that may contribute to informant discrepancies in this population. Hierarchical multiple regression analyses suggested that mothers with higher levels of education and psychopathology (i.e., ADHD symptom severity, parenting stress) may be most likely to report adolescent ADHD symptom severity that is higher than reported by teachers. Reports from general education teachers (vs. special education) were associated with lower symptom severity compared to mothers. Finally, a documented diagnosis of ADHD in the school was predictive of more severe reports from mothers. We discuss explanations for these findings and implications for assessment of middle school students with ADHD

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Seminars in Perinatology. 2016;40:497-509.

**EARLY NEURODEVELOPMENTAL OUTCOMES OF EXTREMELY PRETERM INFANTS.**

***Rogers EE, Hintz SR***.

Infants born at extreme preterm gestation are at risk for both death and disability. Although rates of survival have improved for this population, and some evidence suggests a trend toward decreased neuromotor impairment over the past decades, a significant improvement in overall early neurodevelopmental outcome has not yet been realized. This review will examine the rates and types of neurodevelopmental impairment seen after extremely preterm birth, including neurosensory, motor, cognitive, and behavioral outcomes. We focus on early outcomes in the first 18ΓÇô36 months of life, as the majority of large neonatal studies examining neurodevelopmental outcomes stop at this age. However, this early age is clearly just a first glimpse into lifetime outcomes; the neurodevelopmental effects of extreme prematurity may last through school age, adolescence, and beyond. Importantly, prematurity appears to be an independent risk factor for adverse development, but this population demonstrates considerable variability in the types and severity of impairments. Understanding both the nature and prevalence of neurodevelopmental impairment among extremely preterm infants is important because it can lead to targeted interventions that in turn may lead to improved outcomes

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Sleep Med Rev. 2016.

**INTRAINDIVIDUAL VARIABILITY OF SLEEP/WAKE PATTERNS IN RELATION TO CHILD AND ADOLESCENT FUNCTIONING: A SYSTEMATIC REVIEW.**

***Becker SP, Sidol CA, Van Dyk TR, et al***.

Substantial research attention has been devoted to understanding the importance and impact of sleep in children and adolescents. Traditionally, this has focused on mean sleep variables (e.g., a child's "typical" or average sleep duration), yet research increasingly suggests that intraindividual variability (IIV) of sleep/wake patterns (sometimes referred to as sleep variability or night-to-night variability) regularly occurs and may have implications for adjustment. A systematic search of five electronic databases identified 52 empirical studies published between 2000 and 2015 that examined correlates of sleep IIV in children and adolescents, with a recent increase in the publication rate of such studies. Identified studies were often atheoretical and included post hoc analyses, though IIV in select aspects of sleep does appear to be associated with increasing age/pubertal status, non-White race, physical and neurodevelopmental conditions (e.g., attention-deficit/hyperactivity disorder; autism), psychopathology symptoms (e.g., anxiety, depression, inattention), body weight, stress, aspects of cognitive functioning, and poorer sleep functioning/habits. The limited intervention work examining sleep IIV in adolescents is promising, though studies are needed using more rigorous intervention designs. Clinical sleep recommendations may not only need to address overall sleep duration and sleep habits but also the stability of sleep duration and timing. It will be important for future research examining sleep IIV in children and adolescents to use a developmental framework in advancing theory pertaining to the causes, mechanisms, moderators, and outcomes of sleep IIV in youth, and a conceptual model is proposed to help guide such efforts

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Toxicol Lett. 2016;259:S169.

**BLOOD LEAD LEVEL AND PRESENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN SCHOOL CHILDREN.**

***Pereira K, Aular Y, Nunez C, et al***.

**Introduction**: Lead (Pb) is a toxic metal naturally present in the earth's crust. Pb exposure may cause neurodevelopmental disorders, especially attention deficit hyperactivity disorder (ADHD).

**Objective**: To analyze the blood lead level (PbB) and the presence of ADHD in school children from first to third grade of the Bolivarian School Bìrbula II Battle of Bombon, Naguanagua Carabobo State.

**Materials and method**: Descriptive and correlational study in which 47 schoolchildren of both sexes participated. Venous blood samples for the determination of PbB were taken, and to identify children with

suspected ADHD behavior, a questionnaire for parents and teachers Conners (10 items), and home and school (48 and 28 items) was applied .We calculated descriptive statistics (average, minimum and maximum), and absolute frequencies, and percentages. Student's t test was used for differences between groups when the study variables had a normal distribution, when variables did not follow a normal distribution, nonparametric statistics (Mann-Whitney U test) were applied using the free package and PASTv.2.04 level of significance was $p < 0.05$.
**Results**: 55% of the students were female and the average age was 7.30-¦0.70 years. 91% of children had levels of PbB (10.90-¦4.20++g/dL) statistically higher ($p < 0.05$) than the permissible limit set by the Centers for Disease Control and Prevention (CDC). However, 93.7% of children regardless of sex, had PbB levels> 5++g/dL. 16 children suspected for ADHD were observed, ADHD subtypes (as parents) were combined (56.3%), 31.2% were hyperactive, and 12.5% unspecified. There were no inattentive, and ADHD (as teachers) combined (37.5%), hyperactive and inattentive (25%), and unspecified (12.5%). There was a statistically significant association ($p < 0.05$) in males with the combined subtype (ADHD as teachers).
**Conclusions**: Most students and suspected ADHD (as parents or teachers) presented PbB levels above the permissible limit set by the Centers for Disease Control and Prevention (CDC, 2012)

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Turk J Pediatr. 2016;58:94-96.

**LATE-DIAGNOSED PHENYLKETONURIA IN AN EIGHT-YEAR-OLD BOY WITH DYSLEXIA AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER.**

***Yıldız Y, Dursun A, Tokatlı A, Coşkun T, Sivri HS.***

Phenylketonuria, previously a common cause of severe intellectual disability, is a metabolic disorder now promptly diagnosed and effectively treated thanks to newborn screening programs. Here, we report a male patient presenting with dyslexia and attention-deficit hyperactivity disorder, who was diagnosed with mild phenylketonuria at eight years of age. Earlier recognition and treatment before the establishment of irreversible brain damage would have resulted in better neurobehavioural outcomes. Classical phenylketonuria and milder phenotypes of phenylalanine hydroxylase deficiency need to be considered in the differential diagnosis of all cognitive and behavioural problems of unknown cause

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Twin Res Hum Genet. 2016;19:647-51.

**GENETIC ETIOLOGIES OF COMORBIDITY AND STABILITY FOR READING DIFFICULTIES AND ADHD: A REPLICATION STUDY.**

***Wadsworth SJ, DeFries JC, Willcutt EG, et al.***

Because of recent concerns about the replication of published results in the behavioral and biomedical sciences (Ioannidis, PLoS Medicine, Vol. 2, 2005, p. e124; Open Science Collaboration, Science, Vol. 349, 2015, p. 943; Pashler & Wagenmakers, Perspectives on Psychological Science, Vol. 7, 2012, pp. 528-530), we have conducted a replication of our recently published analyses of longitudinal reading performance and attention deficit-hyperactivity disorder data from twin pairs selected for reading difficulties (Wadsworth et al., Twin Research and Human Genetics, Vol. 18, 2015, pp. 755-761). Results obtained from univariate and bivariate (DeFries & Fulker, Behavior Genetics, Vol. 15, 1985, pp. 467-473; Acta Geneticae Medicae et Gemellologiae: Twin Research, Vol. 37, 1988, pp. 205-216) analyses of data from a subset of twin pairs tested in the International Longitudinal Twin Study of Early Reading Development at post-4th grade, and its continuation into high school at post-9th grade, were compared to those from our previous report. Similar measures of reading performance, the same measures of inattention and hyperactivity/impulsivity, and similar selection criteria were used in the two studies. In general, the patterns of results obtained from these two independent studies were highly similar. Thus, these results clearly illustrate the principle that findings from studies in quantitative behavioral genetics often replicate (Plomin et al., Perspectives on Psychological Science, Vol. 11, 2016, pp. 3-23)

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REVIEW

# The potential relevance of docosahexaenoic acid and eicosapentaenoic acid to the etiopathogenesis of childhood neuropsychiatric disorders

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**Abstract** Over the last 15 years, considerable interest has been given to the potential role of omega-3 polyunsaturated fatty acids (PUFAs) for understanding pathogenesis and treatment of neurodevelopmental and psychiatric disorders. This review aims to systematically investigate the scientific evidence supporting the hypothesis on the omega-3 PUFAs deficit as a risk factor shared by different pediatric neuropsychiatric disorders. Medline PubMed database was searched for studies examining blood docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA) status in children with neuropsychiatric disorders. Forty-one published manuscripts were compatible with the search criteria. The majority of studies on attention-deficit/hyperactivity disorder (ADHD) and autism found a significant decrease in DHA levels in patients versus healthy controls. For the other conditions examined—depression, juvenile bipolar disorder, intellectual disabilities, learning difficulties, and eating disorders (EDs)—the literature was too limited to draw any stable conclusions. However, except EDs, findings in these conditions were in line with results from ADHD and autism studies. Results about EPA levels were too inconsistent to conclude that EPA could be associated with any of the conditions examined. Finally, correlational data provided, on one hand, evidence for a negative association between DHA and symptomatology, whereas on the other hand, evidence for a positive association between EPA and emotional well-being. Although the present review underlines the potential involvement of omega-3 PUFAs in the predisposition to childhood neuropsychiatric disorders, more observational and intervention studies across different diagnoses are needed, which should integrate the collection of baseline PUFA levels with their potential genetic and environmental influencing factors.

**Keywords** Docosahexaenoic acid (DHA) · Eicosapentaenoic acid (EPA) · ADHD · Autism · Juvenile bipolar disorder · Intellectual disability

## Introduction

Childhood neurodevelopmental and psychiatric disorders are known to be complex conditions of multifactorial aetiology, involving both genetic and environmental determinants. Autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), learning disability (LD), and intellectual disability (ID) are among the most common neurodevelopmental disorders, of which the estimated prevalence in Europe ranges between 1 and 5%, depending on the condition being studied (see [1] and see [2] for ASD; see [3] for ADHD; see [4] for ID; and see [5] for LD). In addition, psychiatric disorders, such as emotional disorders, represent an important public health problem. We use here the term 'emotional disorders' to refer to those psychopathological conditions encompassing mood and anxiety disorders which are estimated to affect between 1 and 6% of children and adolescents in Europe [6, 7]. Although these diagnoses

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are categorical in nature, they frequently show clinical overlap. For example, in ADHD children, approximately 20% of cases have a comorbid diagnosis of ASD [8], whereas 30–50% have a comorbid diagnosis of LD [9, 10]. Co-occurrence between ADHD and mood disorders appears to be even higher, with about 60% of ADHD patients reported to have a mood disorder [11, 12]. A frequent co-occurrence between ASD and both ID and emotional disorders has also been reported [13–15]. Knowing that a significant comorbidity exists between these disorders and that they all have a heritable component, the hypothesis that neurodevelopmental and psychiatric disorders may share risk factors at the level of biological predisposition has been raised [16]. Specifically, over the last 15 years, considerable interest has been given to the potential role of polyunsaturated fatty acid (PUFA) deficiencies for pathogenic understanding of these disorders and, subsequently, to the possible role of PUFAs as adjuvants to pharmacological treatment.

PUFAs include two series of fatty acids: omega-3 and omega-6 series. The long-chain PUFAs (LC-PUFAs) of both series are known to play major biological roles, being structural and functional components of cell membranes and having an even more profound influence in the development of the central nervous system. The omega-3 docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), in addition to the omega-6 arachidonic acid (AA), are three LC-PUFAs of particular importance for optimal brain development and functioning, having both independent and shared effects [17].

DHA and to, a lesser extent, AA are the two most abundant long-chain PUFAs in the brain, where they are key components of neuronal membranes. The metabolic precursor of DHA, i.e., EPA, although not present in large amounts in the central nervous system, stands out for its anti-inflammatory properties, which may have neuroprotective effects on brain [17].

DHA is critical for maintaining both membrane integrity and fluidity and synaptic transmission [18]. Moreover, DHA is the most abundant PUFA in photoreceptor cell membranes of the retina and in brain grey matter, making up 15–20% of the total fatty acid composition in the frontal cortex [19–21]. Thus, DHA is likely involved in executive functions, such as planning, focussed attention, and behavioural regulation, which are known to be primarily located in the frontal lobe. Accumulation of DHA in the brain is particularly relevant during the last trimester of fetal development until 2 years of age when the infant's brain undergoes a rapid increase in growth and cellular proliferation, reaching 80% of its adult size [22]. During this period, known as the 'brain growth spurt', there is an approximate 30-fold increase in DHA content [23]. Throughout childhood, DHA continues to accumulate in the brain, in association with the maturation of frontal cortex grey matter [21].

