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**DEVELOPMENT OF A NEW ATTENTION RATING SCALE FOR CHILDREN WITH INTELLECTUAL DISABILITY: THE SCALE OF ATTENTION IN INTELLECTUAL DISABILITY (SAID).**  
Freeman NC, Gray KM, Taffe JR, et al.  
Difficulties with attention, impulsivity, and hyperactivity are thought to be as common among children with intellectual disability (ID) as they are in children without ID. Despite this, there is a lack of scales to specifically assess ADHD symptomatology in children and adolescents with ID. This article describes the development and evaluation of a teacher-completed measure; the Scale of Attention in Intellectual Disability (SAID). A community survey of 176 teachers of children 5-13 years of age, with ID at all levels of impairment indicated that the T-SAID is a reliable and valid measure. Integrating this scale with neuropsychological and clinical research holds exciting promise for enhancing our understanding of the nature of attention difficulties within populations with ID.

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**INTERVENTION FOR EXECUTIVE FUNCTIONS IN ATTENTION DEFICIT AND HYPERACTIVITY DISORDER.**  
Menezes A, Dias NM, Trevisan BT, et al.  
This study aimed to investigate if an executive functions (EF) intervention could promote these skills in individuals with attention deficit and hyperactivity disorder (ADHD). Eighteen children and adolescents, 7-13 years old, divided into experimental (EG, N = 8) and control (CG, N = 10) groups, were assessed in the Block Design and Vocabulary subtests of the WISC III and seven tests of EF. Parents answered two scales, measuring EF and inattention and hyperactivity signs. EG children participated in a program to promote EF in twice-weekly group sessions of one hour each. After 8 months of intervention, groups were assessed again. ANCOVA, controlling for age, intelligence quotient and pretest performance, revealed gains in attention/inhibition and auditory working memory measures for the EG. No effect was found for scales or measures of more complex EF. Results are not conclusive, but they illustrate some promising data about EF interventions in children and adolescents 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.
AN EIGHTEEN-MONTH FOLLOW-UP OF A PILOT PARENT-DELIVERED PLAY-BASED INTERVENTION TO IMPROVE THE SOCIAL PLAY SKILLS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND THEIR PLAYMATES.


Background: Children with attention deficit hyperactivity disorder (ADHD) experience significant ongoing social difficulties which occur in multiple contexts. Interventions designed to improve these social difficulties have demonstrated minimal effectiveness. Thus, there is a clear need to establish interventions that are effective in addressing the social difficulties of children with ADHD across contexts and in the long term.

Aim: To examine the long-term effectiveness and appropriateness of a pilot parent-delivered intervention designed to improve the social play skills of children with ADHD and their playmates.

Method: Participants included five children with ADHD who had completed the intervention 18-months prior, their typically developing playmates and mothers of children with ADHD. Blinded ratings from the Test of Playfulness were used to measure children's social play: post-intervention and 18-months following the intervention in the home and clinic. Wilcoxon signed-ranks and Cohen's-d calculations were used to measure effectiveness. Parents' perspectives of the appropriateness of the intervention were explored through semi-structured interviews and data were analysed thematically.

Results: The social play skills of children with ADHD and their playmates were maintained following the intervention in the home and clinic. Thematic analysis revealed four core-themes against an intervention appropriateness framework: new parenting tools, a social shift, adapting strategies over time and the next developmental challenge.

Conclusion: The parent-delivered intervention demonstrated long-term effectiveness and appropriateness for improving children's social play skills. Significance: These preliminary results are promising as maintaining treatment effects and achieving generalisation across contexts has remained an unachieved goal for most psycho-social interventions.

IMPACT OF A BEHAVIOURAL SLEEP INTERVENTION ON SYMPTOMS AND SLEEP IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, AND PARENTAL MENTAL HEALTH: RANDOMISED CONTROLLED TRIAL.


OBJECTIVE: To examine whether behavioural strategies designed to improve children's sleep problems could also improve the symptoms, behaviour, daily functioning, and working memory of children with attention deficit hyperactivity disorder (ADHD) and the mental health of their parents.

DESIGN: Randomised controlled trial.

SETTING: 21 general paediatric practices in Victoria, Australia.

PARTICIPANTS: 244 children aged 5-12 years with ADHD attending the practices between 2010 and 2012.

INTERVENTION: Sleep hygiene practices and standardised behavioural strategies delivered by trained psychologists or trainee paediatricians during two fortnightly consultations and a follow-up telephone call. Children in the control group received usual clinical care.

MAIN OUTCOME MEASURES: At three and six months after randomisation: severity of ADHD symptoms (parent and teacher ADHD rating scale IV-primary outcome), sleep problems (parent reported severity, children's sleep habits questionnaire, actigraphy), behaviour (strengths and difficulties questionnaire), quality of life (pediatric quality of life inventory 4.0), daily functioning (daily parent rating of evening and morning behavior), working memory (working memory test battery for children, six months only), and parent mental health (depression anxiety stress scales).

RESULTS: Intervention compared with control families reported a greater decrease in ADHD symptoms at three and six months (adjusted mean difference for change in symptom severity -2.9, 95% confidence interval -5.5 to -0.3, P=0.03, effect size -0.3, and -3.7, -6.1 to -1.2, P=0.004, effect size -0.4, respectively). Compared with control children, intervention children had fewer moderate-severe sleep problems at three months (56% v 30%; adjusted odds ratio 0.30, 95% confidence interval 0.16 to 0.59; P<0.001) and six months (46% v 34%; 0.58, 0.32 to 1.0; P=0.07). At three months this equated to a reduction in absolute risk of 25.7% (95% confidence interval 14.1% to 37.3%) and an estimated number needed to treat of 3.9. At six
months the number needed to treat was 7.8. Approximately a half to one third of the beneficial effect of the intervention on ADHD symptoms was mediated through improved sleep, at three and six months, respectively. Intervention families reported greater improvements in all other child and family outcomes except parental mental health. Teachers reported improved behaviour of the children at three and six months. Working memory (backwards digit recall) was higher in the intervention children compared with control children at six months. Daily sleep duration measured by actigraphy tended to be higher in the intervention children at three months (mean difference 10.9 minutes, 95% confidence interval -19.0 to 40.8 minutes, effect size 0.2) and six months (9.9 minutes, -16.3 to 36.1 minutes, effect size 0.3); however, this measure was only completed by a subset of children (n=54 at three months and n=37 at six months).

**CONCLUSIONS:** A brief behavioural sleep intervention modestly improves the severity of ADHD symptoms in a community sample of children with ADHD, most of whom were taking stimulant medications. The intervention also improved the children's sleep, behaviour, quality of life, and functioning, with most benefits sustained to six months post-intervention. The intervention may be suitable for use in primary and secondary care.

Trial registration Current Controlled Trials ISRCTN68819261

Canadian Psychology/Psychologie canadienne. 2015 Aug;56:295-300.

**ADHD IN SCHOOLS: ADOPTING A STRENGTHS-BASED PERSPECTIVE.**

*Climie EA, Mastoras SM.*

Children with attention-deficit/hyperactivity disorder (ADHD) present with a number of behavioural, social, and academic challenges. However, the importance of understanding the strengths and abilities of these children should not be overlooked, particularly in the school environment. This brief report highlights the application of positive psychology to a population typically portrayed in a negative light—children with ADHD. Specifically, this article provides an argument for seeking a more positive understanding of children with ADHD and illustrates the necessity of taking a strengths-based approach in working with and supporting these students. Avenues for adopting a strengths-based approach to ADHD within both research and practice are discussed, informed by concepts from related areas of positive psychology, strengths perspectives, and resilience. The benefits of and potential directions for integrating positive psychology frameworks into the ADHD research field are outlined, emphasising the need to link findings to evidence-based practice. Implications for school-based practice will also be examined, highlighting the importance of strengths-based assessment and intervention approaches in school environments so as to provide more positive and well-rounded support for children with ADHD. Ultimately, positive psychology offers a more balanced, holistic, and hopeful approach to a population typically viewed through a deficit lens and has the potential to inspire a greater emphasis on building capacity in these children and their families and schools.


