NEWSLETTER

INDICE:

SAVE THE DATE

Meeting:

USO RAZIONALE DEGLI PSICOFARMACI IN ETÀ EVOLUTIVA PER IL TRATTAMENTO DELL'ADHD.

IRCCS Istituto di Ricerche Farmacologiche Mario Negri
Milano 21 giugno 2016

BIBLIOGRAFIA ADHD marzo 2016

Acta Psychiatr Scand. 2016;133:310-23.

NEURAL CORRELATES OF REACTIVE AGGRESSION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND COMORBID DISRUPTIVE BEHAVIOUR DISORDERS.

Bubenzer-Busch S, Herpertz-Dahlmann B, Kuzmanovic B, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is often linked with impulsive and aggressive behaviour, indexed by high comorbidity rates between ADHD and disruptive behaviour disorders (DBD). The present study aimed to investigate underlying neural activity of reactive aggression in children with ADHD and comorbid DBD using functional neuroimaging techniques (fMRI).

Method: Eighteen boys with ADHD (age 9-14 years, 10 subjects with comorbid DBD) and 18 healthy controls were administered a modified fMRI-based version of the 'Point Subtraction Aggression Game' to elicit reactive aggressive behaviour. Trials consisted of an 'aggression phase' (punishment for a fictitious opponent) and an 'outcome phase' (presentation of the trial outcome).

Results: During the aggression phase, higher aggressive responses of control children were accompanied by higher activation of the ventral anterior cingulate cortex and the temporoparietal junction. Patients displayed inverted results. During the outcome phase, comparison between groups and conditions showed differential activation in the dorsal striatum and bilateral insular when subjects gained points. Losing points was accompanied by differential activation of regions belonging to the insula and the middle temporal sulcus.

Conclusion: Data support the hypothesis that deficient inhibitory control mechanisms are related to increased impulsive aggressive behaviour in young people with ADHD and comorbid DBD

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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;133:324-34.

THE INFLUENCE OF COMORBID DISORDERS ON THE EPISODICITY OF BIPOLAR DISORDER IN YOUTH.

Yen S, Stout R, Hower H, et al.

Objective: Bipolar disorder (BP) frequently co-occurs with other psychiatric disorders. We examine whether course of anxiety disorders (ANX), attention deficit hyperactivity disorder (ADHD), disruptive behavior disorders (DBD), and substance use disorders (SUD) influence likelihood of recovery and recurrence of depression and mania in BP youth.

Method: Weekly ratings of psychiatric disorder intensity were obtained from 413 participants of the Course and Outcome of BP Youth project, followed for an average of 7.75 years. Multiple-event Cox proportional hazards regression analyses examined worsening of comorbid disorders as predictors of mood episode recovery and recurrence.

Results: Increased severity in ANX and SUD predicted longer time to recovery and less time to next depressive episode, and less time to next manic episode. Multivariate models with ANX and SUD found that significant effects of ANX remained, but SUD only predicted longer time to depression recovery. Increased severity of ADHD and DBD predicted shorter time to recurrence for depressive and manic episodes.

Conclusion: There are significant time-varying relationships between the course of comorbid disorders and episodicity of depression and mania in BP youth. Worsening of comorbid conditions may present as a precursor to mood episode recurrence or warn of mood episode protraction

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ADHD Atten Deficit Hyperact Disord. 2016;8:53-58.

THE IMPACT OF SLEEP RESTRICTION ON DAYTIME MOVEMENT IN TYPICALLY DEVELOPING CHILDREN.

Poirier A, Gendron M, Vriend J, et al.

The current study investigated the link between poor sleep and ADHD symptomatology. The effects of extending versus restricting sleep on subjective (questionnaires) and objective (actigraphy) measures of daytime movement were examined in 25 typically developing children aged 8ΓÇô12-áyears. Subjective measures demonstrated an increase in ADHD symptomology following sleep restriction, with follow-up analyses indicating that findings were due to poorer attention, not changes in hyperactivity. The results of actigraphy data indicated that there were no differences found for mean or median daytime activity, but the standard deviation of activity was found to be significantly higher following sleep restriction. Contrary to the popular belief that sleep restriction results in increased overall activity, this study instead found an increase in variability of activity. This suggests that a sleep-restricted childΓÇÖs activity level may appear as alternating periods of high and low activity levels throughout the day

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Afr J Psychiatry (South Africa). 2016;19.

SALIVARY CORTISOL LEVELS IN ABUSED CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Meguid N, Reda M, El Sheikh M, et al.

Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder during childhood. Family violence is a psychosocial factor that has been recently introduced in the literature about ADHD, with indications that parents of hyperactive children are more likely to use physical methods to their discipline. Cortisol as the primary stress hormone and as an index of the hypothalamic-pituitary-adrenal axis regulation has been used to study the neurobiological profile of ADHD patients.