Compared to DHA, EPA concentration within brain phospholipids is typically 250–300-fold lower [17]. However, EPA, but not DHA, is a precursor of the series 3 and 5 eicosanoids, which are lipid mediators able to promote beneficial effects, such as anti-inflammation, vasodilatation and anti-aggregation. Biosynthesis of EPA-derived eicosanoids requires the enzymes cyclooxygenases (COX) and lipoxygenases (LOX). These same enzymes are also involved in the formation of the series 2 and 4 eicosanoids derived from AA that have mainly pro-inflammatory and pro-aggregatory effects [24, 25]. Consequently, as more EPA is present into cell membranes, fewer amount of enzyme will be available for converting AA into pro-inflammatory eicosanoids. AA/EPA ratio is, therefore, considered an important indicator of cellular inflammation and EPA can act as modulator of inflammation in brain tissues [26]. In contrast, due to its greater spatial size, DHA is a poor substrate for COX and LOX enzymes [26]. DHA, however, can also exert anti-inflammatory effects through the production of the 'Specialized Pro-resolving Mediators', a recently identified class of lipid mediators which prevent excessive inflammation and promote active resolution of inflammatory responses [27].

Due to the differential effects of omega-6 and omega-3 on inflammation, a balance between them is considered critical for optimal brain function and, in general, more beneficial effects are attributed to a low omega-6-to-omega-3 ratio [25].

The human body is able to endogenously synthesise DHA and EPA from their dietary essential fatty acid precursors (alpha-linoleic acid and its byproducts), but the conversion process has been shown to be highly variable and relatively inefficient [28, 29].

Approximately 0.2–8% of dietary alpha-linoleic acid is converted to EPA and less than 4% is converted to DHA [28, 30]. In women, the conversion process appears to be more efficient: approximately 21 and 9% of alpha-linoleic acid is converted to EPA and DHA, respectively [25, 30]. Given the limited conversion rate, a dietary supply of adequate amounts of preformed DHA and EPA appears to be essential to support neuronal development, not only during the prenatal period but also during infancy and childhood.

Several observational studies have been conducted in the last 30 years to investigate the potential connection between low blood levels of different PUFAs and the occurrence of childhood neuropsychiatric disorders. Since blood measures of PUFA correlate well with brain PUFA levels and intake [31, 32], the studies usually compared the blood PUFA profiles of affected children with the profiles of typically developing children. A wide range of conditions has been studied, including ADHD, autism, major depression, and juvenile bipolar disorder (JBD).

The hypothesis that omega-3 fatty acid deficiency may represent a risk factor in the pathogenesis of neuropsychiatric disorders has also driven the conduction of supplementation trials to evaluate possible beneficial effects of PUFAs in the treatment of childhood neuropsychiatric disorders [33].

The purpose of the current review is to investigate whether there is scientific evidence to support the hypothesis of omega-3 fatty acid deficiency as a risk factor shared by different neuropsychiatric disorders. Thus, we aim to systematically investigate the current body of knowledge about the association between low blood DHA and EPA levels and the risk of neurodevelopmental and psychiatric disorders in children and adolescents. We choose to focus on DHA and EPA, because—as stated before—they have an essential role in normal neural and cognitive development. To the best of our knowledge, this is the first review addressing this topic systematically. We also make a critical reflection with the goal of sensitising and encouraging further studies on blood PUFA levels of both typically developing children and those with a neuropsychiatric diagnosis.

## Method

### Search strategy

This review is reported according to the Systematic Reviews and Meta-Analyses (PRISMA) statement [34].

PubMed (1965 through March 2016) was searched by two reviewers (A. T. and A. C.) for relevant papers using a combination of indexing terms with free text searching. The form of our general search strategy was the following: ([blood] AND [docosahexaenoic acid] OR [eicosapentaenoic acid]) AND ([mental disorders] OR [psychiatric disorders] OR [psychiatric diseases]) AND ([child, preschool] OR [child] OR [adolescent]). All search criteria were specified before conducting the review but were not registered online. The electronic search was supplemented by hand searches of journals and individual article reference lists. In addition, review articles and meta-analyses were checked to identify additional studies.

### Inclusion criteria

We included in this review only original studies examining DHA or EPA status in blood components of diagnosed or typically developing children. Other inclusion criteria were as follows: (1) the values of DHA and EPA were reported in the text, tables, or supplements; (2) subjects were limited to children aged 2–18; and (3) the English language was the language of publication.

### Data collection, extraction, and quality assessment

Title, abstract, and subsequent full-text screening were carried out to determine the eligibility of potentially relevant articles on the basis of inclusion and exclusion criteria.

Data from each study were independently extracted by two reviewers (A. T. and A. C.) into a Microsoft Excel 2010 file. Extracted variables included country of study, study population (age, sample size, and condition), study design, assessment and diagnostic tools, DHA and EPA data, levels of significance, and main findings.

In the majority of studies, DHA and EPA values were expressed as percentage contribution, by weight, to total fatty acids. Thus, to make comparisons across studies easier, we converted—if published data rendered it possible—DHA and EPA values expressed in absolute values to percent values. DHA and EPA data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), based on how they were reported in the original article. If necessary, a standard error of the mean (SEM) was transformed to an SD using the conversion methods described in the Cochrane Handbook [35]. Across studies, investigators measured the fatty acid composition in various blood fractions, including plasma, serum, red blood cells (RBCs), and whole blood. Since there is no significant difference in the fatty acid composition percent of plasma and serum (see [36]), we use the term 'plasma' throughout the paper for the uniformity of discussion. Plasma fatty acid composition is considered a reflection of recent fat intake (last 24 h), whereas RBC fatty acids reflect long-term fatty acid intake (from 3 weeks to 3 months), because their turnover is much slower than that of plasma [37]. Whole blood EPA and DHA (i.e., derived from both plasma and circulating cells) have been shown to be highly correlated with that of RBCs [38].

Quality assessment of studies was carried out using an adapted version of the Newcastle-Ottawa Scale for observational studies [39]. The following items were collected: adequacy of case definition, representativeness of cases, selection of controls, definition of controls, comparability on the basis of the design or analysis (whether main potential confounders of DHA status, such as omega-3 dietary intake, were taken into account as potential explanations for observed differences between cases and controls in DHA status), and evaluation of DHA status (clear description of fatty acid analysis and the source unit for expressing blood fatty acid values).

## Results

Figure 1 presents a flow diagram depicting the selection procedure for this systematic review, together with the

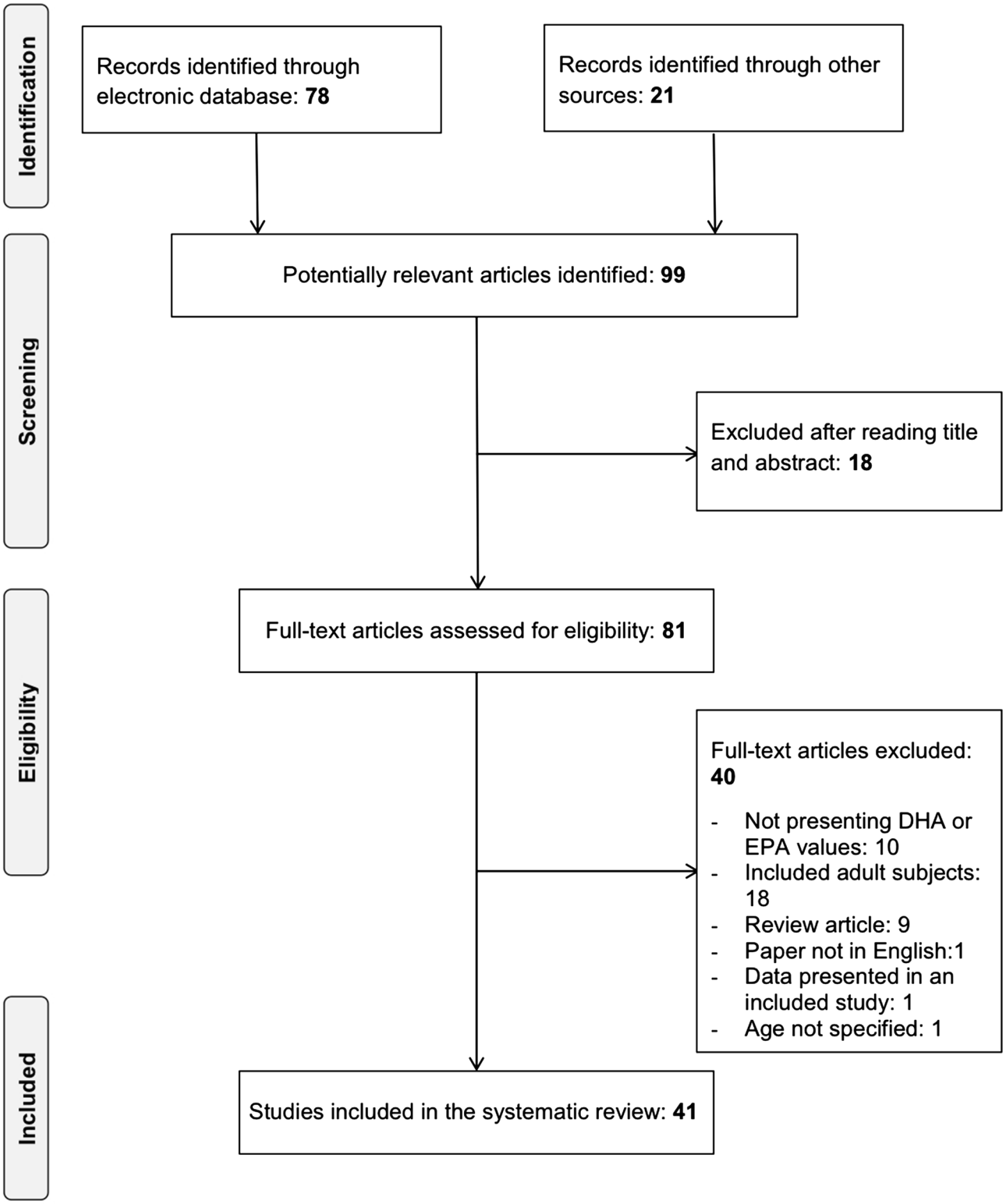


**Fig. 1** Flow diagram of the study selection process

number of articles identified. Altogether, 99 potentially relevant articles were identified and screened. After the initial screening, 81 articles were found to be relevant for the present review, and the full text of each was collected and examined. Of these papers, 41 respected all the eligible criteria and were included in the review. Conversely, 40 full-text articles were excluded due to reasons, as presented in Fig. 1.

Of these 41 studies, 24 examined the PUFA profiles of children with a diagnosis of neuropsychiatric disorder in the context of case–control studies, comparing the PUFA levels of diagnosed children with those of healthy children or those with other diseases. The other study designs were randomised clinical trials (RCTs; 9), non-randomised controlled clinical trials (CCTs; 3), open-label clinical trials (2), and cross-sectional studies without a control group (3). Of these 14 clinical trials, 4 included the recruitment of a healthy reference sample to compare blood PUFA values [40–43]. Only three of these published the PUFA values of the reference sample [41–43].

For the clarity of discussion, we have gathered the results about different disorders into distinct tables. In each table, we report blood DHA and EPA values of both cases and controls extracted from case–control studies, as well as baseline blood DHA and EPA values of both interventions and, if available, reference samples extracted from clinical trials. The studies included a total of 3743 subjects and were heterogeneous in terms of sample size, which ranged from 7 [44] to 493 [45] for clinical groups, whereas for control children, it ranged between 12 [46] and 161 [47]. Two studies involved only preschool children (2–5 years) [48, 49], 17 studies involved only school-age children (6–18 years) [43–46, 50–62], and 5 studies were conducted on adolescents (12–18 years) [47, 63–66]. In 11 studies, there was a broader age range, extending from 3 to 18 years of age [40, 42, 67–75]. In the remaining six studies, age range was not specified, as they only reported mean age [41, 76–80]. Vancassel and colleagues recruited as controls children between 1 and 19 years of age [74], whereas Sliwinski and colleagues' study accepted into their control group children from age 12 to age 20 [65]. The studies were carried out in 17 different countries. Fifteen of the populations investigated were from Europe, 12 were from North America, 7 were from Asia, 3 were from Africa, and 4 were from Oceania. The neuropsychiatric disorders examined were ADHD (20), autism (13), JBD (3), depression (1), eating disorders (2), and ID (1). In addition, the study of Montgomery and colleagues [45] involved healthy children with below-average reading ability without a diagnosis of learning disorder.

The definition and the representativeness of cases and the definition and selection of controls were adequate in the large majority of studies. However, in three studies, case definition relied partially [55] or totally [60, 77] on parent- or teacher-reported questionnaires. Of the 28 studies using a control group, most ($n = 19$) declared using age- and sex-matched subjects with no history of neuropsychiatric disorders as controls. Subjects with developmental delay were recruited as controls in three studies [49, 74, 76], whereas in Milte and colleagues' study [55], control subjects were ADHD children with no apparent learning difficulties. Cases and controls were assessed for dietary intake in only 10 of the 28 studies that used a control group. The source unit used to express blood fatty acid values was not declared in five studies [40, 53, 58, 63, 66].