**MEDIATING EFFECT OF PSYCHOPATHY ON THE RISK OF SOCIAL PROBLEMS AMONG CHILDREN WITH ADHD VERSUS SLUGGISH COGNITIVE TEMPO SYMPTOMS.**

*Raiker JS, Greening L, Stoppelbein L, et al.*

Sluggish cognitive tempo (SCT) has been proposed as a unique syndrome; however research examining how it is different from attention-deficit/hyperactivity disorder (ADHD) is just starting to emerge. The present study extends this research by examining how specific personality features (i.e., psychopathy) may mediate the relation between ADHD and social problems, but not between SCT and social problems. Caregivers of 198 children (6–12 years old) that presented for an inpatient psychiatric evaluation completed standardized measures of childhood behavior problems. Bootstrapped mediational analyses were performed to evaluate the mediating role of psychopathy on the relation between social problems and symptoms of ADHD versus SCT. Two sub-domains of psychopathy—impulsivity and narcissism—emerged as partial mediators for the relation between social problems and ADHD symptoms; whereas SCT
symptoms were not found to be related to psychopathy after controlling for ADHD symptoms. These findings provide support for conceptualizing ADHD and SCT as discrete syndromes as well as for the mediating role of psychopathy domains on the risk of social problems among a clinical sample of youth with symptoms of ADHD.

COMORBIDITY OF AUTISM SPECTRUM DISORDER AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A REVIEW.
Attention-deficit/hyperactivity disorder (ADHD) is one of the most common comorbidities of ASD. This article reviews the assessment tools and clinical research (prevalence, clinical characteristics and treatment) and fundamental research (iconography, genetics, neurophysiology, electronerophysiology) of ASD with ADHD according to lately related articles. The findings suggested that there was lack of researches on treatment and iconography of ASD with ADHD and the conclusions were inconformity. Furthermore, most of the objects in these researches were children of normal intelligence. Thus future research should expand its objects to patients of adult and children with mental retardation and do further explore in iconography and treatment.

LOW-DOSE METHYLPHENIDATE MONOTHERAPY FOR FEATURES OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SECONDARY TO HEREDITARY CEREBELLAR ATAXIA.
Hu LY, Lin YL, Chang HS, et al.
Presents a case report of a 16-year-old unmarried female student presented to the outpatient department with acute onset of easy distractibility, hyperactivity, hypertalkativeness, decreased need for sleep, and distorted interpersonal behaviors, including lack of respect for interpersonal boundaries or appropriate social limits for 2 weeks. She was taken to a local medical doctor, who initially suspected the presence of a manic episode of bipolar disorder. The sudden onset of psychiatric symptoms mentioned above in the absence of a psychiatric history indicated an atypical presentation. She was admitted to the psychiatric ward for further evaluation and treatment. Brain magnetic resonance imaging showed mild bilateral atrophy of the cerebellum. Because of her sudden-onset psychiatric symptoms, attention-deficit/hyperactivity disorder-cerebellar ataxia (ADHD/CA) was suspected and methylphenidate (MPH) was prescribed. The patient showed dramatic improvement in her features of ADHD after starting on the low-dose MPH monotherapy. These findings might alert clinicians to be aware of the possibility that features of ADHD might accompany hereditary cerebellar ataxia and also to the possibility that ADHD features might respond to treatment with low-dose MPH in this situation.

COMORBIDITIES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: PREGNANCY RISK FACTORS AND PARENT MENTAL HEALTH.
Silva D, Houghton S, Hagemann E, et al.
Our study examined the risk of maternal smoking and alcohol consumption in pregnancy associated with child comorbidity in a community sample of children diagnosed with attention deficit hyperactivity disorder (ADHD). We used a cross sectional community retrospective questionnaire of 321 children diagnosed with ADHD. Our results suggest that maternal smoking increased the risk of oppositional defiant behavior (ODB) in children with ADHD twofold (OR 2.27; CI 1.29–4.11). Maternal alcohol consumption increased the risk although not significantly for ADHD child comorbid ODB, anxiety disorder and depression. Parent mental health significantly impacted on child comorbidity. Our study suggests that smoking in pregnancy is associated with comorbid ODB, independent of parent mental health, family history of ADHD and...
socioeconomic factors. Parent mental health is independently associated with comorbid ODB, anxiety disorder and depression.

**Grey Matter Volume Differences Associated with Gender in Children with Attention-Deficit/Hyperactivity Disorder: A Voxel-Based Morphometry Study.**  
Female participants have been underrepresented in previous structural magnetic resonance imaging reports on attention-deficit/hyperactivity disorder (ADHD). In this study, we used optimized voxel-based morphometry to examine grey matter volumes in a sample of 33 never-medicated children with combined-type ADHD and 27 typically developing (TD) children. We found a gender-by-diagnosis interaction effect in the ventral anterior cingulate cortex (ACC), whereby boys with ADHD exhibited reduced volumes compared with TD boys, while girls with ADHD showed increased volumes when compared with TD girls. Considering the key role played by the ventral ACC in emotional regulation, we discuss the potential contribution of these alterations to gender-specific symptoms’ profiles in ADHD.

**Use of Paracetamol During Pregnancy and Child Neurological Development.**  
Paracetamol (acetaminophen) remains the first line for the treatment of pain and fever in pregnancy. Recently published epidemiological studies suggested a possible association between paracetamol exposure in utero and attention-deficit–hyperactivity disorder/hyperkinetic disorder (ADHD/HKD) or adverse development issues in children. However, the effects observed are in the weak to moderate range, and limitations in the studies’ design prevent inference on a causal association with ADHD/HKD or child neurological development. In parallel, recent animal data showed that cognition and behaviour may be altered following exposure to therapeutic doses of paracetamol during early development. These effects may be mediated by interference of paracetamol with brain-derived neurotrophic factor, neurotransmitter systems (including serotonergic, dopaminergic, adrenergic, as well as the endogenous endocannabinoid systems), or cyclooxygenase-2. However, no firm conclusion can be made on the relevance of these observations to humans. We conclude that additional well-designed cohort studies are necessary to confirm or disprove the association. In the context of current knowledge, paracetamol is still to be considered safe in pregnancy and should remain the first-line treatment for pain and fever.

**Prevalence of Incontinence, Attention Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder in Preschool Children.**  
Externalizing disorders as attention deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) are common in children with nocturnal enuresis (NE), daytime urinary incontinence (DUI) and faecal incontinence (FI). We examined the prevalence rates of ADHD, ODD and incontinence in a defined geographical area and analysed the association between externalizing disorders and subtypes of incontinence. 1,676 parents of children who were presented at the mandatory school-entry medical examination completed a questionnaire with all DSM-IV items of ADHD, ODD and six questions regarding incontinence. 50.2 % were male and mean age was 5.7 years. 9.1 % had at least one subtype of incontinence (8.5 % had NE, 1.9 % DUI and 0.8 % FI). Boys were significantly more affected by incontinence overall, NE, FI and ADHD than girls. 6.4 % had ADHD, 6.2 % had ODD and 2.6 % were affected by ADHD and ODD. 10.3 % of the children with incontinence had ADHD and 10.3 % ODD.
Children with FI were significantly more affected by externalizing disorders (50%) than children with isolated NE (14.5%), children with DUI (9.5%) and continent children (9.5%). Children with incontinence, especially those with FI, are at much higher risk of externalizing disorders. An additional effect of children with both ADHD and ODD having higher rates of incontinence than children with only one disorder could not be found. However, these children represent a high-risk group with lower compliance to treatment and worse outcome. Therefore, screening not only for ADHD but also for ODD should be implemented for all children with incontinence.

Eur Child Adolesc Psychiatry. 2015.