Methods: This study was conducted on 50 ADHD children & 30 matched controls, severity was assessed using the Conners' Parent Rating Scales-Revised long version, children IQ and exposure to abuse was measured; salivary cortisol levels was measured using enzyme-linked immunosorbent assay in two samples (ELISA). Aim of the study was to measure prevalence and impact of abuse on ADHD children and correlate results with salivary cortisol level.

Results: Results showed significant higher exposure of ADHD children to parental abuse than control group. Executive function showed to be impaired in abused ADHD children, lower bedtime cortisol level in abused ADHD children compared to control. There was a negative correlation between cortisol level and child abuse.

In addition, there was a negative correlation between different types of abuse and components of WCST. While no correlation between both cortisol samples and components of WCST.
Conclusion: We concluded that children with ADHD displayed higher exposure to parental abuse, lower cognitive function and this was linked to their lower levels of cortisol level

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Am J Med Genet Part A. 2016;170:799-800.
DEPRESSION AND HYPERACTIVITY IN TWO PATIENTS WITH CRANIOFRONTONASAL SYNDROME.
Fischer M, Bänsch PS, Unterecker S, et al.

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Arch Psychiatry Psychother. 2015;17:32-38.
TREATMENT OF ADHD: COMPARISON OF EEG-BIOFEEDBACK AND METHYLPHENIDATE.
Flisiak-Antonijczuk H, Adamowska S, Chladzi+¦ska-Kiejna S, et al.
Aim of the study: The purpose of the study was to evaluate the efficacy of the electroencephalogram (EEG)-biofeedback (NF) method in attention-deficit hyperactivity disorder (ADHD) treatment in each of the three basic DSM-IV-TR clinical types.
Materials and method: 85 patients aged 6 to 14 years treated in an outpatient department and a day care department (S) were qualified for the EEG-biofeedback therapy, whereas the control group consisted of 30 patients (C) who were treated with methylphenidate. For the purpose of evaluating the efficacy of treatment, a structured interview on the presence of the ADHD symptoms was used. The S group patients participated in 20 NF therapy sessions throughout a six-month period. An analysis of electrophysiological parameters of EEG was additionally conducted in group S theta/sensorimotor rhythm (SMR) and theta/beta ratios in C3 and C4 channels at three points in time (at the beginning, during and at the end of the EEG-biofeedback therapy).
Results: Both types of S and C group therapies significantly reduce ($p<0.01$) the number of attention deficit, hyperactivity and impulsiveness symptoms in subgroups with attention deficit prevalence and mixed type ADHD. In all ADHD types a significant decrease in values of the examined theta/SMR and theta/beta ratios was noted between sessions 1 and 10.
Conclusions: The NF method proved similarly effective to methylphenidate in reducing the number of symptoms in two types of ADHD: ADHD with the prevalence of attention deficit and in mixed type ADHD

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Behavior Analysis in Practice. 2016 Mar;9:64-76.
A FLOW CHART OF BEHAVIOR MANAGEMENT STRATEGIES FOR FAMILIES OF CHILDREN WITH CO-OCCURRING ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND CONDUCT PROBLEM BEHAVIOR.
Danforth JS.
Behavioral parent training is an evidence-based treatment for problem behavior described as attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, and conduct disorder. However, adherence to treatment fidelity and parent performance of the management skills remains an obstacle to optimum outcome. One variable that may limit the effectiveness of the parent training is that demanding behavior management procedures can be deceptively complicated and difficult to perform. Based on outcome research for families of children with co-occurring ADHD and conduct problem behavior, an example of a visual behavior management flow chart is presented. The flow chart may be used to help teach specific behavior management skills to parents. The flow chart depicts a chain of behavior management strategies taught with explanation, modeling, and role-play with parents. The chained steps in the flow chart are elements common to well-known evidence-based behavior management strategies, and perhaps, this depiction well serve as a setting event for other behavior analysts to create flow charts for their own parent

training, Details of the flow chart steps, as well as examples of specific applications and program modifications conclude

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Behav Ther. 2016;47:339-54.

TRAJECTORIES AND PREDICTORS OF RESPONSE TO THE CHALLENGING HORIZONS PROGRAM FOR ADOLESCENTS WITH ADHD.

Langberg JM, Evans SW, Schultz BK, et al.