### Association between blood DHA and EPA levels and ADHD

The main characteristics of the 20 studies investigating the possible association between ADHD, and DHA and EPA concentrations are shown in Table 1.

Nine out of 20 studies compared the blood levels of DHA and EPA of patients with those of a reference group of typically developing children [41, 43, 46, 51, 59, 60, 64, 68, 77]. The majority of these studies indicated lower levels of DHA in ADHD children at a significant level [43, 46, 51, 60, 68, 77] or at least showed a general trend—although not significant—in the same direction [41, 64]. Worthy of separate attention is Milte and colleagues' study [55], which involved ADHD children with and without learning difficulties and found that the former subgroup had significantly lower DHA than the latter one. Considering the six independent studies that observed significant DHA reduction in ADHD children as compared to healthy controls [43, 46, 51, 60, 68, 77], the percentage decrease in DHA ranged from 10 [77] to 35% [68]. With respect to EPA levels, the majority of the studies did not indicate any case–control difference. Only Stevens and colleagues [60] reported a significant decrease of EPA levels in children with ADHD (percentage decrease: 37.5%; specimen: plasma).

The contribution of DHA and EPA to plasma, RBCs, or total blood phospholipids exhibited a variation among geographic areas. The highest DHA value expressed as percentage of total fatty acids was found in India [41] and the lowest in Canada [59], with a six-fold variation. The highest percentage of EPA was reported in New Zealand [77], the lowest in Taiwan [68].

The relationship between blood DHA and behaviour, quality of life, neuropsychological functioning, or brain functions was also assessed in seven studies [46, 51, 55, 60, 63, 64, 66]. Three studies [46, 51, 60] observed significant negative correlations in the total sample of participants with or without ADHD between DHA levels and parental rates of ADHD symptoms or associated

**Table 1** Main characteristics of studies on ADHD

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Chen [68] | Taiwan | CCS | 58 | 4–12 | Pl<br>RBC | 5.07 ± 4.26<br>1.35 ± 0.37 | N/A<br>0.15 ± 0.02 | 52 | 4–12 | Pl<br>RBC | 3.91 ± 1.58<br>2.08 ± 0.94* | N/A<br>0.18 ± 0.11 | Area % | Diagnostic interviews with DSM-IV criteria | – |
| Colter [46] | Canada | CCS | 11 | 10–16 | RBC | 3.12 ± 0.75 | 0.51 ± 0.21 | 12 | 10–16 | RBC | 4.39 ± 1.34* | 0.64 ± 0.24 | Mol % | DSM-IV criteria, CPRS | Negative association of **DHA** with CPRS scales |
| Crippa [51] | Italy | CCS | 48 | 7–14 | WB | 1.71 ± 0.46 | 1.04 ± 0.78 | 22 | 7–14 | WB | 1.93 ± 0.53* | 1.13 ± 0.45 | % Tot FAs | DAWBA, WISC-III, ANT, CPRS, ADHD-RS, SDQ, CHQ, CGI-S, C-GAS | Negative association of whole sample **DHA** with ADHD-RS, CGI and SDQ scales. Positive association of **DHA** with CHQ<br>Negative association of **EPA** with the SDQ impact scale. Positive association of **EPA** with CHQ |
| Germano [40] | Italy | CCT | 16 | 3.5–16 | RBC | 1.99 ± 0.64 | 0.99 ± 0.44 | 36 | 3.5–16 | N/A | N/A | N/A | N/A | DSM-IV criteria, CPRS | – |
| Gow [63] | UK | CSS | 20 | 12–16 | RBC | 3.6 ± 0.85 | 0.53 ± 0.13 | – | – | – | – | – | N/A | CPRS, CTRS, ChIPS | Positive association of **DHA** with right temporal N170 amplitude in response to covert expressions of fear<br>Positive association of **EPA** with a cognitive bias in orientation to positive emotions |
| Gow [64] | UK | CCS | 29 | 12–16 | Pl | 3.18 ± 1.0 | 1.04 ± 0.49 | 43 | 12–16 | Pl | 3.64 ± 0.95 | 0.99 ± 0.44 | ng/mL | ChIPS SDQ, CPRS, CTRS, BYI-II, DASS, BIS, APSD, ICU | Negative trend association of **DHA** with ICU traits<br>Negative association of **EPA** with ICU traits |

**Table 1** continued

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Gustafsson [53] | Sweden | RCT | 1st group 37<br>2nd group 36 | 7–12 | Pl 1st group<br>Pl 2nd group<br>RBC 1st group<br>RBC 2nd group | 4.12 ± 1.16<br>4.19 ± 1.04<br>5.6 ± 0.97<br>5.89 ± 1.03 | 1.17 ± 0.44<br>1.36 ± 0.80<br>0.92 ± 0.26<br>1.02 ± 0.30 | – | – | – | – | – | N/A | DSM-IV criteria, CTRS, CPT, ADHD-RS | – |
| Johnson [54] | Sweden | RCT | 1st group 20<br>2nd group 25 | 8–18 | Pl 1st group<br>Pl 2nd group | 2.97 ± 0.82<br>3.06 ± 0.73 | 1.08 ± 0.42<br>1.08 ± 0.42 | – | – | – | – | – | Mol % | DSM-IV criteria, ADHD-RS | – |
| Joshi [41] | India | CCT | 30 | 8.0 | RBC | 5.7 ± 2.8 | 0.55 ± 0.33 | 29 | 7.5 | RBC | 5.83 ± 2.52 | 0.56 ± 0.33 | % Tot FAs | DSM-IV criteria, Parent Rating Scale | – |
| Milte [55] | Australia | CCS | 27 ADHD with LD | 7–12 | RBC | 3.26 ± 2.8 | N/A | 48 ADHD without LD | 7–12 | RBC | 3.68 ± 5.25* | N/A | % Tot FAs | Official ADHD diagnosis, CPRS, parent-reported learning difficulties, WIAT-III, WISC-III, creature counting | Positive association of whole sample **DHA** with word reading at WIAT-III |
| Milte [56] | Australia | RCT | 75 | 7–12 | RBC 1st group<br>RBC 2nd group<br>RBC 3rd group | 3.64 ± 0.95<br>3.71 ± 0.75<br>3.42 ± 0.79 | 0.61 ± 0.23<br>0.66 ± 0.30<br>0.56 ± 0.17 | – | – | – | – | – | % Tot FAs | Official ADHD diagnosis, CPRS, parent-reported learning difficulties, WIAT-III, WISC-III, Creature Counting, Sky Search Dual Task | – |
| Mitchell [77] | New Zealand | CCS | 44 | 9.1 | Pl | 3.02 ± 1.32 | 1.3 ± 0.69 | 45 | 8.7 | Pl | 3.35 ± 1.35* | 1.39 ± 0.64 | % Tot FAs | RBPC, CTRS | – |
| Sorgi [58] | USA | OPS | 9 | 8–16 | Pl | 2.30 ± 0.88 | 0.49 ± 0.12 | – | – | – | – | – | N/A | DSM-IV criteria, ADHD SC-4, CGI-S | – |

**Table 1** continued

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Spahis [59] | Canada | CCS | 37 | 6–12 | Pl | 1.14 ± 0.42 | 0.41 ± 0.18 | 35 | 6–12 | Pl | 0.94 ± 0.35* | 0.33 ± 0.12* | % Tot FAs | DISC-4, CPRS, CTRS, WISC-III | – |
| | | | | | RBC | 3.23 ± 0.98 | 0.46 ± 0.2 | | | RBC | 2.29 ± 0.98** | 0.31 ± 0.12** | | | |
| Stevens [60] | USA | CCS | 53 | 6–12 | Pl | 1.78 ± 0.45 | 0.15 ± 0.21 | 43 | 6–12 | Pl | 2.04 ± 0.58* | 0.24 ± 0.21* | Area % | CPRS, CTRS | Negative association of whole sample **DHA** with CPRS |
| | | | | | RBC | 1.61 ± 1.31 | N/A | | | RBC | 2.18 ± 1.45 | N/A | | | |
| Stevens [43] | USA | RCT | 50 | 6–13 | Pl | 1.74 ± 0.48 | 0.31 ± 0.19 | 24 | 6–13 | Pl | 2.16 ± 0.64** | 0.35 ± 0.36 | Area % | Official ADHD diagnosis, DBD | – |
| | | | | | RBC | 3.52 ± 0.83 | 0.39 ± 0.07 | | | RBC | 2.88 ± 0.4** | 0.31 ± 0.13** | | | |
| Sumich [66] | UK | CSS | 46 | 12–16 | RPC in RBC | 1.4 ± 0.67 | 0.39 ± 0.16 | – | – | – | – | – | N/A | ChIPS, CPRS, CTRS, Kaufman Brief Intelligence test | Positive association of **DHA** with EEG alpha activity. Alpha activity correlated inversely with inattention scale of CTRS<br>Positive association of **EPA** with EEG theta activity. Theta activity correlated inversely with episodic memory |
| | | | | | RPE in RBC | 4.07 ± 0.87 | 0.79 ± 0.25 | | | | | | | | |
| Vaisman [61] | Israel | RCT | 1st group 18<br>2nd group 21<br>3rd group 21 | 8–13 | Pl 1st group | 4.4 ± 1.5 | 0.7 ± 1.2 | – | – | – | – | – | % Tot FAs | Official ADHD diagnosis, CPT, TOVA | – |
| | | | | | Pl 2nd group | 4.0 ± 1.4 | 0.6 ± 0.6 | | | | | | | | |
| | | | | | Pl 3rd group | 4.8 ± 2.0 | 0.7 ± 0.5 | | | | | | | | |
| | | | | | RBC 1st group | 4.1 ± 2.1 | 0.8 ± 0.6 | | | | | | | | |
| | | | | | RBC 2nd group | 3.4 ± 1.5 | 1.0 ± 0.7 | | | | | | | | |
| | | | | | RBC 3rd group | 3.7 ± 1.5 | 1.2 ± 0.6 | | | | | | | | |
| Voigt [80] | USA | RCT | 1st group 27<br>2nd group 27 | 9.3 | Pl 1st group | 1.89 ± 0.45 | 0.32 ± 0.09 | – | – | – | – | – | Mol % | Official ADHD diagnosis, DSM-IV criteria, TOVA, CCTT, CBCL, CPRS | – |
| | | | | | Pl 2nd group | 1.96 ± 0.4 | 0.33 ± 0.12 | | | | | | | | |

**Table 1** continued

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Widenhorn-Müller [62] | Germany | RCT | 1st group 43<br>2nd group 45 | 6–12 | RBC 1st group<br>RBC 2nd group | 3.51 ± 0.59<br>3.47 ± 0.67 | 0.62 ± 0.19<br>0.58 ± 0.13 | – | – | – | – | – | % Tot FAs | DSM-IV criteria, DISYPS-II, CBCL, TRF, HAWIK-IV | – |

Age values are expressed as range or mean. DHA and EPA values are expressed as mean ± standard deviation

*Asterisks* Significant difference between cases and controls, ** $p < 0.01$, * $p < 0.05$

*CCS* case–control study, *CCT* controlled clinical trial, *CSS* cross-sectional study, *RCT* randomised controlled trial, *OLS* open-label study, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *Pl* plasma, *RBC* red blood cells, *WB* whole blood, *RPC* red blood choline phosphoglycerides, *RPE* red blood ethanolamine phosphoglycerides, *FAs* fatty acids, *N/A* data not available, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition, *CPRS* Conners' Parent Rating Scale, *DAWBA* Development and Well-Being Assessment, *WISC-III* Wechsler Intelligence Scale for Children-III, *ANT* Amsterdam Neuropsychological Task, *ADHD-RS* ADHD Rating Scale, *SDQ* Strengths and Difficulties Questionnaire, *CHQ* Child Health Questionnaire, *CGI-S* Clinical Global Impression-Severity scale, *C-GAS* Children Global Assessment Scale, *CTRS* Conners' Teacher Rating Scale, *ChIPS* Children's Interview of Psychiatric Syndromes, *BYI-II* Beck's Youth Inventories-II, *DASS* Depression, Anxiety and Stress Scales, *BIS* Barratt Impulsiveness Scale, *APSD* Anti-Social Process Screening Device, *ICU* Inventory of Callous-Unemotional Traits, *CPT* Continuous Performance Test, *WIAT-III* Wechsler Individual Achievement Test-III, *RBPC* Revised Behaviour Problem Checklist, *ADHD SC-4* ADHD Symptom Checklist-4, *DISC-4* Diagnostic Interview Schedule for Children-IV, *DBD* Disruptive Behaviour Disorders Rating scale, *TOVA* Test of Variables of Attention, *CCTT* Children Colour Trails Test, *CBCL* Child Behaviour Checklist; *DISYPS-II* Diagnostic System for Mental Disorders in Childhood and Adolescence, *TRF* Teacher's Report Form, *HAWIK-IV* Hamburg Wechsler Intelligence Scales for Children–IV

difficulties; one of these [51] reported the same inverse relationship also for EPA. Interestingly, a trend association between low DHA levels and high callous-unemotional traits among ADHD children was reported by Gow and colleagues [64]. This trend association became significant when EPA was taken into account. In addition, ADHD symptom severity was found to be negatively correlated with DHA by Crippa and colleagues [51], who also reported—for the first time—an association between lower blood levels of DHA and EPA, and poorer quality of life. Concerning neuropsychological functioning, two studies examined attentional performance on cognitive tasks [51, 55] and came to similar results, indicating a lack of association between neuropsychological outcomes of attention and DHA or EPA. However, Milte and colleagues [55] observed that increased DHA correlated significantly with reading ability. Finally, two studies explored the association between DHA and brain functions [i.e., electroencephalography (EEG) and event-related potential (ERP)] among ADHD children [63, 66]. They reported lower DHA and EPA levels being correlated with a high- and slow-frequency EEG activity reduction, respectively [66]. In addition, positive associations were found between DHA and ERP responses to facial expressions of fear and between EPA and a cognitive bias in orientation to overt expressions of happiness over both sad and fearful faces [63].