HOW 'CORE' ARE MOTOR TIMING DIFFICULTIES IN ADHD? A LATENT CLASS COMPARISON OF PURE AND COMORBID ADHD CLASSES.
Van Der Meer JMJ, Hartman CA, Thissen AJAM, et al.
Children with attention-deficit/hyperactivity disorder (ADHD) have motor timing difficulties. This study examined whether affected motor timing accuracy and variability are specific for ADHD, or that comorbidity with autism spectrum disorders (ASD) contributes to these motor timing difficulties. An 80-trial motor timing task measuring accuracy (++) and infrequent long response times (−−) in estimating a 1-s interval was administered to 283 children and adolescents (8-17 years) from both a clinic and population based sample. They were divided into four latent classes based on the SCQ and CPRS-R:L data. These classes were: without behavioral problems (Normal-class, n = 154), with only ADHD symptoms (ADHD-class, n = 49), and two classes with both ASD and ADHD symptoms; ADHD(+ASD)-class (n = 39) and ASD(+ADHD)-class (n = 41). The pure ADHD-class did not deviate from the Normal class on any of the motor timing measures (mean RTs 916 and 925 ms, respectively). The comorbid ADHD(+ASD) and ASD(+ADHD) classes were significantly less accurate (more time underestimations) compared to the Normal class (mean RTs 847 and 870 ms, respectively). Variability in motor timing was reduced in the younger children in the ADHD(+ASD) class, which may reflect a tendency to rush the tedious task. Only patients with more severe behavioral symptoms show motor timing deficiencies. This cannot merely be explained by high ADHD severity with ASD playing no role, as ADHD symptom severity in the pure ADHD-class and the ASD(+ADHD) class was highly similar, with the former class showing no motor timing deficits.


THE ROLE OF ADVERSE LIFE EVENTS ON DEPRESSION IN OLDER ADULTS WITH ADHD.
Semeijn EJ, Comijs HC, Kooij JJ, et al.
BACKGROUND: Comorbidity between Attention-Deficit/Hyperactivity Disorder (ADHD) and depression is high, also in older adults. Thus far it is not well understood why ADHD and depression are so strongly interrelated. One factor that may play a role in older adults with ADHD is an increased risk of experiencing adverse life events.

METHODS: Six year follow-up data were used from the Longitudinal Aging Study Amsterdam (LASA). To diagnose ADHD, the DIVA 2.0, a diagnostic interview was administered among a subsample (N=230, age 60-94). In addition to the ADHD diagnosis, the associations between the number of ADHD symptoms, depressive symptoms and adverse life events were examined. Data were analyzed by means of logistic and linear regression analyses.

RESULTS: Compared to older adults without ADHD, those with ADHD reported more serious conflicts. The risk of depression in older adults with ADHD was partly explained by serious conflicts. Furthermore, the association between ADHD severity and depression was stronger in those who experienced serious conflicts and those who experienced more adverse life events.

LIMITATIONS: The ADHD diagnosis was based on the DSM-IV criteria, which were developed for children, and have not yet been validated in (older) adults.
CONCLUSIONS: Having conflicts with others and accumulation of adverse life events over time partly explained the association between ADHD and depression. Better and earlier treatment of ADHD may prevent the development of depression in the presence of life events associated with ADHD.

J Clin Endocrinol Metab. 2015 Apr;100:1245-55.

ESTIMATING BURDEN AND DISEASE COSTS OF EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS IN THE EUROPEAN UNION.

CONTEXT: Rapidly increasing evidence has documented that endocrine-disrupting chemicals (EDCs) contribute substantially to disease and disability.

OBJECTIVE: The objective was to quantify a range of health and economic costs that can be reasonably attributed to EDC exposures in the European Union (EU).

DESIGN: A Steering Committee of scientists adapted the Intergovernmental Panel on Climate Change weight-of-evidence characterization for probability of causation based upon levels of available epidemiological and toxicological evidence for one or more chemicals contributing to disease by an endocrine disruptor mechanism. To evaluate the epidemiological evidence, the Steering Committee adapted the World Health Organization Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group criteria, whereas the Steering Committee adapted definitions recently promulgated by the Danish Environmental Protection Agency for evaluating laboratory and animal evidence of endocrine disruption. Expert panels used the Delphi method to make decisions on the strength of the data.

RESULTS: Expert panels achieved consensus at least for probable (>20%) EDC causation for IQ loss and associated intellectual disability, autism, attention-deficit hyperactivity disorder, childhood obesity, adult obesity, adult diabetes, cryptorchidism, male infertility, and mortality associated with reduced testosterone. Accounting for probability of causation and using the midpoint of each range for probability of causation, Monte Carlo simulations produced a median cost of euro157 billion (or $209 billion, corresponding to 1.23% of EU gross domestic product) annually across 1000 simulations. Notably, using the lowest end of the probability range for each relationship in the Monte Carlo simulations produced a median range of euro109 billion that differed modestly from base case probability inputs.

CONCLUSIONS: EDC exposures in the EU are likely to contribute substantially to disease and dysfunction across the life course with costs in the hundreds of billions of Euros per year. These estimates represent only those EDCs with the highest probability of causation; a broader analysis would have produced greater estimates of burden of disease and costs.

J Clin Endocrinol Metab. 2015 Apr;100:1256-66.

NEUROBEHAVIORAL DEFICITS, DISEASES, AND ASSOCIATED COSTS OF EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS IN THE EUROPEAN UNION.

CONTEXT: Epidemiological studies and animal models demonstrate that endocrine-disrupting chemicals (EDCs) contribute to cognitive deficits and neurodevelopmental disabilities.

OBJECTIVE: The objective was to estimate neurodevelopmental disability and associated costs that can be reasonably attributed to EDC exposure in the European Union.

DESIGN: An expert panel applied a weight-of-evidence characterization adapted from the Intergovernmental Panel on Climate Change. Exposure-response relationships and reference levels were evaluated for relevant EDCs, and biomarker data were organized from peer-reviewed studies to represent European exposure and approximate burden of disease. Cost estimation as of 2010 utilized lifetime economic productivity estimates, lifetime cost estimates for autism spectrum disorder, and annual costs for attention-deficit hyperactivity disorder. Setting, Patients and Participants, and Intervention: Cost estimation
was carried out from a societal perspective, ie, including direct costs (eg, treatment costs) and indirect costs such as productivity loss.

RESULTS: The panel identified a 70-100% probability that polybrominated diphenyl ether and organophosphate exposures contribute to IQ loss in the European population. Polybrominated diphenyl ether exposures were associated with 873,000 (sensitivity analysis, 148,000 to 2.02 million) lost IQ points and 3290 (sensitivity analysis, 3290 to 8080) cases of intellectual disability, at costs of euro9.59 billion (sensitivity analysis, euro1.58 billion to euro22.4 billion). Organophosphate exposures were associated with 13.0 million (sensitivity analysis, 4.24 million to 17.1 million) lost IQ points and 59 300 (sensitivity analysis, 16,500 to 84,400) cases of intellectual disability, at costs of euro146 billion (sensitivity analysis, euro46.8 billion to euro194 billion). Autism spectrum disorder causation by multiple EDCs was assigned a 20-39% probability, with 316 (sensitivity analysis, 126-631) attributable cases at a cost of euro199 million (sensitivity analysis, euro79.7 million to euro399 million). Attention-deficit hyperactivity disorder causation by multiple EDCs was assigned a 20-69% probability, with 19 300 to 31 200 attributable cases at a cost of euro1.21 billion to euro2.86 billion.

CONCLUSIONS: EDC exposures in Europe contribute substantially to neurobehavioral deficits and disease, with a high probability of >euro150 billion costs/year. These results emphasize the advantages of controlling EDC exposure.


EFFECTS OF PRENATAL EXPOSURE TO AIR POLLUTANTS (POLYCYCLIC AROMATIC HYDROCARBONS) ON THE DEVELOPMENT OF BRAIN WHITE MATTER, COGNITION, AND BEHAVIOR IN LATER CHILDHOOD.

Peterson BS, Rauh VA, Bansal R, et al.

IMPORTANCE: Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous and neurotoxic environmental contaminants. Prenatal PAH exposure is associated with subsequent cognitive and behavioral disturbances in childhood.

OBJECTIVES: To identify the effects of prenatal PAH exposure on brain structure and to assess the cognitive and behavioral correlates of those abnormalities in school-age children.

DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional imaging study in a representative community-based cohort followed up prospectively from the fetal period to ages 7 to 9 years. The setting was urban community residences and an academic imaging center. Participants included a sample of 40 minority urban youth born to Latina (Dominican) or African American women. They were recruited between February 2, 1998, and March 17, 2006.

MAIN OUTCOMES AND MEASURES: Morphological measures that index local volumes of the surface of the brain and of the white matter surface after cortical gray matter was removed.