The Challenging Horizons After School Program is one of the only psychosocial interventions developed specifically for adolescents with attention-deficit/hyperactivity disorder (ADHD) that has demonstrated efficacy in multiple randomized controlled trials. To date, however, all research with the intervention has evaluated outcomes at the group level, and it is unclear whether all adolescents respond similarly, or if the intervention is particularly well suited for certain adolescents with ADHD. This type of information is needed to guide stakeholders in making informed choices as part of dissemination and implementation efforts. The purpose of this study was to evaluate trajectories of response to intervention for a large sample of middle-school age adolescents with ADHD (grades 6-8) who received the after-school intervention (N = 112). An additional goal of the study was to evaluate potential predictors of response trajectories, focusing on determining what factors best distinguished between intervention responders and nonresponders. Latent trajectory analyses consistently revealed four or five distinct classes. Depending on the outcome, between 16% and 46% of participants made large improvements, moving into the normal range of functioning, and between 26% and 65% of participants made small or negligible improvements. Multivariate predictor analyses revealed that a strong counselor/adolescent working alliance rated from the adolescent perspective and lower levels of parenting stress and parent-adolescent conflict consistently predicted an increased likelihood of intervention response. Implications of these findings for disseminating the after school intervention and for further intervention development are discussed

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Behav Brain Funct. 2016;12.

NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL BENEFITS FROM WHITE NOISE IN CHILDREN WITH AND WITHOUT ADHD.

Baijot S, Slama H, S+Âderlund G, et al.

Background: Optimal stimulation theory and moderate brain arousal (MBA) model hypothesize that extra-task stimulation (e.g. white noise) could improve cognitive functions of children with attention-deficit/hyperactivity disorder (ADHD). We investigate benefits of white noise on attention and inhibition in children with and without ADHD (7-12 years old), both at behavioral and at neurophysiological levels.

Methods: Thirty children with and without ADHD performed a visual cued Go/Nogo task in two conditions (white noise or no-noise exposure), in which behavioral and P300 (mean amplitudes) data were analyzed. Spontaneous eye-blink rates were also recorded and participants went through neuropsychological assessment. Two separate analyses were conducted with each child separately assigned into two groups (1) ADHD or typically developing children (TDC), and (2) noise beneficiaries or non-beneficiaries according to the observed performance during the experiment. This latest categorization, based on a new index we called "Noise Benefits Index" (NBI), was proposed to determine a neuropsychological profile positively sensitive to noise.

Results: Noise exposure reduced omission rate in children with ADHD, who were no longer different from TDC. Eye-blink rate was higher in children with ADHD but was not modulated by white noise. NBI indicated a significant relationship between ADHD and noise benefit. Strong correlations were observed between noise benefit and neuropsychological weaknesses in vigilance and inhibition. Participants who benefited from noise had an increased Go P300 in the noise condition.

Conclusion: The improvement of children with ADHD with white noise supports both optimal stimulation theory and MBA model. However, eye-blink rate results question the dopaminergic hypothesis in the latter.

The NBI evidenced a profile positively sensitive to noise, related with ADHD, and associated with weaker cognitive control

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BJOG Int J Obstet Gynaecol. 2016.

GESTATIONAL WEIGHT GAIN, PREPREGNANCY BODY MASS INDEX AND OFFSPRING ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND BEHAVIOUR AT AGE 10.

Pugh SJ, Hutcheon JA, Richardson GA, et al.

OBJECTIVE: To assess offspring attention-deficit hyperactivity disorder (ADHD) symptoms and emotional/behavioural impairments at age 10 years in relation to maternal gestational weight gain (GWG) and prepregnancy body mass index (BMI).

DESIGN AND SETTING: Longitudinal birth cohort from Magee-Womens Hospital, Pittsburgh, Pennsylvania (enrolled 1983-86).

POPULATION: Mother-infant dyads (n = 511) were followed through pregnancy to 10 years.

METHODS: Self-reported total GWG was converted to gestational-age-standardised z-scores. Multivariable linear and negative binomial regressions were used to estimate effects of GWG and BMI on outcomes.

MAIN OUTCOME MEASURES: Child ADHD symptoms were assessed with the Conners' Continuous Performance Test. Child behaviour was assessed by parent and teacher ratings on the Child Behaviour Checklist (CBCL) and Teacher Report Form, respectively.

RESULTS: The mean (SD) total GWG (kg) was 14.5 (5.9), and 10% of women had a pregravid BMI ≥30 kg/m2 . Prepregnancy obesity (BMI of 30 kg/m2) was associated with increased offspring problem behaviours including internalising behaviours (adjusted β 3.3 points, 95% CI 1.7-4.9), externalising behaviours (adjusted β 2.9 points, 95% CI 1.4-4.6), and attention problems (adjusted β 2.3 points, 95% CI 1.1-3.4) on the CBCL, compared with normal weight mothers (BMI of 22 kg/m2). There were nonsignificant trends towards increased offspring impulsivity with low GWG among lean mothers (adjusted incidence rate ratio 1.2, 95% CI 0.9-1.5) and high GWG among overweight mothers (adjusted incidence rate ratio 1.7, 95% CI 0.9-2.8), but additional outcomes did not differ by GWG z-score. Results were not meaningfully different after excluding high-substance users.