## Association between blood DHA and EPA levels and autism

The main characteristics of studies focussing on autism are shown in Table 2.

Most studies (eight out of nine studies with only healthy children as the control group) were in agreement on reporting significantly lower levels of DHA in children with autism [42, 48, 67, 69–73]. Significant DHA reduction ranged from 14 [70] to 94% [72]. Three other case/control studies [49, 74, 76] showed a tendency, although not significant, for a reduction in DHA levels. Regarding EPA levels, only one study out of six [70] indicated significantly lower levels of EPA in children with autism, with a reduction of 15.7%.

With respect to differences between geographic areas, weight percentage of DHA reached up to five-fold variation. The highest mean values were described for Italy [70], while the lowest mean values were those of Vancassel and colleagues [74] on French children. The highest EPA value in weight percentage was reported in UK [76], the lowest in USA [49].

Meguid and colleagues [42] found a significant negative correlation between DHA level and autistic behaviour according to the Childhood Autism Rating Scale (CARS).

**Table 2** Main characteristics of studies on autism

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Al-Farsi [48] | Oman | CCS | 40 | 4.1 ± 0.9 | Pl | 4.1 ± 0.3 | – | 40 | 4.1 ± 0.8 | Pl | 8.7 ± 1.1** | – | mg/mL | DSM-IV criteria | – |
| Bell [76] | UK | CCS | 45 | 7.5 | Pl | 2.58 ± 0.78 | 0.6 ± 0.29 | TD 45 DD 38 | 7.5 TD 6.0 DD | Pl TD | 2.81 ± 0.72 | 0.69 ± 0.32 | wt% | ADI-R, evidence-based guidelines | – |
| | | | | | RBC | 3.3 ± 1.04 | 0.53 ± 0.24 | | | Pl DD | 2.57 ± 0.80 | 0.60 ± 0.26 | | | |
| | | | | | | | | | | RBC TD | 3.61 ± 0.93 | 0.58 ± 0.20 | | | |
| | | | | | | | | | | RBC DD | 3.36 ± 0.95 | 0.54 ± 0.22 | | | |
| Brigandi [67] | USA | CCS | 121 | 3–17 | RBC | 1.4 ± 0.74 | 0.22 ± 0.22 | 110 | 3–17 | RBC | 1.76 ± 0.89** | 0.22 ± 0.22 | % Tot FAs | DSM-IV criteria, CARS | – |
| Bu [49] | USA | CCS | 40 | 2.1–5 | RBC | 2.12 ± 1.38 | 0.3 ± 0.47 | TD 20 | TD 2.3–5 | RBC TD | 2.17 ± 1.00 | 0.21 ± 0.14 | wt% | DSM-IV criteria, CPRS | – |
| | | | | | | | | DD 20 | DD 2–4.6 | RBC DD | 1.81 ± 0.64 | 0.22 ± 0.12 | | | |
| El-Ansary [69] | Saudi Arabia | CCS | 26 | 4–12 | Pl | 0.38 ± 0.1 | 0.28 ± 0.14 | 26 | 4–11 | Pl | 0.75 ± 0.34** | 0.33 ± 0.11 | mmol/L | ADI-R, ADOS, 3DI | – |
| Ghezzo [70] | Italy | CCS | 21 | 5–12 | RBC | 4.8 ± 1.08 | 0.43 ± 0.16 | 20 | 5–12 | RBC | 5.62 ± 0.67** | 0.51 ± 0.14* | % Tot FAs | DSM-IV criteria, ADOS, CARS, PEP-3, Leiter-R | – |
| Meguid [42] | Egypt | CCT | 30 | 3–11 | WB | 0.95 ± 0.2 | – | 30 | 3–11 | WB | 2.85 ± 0.65** | – | µg/mL | DSM-IV criteria, CARS | Negative association of **DHA** with CARS before treatment in the ten children with autism who did not improve clinically |
| Mostafa [71] | Egypt | CCS | 30 | 4–12 | Pl | 0.59 ± 0.76 | – | 30 | 4–12 | Pl | 2.37 ± 0.55** | – | µg/ml | DSM-IV criteria, CARS | – |

**Table 2** continued

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Mostafa [73] | Egypt | CCS | 80 | 4–12 | Pl | 0.28 ± 0.03 | – | 80 | 4–12 | Pl | 0.98 ± 0.3** | – | mmol/L | DSM-IV criteria, CARS | – |
| Mostafa [72] | Saudi Arabia | CCS | 100 | 3–10 | Pl | 3.1 (0.8) | – | 100 | 3–10 | Pl | 0.18 (1.2)** | – | µg/ml | DSM-IV criteria, CARS Questionnaire on Pediatric Gastrointestinal Symptoms | – |
| Sliwinski [65] | Belgium | CCS | 16 | 12–18 | Pl | 3.40 (no sd reported) | 0.69 (no sd reported) | 22 | 12–20 | Pl | 2.83* (no sd reported) | 0.67 (no sd reported) | wt% | ADI-R, CBCL, YSR, ABC | – |
| Vancassel [74] | France | CCS | 15 | 3–17 | Pl | 1.1 ± 0.2 | – | DD 18 | 1–19 | Pl | 1.4 ± 0.7 | – | wt% | DSM-IV criteria | – |
| Voigt [75] | USA | RCT | 48 | 3–10 | Pl | 117.0 ± 80.7 | 54.6 ± 33.6 | – | – | – | – | – | µmol/L | DSM-IV criteria, CARS, CGI-I, BASC, ABC, CDI | – |

Age values are range or mean ± standard deviation. DHA values are expressed as mean ± standard deviation or median (interquartile range). If not specified, the control group did not have any neuropsychiatric diagnoses

*Asterisks* Significant difference between cases and controls, ** $p < 0.01$, * $p < 0.05$

*CCS* case–control study, *CCT* controlled clinical trial, *RCT* randomised controlled trial, *TD* typically developing children, *DD* developmentally delayed children, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *Pl* plasma, *RBC* red blood cells, *WB* whole blood, *FAs* fatty acids, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, *ADI-R* Autism Diagnostic Interview—Revised, *CARS* Childhood Autism Rating Scale, *ADOS* Autism Diagnostic Observation Schedule, *3DI* Developmental Dimensional Diagnostic Interview, *PEP-3* Psychoeducational Profile-3, *Leiter-R* Leiter International Performance Scale—Revised, *CBCL* Child Behaviour Checklist, *YSR* Youth Self-Report, *ABC* Aberrant Behaviour Checklist, *CGI-I* Clinical Global Impression-Global Improvement Scale, *BASC* Behaviour Assessment Scale for Children, *CDI* Child Development Inventory

**Table 3** Main characteristics of studies on mood disorders

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Clayton [50] | Australia | CCS | 15 with JBD | 9–18 | RBC | 22.08 ± 8.65 | 3.37 ± 1.0 | 15 | 9–18 | RBC | 24.61 ± 9.23* | 3.69 ± 1.04* | µg/mL | WASH-U-K-SADS, YMRS, P-YMRS, HAM-D, CGI-S, C-GAS, CBCL, BYI, Tripartite Mood Rating Scale | Negative association of **DHA** with clinician-rated depression severity on the CGI and participant ratings of aggression on the BYI. |
| Gracious [52] | USA | RCT | 1st group 26 with JBD<br>2nd group 19 with JBD | 6–17 | Pl 1st group<br>Pl 2nd group | 1.09 ± 0.32<br>1.03 ± 0.37 | 0.45 ± 0.35<br>0.37 ± 0.18 | – | – | – | – | – | % Tot FAs | K-SADS-PL, YMRS, CDRS-R, CPRS modified for psychosis, SEFCA, K-SADS Suicidality subscale, GAF, CGI-BP | Negative association of **EPA** with global severity of bipolar illness on the CGI-BP |
| Pottala [47] | USA | CCS | 150 with a diagnosis of depression | 13–18 | RBC | 3.15 (0.82) | 0.32 (0.16) | 161 | 13–18 | RBC | 3.39 (1.2)* | 0.32 (0.16) | wt% | ICD-9 criteria | – |
| Wozniak [44] | USA | OLS | 7 with JBD | 6–17 | RBC<br>Pl | 1.09 ± 0.65<br>0.93 ± 0.45 | 0.54 ± 0.88<br>0.46 ± 0.75 | – | – | – | – | – | % Tot FAs | K-SADS, YMRS, CDRS, CGI-S, BPRS | – |

Age values are range or mean ± standard deviation. DHA values are expressed as mean ± standard deviation or median (interquartile range). If not specified, the control group did not have any neuropsychiatric diagnoses

*Asterisks* Significant difference between cases and controls, ** $p < 0.01$, * $p < 0.05$

*CCS* case–control study, *RCT* randomised controlled trial, *OLS* open-label study, *JBD* juvenile bipolar disorder, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *Pl* plasma, *RBC* red blood cells, *FAs* fatty acids, *WASH-U-K-SADS* Washington University at St Louis Schedule for Affective Disorders and Schizophrenia, *YMRS* Young Mania Rating Scale, *P-YMRS* Parent Young Mania Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *CGI-S* Clinical Global Impression-Severity scale, *C-GAS* Children Global Assessment Scale, *CBCL* Child Behaviour Checklist, *BYI* The Beck Youth Inventories, *K-SADS-PL* Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version, *CDRS-R* Children's Depression Rating Scale, *CPRS* Children's Psychiatric Rating Scale, *SEFCA* Side Effects Form for Children and Adolescents, *GAF* Global Assessment of Functioning, *CGI-BP* Clinical Global Impression for Bipolar Disorder, *ICD-9* International Classification of Diseases Ninth Revision, *BPRS* Brief Psychiatric Rating Scale

**Table 4** Main characteristics of studies on intellectual disabilities or learning difficulties

| References | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Montgomery [45] | UK | CSS | 493 poor readers children | 7–9 | WB | 1.9 ± 0.53 | 0.56 ± 0.2 | – | – | – | – | – | % Tot FAs | BAS-II, CPRS, CTRS | Positive association of **DHA** and **EPA** with reading scores and working memory performance. Negative association of **DHA** with CPRS scales |
| Neggers [57] | South Korea | CCS | 31 with ID | 6–12 | Pl | 2.93 ± 1.71 | 0.47 ± 0.28 | 31 | 6–12 | Pl | 5.14 ± 1.03** | 0.42 ± 0.22 | % Tot FAs | DSM-III-R criteria, DSM-IV criteria | Negative association of **DHA** with ID |

Age values are range. DHA values are expressed as mean ± standard deviation. If not specified, the control group didn't have any neuropsychiatric diagnoses

*Asterisks* Significant difference between cases and controls, ** $p < 0.01$, * $p < 0.05$

*CSS* cross-sectional study, *CCS* case–control study, *ID* intellectual disabilities, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *Pl* plasma, *WB* whole blood, *FA* fatty acids, *BAS-II* British Ability Scales-II, *CPRS* Conners' Parent Rating Scale, *CTRS* Conners' Teacher Rating Scale, *DSM-III* Diagnostic and Statistical Manual of Mental Disorders Third Edition—Revised, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

**Table 5** Main characteristics of studies on eating disorders (anorexia nervosa)

| First author | Country | Study type | Characteristics of cases | | | | | Characteristics of controls | | | | | Source unit | Main assessment and diagnostic tools | Correlation between DHA/EPA and other measures |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No | Age | Specimen | DHA | EPA | No | Age | Specimen | DHA | EPA | | | |
| Swenne [78] | Sweden | CCS | 220 | 15.3 | PI | 4.20 ± 1.37 | 1.13 ± 0.66 | 39 | 15.5 | PI | 4.0 ± 0.97 | 1.04 ± 0.6 | % Tot FAs | DSM-IV criteria | – |
| | | | | | RBC | 4.82 ± 1.19 | 1.05 ± 0.46 | | | RBC | 4.88 ± 0.85 | 0.97 ± 0.27 | | | |
| Swenne [79] | Sweden | CCS | 24 12 of them diagnosed with depression | 14.3 | RBC | 4.71 ± 0.73 | 0.88 ± 0.31 | 39 | 15.5 | RBC | 4.88 ± 0.85 | 0.97 ± 0.27 | % Tot FAs | DSM-IV criteria | – |

Age values expressed as mean. DHA values are expressed as mean ± standard deviation. If not specified, the control group did not have any neuropsychiatric diagnoses

*Asterisks* Significant difference between cases and controls, $^{**}p < 0.01$, $^{*}p < 0.05$

*CCS* case–control study, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *PI* plasma, *RBC* red blood cells, *FAs* fatty acids, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders Fourth Edition

### Association between blood DHA and EPA levels and mood disorders

Only two [47, 50] of the four reviewed studies on mood disorders (see Table 3 for the main characteristics of the studies) compared the blood DHA and EPA values of patients with those of healthy controls of similar age.