RESULTS: We detected a dose-response relationship between increased prenatal PAH exposure (measured in the third trimester but thought to index exposure for all of gestation) and reductions of the white matter surface in later childhood that were confined almost exclusively to the left hemisphere of the brain and that involved almost its entire surface. Reduced left hemisphere white matter was associated with slower information processing speed during intelligence testing and with more severe externalizing behavioral problems, including attention-deficit/hyperactivity disorder symptoms and conduct disorder problems. The magnitude of left hemisphere white matter disturbances mediated the significant association of PAH exposure with slower processing speed. In addition, measures of postnatal PAH exposure correlated with white matter surface measures in dorsal prefrontal regions bilaterally when controlling for prenatal PAH.

CONCLUSIONS AND RELEVANCE: Our findings suggest that prenatal exposure to PAH air pollutants contributes to slower processing speed, attention-deficit/hyperactivity disorder symptoms, and externalizing problems in urban youth by disrupting the development of left hemisphere white matter, whereas postnatal PAH exposure contributes to additional disturbances in the development of white matter in dorsal prefrontal regions.
Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity Disorder and Cocaine Use Disorder: A Randomized Clinical Trial.

Levin FR, Mariani JJ, Specker S, et al.

Importance: Adult attention-deficit/hyperactivity disorder (ADHD) is prevalent but often unrecognized, in part because it tends to co-occur with other disorders such as substance use disorders. Cocaine use disorder is one such disorder with high co-occurrence of ADHD.

Objective: To examine whether treatment of co-occurring ADHD and cocaine use disorder with extended-release mixed amphetamine salts is effective at both improving ADHD symptoms and reducing cocaine use.

Design, Setting, and Participants: Thirteen-week, randomized, double-blind, 3-arm, placebo-controlled trial of participants meeting DSM-IV-TR criteria for both ADHD and cocaine use disorder conducted between December 1, 2007, and April 15, 2013, at 2 academic health center substance abuse treatment research sites. One hundred twenty-six adults diagnosed as having comorbid ADHD and cocaine use disorder were randomized to extended-release mixed amphetamine salts or placebo. Analysis was by intent-to-treat population.

Interventions: Participants received extended-release mixed amphetamine salts (60 or 80 mg) or placebo daily for 13 weeks and participated in weekly individual cognitive behavioral therapy.

Main Outcomes and Measures: For ADHD, percentage of participants achieving at least a 30% reduction in ADHD symptom severity, measured by the Adult ADHD Investigator Symptom Rating Scale; for cocaine use, cocaine-negative weeks (by self-report of no cocaine use and weekly benzoylecgonine urine screens) during maintenance medication (weeks 2-13) and percentage of participants achieving abstinence for the last 3 weeks.

Results: More patients achieved at least a 30% reduction in ADHD symptom severity in the medication groups (60 mg: 30 of 40 participants [75.0%]; odds ratio [OR] = 5.23; 95% CI, 1.98-13.85; P < .001; and 80 mg: 25 of 43 participants [58.1%]; OR = 2.27; 95% CI, 0.94-5.49; P = .07) compared with placebo (17 of 43 participants [39.5%]). The odds of a cocaine-negative week were higher in the 80-mg group (OR = 5.46; 95% CI, 2.25-13.27; P < .001) and 60-mg group (OR = 2.92; 95% CI, 1.15-7.42; P = .02) compared with placebo. Rates of continuous abstinence in the last 3 weeks were greater for the medication groups than the placebo group: 30.2% for the 80-mg group (OR = 11.87; 95% CI, 2.25-62.62; P = .004) and 17.5% for the 60-mg group (OR = 5.85; 95% CI, 1.04-33.04; P = .04) vs 7.0% for placebo.

Conclusions and Relevance: Extended-release mixed amphetamine salts in robust doses along with cognitive behavioral therapy are effective for treatment of co-occurring ADHD and cocaine use disorder, both improving ADHD symptoms and reducing cocaine use. The data suggest the importance of screening and treatment of ADHD in adults presenting with cocaine use disorder.

Trial Registration: clinicaltrials.gov Identifier:NCT00553319


The purpose of the research study was to determine whether ADHD- and texting-related driving impairments are mediated by extended visual glances away from the roadway. Sixty-one adolescents (ADHD = 28, non-ADHD = 33; 62% male; 11% minority) aged 16–17 with a valid driver’s license were videotaped while engaging in a driving simulation that included a No Distraction, Hands-Free Phone Conversation, and Texting condition. Two indicators of visual inattention were coded: 1) percentage of time with eyes diverted from the roadway; and 2) number of extended (greater than 2 s) visual glances away from the roadway. Adolescents with ADHD displayed significantly more visual inattention to the roadway on both visual inattention measures. Increased lane position variability among adolescents with ADHD compared to those without ADHD during the Hands-Free Phone Conversation and Texting conditions was mediated by an increased number of extended glances away from the roadway. Similarly, texting resulted in decreased visual attention to the roadway. Finally, increased lane position variability during texting was...
also mediated by the number of extended glances away from the roadway. Both ADHD and texting impair visual attention to the roadway and the consequence of this visual inattention is increased lane position variability. Visual inattention is implicated as a possible mechanism for ADHD- and texting-related deficits and suggests that driving interventions designed to address ADHD- or texting-related deficits in adolescents need to focus on decreasing extended glances away from the roadway.


ONLINE SOCIAL COMMUNICATION PATTERNS AMONG EMERGING ADULT WOMEN WITH HISTORIES OF CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Mikami AY, Szwedo DE, Ahmad SI, et al.
Little is known about adult women with attention-deficit/hyperactivity disorder (ADHD); however, available evidence suggests that they experience social impairment. Online social networking websites such as Facebook have become endemic outlets through which emerging adults communicate with peers. No study has examined the peer interactions of emerging adults with childhood histories of ADHD in this developmentally relevant online domain. Participants in the current study were an ethnically diverse sample of 228 women, 140 of whom met diagnostic criteria for ADHD in childhood and 88 who composed a matched comparison sample. These women were assessed at 3 time points spanning 10 years (mean age = 9.6 at Wave 1, 14.1 at Wave 2, 19.6 at Wave 3). After statistical control of demographic covariates and comorbidities, childhood ADHD diagnosis predicted, by emerging adulthood, a greater stated preference for online social communication and a greater tendency to have used online methods to interact with strangers. A childhood diagnosis of ADHD also predicted observations of fewer Facebook friends and less closeness and support from Facebook friends in emerging adulthood. These associations were mediated by a composite of face-to-face peer relationship impairment during childhood and adolescence. Intriguingly, women with persistent diagnoses of ADHD from childhood to emerging adulthood differed from women with consistent comparison status in their online social communication; women with intermittent diagnoses of ADHD had scores intermediate between the other 2 groups. Results are discussed within the context of understanding the social relationships of women with childhood histories of ADHD.


SUMMER TREATMENT PROGRAM IMPROVES BEHAVIOR OF CHILDREN WITH HIGH-FUNCTIONING AUTISM SPECTRUM DISORDER.
This study evaluated the effects of a behavioral summer treatment program for children with high-functioning autism spectrum disorder (HFASD). Twenty boys (M = 9.2 years) diagnosed with HFASD participated in the 6-week program across 6 years. Detailed daily behavioral data were collected on a variety of positive and negative social behaviors. Repeated measures ANOVAs of weekly behavior frequencies indicated substantial improvements in a number of behaviors over the 6 weeks of the program, including following activity rules, contributing to a group discussion, paying attention, and less complaining/whining. Overall, results highlight the potential efficacy of treating chronic functional impairments of HFASD and associated problem behaviors in the context of an intensive behavioral summer treatment program.
The diagnosis of attention deficit hyperactivity disorder (ADHD) distinguishes two dimensions of symptoms, inattention and hyperactivity-impulsivity for ages 3 to adulthood. Currently, no separate classification for preschool-age children exists, whereas preliminary research suggests that the two-factor structure of ADHD may not match the presentation of symptoms in a preschool sample. The present study explored this incongruity by examining the factor structure of the 18 Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev; DSM-IV-TR) ADHD symptoms on the ADHD-Rating Scale-IV–Preschool Version within a normative preschool sample (n = 976). Confirmatory factor analyses (CFAs) were performed on results from teacher and parent ratings. The findings indicate a three-factor model, inattention, hyperactivity, and impulsivity, for the presentation of ADHD in preschoolers based on both parent and teacher report data.