CONCLUSIONS: In a low-income and high-risk sample, we observed a small increase in child behaviour problems among children of obese mothers, which could have an impact on child behaviour in the population.

TWEETABLE ABSTRACT: Maternal obesity is associated with a small increase in child behaviour problems

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BMC Psychiatry. 2016;16.

CO-OCCURRING SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN A POPULATION-BASED SAMPLE OF ADOLESCENTS SCREENED FOR DEPRESSION.

Lundervold AJ, Hinshaw SP, Sørensen L, et al.

Background: Depression is common in adolescents, with a gender bias towards girls. Symptoms associated with attention deficit hyperactivity disorder (ADHD) tend to co-occur in depressed adolescents. This may be related to common features between the two symptom domains, but co-occurring ADHD symptoms may also inflate the severity of depression. The present study investigates the frequency and influence of ADHD symptoms co-occurring with depression in a gender balanced population-based sample of Norwegian adolescents.

Methods: A sample of 9614 adolescents (16-19 years) completed a questionnaire including the short version of the Mood and Feelings Questionnaire (sMFQ) and the Adult ADHD Self-Report Scale (ASRS), with items reflecting symptoms associated with depression and ADHD, respectively. The sMFQ sum score was used as a proxy for severity of depression, and adolescents with a score equal to or above the 90th percentile were defined as depressed. A high response on any of the ASRS items was used to define the presence of an ADHD symptom, and the number of high scores was used to indicate severity.

Results: ADHD symptoms were frequently reported by the adolescents, with a higher frequency in girls than in boys. The gender differences were, however, minor when the analysis was restricted to the adolescents

defined as depressed. Each severe symptom reported on the ASRS contributed significantly to increase the sum score on the sMFQ, and more than 20 % of the adolescents defined as depressed reported six or more symptoms within the ASRS inattention subscale.
Conclusions: The results emphasize the importance of screening for symptoms associated with ADHD when assessing adolescents presenting symptoms indicating depression. Although girls reported higher frequency of symptoms within both domains, the gender bias was dependent on the overall symptom severity. Awareness of co-occurrence of symptoms and gender biases are of importance for both clinical work and future research on mental health and service use in adolescence

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BMC Psychiatry. 2016;16.

DEVELOPMENTAL BRAIN TRAJECTORIES IN CHILDREN WITH ADHD AND CONTROLS: A LONGITUDINAL NEUROIMAGING STUDY.

Silk TJ, Genc S, Anderson V, et al.

Background: The symptom profile and neuropsychological functioning of individuals with Attention Deficit/Hyperactivity Disorder (ADHD), change as they enter adolescence. It is unclear whether variation in brain structure and function parallels these changes, and also whether deviations from typical brain development trajectories are associated with differential outcomes. This paper describes the Neuroimaging of the Children's Attention Project (NICAP), a comprehensive longitudinal multimodal neuroimaging study. Primary aims are to determine how brain structure and function change with age in ADHD, and whether different trajectories of brain development are associated with variations in outcomes including diagnostic persistence, and academic, cognitive, social and mental health outcomes.
Methods/Design: NICAP is a multimodal neuroimaging study in a community-based cohort of children with and without ADHD. Approximately 100 children with ADHD and 100 typically developing controls will be scanned at a mean age of 10 years (range; 9-11years) and will be re-scanned at two 18-month intervals (ages 11.5 and 13 years respectively). Assessments include a structured diagnostic interview, parent and teacher questionnaires, direct child cognitive/executive functioning assessment and magnetic resonance imaging (MRI). MRI acquisition techniques, collected at a single site, have been selected to provide optimized information concerning structural and functional brain development.
Discussion: This study will allow us to address the primary aims by describing the neurobiological development of ADHD and elucidating brain features associated with differential clinical/behavioral outcomes. NICAP data will also be explored to assess the impact of sex, ADHD presentation, ADHD severity, comorbidities and medication use on brain development trajectories. Establishing which brain regions are associated with differential clinical outcomes, may allow us to improve predictions about the course of ADHD

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Brain Dev. 2016.

SELF-CONCEPT IN CHILDREN AND ADOLESCENTS WITH EPILEPSY: THE ROLE OF FAMILY FUNCTIONING, MOTHERS' EMOTIONAL SYMPTOMS AND ADHD.

Ekinci O, Isik U, Gunes S, et al.