One reported in patients with JBD compared with controls a significant reduction in RBC concentrations of 10% for DHA, and of 8.7% for EPA, respectively [50]; the other reported a slight but significant reduction of DHA levels in a clinical group of depressed patients [47]. It is noteworthy that Clayton and colleagues depicted a negative relationship between DHA concentration and the clinician ratings of depression severity [50], whereas Gracious and colleagues found a negative association of EPA with severity of bipolar illness [52].

### Association between blood DHA and EPA levels and intellectual disabilities or learning difficulties

Key characteristics of the studies are summarised in Table 4.

Only Neggers and colleagues [57] compared the plasma fatty acid composition between children with ID and age-matched healthy controls from South Korea. They found a 43% reduction in DHA levels in cases compared to controls and a significant inverse association between plasma DHA and ID, while they did not reported significant differences for EPA levels.

With respect to LD, Montgomery and colleagues [45] reported that better reading ability and working memory performance were positively associated with both DHA and EPA in UK mainstream schoolers.

### Association between blood DHA and EPA levels and eating disorders

Two studies from the same research group in Sweden [78, 79] examined DHA and EPA status in adolescent girls with anorexia nervosa (see Table 5 for details), finding that the proportions of DHA or EPA in plasma and red blood cell did not differ from controls.

However, a subset of patients with comorbid depression exhibited lower proportions of DHA compared to those without depression [79].

## Discussion

The aim goal of this review was to investigate the current body of knowledge about the association between blood DHA and EPA levels and the risk for different

neurodevelopmental and psychiatric disorders in children and adolescents across different countries all over the world. The most robust data we observed were those from studies examining blood DHA in ADHD and autism, as the large majority of findings showed a significant decrease in DHA levels in patients in comparison with typically developing children. Few other studies indicated an opposite pattern of findings [59, 65], although their generalisability might be limited by factors, such as small sample size [65] or founder effect experienced by the original population, which imply the loss of genetic variation [59]. The percentage decrease in blood DHA ranged from 10 to 35% in ADHD, whereas for children with autism, the range was even wider, ranging from 14 to 94%. For the other conditions examined—depression, bipolar disorder, intellectual disabilities, learning difficulties, and eating disorders—the literature is still too limited at this time to allow for any firm conclusions. Nonetheless, with the notable exception of eating disorders, findings on these conditions were in line with results from the ADHD and autism studies, showing decreases in the levels of DHA for clinical groups.

Although not entirely concordant, the findings from articles examined in the present review support the hypothesis that a poor DHA status might be involved in the pathophysiology of some neurodevelopmental and psychiatric disorders. This hypothesis is particularly strengthened by the consistent and systematic observation of a similar pattern of results across different diagnoses, different geographical areas, and different blood sample specimens revealed by the present review. Within the exception represented by eating disorders, anorexia nervosa is the only condition wherein the findings were consistently coherent in showing a lack of association with DHA status. However, data are hard to interpret in this case, given the abnormal eating habits that characterise the disorder. Interestingly, we found that when anorexic patients had comorbid depression, blood DHA levels saw a reduction compared to the non-depressed group, in agreement with reviewed studies on mood disorders that indicate an association between lower DHA levels and clinical condition.

The suggestion of a possible involvement of DHA in neurodevelopmental and psychiatric disorders seems to also be supported by the significant relationship between blood DHA status and behavioural measures. Specifically, among children with autism, a statistically negative correlation between levels of autistic behaviour, as measured by the CARS, and DHA levels was reported by Meguid and colleagues [42]. Moreover, in children and adolescents with JBD, DHA status was negatively correlated with clinician-rated severity of depression [81]. Other compelling suggestions come from studies that tested correlations in mixed samples of clinical (ADHD) and non-clinical children—regardless of diagnostic category—where measures were more likely to be distributed along a continuum ranging from well-functioning to mild-to-severe symptomatology. Higher blood DHA was found to be associated with reduced ADHD symptoms, such as lack of attention and excessive motor activity, as well as lower oppositional behaviour and better physical and psychosocial functioning [46, 51, 60]. These results seem to support the view that DHA, besides having an involvement in the etiopathogenesis of neuropsychiatric disorders, has an important role in promoting normal development and functioning. Data on neuropsychological performance, however, returned weaker results, as no reviewed study observed an association between DHA and attentional performance; of the three studies exploring the association between DHA and reading ability, two (Milte and colleagues in a sample composed of ADHD children [55] and Montgomery and colleagues in a sample of poor readers [45]) found a significant positive correlation, whereas the other did not (Crippa and colleagues in a sample composed of ADHD and healthy controls [51]). Another aspect worthy of attention is that DHA seems to be associated with emotional processing, as lower DHA was found to be associated with higher self-reported callous-unemotional traits and poorer brain response to facial expressions of fear, both of which are features related to conduct problems [63, 64].

Contrary to what has been observed for DHA, results from case–control comparisons of blood levels were too inconsistent to conclude that EPA could be associated with any of the neuropsychiatric conditions examined. The discrepancy between findings upon EPA compared to DHA becomes more evident when looking at neurodevelopmental disorders, i.e., ADHD, ASD, and ID. However, results of correlation analyses from ADHD and mood disorder studies using both behavioural and electrophysiological measurements indicate that, despite not being associated with core diagnostic features, EPA might modulate children's emotional state [51, 63, 64], global functioning [51], and bipolar illness severity [52]. Indeed, these observational findings suggest a role of EPA in supporting emotional well-being and appear to be in good agreement with those of RCTs involving adults with mood disorders, which have shown that EPA is more effective than DHA in treating depression [82].

At the biological level, there are several possible mechanisms by which a lack of DHA or EPA could exert an effect on brain functioning and, ultimately, on emotion, behaviour, and cognition. One way is through immune function, as a relative lack of omega-3 increases the tendency for inflammation, which in turn can alter neuronal morphology and function, resulting in possible behavioural or cognitive disorders [83]. Another mechanism is related to neurotransmitter function. It has been shown that omega-3 deficiency affects membrane fluidity and receptor functions, leading

to impaired neurotransmission of serotonin and dopamine in particular, both of which are involved in ADHD, ASD, and mood disorders [83–85].

Primary causes underlying both the DHA deficiency observed in children with a neuropsychiatric diagnosis and the association observed between lower EPA levels and emotional problems are probably multifactorial and involve constitutional as well as environmental determinants. Recent research is trying to clarify this issue, defining which factors could influence fatty acids' status. Amongst the environmental factors, an omega-3-deficient diet has been linked with a higher risk for many different health problems, both physical and mental, such as cardiovascular disease, autoimmune disorders, and mood disorders [86, 87]. A low supply of preformed omega-3 EPA and DHA and the consequent increase in the omega-6-to-omega-3 ratio reflects the typical diet in Western countries. During the last 100 years, the omega-6-to-omega-3 ratio in average Western-type diet underwent an increase from about 3:1 to approximately 20:1 [30]. This increase is probably related to the widespread use of seed- and vegetable oils rich in omega-6, such as soybean oil, corn oil, and safflower oil. Asian and Mediterranean populations, on the other hand, generally consume more foods rich in omega-3 and have a more balanced omega-6-to-omega-3 intake in their diet. An indication of the difference in omega-3 dietary intake across geographic areas was also provided by the studies reviewed here. Accordingly, higher DHA values were observed in Asian countries, such as South Korea and India, and in coastal European countries, such as Italy and Sweden, while the highest EPA levels were reported for New Zealand, together with Israel and Italy. Conversely, as we moved towards Western countries, such as the USA or Canada, we observed—compared to the former countries—the lowest DHA and EPA values, showing up to a six- and nine-fold variation, respectively. Interestingly, even in countries with probable higher DHA consumption, such as South Korea, Taiwan, or Italy, we observed a significant difference in blood DHA values between clinical and non-clinical groups, which appear not to be related to differences in omega-3 dietary intake [51, 57, 68]. This observation leads to the additional consideration of constitutional factors as potential modulators of omega-3 status, as might be the conversion efficiency of fatty acid precursors to their long-chain derivates, including DHA and EPA. Conversion efficiency has been shown to be associated with genetic variability in the fatty acid desaturase (FADS) gene cluster, which codes for enzymes that metabolise omega-3 PUFAs. Caspi and colleagues [88], for instance, indicated an association between a child's genotype for single-nucleotide polymorphism (SNP) rs174575 within FADS and his or her AA and DHA levels. In addition, FADS minor allele carriers have been reported to have lower EPA levels [89]. Another association of a SNP in the FADS gene cluster, rs498793, was described in ADHD children [90], suggesting a possible correlation between genes that regulate fatty acid metabolism and ADHD. In the last few years, studies investigating the efficacy of omega-3 PUFA supplementation started to weigh these gene–diet interaction effects to explain inter-individual variability in blood PUFA levels after fish oil consumption [91]. Only a small number of RCTs in the literature have measured the baseline PUFA status or genetic constitution of participants. Future observational, matched case/control studies could help to deepen knowledge about multiple genetic and environmental factors underlying blood levels of omega-3 through the collection of actual dietary intake of omega-3 PUFAs and genotypic data, in addition to baseline PUFA levels. Having these measurements can also help to better characterise more vulnerable groups, for whom omega-3 supplementation may be more efficacious.

Finally, a recent meta-analysis [92] has indicated a small evidence of benefit from omega-3 supplementation limited to ADHD children with low levels of blood omega-3 at baseline. The decision to promote omega-3 supplementation should, therefore, be guided by scientific evidence coming from randomised intervention controlled trials, carefully designed in terms of blood PUFA levels, dietary intake, and genetic constitution.

In conclusion, the present review supports the hypothesis that DHA abnormalities may play a role in the predisposition towards different childhood developmental and psychiatric disorders, regardless of geographic context. Although more studies are required, there are scientific grounds for considering ADHD, autism, ID, and mood disorders part of a 'phospholipid spectrum disorder', which comprise conditions characterised by the involvement—at least to some extent—of DHA abnormalities [83, 93]. DHA alteration may hence represent a promising biomarker that can help make a more precise and earlier diagnosis, as well as suggest opportune, tailored omega-3 supplementation, or diet interventions. EPA, on the other hand, appears less plausible as biological marker for childhood neuropsychiatric disorders, but seems to have a role in reducing symptoms severity and functional impairment, and, eventually, it may act as a promoter of emotional well-being. These observations support the hypothesis—also confirmed by several RCTs—that higher dose of EPA has significant beneficial effects on neuropsychiatric disorders [94, 95].

There were some limitations in the present review. These results should be interpreted while keeping in mind that the different source units on which the PUFA analyses were performed (plasma, whole blood, and RBC) represent a possible case of heterogeneity making more difficult the interpretation of blood biochemical measures, making data difficult to compare between different works. Indeed, PUFA levels sensibly

vary not only according to the analytical method or the technique used to prepare samples but mostly according to the type of source unit on which the analysis is carried out, as demonstrated by Risè and colleagues [37] and confirmed by the meta-analysis of Fekete and colleagues [96]. Although there were no a priori language limitations, only papers in English were considered for the review; furthermore, the authors of the articles were not contacted if blood DHA values were not reported in the text. This limited our ability to fully report and compare results published in the literature. Nevertheless, due to the significant heterogeneity of the studies included, we feel that these limitations have not biased our major findings. Another limitation of the present work is that we did not contact experts in the field to identify additional possible unpublished data. Since we focussed on observational data, we cannot indicate any causal relationship, as the strongest evidence about a causal role can only be provided by RCTs. Supplementation studies have provided some promising evidence that DHA plus EPA can have beneficial effects on neuropsychiatric disorders [42, 81, 94, 95]. However, to elucidate the issue, there is a strong need for further observational and intervention studies investigating different childhood psychiatric disorders through large sample sizes and the collection of both baseline PUFA levels and potential influencing factors, such as diet and genotype.