Role of ADHD Symptoms as a Contributing Factor to Obesity in Patients with MC4R Mutations.
Besides the crucial role of genetic susceptibility in the development of early-onset obesity, it has been shown that feeding behavior could contribute to increased body weight. A significant association between obesity/overweight and ADHD has been reported, suggesting that these two conditions, despite their heterogeneity, might share common molecular pathways. Although the co-occurrence of obesity and ADHD is increasingly supported by empirical evidence, the complex pathogenetic link between these two conditions is still unclear. Here, we focus on the relationship between MC4R gene mutations and ADHD in children with early-onset obesity. Mutations in the gene MC4R lead to the most common form of monogenic obesity. We hypothesize that dysregulated eating behavior in a subset of patients with MC4R mutation might be due to comorbid ADHD symptoms, underpinned by abnormal reward mechanisms. Therefore, we speculate that it is possible to prevent obesity in a subset of patients with MC4R mutation, even if these patients are genetically programmed to "be fat", via an appropriate treatment of ADHD symptoms. We hope that our paper will stimulate further studies testing if the early screening for ADHD symptoms and their appropriate treatment may be an effective way to prevent obesity in a subset of children with MC4R mutation.
Llyod PC, Simon AE, Parker JD.
OBJECTIVES: Medicaid claims have been used to characterize utilization patterns of child Medicaid beneficiaries. However, because states are increasingly adopting Medicaid managed care plans, analyses of children enrolled in Medicaid based only on claims for fee-for-service (FFS) programs may not apply to the general Medicaid population.
METHODS: The 2003-2005 National Health Interview Survey and 2003-2005 Medicaid Analytic eXtract linked files were used to examine associations between sociodemographic, health, and geographic characteristics of children aged 0-17 years and enrollment in Medicaid FFS compared with a comprehensive managed care (CMC) program. Additional analyses of age-specific health outcomes were performed on a subset of children aged 6-17 years. Chi-square tests were used to assess associations, and 95% confidence intervals are provided for point prevalence estimates.
RESULTS: Higher percentages of children in CMC compared with FFS were non-Hispanic white, lived in families with income less than 100% of the federal poverty level, had excellent or very good health, lived in the Northeast and West, and lived in large central metro areas. No significant differences were observed by sex, age, and asthma diagnoses between children enrolled in CMC and FFS. Among children aged 6-17 years, higher percentages of children enrolled in FFS compared with children in CMC were diagnosed with learning disabilities or developmental delays and attention deficit hyperactivity disorder. Researchers using data from children enrolled only in Medicaid FFS programs to describe children enrolled in Medicaid should understand differences between children in CMC and FFS. Generalization of study results from FFS claims may depend on the outcomes examined.

TIME WINDOWS MATTER IN ADHD-RELATED DEVELOPING NEUROPSYCHOLOGICAL BASIC DEFICITS: A COMPREHENSIVE REVIEW AND META-REGRESSION ANALYSIS.
Pauli-Pott U, Becker K.
Normative development of neuropsychological functions that are assumed to underlie attention deficit/hyperactivity disorder (ADHD) may show transition periods, i.e., periods of heightened developmental discontinuity and reduced differential continuity. During such periods differences between ADHD cases and controls in these functions might be obscured because assessments probably not only reflect individual differences in the ADHD-related deviation but also individual differences in speed/onset of the transition. Our review focuses on executive inhibitory control (IC) and delay aversion/discounting (DA) because normative developmental processes of these characteristics are relatively well described. For complex IC performance a transition period can be assumed in preschool years, for DA around puberty. Published meta-analyses on neuropsychological IC tasks and a meta-regression analysis of 23 case-control comparisons in DA tasks comprising 1395 individuals with ADHD and 1195 controls confirmed our assumption. Effect sizes of case-control comparisons were significantly larger outside transition periods, i.e., in age-periods of relative developmental continuity. An increasingly precise identification of such time windows could contribute to the understanding of the etiological pathways of ADHD.

ZOLPIDEM AND SLEEP IN PEDIATRIC BURN PATIENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.
Cronin SD, Gottschlich MM, Gose LM, et al.
Existing research shows that hospitalized patients, especially pediatric burn patients, are often sleep deprived. A pre-existing diagnosis of attention deficit/hyperactivity disorder (ADHD) further compounds a burn patient’s inability to sleep. This retrospective study compared the effectiveness of zolpidem on patients with acute burns with ADHD (n = 23) and patients with acute burns without ADHD (n = 23). Effectiveness was defined based on the need for a change in the sleep medication or an increase in the
zolpidem dose during the first 12 days of treatment. This study found that sleep dysfunction was similar in pediatric burn patients with and without a concurrent diagnosis of ADHD. Sixteen (69.6%) patients with and 13 (56.5%) patients without ADHD required a sleep medication change (p = 0.541). Further, while patients with ADHD required a sleep medication change (median = 5 days) sooner than those without ADHD (median = 9 days), it appears that zolpidem is not an effective drug for managing sleep in pediatric burn patients with or without ADHD.


MENTAL HEALTH OF EXTREMELY LOW BIRTH WEIGHT SURVIVORS IN THEIR 30S.


OBJECTIVE: To determine the risk for psychiatric disorders among extremely low birth weight (ELBW) survivors in their early to mid-30s and to determine whether those born small for gestational age or those exposed to a full course of antenatal corticosteroids (ACS) were at particularly high risk.

METHODS: A prospective, longitudinal, population-based cohort of 84 ELBW survivors and 90 normal birth weight (NBW) control participants born in Ontario, Canada from 1977 to 1982 were assessed by interviewers naive to birth weight status using the Mini-International Neuropsychiatric Interview.

RESULTS: ELBW survivors had lower odds of an alcohol or substance use disorder but higher odds of current non-substance-related psychiatric problems (odds ratio [OR] = 2.47; 95% confidence interval [CI], 1.19-5.14). Those born ELBW and SGA exhibited the same patterns with larger effects. ACS-exposed ELBW survivors had even higher odds of any current non-substance-related psychiatric disorder (OR = 4.41; 95% CI, 1.65-11.82), particularly generalized anxiety disorder (OR = 3.42; 95% CI, 1.06-11.06), the generalized type of social phobia (OR = 5.80; 95% CI, 1.20-27.99), and the inattentive subtype of attention-deficit/hyperactivity disorder (OR = 11.45; 95% CI, 2.06-63.50).

CONCLUSIONS: In their early to mid-30s, ELBW survivors were less likely to have alcohol or substance use disorders but may be at greater risk for other psychiatric problems. Those exposed to ACS were at especially high risk and manifested no reduction in alcohol or substance use disorders. ELBW survivors exposed to ACS may be a special group at risk for psychopathology in adulthood.


AGREEMENT OF ADOLESCENT RATINGS WITH MOTHER RATINGS AND TEACHER RATINGS OF ADHD SYMPTOM GROUPS: A CORRELATED TRAIT-CORRELATED METHOD MINUS ONE ANALYSIS.

Gomez R, Gomez A.

This study examined the level of agreement of adolescent ratings with mother ratings, and adolescent ratings with teacher ratings of the inattention (IA) and hyperactivity/impulsivity (HI) symptom groups of ADHD. A total of 214 adolescents provided self-ratings of IA and HI, and their IA and HI were also rated by their mothers and teachers. The correlated trait-correlated method minus one model was applied, with adolescent ratings as the reference method, and the other two ratings as the non-reference methods. The findings indicated no additional variance in adolescent ratings for IA and HI that could not be accounted by mother ratings of IA and HI, respectively. In contrast, there was additional variance in adolescent ratings for IA and HI that could was not accounted by teacher ratings of IA and HI, respectively. The findings suggest that when diagnosing ADHD in adolescents, their reports of their own ADHD behaviors are not needed when mother reports of such behaviors are used.
CONDUCT BEHAVIORS AND OPPOSITIONAL DEFIANT BEHAVIORS IN CHILDREN AND ADOLESCENTS WITH ADHD.