Purpose: This study aimed to identify the associated factors of poor self-concept in children and adolescents with epilepsy.
Methods: Fifty-three patients with uncomplicated epilepsy (aged 7-18. years) and 28 healthy controls were included. Study measures included the Piers-Harris 2 Self-Concept Scale, Family Assessment Device (FAD), Turgay DSM-IV based ADHD rating Scale (T-DSM-IV-S), Conners' Teacher Rating Scale (CTRS-R), Beck Depression Inventory and State-Trait Anxiety Inventory (STAI). Neurology clinic charts were reviewed for the epilepsy-related variables.
Results: While the Piers-Harris 2 total score was not significantly different between the groups, patients with epilepsy had lower (poorer) scores on freedom from anxiety and popularity subscales. Linear regression analysis revealed that the problem solving, affective responsiveness, general functioning and communication scores of FAD; total and inattentiveness scores of T-DSM-IV-S and mothers' Beck scores were associated

with the total score of Piers-Harris 2. Epilepsy-related factors were not found to be associated with self-concept scores.
Conclusion: Poor self-concept in children with epilepsy is associated with negative family functioning, mothers' emotional symptoms and ADHD, especially the symptoms of inattentiveness

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Brain Research Bulletin. 2016;124:12-20.
COMPLEXITY ANALYSIS OF BRAIN ACTIVITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A MULTISCALE ENTROPY ANALYSIS.
Chenxi L, Chen Y, Li Y, et al.
The multiscale entropy (MSE) is a novel method for quantifying the intrinsic dynamical complexity of physiological systems over several scales. To evaluate this method as a promising way to explore the neural mechanisms in ADHD, we calculated the MSE in EEG activity during the designed task. EEG data were collected from 13 outpatient boys with a confirmed diagnosis of ADHD and 13 age- and gender-matched normal control children during their doing multi-source interference task (MSIT). We estimated the MSE by calculating the sample entropy values of delta, theta, alpha and beta frequency bands over twenty time scales using coarse-grained procedure. The results showed increased complexity of EEG data in delta and theta frequency bands and decreased complexity in alpha frequency bands in ADHD children. The findings of this study revealed aberrant neural connectivity of kids with ADHD during interference task. The results showed that MSE method may be a new index to identify and understand the neural mechanism of ADHD

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Child Adolesc Ment Health. 2016.
CAUGHT IN THE EYE OF THE STORM: A QUALITATIVE STUDY OF VIEWS AND EXPERIENCES OF PLANNED DRUG HOLIDAYS FROM METHYLPHENIDATE IN CHILD AND ADOLESCENT ADHD TREATMENT.
Ibrahim K, Vogt C, Donyai P.
Background: Attention deficit hyperactivity disorder (ADHD) can be treated with stimulant medication such as methylphenidate. Although effective, methylphenidate can cause serious side-effects, including suppressed appetite, growth retardation and sleep problems. A drug holiday is a deliberate interruption of pharmacotherapy for a defined period of time and for a specific clinical purpose, for example for appeasing side-effects. While some international guidelines recommend introducing drug holidays in ADHD treatment, this is not practised routinely. Our aim was to examine the views and experiences of planned drug holidays from methylphenidate with adults who have responsibility for treatment decisions in children and adolescents with ADHD.
Method: In-depth interviews were carried out. Child and Adolescent Mental Health Services practitioners (n = 8), General practitioners (n = 8), teachers (n = 5) and mothers of children with ADHD (n = 4) were interviewed in a UK setting. Interview transcripts were analysed using grounded theory.
Results: Methylphenidate eases the experience of the child amid problems at home and at school and once started is mostly continued long term. Some families do practise short-term drug holidays at weekends and longer term ones during school holidays. The decision to introduce drug holidays is influenced by the child's academic progress, the parents' ability to cope with the child, as well as medication beliefs. Trialling a drug holiday is thought to allow older children to self-assess their ability to manage without medication when they show signs of wanting to discontinue treatment prematurely.
Conclusions: Planned drug holidays could address premature treatment cessation by enabling adolescents to assess repercussions under medical supervision. Child and Adolescent Mental Health

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Climacteric. 2016;1-3.

MIDLIFE ADHD IN WOMEN: ANY RELEVANCE TO MENOPAUSE?

Pines A.

Recently, there has been a growing interest in better understanding of the adult-type attention deficit hyperactive disorder (ADHD). It is now accepted that many children with ADHD continue to have symptoms later in life, although the characteristics of the disease may change substantially in adults. Data are emerging on ADHD in midlife and old age and some studies analyze gender differences and co-morbidities during the lifespan of ADHD patients. This short communication discusses the possible resemblance of certain menopausal symptoms and those of adult ADHD and the potential contribution of the female hormonal environment. Further, there might be a promising role for psychostimulants, the mainstay of ADHD management, as treatment of impairment of some executive function domains in menopausal women

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Clinical Journal of Sport Medicine. 2016;26:120-27.