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**Compliance with ethical standards**

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Neuropsychology

# Evaluation of Relational Reasoning by a Transitive Inference Task in Attention-Deficit/Hyperactivity Disorder

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# Evaluation of Relational Reasoning by a Transitive Inference Task in Attention-Deficit/Hyperactivity Disorder

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***Objective:*** Here we explored whether children with ADHD have a deficit in relational reasoning, a skill subtending the acquisition of many cognitive abilities and social rules. ***Method:*** We analyzed the performance of a group of children with ADHD during a transitive inference task, a task requiring first to learn the reciprocal relationship between adjacent items of a rank ordered series (e.g., A>B; B>C; C>D; D>E; E>F), and second, to deduct the relationship between novel pairs of items never matched during the learning (e.g., B>D; C>E). ***Results:*** As a main result, we observed that children with ADHD were impaired in performing inferential reasoning problems. The deficit in relational reasoning was found to be related to the difficulty in managing a unified representation of ordered items. ***Conclusion:*** The present finding documented a novel deficit in ADHD, contributing to improving the understanding of the disorder.

*Keywords:* ADHD, inferential reasoning, problem solving



Inferential reasoning is the ability to conclude the relationship among ideas or items by using logical processes and information or facts previously learned (Preston & Eichenbaum, 2013; Ryan, Moses, & Villate, 2009; Vasconcelos, 2008; Zeithamova, Schlichting, & Preston, 2012). With regard to an instance, it could be possible to conclude that Tom is taller than John after experiencing the following high-hierarchy; Paul > Tom > Marc > John > Luc. This ability is involved in several aspects of our daily life. For example, it subtends the mathematical abilities or the comprehension of the reciprocal relationships between the roles of the individuals of a social context.

The efficient use of inferential reasoning, requires the correct learning and storage of different memories and the ability to make flexible relational links between them, for instance, by encoding items with common elements (Moses, Villate, Binns, Davidson, & Ryan, 2008; Ryan et al., 2009; Schlichting & Preston, 2015).

To study the cognitive abilities involved in inferential reasoning controlled versions of the Transitive Inference (TI) tasks have been developed experimentally (Acuna, Eliassen, Donoghue, & Sanes, 2002; Brunamonti, Genovesio, Carbè, & Ferraina, 2011; Bryant & Trabasso, 1971; Vasconcelos, 2008; Zeithamova, Dominick, & Preston, 2012; Zeithamova et al., 2012). A typical TI task is divided in a *learning* and in a *test* phase. During the learning phase, it is required to learn the reciprocal relationships between pairs of stimuli of a rank ordered set, for example, A > B; B > C; C > D; D >E; E > F. In the test phase, it is required to deduct the relationship between items never paired during the learning as:

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A>C, A>D, A>E, A>F, B>D, B>E, B>F, C>E, C>F, D>F. The TI task has been employed to evaluate inferential reasoning abilities in humans and in several animal species to verify whether they are able to solve inferential reasoning problems (for review see Vasconcelos, 2008), in children (Bryant & Trabasso, 1971; Wright & Smailes, 2015), as well as in patients with brain injuries (Koscik & Tranel, 2012; Waechter, Goel, Raymont, Kruger, & Grafman, 2013). The picture which has emerged from these studies is that TI is a complex task which solution relies on different cognitive abilities (Libben & Titone, 2008; Moses, Ostreicher, & Ryan, 2010; Ryan et al., 2009; Solomon, Frank, Smith, Ly, & Carter, 2011) involving different brain systems (Brunamonti et al., 2014; Moses et al., 2008; Preston & Eichenbaum, 2013). The main mechanisms raised to account for TI task performance are a *relational flexibility* higher-level mechanism and lower level *associative strategies* (Libben & Titone, 2008; Moses et al., 2008). The *relational flexibility* mechanism counts on the encoding of the reciprocal relationship between the items within a unified mental representation, which is then explored in order to make comparisons in the case of inexperienced pairs. Strategies based on this cognitive mechanism require the temporary activation of a spatially organized mental schema of the ranked items, and the comparison between their relative positions (Acuna et al., 2002; Brunamonti et al., 2014; Libben & Titone, 2008; Zeithamova et al., 2012). In fact, both spatial and nonspatial ordered information were often found to be cognitively represented as a spatially organized "mental line" (Brunamonti, Falcone, Genovesio, Costa, & Ferraina, 2012; Holmes & Lourenco, 2011; Prado, Noveck, & Van Der Henst, 2010; Previtali, de Hevia, & Girelli, 2010; Schwarz & Keus, 2004; Shaki & Fischer, 2008). In a TI task, the mental line is represented with item A on one end (e.g., right), item F on the other end (e.g., left), and items B, C, D, and E located linearly between (Brunamonti et al., 2011; Chen, Swartz, & Terrace, 1997; D'Amato & Colombo, 1990; Prado et al., 2010; Roberts & Phelps, 1994). To properly solve TI tasks, it is required to maintain the linear representation of the ordered items active by efficient working and long-term memory abilities and to extract reciprocal representation of the mental line (Brunamonti et al., 2011, 2014; Libben & Titone, 2008).

Conversely, the *associative strategies* count on the reinforcement history of each item during the learning phase. A way to account for the reinforcement history is to consider that during the learning phase the two extreme items A (always the winner) and F (always the looser) acquire opposite strength in driving the choice. The intermediate items, with a probability to be chosen close to 50%, acquire intermediate value strengths, proportional to their proximity to the two extreme items (Frank, Rudy, & O'Reilly, 2003). Therefore, a strategy relying on the *relational flexibility* could be favored in comparing two middle items in which their value is balanced. On the contrary, if one of the extreme items occurs during a pair comparison, the choice is likely driven by its strength to attract the response, and a decision relying on the associative mechanism is more likely adopted.

Furthermore, if during the test phase, pairs of items used during learning are presented, a retrieval process mediated by long-term memory is thought to intervene (Frank et al., 2003; Heckers, Zalesak, Weiss, Ditman, & Titone, 2004; Ryan et al., 2009).

The complexity of TI tasks is believed to be a valuable tool to estimate the efficiency of the cognitive functions involved in the task and the integrity of the underlying neural circuits in population of patients with psychiatric diseases (Titone, Ditman, Holzman, Eichenbaum, & Levy, 2004), in older age populations (Moses et al., 2010; Ryan et al., 2009) or in neurodevelopmental disorders (Solomon et al., 2011). For example, it has been observed that adults suffering from autism spectrum disorders failed to solve TI tasks relying on the associative learning strategy whereas they were good as controls in solving problems through the relational reasoning mechanism (Solomon et al., 2011).

In Attention-Deficit/Hyperactivity Disorder (ADHD), deficits in attention, working memory, and executive control, but also in learning, have been regularly observed in both children and adult populations (Di Trani et al., 2011; Pani et al., 2013; Rhodes, Park, Seth, & Coghill, 2012; Skodzik, Holling, & Pedersen, 2013). Even if the neuropsychological deficits found in ADHD are strictly entailed in inferential reasoning, this ability is not yet explored in this population of children.

We were interested in understanding whether children with ADHD proficiently solve a six-item TI task and to find out which strategy they adopt, whether they rely their performance more on a relational flexibility mechanism or on an associative strategy. To better clarify the cognitive processes involved in inferential reasoning, we also explored the relationship between working memory, long-term memory, linear spatial organization measures obtained from neuropsychological tasks and the results in TI task.

## Method

### Participants

Thirty-seven (33 males) with diagnosis of ADHD and 33 typically developing (TD) children (29 males) were included in the study. Children with ADHD were recruited form the Child Neuropsychiatry Unit at the Bambino Gesù Children's Hospital, and TD children from local primary and secondary schools. For both groups, exclusion criteria were: IQ below 85, as assessed by the Colored Progressive Matrices (CPM; Raven, 2008); evidence of neurological disorders, pervasive developmental disorders, and receptive language disorders. The two groups did not differ for Chronological Age (CA; ADHD: 10.2 ± 1.1; TD: 9.9 ± 1.1; $t_{68} = 1.0$; $p = 0.31$) and for IQ (ADHD: 108.3 ± 13.0; TD: 111.5 ± 12.5; $t_{68} = 1.0$; $p = 0.3$).

Children with ADHD underwent a child psychiatric examination conducted by experienced developmental psychiatrists and neuropsychologists. ADHD diagnosis was based on developmental history, extensive clinical examination and the semistructured interview K-SADS-PL (Kaufman et al., 1997; Kaufman, Brent, Rao, & Ryan, 2004) conducted to parent and child separately. Following the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM–5*; American Psychiatric Association, 2013), children with ADHD were characterized as: 28 fulfilled diagnostic criteria for ADHD Combined presentation, 2 for ADHD Hyperactive-Impulsive and none for the ADHD Inattentive presentation. Patients with ADHD NOS (Not Otherwise Specified) were not included in the study.

All participants and their parents gave written informed consent after receiving a comprehensive description of the study. The study was approved by the local Ethics Committee (reference number: 1111_OPBG_2016).

## Measures: Transitive Inference Task

All participants were submitted to a computerized TI task adapted for children. The task was composed by the learning phase and the test phase.

During the learning phase the participants were required to learn the relationship between 6 items (black and white bitmaps −30 × 30 mm - abstract images, each with the same proportion of white area over a black background) that were ranked arbitrarily by one of the authors (Figure 1, *Panel A*; A > B > C > D > E > F). To allow the children to figure out the relationship between the six items, they were instructed to select the higher between adjacent items in the sequence (AB, BC, CD, DE, EF) by using a trial and error strategy. This learning phase was composed by two steps: a *study phase* and a *recall phase*. During the study phase, each pair of the same adjacently ranked items (for instance AB) were presented in blocks of 15. Each block was repeated until the percentage of correct responses was at least 80% for each pair. Then, the next pair (for instance BC) was presented with the same rule. Once the participant reached the learning criterion for all pairs, they moved to the recall phase. In this phase, adjacent studied pairs were presented randomly in a block of 100 trials (20 presentations of each pair, 10 times with the target item in the upper position and 10 times in the lower position). At the end of each block an automated procedure provided to the participant a feedback on his or her performance by displaying on the screen a number of smiley faces proportional to the proportion of correct responses (☺ < 20%; ☺☺ = > 20 < 40%; ☺☺☺ = > 40 < 60%; ☺☺☺☺ > 60 < 80%; ☺☺☺☺☺ = > 80%). Children were told that they could move to the test phase once they achieved at least four smiley faces. One or more blocks of 100 trials were presented until the percentage of correct responses reached the criterion.

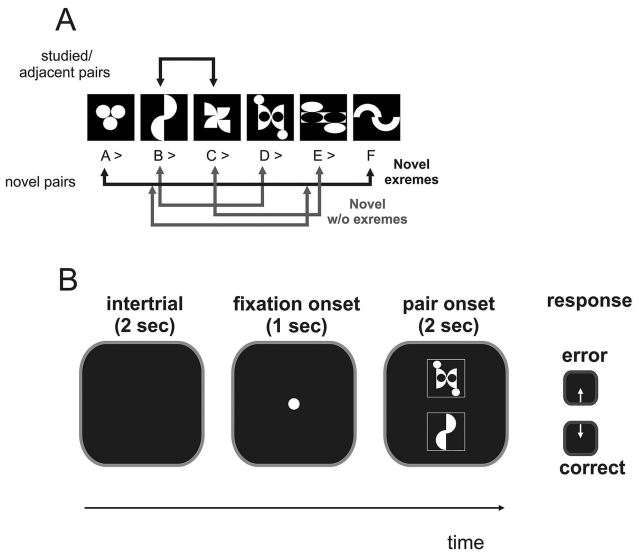


*Figure 1.* Transitive Inference (TI) task. (A) Rank-ordered items. Different categories of problems are illustrated. (B) Sequence of the task events. One second after the presentation of a fixation point (white spot) at the middle of a screen, a pair of items (30 × 30 mm each) were presented on the display, centered 20 mm above and below the fixation spot. The participants had to indicate the higher item in rank between the two, by typing the upper or the lower pointing arrow on a computer keyboard.

In the test phase, the participants were required to infer the relationship between pairs of items never presented together during the learning (AC, AD, AE, AF, BD, BE, BF, CE, CF, DF). These 10 novel pairs of items were randomly intermixed with the 5 learned pairs (AB, BC, CD, DE, EF). In the test phase, for each Participant 150 trials (10 presentations of each pair, 5 times with the target item in the upper position and 5 times in the lower position) were collected.

In the study phase, recall phase and test phase, the trial began with a fixation point appearing at the middle of a screen (Figure 1, *Panel B*). After 1 sec, a pair of items, located one above and one below the fixation point, appeared on the display. The participants had to indicate the higher item in rank between the two, by typing the upper or the lower pointing arrow on a computer keyboard. If no response was provided within 2 sec from the items onset, the trial was aborted and a new trial was presented. Two different acoustic feedbacks informed the participants whether they have responded correctly or not.