Ghanizadeh A.

There is controversy about the association among attention deficit hyperactivity disorder (ADHD), conduct disorder behaviors, and oppositional defiant behaviors. This study examines whether different subcategories of conduct behaviors co-occur in children with ADHD, and investigates the association of conduct behaviors with ADHD symptoms and oppositional defiant behavior, considering the covariant factors of parental age and educational level. A total of 441 children and adolescents with ADHD participated in this study - 342 (77.6%) boys and 99 girls (22.4%). Their mean age was 9.1 (standard deviation = 2.2) years. They came from families with 1 to 8 children. There were statistically significant correlations among different subcategories of conduct disorder (p < 0.001 for all the correlations). Oppositional behavior scores were associated with all 4 subcategories of conduct behaviors. The severity of hyperactivity/impulsivity was associated with the subcategory of “destruction of property.” The inattentiveness score was associated with “aggression to people and animals.” The current results do not suggest that conduct behaviors exclude oppositional defiant behaviors. The subcategories of conduct behaviors occur in a cluster rather than as a solitary behavior. Larger family size and lower educational level of the father increase the risk of aggression to people and animals in children with ADHD.

DELIQUENCY AND ASSOCIATION WITH BEHAVIORAL DISORDERS AND SUBSTANCE ABUSE.


OBJECTIVE: to determine the incidence and associations of attention deficit-hyperactivity disorder (ADHD), conduct disorder (CD), and substance abuse disorder (SAD) in adolescents in conflict with the law in a Brazilian cohort.

METHODS: the Brazilian version of the Schedule for Affective Disorders and Schizophrenia for School Aged-Children (K-SADS-PL) was administered to 69 adolescent boys who were incarcerated for 45 days in the city of Curitiba, Brazil.

RESULTS: mean age was 15.5 years (range, 12-16.9 years) and most adolescents originated from disadvantaged social classes (87%). They resided in neighborhoods on the outskirts of the city or towns in the greater metropolitan area. Truancy and low educational achievement were common, with 73.9% not currently attending school and 43.4% not having finished the 5th grade. The great majority lived in single-parent families and many had relatives who themselves had problems with the law. Psychiatric disorders were apparent in 81.1% of the subjects, with the most common disorders being CD (59.4%), SAD (53.6%), and ADHD (43.5%). Both ADHD (p <0.001) and CD (p <0.01) had significant associations with substance abuse.

CONCLUSION: in male adolescents in conflict with the law, ADHD, CD, and SAD were all found to be associated with delinquency.

TREATMENT OF ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD): NURSING IMPLICATIONS. LUNA DL, Moriones JO.

OBJECTIVE: This review aims to know the role of the nurse in ADHD treatment, identifying the most appropriate therapeutic options between nursing interventions and pharmacological treatment.

DEVELOPMENT: In ADHD, the role of the nurse is to respond family needs about the effectiveness of medication, behavior modification treatment and other alternatives. There are family interventions of psychoeducation that assist the child in the recovery process. Through the education for health, the nurse should promote the combination of behavioral therapy and pharmacological as the only one able to improve child's quality of life.
CONCLUSIONS: Nurses have a privileged role due to its experience in education for health; this contributes to being a competent agent that provides families essential information about the disease treatment. Spanish schools are lacking a figure that represent health as a relevant subject in the vital process, hence the need of the school nurse.

DISTINGUISHING ADOLESCENTS WITH ADHD FROM THEIR UNAFFECTED SIBLINGS AND HEALTHY COMPARISON SUBJECTS BY NEURAL ACTIVATION PATTERNS DURING RESPONSE INHIBITION.
van Rooij D, Hoekstra PJ, Mennes M, et al.
Objective: Dysfunctional response inhibition is a key executive function impairment in attention deficit hyperactivity disorder (ADHD). Still, behavioral response inhibition measures do not consistently differentiate affected from unaffected individuals. The authors therefore investigated neural correlates of response inhibition and the familial nature of these neural correlates.
Methods: Functional MRI measurements of neural activation during the stop-signal task and behavioral measures of response inhibition were obtained in adolescents and young adults with ADHD (N = 185), their unaffected siblings (N = 111), and healthy comparison subjects (N = 124).
Results: Stop-signal task reaction times were longer and error rates were higher in participants with ADHD, but not in their unaffected siblings, while reaction time variability was higher in both groups than in comparison subjects. Relative to comparison subjects, participants with ADHD and unaffected siblings had neural hypoactivation in frontal-striatal and frontal-parietal networks, whereby activation in inferior frontal and temporal/parietal nodes in unaffected siblings was intermediate between levels of participants with ADHD and comparison subjects. Furthermore, neural activation in inferior frontal nodes correlated with stop-signal reaction times, and activation in both inferior frontal and temporal/parietal nodes correlated with ADHD severity.
Conclusions: Neural activation alterations in ADHD are more robust than behavioral response inhibition deficits and explain variance in response inhibition and ADHD severity. Although only affected participants with ADHD have deficient response inhibition, hypoactivation in inferior frontal and temporal/parietal nodes in unaffected siblings supports the familial nature of the underlying neural process. Activation deficits in these nodes may be useful as endophenotypes that extend beyond the affected individuals in the family.

Z Kinder Jugendpsychiatr Psychother. 2015 May;43:185-93.
THE COMORBIDITY OF LEARNING DIFFICULTIES AND ADHD SYMPTOMS IN PRIMARY-SCHOOL-AGE CHILDREN.
Children having difficulties in acquiring early literacy and mathematical skills often show an increased rate of inattention, hyperactivity, and impulsivity. This study provides data on the comorbidity rates of specific learning difficulties and ADHD symptoms. We analyzed the data of 273 children with learning difficulties despite an at least average IQ, 57 children with low IQ, and 270 children without learning difficulties and average IQ (comparison group). We assessed children's IQ and school achievement using standardized achievement tests. ADHD symptoms were assessed via parents' ratings. Our results showed that only 5% of both the control group and the group with solely mathematical difficulties fulfilled the criteria of an ADHD subtype according to the DSM-IV based on parents' ratings. In contrast, this was the case in even 20% of the children with difficulties in reading/writing and of those with low IQ. Compared to girls, boys in the control group had a 150% higher risk for matching the criteria of one of the ADHD subtypes in parents' ratings, whereas boys with learning difficulties and those with low IQ had an even 200% to 600% higher risk for it. The relationship between learning difficulties and ADHD symptoms can be found predominantly in the inattentive type. Possible reasons for the results are discussed.

SCREENING INTERVIEW FOR EARLY DETECTION OF HIGH-FUNCTIONING AUTISM SPECTRUM DISORDERS.

OBJECTIVE: Various different questionnaires are available for the screening of autism spectrum disorders (ASD). These screening instruments show high sensitivity and are able to identify a large number of individuals with ASD, but they lack the specificity to differentiate individuals with ASD from those children and adolescents with other complex neurobehavioural disorders (such as attention-deficit/hyperactivity disorder, emotional disorders, and others), especially for those without intellectual disabilities.

METHOD: The present study evaluates the data of 309 individuals (153 with high-functioning ASD, 156 with other psychiatric disorders, IQ > 70) to find out whether selected items of the ADI-R can be used for an economic and sensitive screening of high-functioning ASD.

RESULTS: The results show that 8 items of the ADI-R can be used to discriminate high-functioning ASD and other psychiatric disorders. A cutoff of 5 led to a sensitivity of 0.93 and a cutoff of 6 to a specificity of 0.74.