MULTIPLE SELF-REPORTED CONCUSSIONS ARE MORE PREVALENT IN ATHLETES WITH ADHD AND LEARNING DISABILITY.

Nelson LD, Guskiewicz KM, Marshall SW, et al.

Objective: We evaluated how attention deficit-hyperactivity disorder (ADHD) and learning disability (LD) are associated with concussion history and performance on standard concussion assessment measures. Based on previous reports that developmental disorders are associated with increased injury proneness and poorer cognitive performance, we anticipated that ADHD and LD would be associated with increased history of concussion and poorer baseline performance on assessment measures.

Design: Cross-sectional study.

Setting: Clinical research center.

Participants: The study sample aggregated data from two separate projects: the National Collegiate Athletic Association Concussion Study and Project Sideline.

Interventions: We analyzed preseason baseline data from 8056 high school and collegiate athletes (predominantly male football players) enrolled in prior studies of sport-related concussion.

Main Outcome Measures: Measures included demographic/health history, symptoms, and cognitive performance.

Results: Attention deficit-hyperactivity disorder and LD were associated with 2.93 and 2.08 times the prevalence, respectively, of 3+ historical concussions (for comorbid ADHD/LD the prevalence ratio was 3.38). In players without histories of concussion, individuals with ADHD reported more baseline symptoms, and ADHD and LD were associated with poorer performance on baseline cognitive tests. Interactive effects were present between ADHD/LD status and concussion history for self-reported symptoms.

Conclusions: Neurodevelopmental disorders and concussion history should be jointly considered in evaluating concussed players.

Clinical Relevance: Clinical judgments of self-reported symptoms and cognitive performance should be adjusted based on athletes' individual preinjury baselines or comparison with appropriate normative samples

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Clin Neurophysiol. 2016;127:2161-66.

COHERENCE IN CHILDREN WITH AD/HD AND EXCESS ALPHA POWER IN THEIR EEG.

Robbie JC, Clarke AR, Barry RJ, et al.

Objective: This study investigated differences in EEG coherence measures between two groups of children with Attention-Deficit/Hyperactivity Disorder (AD/HD) - one with the more common EEG profile (increased theta), and a group with excess alpha activity as the dominant EEG abnormality.

Methods: 26 children (aged 9-13 years) with AD/HD were included in each of the excess-theta and excess-alpha groups, and were age- and sex-matched with 26 control subjects. EEG was recorded from 19 electrode sites during an eyes-closed resting condition. Wave-shape coherence was calculated for eight intrahemispheric and eight interhemispheric electrode pairs, for the delta, theta, alpha and beta bands.

Results: In comparison with the controls, the excess-theta AD/HD group had increased theta intrahemispheric coherences at short-medium inter-electrode distances. Frontally, the excess-theta AD/HD group had increased interhemispheric theta and reduced beta coherences. The excess-alpha group primarily showed increased slow wave (delta and theta) intrahemispheric coherence at short-medium inter-electrode distances, and reduced alpha coherence at longer inter-electrode distances, compared with controls. An increase in frontal interhemispheric theta coherence was also found.
Conclusions: These results suggest that AD/HD children with excess alpha power have an underlying connectivity dysfunction in the frontal lobes, which is found in common with other subjects with the excess-theta EEG profile. However, a number of qualitative differences exist that could be associated with other aspects of the AD/HD diagnosis. The excess-alpha group appeared to have fewer frontal-lobe abnormalities than the excess-theta AD/HD group. Significance: This is the first study to investigate coherence in AD/HD children who have the atypical profile of increased alpha power in their EEG

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Clin Neurophysiol. 2016;127:2182-91.
POSTERIOR ALPHA OSCILLATIONS REFLECT ATTENTIONAL PROBLEMS IN BOYS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Vollebregt MA, Zumer JM, ter Huurne N, et al.
Objective: This study aimed to characterize alpha modulations in children with ADHD in relation to their attentional performance.
Methods: The posterior alpha activity (8-12 Hz) was measured in 30 typically developing children and 30 children with ADHD aged 7-10 years, using EEG while they performed a visuospatial covert attention task. We focused the analyses on typically developing boys (N = 9) and boys with ADHD (N = 17).
Results: Alpha activity in typically developing boys was similar to previous results of healthy adults: it decreased in the hemisphere contralateral to the attended hemifield, whereas it relatively increased in the other hemisphere. However, in boys with ADHD this hemispheric lateralization in the alpha band was not obvious (group contrast, p = .018). A robust relation with behavioral performance was lacking in both groups.
Conclusions: The ability to modulate alpha oscillations in visual regions with the allocation of spatial attention was clearly present in typically developing boys, but not in boys with ADHD.
Significance: These results open up the possibility to further study the underlying mechanisms of ADHD by examining how differences in the fronto-striatal network might explain different abilities in modulating the alpha band activity