During the experimental sessions, the participants were seated on a chair, facing a 15″ computer screen in a dimly illuminated room. The presentation of the stimuli and the responses were controlled by a custom made routine running in the Matlab (www.mathworks.com; see also Brunamonti, Ferraina & Parè, 2012 for similar methods in other experimental paradigms) and based on the Psychophysical toolbox (Brainard, 1997).

## Neuropsychological Evaluation

**Spatial working memory task.** The *N*-back task required the participants to respond when the current stimulus's location matched the location of the previously presented item. Participants were administered the n-back task by a computerized program (http://brainworkshop.sourceforge.net/) that registered the corrected responses. Participants were told to press the 'l' key on the keyboard denoting target with their right index finger. In the 1-back condition, the target was any location identical to the location immediately preceding it (i.e., the location presented one trial back). In the 2-back condition, the target was any location that was identical to the one presented two trials back. In the 3-back condition, the target was any location that was identical to the one presented three trials back. Stimuli were presented at a rate of one location every 3 seconds. Participants completed 35 trials per condition. The number of corrected detected targets and the errors were considered to calculate a percentage accuracy value. Only when the accuracy was ≥ 80%, the next *N*-back level was submitted. An efficiency index was calculated and considered in the analysis, based on the last n-back span achieved (i.e., percentage accuracy value ≥ 80%) and the percentage of accuracy obtained in the next not achieved n-back (i.e., percentage accuracy value < 80%). For example, if the last *N*-back reached was 2 and the percentage of accuracy of the next not achieved *N*-back was 30%, the score obtained was 2.30.

**Pairing long-term memory task.** The study phase of the task consisted in the presentation of nine pairs of photos vertically arranged, including a butterfly and a flower (for details see Costanzo, Vicari, & Carlesimo, 2013). The test phase was given immediately after the study phase. For each test item, the studied butterfly photos was presented at the center of the PC screen; a horizontal array of three flowers appeared simultaneously in the

lower part of the screen. Each flower triplet was composed by the flower that had been presented together with the probe butterfly during the study phase and two others that had been presented together with two different butterflies during the study phase. The participants were requested to indicate the flower that had been presented with the butterfly during the study phase (maximum score: 9). Study and test phases were presented for three consecutive times and the number of elements correctly recognized in the three trials was considered in the analysis.

## Visual Attentional Shifting Task

Visual Attention was measured by a spatial cuing paradigm in which covert attention (without eye movements) is engaged across two locations of a forthcoming target stimulus by a peripheral, informative spatial cue (i.e., cue location predicts target location) at two variable cue-target intervals (50 and 300 ms). A modified version of the Visual Spatial Attention Task (Ruffino et al., 2014) was used. Two circles (2.5°) were displayed peripherally (8° eccentricity, one to the left and one to the right of the fixation point) and 500 ms later the visual cue was shown, consisting of a narrow (1.5° visual angle) displayed for 50 ms above one of the circles. In the response trials of the present version, a target (dot, 0.5°; duration 50 ms) was presented after one of two cue-target stimulus onset asynchronies (SOA, 50 or 300 ms) in one of the two possible locations. The probability that the cue was presented in the target location was 50% (i.e., the cue location was predictive of target location). In contrast, in catch trials the target was not presented and participants did not have to respond. Catch trials were intermixed with response trials. Participants were instructed to react as quickly as possible to the onset of the visual targets by pressing the spacebar on the computer keyboard (detection task). Simple RTs and error rates were recorded by the computer. The maximum time allowed to respond was 1500 ms. The intertrial interval was 1000 ms; after that time the trial started automatically. The experimental session consisted of 144 trials.

## Number Insertion Task

The subtest is derived from the *Battery for evaluating Math abilities* (Biancardi & Nicoletti, 2004) that explores several aspects of math with 10 different tasks. The Number Insertion subtest required to place a number (one to five digits) in one of four possible positions among three other numbers. Both accuracy (maximum score: 12) and speed were measured and considered in the analysis.

## Data Analysis

**Transitive inference task.** Responses on novel pairs of items (i.e., not adjacent pairs, not experienced during the study phase) and studied pairs (i.e., pairs of adjacent items) were separately analyzed.

**Performance on novel pairs in the test phase.** Novel pairs were grouped into two categories: (a) novel pairs not including extreme items (*Novel w/o extremes*), which were novel pairs not including the item A or the item F (i.e., BD, CE, BE); and (b) novel pairs involving only the extreme items (*Novel extremes*), formed by the always winner item A and the always looser item F (i.e., AF).

Performances on the novel pairs were analyzed on the proportion of correct responses.

**Learning curves and performance on studied pairs in the test phase.** Learning curves were calculated to evaluate, within each group, the process of acquisition of the relationship between the adjacent pairs during the study phase and the recall phase. For each participant the trials obtained during the study phase (each pair presented in blocks of trials) and the recall phase (all the pairs randomly presented) were grouped according to their sequence of presentation, and the sequence of successfully performed trials was evaluated by computing a learning curve based on a nonrandom walk hypothesis (Papazachariadis et al., 2012). Starting from zero, a learning curve of the sequence of trials was built by adding or subtracting the value 0.5 (the probability to respond successfully at each given trial) to the previous value, if a given trial was correct or incorrect, respectively.

## Statistical Analyses

The performances of the two groups were compared by using the Mann–Whitney *U*, because the assumption of homogeneity of the variance, monitored with Levene's test, was violated for some variables (i.e., Pairs: AF, AB, CE, DE; Number insertion accuracy).

Neuropsychological measures were analyzed after converting raw scores to *z* scores based on the mean and the standard deviation of normative data of the task (for the Number Insertion accuracy and speed) or, when normative data were not available, on the mean and standard deviation of TD children (for the *N*-back efficiency index, Pairing Long-term Memory Task, Visual Attention SOA50 score and Visual Attention SOA300 score). Spearman's Rank Correlation Coefficient was used to test correlation between measures.

Each learning curve was modeled with a linear trend-line and the slope of the line was considered as an estimate of the efficiency of the learning process. A 2 × 5 mixed ANOVA with Group (ADHD vs. TD) as between-subjects factors and the Estimate of the Learning Process Efficiency for each studied pairs (AB vs. BC vs. CD vs. DE vs. EF) as within-subject factors. The assumption of homogeneity of the variance was monitored with Levene's test. Tukey's HSD post hoc test was used to qualify significant effects.

# Results

## Transitive Inference Task

**Performance in novel pairs.** The two groups were compared on the mean performance on *Novel w/o extremes* (the mean of BD, CE and BE) and on the mean performance on *Novel extremes* (AF; see Figure 2). The mean performance on *Novel w/o extremes* was significantly lower in children with ADHD than in TD children ($U = 406$; $p = 0.01$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.09$). However, groups did not differ on *Novel extremes* ($U = 492.5$; $p = 0.16$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.05$).

By considering the two groups together, the mean of the correct responses in novel pairs without extremes (*Novel w/o extremes*) was found correlated with the Number Insertion task speed ($r = 0.24$, $p = 0.04$; CI: 0.00; 0.25: better performance in novel w/o extremes corresponding to faster execution in Number Insertion

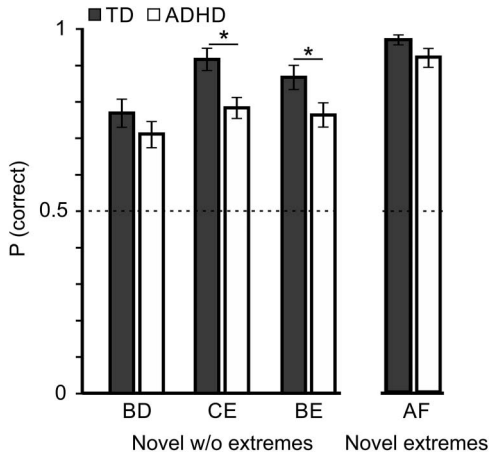


*Figure 2.* Proportion of correct responses, p(correct) of Typically Developing (TD) children and of children with ADHD in trials including the novel pairs without extremes (*w/o extremes*: BD, CE and BE) and the novel pairs with only extremes (*AF*). In the novel pairs without extremes, children with ADHD showed a lower performance than TD children, due to lower scores obtained in CE and BE (CE: $U = 389.5$; $p < 0.01$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.13$; BE: $U = 433.0$; $p = 0.04$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.07$). Vertical bars indicate *SEM*. * indicates statistically significant *p* value.

task) and with the Pairing Long-term Memory task score ($r = 0.24$, $p = 0.04$; CI: 0.01; 0.45: better performance in novel w/o extremes corresponding to higher scores in the Pairing Long-term Memory task). Moreover, also the mean of the correct responses in novel pairs with extremes (*Novel extremes*) was significantly correlated with the Pairing Long-term Memory task score ($r = 0.27$, $p = 0.02$; CI: 0.04; 0.48: better performance in novel extremes corresponding to higher scores in the Pairing Long-term Memory task) and with the N-back efficiency index ($r = 0.38$, $p = 0.001$; CI: 0.16; 0.57: better performance in novel w/o extremes corresponding to higher scores in the *N*-back task).

**Performance in studied pairs.** The performance of the studied pairs was evaluated during learning and during the test phase (see Figure 3).

The learning curves of a TD participant during the acquisition of each adjacent pair of the ordered set was displayed as an example (Figure 3A).

The mixed ANOVA on the estimate of learning process efficiency for each studied pairs (AB vs. BC vs. CD vs. DE vs. EF) documented that the slope of the regression line differed between studied pairs ($F_{4,272} = 22.78$, $p < 0.001$; $\eta_p^2 = 0.25$) because the estimate of learning process efficiency was higher for extreme items (p always <0.001) than for the middle items (AB vs. BC, AB vs. CD, EF vs. BC, EF vs. CD) compared. However, no effect for Group ($F_{1,68} = 0.04$; $p = 0.84$; $\eta_p^2 = 0.006$) nor for the interaction Groups × Studied Pairs ($F_{1,68} = 1.39$; $p = 0.24$; $\eta_p^2 = 0.02$) was found.

The two groups were compared in the same pairs of items (mean of BC, CD, and DE) of the test phase, after the learning had occurred (Figure 3 C). Children with ADHD showed significant lower scores than TD children ($U = 307$; $p = .003$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.0115$).

By considering the two groups together, the mean performance in the middle items (mean of BC, CD, and DE) was correlated to neuropsychological measures to better understand which cognitive process could be related to the performance in the studied pairs. A positive correlation of the mean performance in the middle items was found with the Number Insertion task speed ($r = 0.26$; $p = 0.03$; CI: 0.02; 0.46: better performance in the middle items corresponding to higher speed in Number Insertion task), the

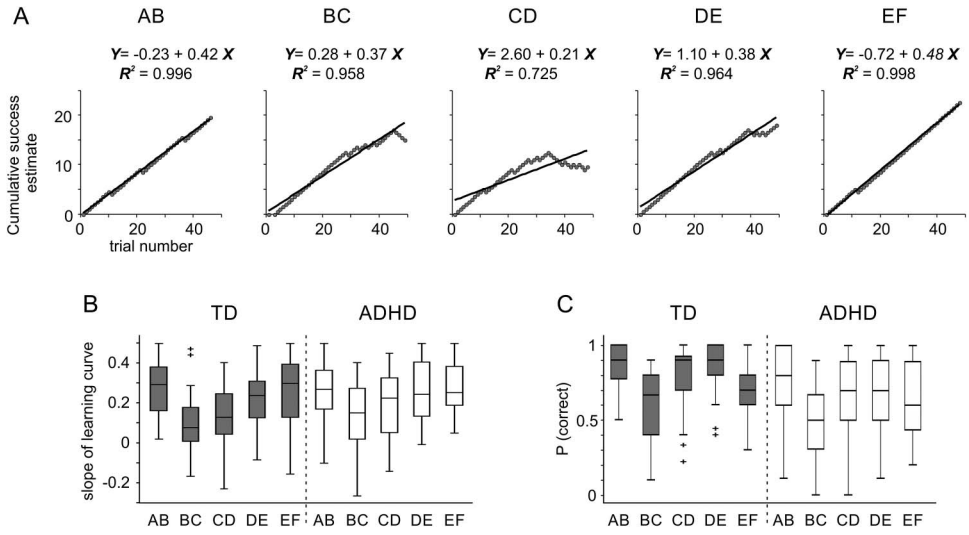


*Figure 3.* Learning curves and performance in the studied pairs during test (A). Learning curves for each pair comparison across the learning and the recall phase for a representative TD child. The parameters of the linear fitting on the observed performance and the goodness of fit are reported (B). Box plot of the distribution of the slopes of the trend-line of the learning curve for each pair across all the TD children (gray boxes) and children with ADHD (white boxes). (C) Performance in studied pairs during the test phase in both groups of children (color group code as in B).

Pairing Long-term Memory task score ($r = 0.28$; $p = 0.02$; CI: 0.05; 0.48: better performance in the middle items corresponding to higher scores in Pairing Long-term Memory), and the *N*-back efficiency index ($r = 0.25$, $p = 0.04$; CI: 0.02; 0.46: better performance in the middle items corresponding to higher scores in the *N*-back task).