CONCLUSION: The combination of early onset, serious abnormalities in social contact with stereotyped or compulsive-ritualized behaviour or interests can be detected with few interview questions for screening of ASD. Nevertheless, a more detailed and specific assessment in an expert setting should follow the screening process.
Role of ADHD symptoms as a contributing factor to obesity in patients with MC4R mutations

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ABSTRACT

Besides the crucial role of genetic susceptibility in the development of early-onset obesity, it has been shown that feeding behavior could contribute to increased body weight. A significant association between obesity/overweight and ADHD has been reported, suggesting that these two conditions, despite their heterogeneity, might share common molecular pathways. Although the co-occurrence of obesity and ADHD is increasingly supported by empirical evidence, the complex pathogenetic link between these two conditions is still unclear. Here, we focus on the relationship between MC4R gene mutations and ADHD in children with early-onset obesity. Mutations in the gene MC4R lead to the most common form of monogenic obesity. We hypothesize that dysregulated eating behavior in a subset of patients with MC4R mutation might be due to comorbid ADHD symptoms, underpinned by abnormal reward mechanisms. Therefore, we speculate that it is possible to prevent obesity in a subset of patients with MC4R mutation, even if these patients are genetically programmed to “be fat”, via an appropriate treatment of ADHD symptoms. We hope that our paper will stimulate further studies testing if the early screening for ADHD symptoms and their appropriate treatment may be an effective way to prevent obesity in a subset of children with MC4R mutation.

INTRODUCTION

In the last decade the prevalence of obesity has dramatically increased among children and adolescents, not only in developed but also in low-middle income countries, with enormous implications in terms of public health [1]. In 2010, according to the World Health Organization, 42 millions children under the age of 5 were estimated to be overweight worldwide [2].

Besides the crucial role of genetic susceptibility in the development of early-onset obesity, it has been shown that feeding behavior could contribute to increased body weight. However, there is a group of patients in which early obesity is mostly due to genetic factors, including melanocortin-brain-receptor-4 (MC4R) mutations, which represent the most common form of monogenic severe obesity [3].

The hypothesis

In this paper, we hypothesize that, in a subset of patients with MC4R mutation, dysregulated eating behavior could be primary correlated to Attention Deficit/Hyperactivity Disorder (ADHD) symptoms, starting in childhood. Therefore, the assessment for the presence of ADHD and its early pharmacological treatment could be an effective strategy to prevent obesity in a subset of patients with MC4R mutation, even if they are genetically programmed to become obese.

Evaluation of hypothesis

MC4R is a 7-trans-membrane receptor highly expressed in several hypothalamic nuclei and also on target neurons of the
paraventricular nucleus, involved in the regulation of energy homeostasis [3]. This receptor is activated by alpha-melanocyte stimulating hormone (α-MHS), its endogenous agonist, and is antagonized by agouti-related peptide (AgRP). Leptin stimulates the production of pro-opiomelanocortin (POMC), the precursor of alpha-MHS, and inhibits the expression of AgRP, generating an orexigenic signal [3]. MC4R is also expressed on the surface of target neurons of the paraventricular nucleus, having a role in the mechanism of appetite [4].

Prevalence of MC4R deficit ranges from 0.2% to 5.8% (1.8% of children in the European population) and is characterized clinically by early hyperphagia and severe obesity, with a Body Mass Index >35 in adults and with onset during the first year of life [5,6]. The study of the behavioral phenotypes in genetically determined obese patients could offer clinically useful insights to understand which factors contribute to early hyperphagia; this in turn may be informative for the prevention of obesity. However, little is known about eating patterns in MC4R mutation carriers, and only rarely Binge Eating Disorder (BED) appears as a relevant phenotype [7]. Besides the eating patterns, other behavioral features have been poorly investigated in patients with MC4R gene mutation. However, three reports [8–10] consistently found severe symptoms of ADHD, as summarized in Table 1. Interestingly, one of these studies pointed out that 80% of subjects carrying homozygous and 20% of subjects carrying heterozygous mutations of MC4R, presented symptoms of ADHD since childhood [9], which is significantly higher than the estimated prevalence of ADHD in school-aged children in the general population, amounting at approximately 5% [11].

Indeed, a significant association between obesity/overweight and ADHD has been reported, suggesting that these two conditions, despite their heterogeneity, might share common molecular pathways [11]. Recent evidence also shows that ADHD temporally, and, thus, probably causally precedes obesity [12,13]. However, although the co-occurrence of obesity and ADHD is well known, the complex pathogenetic links between these two conditions still needed to be elucidated. It is not clear what dimension of ADHD could be specifically associated with abnormal eating behaviors [11,14]. A first possibility is that impulsivity and poor planning skills lead to overconsumption when not hungry. Another hypothesis is that patients may be inattentive to internal signs of hunger and satiety, or they perceive subjectively greater stress, and this may predispose to compulsive and compensatory overfeeding, due to the anxiolytic-like quality of eating. An alternative option is that the loss of control over food intake could be compared to other addictive behaviors, common in ADHD patients. ADHD is a subtype of “reward deficiency syndrome” that is characterized by an insufficient dopamine-related natural reward that leads to use “unnatural” immediate rewards, such as abnormal eating behaviors. These may lead to the co-occurrence of overweight/obesity in ADHD patients [12]. However, the pathways that link ADHD and obesity are probably multiple and complex. Here, we specifically discuss how MC4R mutation may underpin reward deficiency syndrome in patients with obesity and ADHD. We also discuss the possible treatment implications of the link MC4R–ADHD-obesity.

Evidence from genetic, brain imaging and environmental studies has suggested a functional and anatomical link between dopaminergic and melanocortinergic systems [15]. MC4R is expressed in virtually all brain regions, including the ventral tegmental area (VTA), hypothalamus, thalamus, amygdala, cortex, brainstem and spinal cord [16,17]. Melanocortin administered intracerebroventricularly or into the ventral tegmental area (VTA) stimulates the release of dopamine in the striatum, binding to MC4R [18,19]. Furthermore, through the hypothalamus and limbic regions, the melanocortin system modulates the activity of dopamine cells and their projections into nucleus accumbens and frontal cortex, which are also involved in the rewarding process [20]. Both individuals with ADHD and subjects with obesity show low dopamine receptor availability, respectively D2/D3 in the hypothalamus and D2 receptor levels in the striatum [21,22]. Some evidences from animal models confirmed that MC4R mutations are potentially associated with a hypodopaminergic activity. MC4R knockout mice (MC4RKO) are hyperphagic and become obese [23]. Weight gain in the MC4R knockout animals has also been conceived as the result of increased food consumption and low locomotor activity [4]. Therefore, the low dopamine availability observed also in MC4R mutation carriers, could lead them to use “unnatural” immediate rewards, such as snacking or hyperphagia.

The melanocortin system is also involved in rewarding and reinforcing properties of drugs. Repeated cocaine administration have been shown to increase the expression of MC4R in nucleus accumbens and striatum, and the infusion of a MC4R antagonist blocked the locomotor responses to drug in MC4R mutated mice [24]. Cocaine and amphetamine-related transcript (CART), which is stimulated by leptin secretion, is involved in locomotor activity and in the appraisal of rewarding/reinforcing stimuli [25,26]. Interestingly, CART expression in serum and hypothalamus is increased in both MC4R+/– and +/+ mice [27]. These findings could explain the efficacy on weight loss of both Methylphenidate (MPH) and Atomoxetine (ATMX), respectively the first and the second line pharmacological treatments for ADHD, in MC4R mutation carriers, as described in Table 1. More specifically, ATMX selectively inhibits noradrenergic re-uptake in those regions generating a signal of satiety, as well as paraventricular nuclei. Adults with reduced MC4R function show a lowered adrenergic level [10]. Therefore, elevation of noradrenergic levels due to ATMX might be beneficial in conditions associated with a low noradrenergic/sympathetic tone, as well as in MC4R mutation. Methylphenidate is a dopamine-reuptake modulator and induces anorexigenic effects, by increasing dopamine signaling in brain regions involved in food intake, reward and motivation, as well as hypothalamus, striatum, frontal cortex. Weight loss, usually regarded as an adverse effect of MPH in normal weight populations, may constitute a therapeutic effect in severe obese patients with ADHD. Furthermore, the pre-treatment children’s weight is a positive predictor for MPH efficacy on weight loss, with the evidence that “heavier” children have more weight loss than “thinner” children [28]. Finally, MPH anorexigenic effect could be stronger in MC4R-mutated subjects than normally observed in subjects with ADHD, since a reduced MC4R activity could contribute to higher MPH efficacy [8].

In clinical practice, appetite suppression caused by MPH may result in a more considerable weight reduction for obese patients with dysregulated eating behavior. Since no differences have been found in weight loss between carriers and not-carriers of MC4R mutation under weight-reduction regimen, it has been postulated that MC4R deficit does not influence per-se the ability to lose weight [29].