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Clin Pediatr. 2016;55:326-32.
USING CLINICAL DATA TO PREDICT ACCURATE ADHD DIAGNOSES AMONG URBAN CHILDREN.
Silverstein M, Hironaka LK, Feinberg E, et al.
Diagnosing attention deficit hyperactivity disorder (ADHD) requires reports of child behavior from 2 settings - most commonly home and school. Obtaining this information from teachers, however, is often challenging. We sought to determine if clinical data, supplementary to parent symptom scales, could be useful in predicting DSM-compliant diagnoses. Parents and teachers reported ADHD symptoms for 156 children using Vanderbilt scales; care managers collected clinical data; a team of specialists determined whether children met diagnostic criteria for ADHD. The ability of a parent Vanderbilt alone to predict an ADHD diagnosis was 56% (95% confidence interval = 45%, 67%). By adding child age and grade retention history to the multivariable model, the probability rose to 78% (95% confidence interval = 59%, 93%). In the maximally predictive model - which included 5 covariates - the predictive validity rose to 84% (95% confidence interval = 52%, 99%). Supplementing parent symptom reports with clinical data may be a viable alternative in certain cases when teacher reports are unavailable

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Clin Psychopharmacol Neurosci. 2016;14:79-87.

ADVANCED TEST OF ATTENTION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN JAPAN FOR EVALUATION OF METHYLPHENIDATE AND ATOMOXETINE EFFECTS.

Fujioka T, Takiguchi S, Yatsuga C, et al.

Objective: This study was conducted to validate the Advanced Test of Attention (ATA) of the visual attention version of Japanese children with attention deficit/hyperactivity disorder (ADHD) and to evaluate the efficacy of methylphenidate (OROS-MPH) and atomoxetine medications.

Methods: To assess pharmacotherapy efficacy, the visual version of ATA was administered to 42 children with ADHD. Results were assessed using discriminant analysis, ANOVA for indices of ATA before and after medication treatment, and correlation analysis between the improvement of indices of ATA and clinical symptoms during medication treatment.

Results: Discriminant analysis showed that 69.0% of ADHD children were assigned correctly. The T score of commission errors increased as the trial progressed on the medication-off condition. T scores of commission errors and standard deviation of response times on medication-on condition were low compared to the medication-off condition. A few significant correlations were found between the improvements of indices of ATA and ADHD-Rating Scale (RS) during treatment.

Conclusion: The performance of the visual version of ATA on medication-off condition reflected the features of ADHD. Furthermore, the medication treatment effects were confirmed sufficiently. In addition, results suggest that indices of ATA reflected aspects of ADHD symptoms that are difficult to elucidate for ADHD-RS. For assessing symptoms and effects of medical treatment in children with ADHD, ATA might be a useful assessment tool

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CNS and Neurological Disorders - Drug Targets. 2015;14:1283-91.

COMPARING THE EFFECTS OF DRUG THERAPY, PERCEPTUAL MOTOR TRAINING, AND BOTH COMBINED ON THE MOTOR SKILLS OF SCHOOL-AGED ATTENTION DEFICIT HYPERACTIVITY DISORDER CHILDREN.

Yazd SNT, Ayatizadeh F, Dehghan F, et al.

The purpose of this research was to compare the effects of drug therapy, perceptual motor training and a combination of drug therapy and perceptual motor training on gross and fine motor skills of 6 to 12 year-old Iranian attention deficit hyperactivity disorder children. Thirty-six attention deficit hyperactivity disorder children currently under treatment in three Iranian psychological-neurological clinics participated in this research study. Participants were sampled from the accessible population and randomly assigned to three experimental groups (n = 12 each). The Conners Parent Rating Scale was used to classify the children and the Bruininks-Oseretsky Test of Motor Proficiency was administered before and after a three month treatment/ training session. Participants in the first experimental group received drug therapy (including methylphenidate). In the second group participants took part in 18 sessions of perceptual-motor skill training for six consecutive weeks, and in the third group children received both interventions. The results indicated that interventions using perceptual-motor training alone or in combination with a drug therapy significantly improved both gross and fine motor skills over a period of six weeks. Participants in the drug-only group showed no improvement in motor performance

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Cochrane Database Syst Rev. 2016;2016.

PHYSICAL ACTIVITY FOR IMPROVING THE SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.

Parker J, Martyn-St James M, Green MA, et al.