## Neuropsychological Evaluation

The analysis on neuropsychological measures (see Figure 4) documented that children with ADHD had lower scores than TD children in the Pairing Long-term Memory task ($U = 277$; $p < 0.001$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.12$), were slower than TD children in solving the Number Insertion task ($U = 289$; $p < 0.01$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.17$), and showed lower efficiency index than TD children in the *N*-back ($U = 339$; $p = .001$, nADHD = 37; nTD = 33; $\eta_p^2 = 0.14$).

## Discussion

The present study was aimed at evaluating whether TI problems were efficiently solved by children with ADHD and which was the cognitive strategy adopted to solve the task.

Our results documented that children with ADHD had difficulties in solving TI trials including novel pairs without the extremes A and F (i.e., *Novel w/o extremes*). Conversely, their performance did not differ from that of TD children in solving AF trials (i.e., *Novel extremes*). According to the associative learning theory (Frank et al., 2003; Wynne, 1997; Wynne, von Fersen, & Staddon, 1992), to solve TI trials including extremes a reinforcement learning mechanism could mainly drive the choice, because of the presence in a pair of the extreme item A and F (A is always reinforced and F never reinforced) and making the discrimination of the pairs AB and EF less ambiguous than the other pairs. On the other hand, to solve TI trials without extremes a unified mental schema to represent reciprocal relationship between the items and to make comparisons between pairs is needed. Indeed, the recruitment of a *relational flexibility* mechanism has been observed to be related to the capability to extract the relation between items and organize them as a unified representation on a "mental line" (Brunamonti et al., 2011; Gazes, Chee, & Hampton, 2012; Jacobs, 2006; Libben & Titone, 2008; Moses et al., 2010; Ryan et al., 2009).

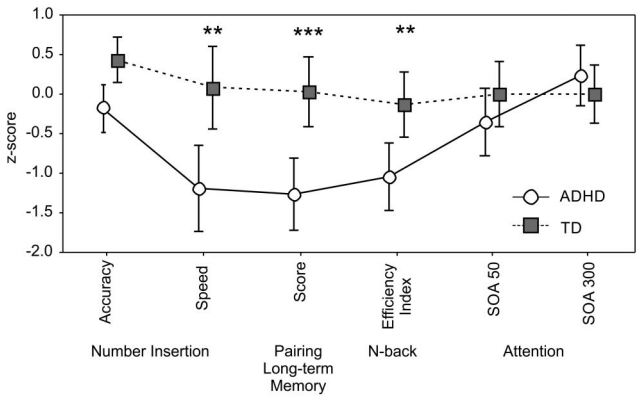


*Figure 4.* Normalized scores of neuropsychological evaluation scales. Significant between groups post hoc comparisons are reported. $^{***}p < 0.001$; $^{**}p < 0.01$. Vertical bars indicate 95% C.I.

Notably, to maintain active the linear representation of the ordered items by memory could help compare items, identify their relation and organize them as a mental line. By considering the two groups together, our correlation analysis documented that the proportion of correct response of *Novel w/o extremes* pairs correlated with the Number Insertion task speed and with the Pairing Long-term Memory task score. The ability to correctly solve pairs without extremes is then associated with the ability to represent a mental line for correctly indicating the position of a given number on a physical line but also requires to memorize the ordered items.

The lower proportion of correct response obtained by children with ADHD in novel pairs *w/o extremes* could be related to their difficulty in manipulating ordered items as numbers on a mental number line and/or to their difficulty in maintaining in memory ordered items to create a unified representation of them (Moses et al., 2010; Prado et al., 2010; Ryan et al., 2009). In elders, for example, the lower performance on *Novel w/o extremes* has been related to their reduced ability to extract relations between items, and to their preference to rely on a bottom up strategy to solve TI problems, driven by the value of the items acquired by the reinforcement during the learning (Moses et al., 2010).

Both the top down relational flexibility and the bottom up value associative mechanisms have been studied in several pathological populations (Koscik & Tranel, 2012; Solomon et al., 2011; Titone et al., 2004; Waechter et al., 2013). For example, Solomon et al. (2011) have verified the efficiency of the value transfer strategy and the relational flexibility mechanism in a group of adults suffering of autism spectrum disorders using a five-items TI task. In these patients results documented difficulties in comparisons strongly driven by the value of the extreme pair AE. On the contrary, patients performed as well as controls with the pair BD, in which the integrity of the relational flexibility mechanism is mainly involved. Notably this pattern is opposite to that seen in our children with ADHD. We interpreted the deficit found in our children with ADHD in using relational flexibility mechanism required for TI as a consequence of their frontal lobe dysfunctions (Ma et al., 2012). However, the performance in TI trials involving novel pairs with extreme items A and F was found related to both long-term memory and working memory processes (with Pairing Long-term Memory task score and with *N*-back task efficiency index), confirming the role of the retrieval process in solving novel pairs with extreme items (Heckers et al., 2004; Ryan et al., 2009). Because our results showed that children with ADHD had lower scores than TD children in working memory, long-term memory, and number insertion task, their preserved abilities in evaluating novel pairs with extremes could be attributable more to their attempts to solve the task based on compensatory strategies using associative mechanisms than memory abilities or the mental representation of the relation between items.

To verify the efficiency of learning abilities, we compared the performance of the children with ADHD to that TD children during the acquisition of the relationship between the studied pairs. Our results documented that the estimate of learning process efficiency of the two groups did not differ. Indeed, the analysis of the slope of the regression line documented that the two groups of children did not differ on their performance in the studied pairs,

both showing more difficulties in learning middle items than extreme items. In other words, the lack of difference in training history between the two groups (the proportion of positive feedback received by each item during the acquisition of the relationship between the studied pairs did not differ in the two groups), the different performance between TD children and children with ADHD found in the subsequent test phase cannot rely on different efficiency of associative mechanisms.

However, groups differed on the scores of the studied pairs (mean of BC, CD, and DE) of the test phase, after the learning had occurred. The proportion of correct responses of children with ADHD was lower than that of TD children. Looking at the correlational analysis, this performance on the studied pairs was linked to long-term memory abilities (the Pairing Long-term Memory task), working memory abilities (the *N*-back task), and the ability to locate numbers in a number line (Number Insertion task). The lower performance in children with ADHD than in TD children could be interpreted, again, as the consequence of the deficits found in children with ADHD in these cognitive domains, as documented by the neuropsychological evaluation.

TI ability is supported by multiple, interacting brain systems. Studies demonstrated important contributions from the frontal regions (Brunamonti et al., 2016; Koscik & Tranel, 2012; Libben & Titone, 2008), parietal regions, medial temporal areas, in particular the hippocampus (Greene, Gross, Elsinger, & Rao, 2006; Heckers et al., 2004; Knauff, Fangmeier, Ruff, & Johnson-Laird, 2003; Nagode & Pardo, 2002), and the basal ganglia (Frank et al., 2006, 2004; Moses et al., 2010). In children with ADHD, neuroimaging studies have reported abnormalities in brain areas crucial for the control of attention and cognition (Bush, 2011; Seidman et al., 2005) as the frontal cortex, the parietal cortex, the cerebellum, but also in brain regions essential for associative learning as thalamus and hippocampus, and in the connectivity between the temporal lobe and the prefrontal cortex (Posner et al., 2014; Xia et al., 2012). Although it is speculative, the impaired performance on TI tasks in children with ADHD may be then interpreted as a consequence of both frontal and temporal lobe dysfunctions.

In sum, our results indicate that the preferential strategy used by children with ADHD to solve the TI task could rely more on associative mechanisms rather than on memory abilities or the mental representation of the relation between items. However, TI ability seemed to be not fully preserved in children with ADHD, because they were less efficient than TD children in making inference between novel items, probably because of their difficulties in controlling and in maintaining in memory a unified representation of related items. Further studies, including direct measures of the awareness of the reciprocal relationship between the items (Libben & Titone, 2008; Moses et al., 2010) are needed to better understand this issue.

The approach used in the present work as well as in previous researches aimed at studying the cognitive mechanisms involved in TI (Libben & Titone, 2008; Moses et al., 2010) had the limitation to fully control the learning processes taking place during the test phase. Indeed, in the test phase, only the first comparison between nonadjacent pairs should be believed as the result of the transitive inference process. Starting from the second comparison between nonadjacent items, this comparison is not novel anymore. The repeated exposure to the same pair of nonadjacent items and the reinforce history of each item are variables that could affect the entire performance of the test phase. To our knowledge this issue was only partially treated in a very few previous studies with monkeys (Brunamonti et al., 2016; Jensen et al., 2013) and should be taken into account in future studies on TI.

Mathematical skills, text-processing skills as well as understanding the social rules, trusting other people or building friendships with a person rather than one other person and many other cognitive and social processes are all influenced by relational reasoning abilities (Carpenter Rich, Loo, Yang, Dang, & Smalley, 2009; Coleman et al., 2010; Favrel & Barrouillet, 2000; Kim & Song, 2011; Markovits, & Dumas, 1999; Ragni & Knauff, 2013; Sedek, Piber-Dabrowska, Maio, & Von Hecker, 2011; Winstanley, Eagle, & Robbins, 2006). Understanding the nature of the deficit reported in these abilities of children with ADHD may improve their cognitive and social development.

In conclusion, our study documents a deficit in relation reasoning in children with ADHD. To the best of our knowledge this is the first report documenting this finding and, because of the implication of relation reasoning in the cognitive and the affective development, it may contribute to some clinical manifestation of the disorders. Moreover, describing which strategy ADHD children use to solve a relation reasoning task offers significant information to the better understanding of the disorder and to guide possible therapeutic approaches.

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Ente Organizzatore

Centro per l'Età Evolutiva
Studio Associato di Psicologia

Con il patrocinio:

# CONVEGNO SCIENTIFICO

## I disturbi del neurosviluppo in età prescolare:

## individuazione precoce e interventi efficaci

Milano, sabato 4 febbraio 2017

Edificio U7 Aula 10 - Università di Milano Bicocca

### PROGRAMMA

8.15 - 9.15. Registrazione dei partecipanti

**9.15. Presentazione della Giornata**

Gian Marco Marzocchi

Moderatore dei lavori del mattino
Federica Zanetto – *Pediatra di Famiglia, Vimercate (MB)*

**9.15 Promozione della salute, prevenzione o diagnosi precoce nei disturbi del neurosviluppo?**
Antonella Costantino - *Direttore UONPIA Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano*

SESSIONE LINGUAGGIO

**9.45 Fino a quanto è possibile fare diagnosi precoce nei DSL? Dalla ricerca scientifica agli strumenti diagnostici del futuro**
Paola Zanchi - *Università di Milano – Bicocca & Centro per l'Età Evolutiva, Bergamo*

**10.05 I Disturbi di Linguaggio: definire gli indicatori precoci e applicare una presa in carico efficace**
Renata Salvadorini – *UO Neurologia e Neuro-riabilitazione, IRCCS Stella Maris, Calambrone (Pisa)*

11.00 - 11.30 Coffee Break offerto dagli sponsor

SESSIONE APPRENDIMENTI SCOLASTICI

**11.30 Prerequisiti dell'apprendimento della letto-scrittura: segnali precoci alla scuola dell'infanzia e studi longitudinali**
Paola Bonifacci - *Laboratorio Assessment Disturbi di Apprendimento (LADA), Dipartimento di Psicologia, Università di Bologna*

**12.15 Conoscere i numeri in età prescolare: segnali di rischio, interventi precoci e risultati alla scuola primaria**
Valentina Tobia *Università di Milano – Bicocca & Centro per l'Età Evolutiva, Bergamo*

12.45 - 14.00 Pausa Pranzo

Moderatore dei lavori del pomeriggio
Leonello Venturelli - *Pediatra di famiglia, Bergamo*

SESSIONE AUTISMO

**14.00 L'importanza della diagnosi precoce nell'autismo: progetti di screening e percorsi intervento nello sviluppo**
Franco Nardocci - *Past President SINPIA, Fondazione Italiana Autismo, Roma*

SESSIONE COMPORTAMENTO E ATTACCAMENTO

**14.45 Difficoltà transitorie e problemi persistenti nei disturbi d'ansia in età prescolare**
Emanuela Iacchia *Didatta SITCC & Comitato Scientifico Aimuse*

**15.30 Disturbi di attenzione, iperattività e disfunzioni esecutive si osservano in età prescolare, ma come riconoscerli clinicamente?**
Gian Marco Marzocchi *Università di Milano – Bicocca & Centro per l'Età Evolutiva, Bergamo*

**16.00 - 16.15 Conclusione dei lavori**

**Per raggiungere la sede del Convegno:**

- In auto (parcheggio): raggiungere zona Bicocca – Greco Pirelli.
- In treno: fermata Milano Greco Pirelli. L'edificio U7dell'Università di Milano Bicocca dista 5 minuti a piedi.
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http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-newsletter

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014 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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