Consequences of the hypothesis and discussion

In summary, our hypothesis points to the role of ADHD in the development of abnormal eating patterns in a subset of obese patients with MC4R gene mutation. The presence of ADHD symptomatology in MC4R mutation carriers could worsen hyperphagic pattern and contribute to the early onset of obesity.

We propose that the presence of ADHD symptoms should be routinely evaluated in obese MC4R mutation carriers, because a subset of them could be particularly prone to develop ADHD which could contribute to weight gain via abnormal eating patterns. Early diagnosis and treatment of ADHD could be an effective method to prevent the onset of hyperphagia and excessive weight
Table 1
Characterization of ADHD phenotype and eating behavior in 9 MC4R mutation carriers.

<table>
<thead>
<tr>
<th>Patient</th>
<th>MC4R mutation</th>
<th>Treatment</th>
<th>BMI</th>
<th>Gender</th>
<th>Age</th>
<th>Psychiatric characteristics</th>
<th>Eating behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albayrak et al. (2011) [8]</td>
<td>Male</td>
<td>2</td>
<td>Hyperactivity, inattention, Hyperphagic, hungry at night</td>
<td>Heterozygous</td>
<td>Missense (C271R) – &gt;97</td>
<td>From 33 to 23 during the treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>&lt;18</td>
<td>Inattention</td>
<td>Hyperphagic, but not fulfill criteria for BED</td>
<td>Heterozygous</td>
<td>Missense (C271R) – &gt;97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>–</td>
<td>Hyperactivity, impulsivity</td>
<td>Hyperphagic, but not fulfill criteria for BED</td>
<td>Heterozygous</td>
<td>Missense (C271R) – &gt;97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>&lt;18</td>
<td>Inattention</td>
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<td>Heterozygous</td>
<td>Missense (C271R) – &gt;97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>13</td>
<td>Hyperactivity, impulsivity</td>
<td>Hyperphagic, snacking</td>
<td>Heterozygous</td>
<td>Missense (C271R) – &gt;97</td>
<td></td>
</tr>
<tr>
<td>Port et al. (2013) [10]</td>
<td>Male</td>
<td>13</td>
<td>Hyperactivity, histrionic</td>
<td>Hyperphagic, snacking</td>
<td>Heterozygous</td>
<td>Missense (C271R) – &gt;97</td>
<td></td>
</tr>
</tbody>
</table>

From 47.4 to 29.6 after 20 months

gain in these children. If our hypothesis is confirmed by further studies, an early behavioral management and appropriate treatment for ADHD could be an useful option for a subgroup of children with MC4R. To our knowledge, whether early treatment ADHD could change the natural course of a subset of children with MC4R mutation has yet to be determined; we hope that our paper stimulates research on this topic, which may have important clinical and public health implications.

Conflict of interest statement

No other conflict of interests to declare.

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References


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

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La partecipazione è gratuita e prevede l’assegnazione di 12 crediti ECM.
L’iscrizione al Convegno è obbligatoria e deve essere effettuata entro il 31 ottobre 2015 accedendo al link: ADHD.marionegri.it

Con il patrocinio della:

SINPIA
Società Italiana di Neuropsichiatria dell’Infanzia e dell’Adolescenza

Con il patrocinio della:

Per il progetto: "Condivisione dei percorsi diagnostico-terapeutici condivisi per l’ADHD" la Regione Lombardia è stato in parte finanziato dalla Regione Lombardia con decreto Dq, Salute n. 378 del 08.02.2014 e n. 77 del 05.02.2015. Il progetto coinvolge 18 Centri di Riferimento per l’ADHD dell’IRCCS - Istituto di Ricerche Farmacologiche Mario Negri. Coordinatore del progetto è la UONPIA degli Spedali Civili di Brescia.
Una risposta alle criticità e ai bisogni inesi

Il Progetto Condivisione dei percorsi diagnostico terapeutici per l’ADHD ha permesso nel triennio 2011-2013 di strutturare un raccordo tra i Centri di Riferimento per l’ADHD in Lombardia e di attivare momenti di formazione e confronto condivisi. Il Registro ha rappresentato un essenziale strumento di monitoraggio continuo e sistematico che ha permesso di programmare e usare in modo appropriato le risorse sulla base dei bisogni (gravità e tipo di domanda), attivando progressivi e significativi miglioramenti nella pratica clinica e garantendo un’efficiente e omogenea qualità delle cure.

Permangono tuttavia significative disomogeneità delle risposte tra i Centri (tempi di attesa per la prima visita, tempi del percorso diagnostico, offerta terapeutica, etc.). L’attività del gruppo formazione/informazione ha evidenziato il bisogno di iniziative continue per le professionalità diversamente implicate nella presa in carico del paziente con ADHD. Anche le famiglie e gli insegnanti dei pazienti necessitano di percorsi informativi e formativi condivisi e partecipati.

Alla luce di queste considerazioni la fase 2014-2015 del Progetto prevedeva di:

- **Migliorare** la struttura della rete curante per l’ADHD: ottimizzando il raccordo e il coordinamento tra i nodi della rete, aumentando il coinvolgimento del territorio, diminuendo e governando la migrazione sanitaria, definendo i livelli di qualità richiesti per i diversi nodi della rete, migliorando l’omogeneità e appropriatezza delle risposte diagnostiche e terapeutiche, definendo la struttura/articolazione della rete regionale dell’ADHD sulla base della qualità delle cure.

- **Implementare** le azioni informative/formative migliorando l’informazione e formazione rivolte alle famiglie, scuole e operatori sulle modalità di presa in carico, gli aggiornamenti normativi e la conoscenza scientifica relativi all’ADHD.

- **Garantire** risposte terapeutiche omogenee e appropriate in tutto il territorio regionale migliorando la capacità di risposta terapeutica dei servizi, sia nell’ambito dei Centri di riferimento che dei Poli territoriali.

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**Percorsi diagnostico-terapeutici condivisi per l’ADHD**

### Lunedì 9 Novembre 2015

**Mattina 09.00 – 13.00**

**La prevalenza dei bisogni: la saga ADHD**

Maurizio Bonati

**Percorso diagnostico condiviso per l’ADHD**

Massimo Molteni

**dal Progetto**

**Daniele Arisi**

**e ancora …**

**Emiddio Fornaro**

Guardando oltre

ADHD-disturbi dirompenti-autismo: appropriatezza, qualità e utilità dei percorsi diagnostici

**Luigi Mazzone**

**Discussione**

**Pomeriggio 14.30 – 18.00**

**Interventi terapeutici condivisi per l’ADHD**

Ottaviano Martinelli

**dal Progetto**

**Monica Saccani**

**e ancora ... dubbi e criticità**

Parent training

Claudio Bissoli

Teacher training

Gianluca Daffi

Child training

- Coping Power Program: evidenze, limiti, prospettive
  - Laura Vanzini
- Esperienze in età scolare e prescolare
  - Davide Villani

Guardando oltre

Strategie di interventi tra ieri e oggi

Dino Maschietto

**Discussione**

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**Martedì 10 Novembre 2015**

**Mattina 09.00 – 13.00**

**Formazione e aggiornamento permanente degli operatori**

Edda Zanetti

**dal Progetto**

Formazione

Paola Effedri

Cento ADHD vs territorio

Paola Morosini

e ancora …

Luoghi e contesti di educazione continua

Elisa Fazzi

Guardando oltre

Quale formazione per quale operatore

Serafino Corti

**Pomeriggio 14.30 – 18.00**

**Struttura della rete curante per l’ADHD**

Antonella Costantino

**dal Progetto**

Monitoraggio e valutazione del funzionamento della rete

Ottaviano Martinelli

e ancora …

Al compimento della maggiore età

Laura Reale

La spesa dei percorsi ADHD per i Servizi

Gianluigi Casadei

Guardando oltre

Organizzazione dei Servizi vs garanzia dei diritti

Francesco Nardocci

**Discussione**

**Ricerca-azione in neuropsichiatria dell’età evolutiva**

Alessandro Zuddas

**Discussione generale e conclusioni**
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”.

Per ricevere la newsletter iscriversi al seguente indirizzo:
http://crc.marionegri.it/bonati/adhdnews/subscribe.html