This is the protocol for a review and there is no abstract. The objectives are as follows: To determine the effects of physical activity interventions for children and adolescents aged 18 years or younger with a diagnosis of attention deficit hyperactivity disorder (ADHD)

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Egypt J Neurol , Psychiatr Neurosurg. 2015;52:270-73.

QUANTITATIVE ELECTROENCEPHALOGRAPHIC CHANGES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER CHILDREN.

Abdel Kader AA, Mohamed NA, Amin OR, et al.

Background The electroencephalogram (EEG) has long been used to pick up and analyze the electrical activity of the outermost layer of the brain. Attention deficit hyperactivity disorder (ADHD) patients revealed increased power in the lower frequency bands (δ and θ power) and a raised θ/β ratio.

Objective The aim of this study was to detect the quantitative EEG changes in children with ADHD compared with normal children.

Patients and methods The sampled group consisted of 45 children suffering from ADHD and represented the patient group, and 45 normal children represented the control group. EEG was recorded under resting conditions for all participants. Data from frontal areas were digitally processed and analyzed to calculate the four frequency bands' power (β, α, θ, and δ) and then θ/β ratio was computed. For the patient group, the Wechsler Intelligence Scale for Children was applied and parents of these patients filled out the Arabic version of Conners' Parent Rating Scale-revised-long version.

Results The patient group showed significantly higher θ/β ratio in frontal areas compared with the control group ($P < 0.05$). There was a significant negative relation between age and θ/β ratios and a significant negative relation between age and Conners' hyperactivity subscale ($P < 0.05$). There was a significant positive relation between Conners' hyperactivity subscale and mean θ/β ratio ($P < 0.05$).

Conclusion Quantitative EEG markers - namely, the θ/β ratio - could play a role in the understanding and identification of ADHD

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Egypt J Neurol , Psychiatr Neurosurg. 2016;53:19-22.

CONTINUOUS PERFORMANCE TASK IN ATTENTION DEFICIT HYPERACTIVITY DISORDER CHILDREN.

Abdel Kader AA, Mohamed NA, El Sayed BB, et al.

Background Poor behavioural inhibition is the central impairment in attention deficit hyperactivity disorder (ADHD). At present, there is no reliable objective measure to detect ADHD. A proper pinpointing evaluation for ADHD depends mainly on the history from parents, family members as well as teachers and schoolmates, by means of questionnaires and conduct rating scales.

Objective The aim of this study was to detect continuous performance task (CPT) (test of variants of attention) changes in children suffering from ADHD compared with normal children.

Patients and methods CPT, Conners' parent rating scale and Wechsler intelligence scale were done for two groups of children each containing 39 children, a group of ADHD children and the other a normal control group.

Results We found a significant difference between the mean total IQ score among the ADHD patients group compared with control group. Comparing both groups revealed statistically significant increase in omission, commission and reaction time among patients. A significant negative correlation was found between age on one side and IQ, hyperactivity and psychosomatic subscales, hyperactivity and total DSM-IV scores on the other hand and between commission and opposition, restlessness subscales and ADHD index and also between reaction time and restlessness and emotional index. There was a significant positive correlation between omission and hyperactivity and anxiety subscales, restlessness and emotional indices and DSM-IV hyperactive and total scores. In addition, there was a significant positive correlation between perfectionism and commission and also between reaction time and inattention and social problems subscales.

Conclusion CPT can have a substantial role in objective identification of ADHD

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EMBO Mol Med. 2015 Apr 16;7(7):904-17.

LACK OF KINASE-INDEPENDENT ACTIVITY OF PI3KΓ IN LOCUS COERULEUS INDUCES ADHD SYMPTOMS THROUGH INCREASED CREB SIGNALING.

D'Andrea I, Fardella V, Fardella S, et al.

Although PI3Kγ has been extensively investigated in inflammatory and cardiovascular diseases, the exploration of its functions in the brain is just at dawning. It is known that PI3Kγ is present in neurons and that the lack of PI3Kγ in mice leads to impaired synaptic plasticity, suggestive of a role in behavioral flexibility. Several neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), involve an impairment of behavioral flexibility. Here, we found a previously unreported expression of PI3Kγ throughout the noradrenergic neurons of the locus coeruleus (LC) in the brainstem, serving as a mechanism that regulates its activity of control on attention, locomotion and sociality. In particular, we show an unprecedented phenotype of PI3Kγ KO mice resembling ADHD symptoms. PI3Kγ KO mice exhibit deficits in the attentive and mnemonic domains, typical hyperactivity, as well as social dysfunctions. Moreover, we demonstrate that the ADHD phenotype depends on a dysregulation of CREB signaling exerted by a kinase-independent PI3Kγ-PDE4D interaction in the noradrenergic neurons of the locus coeruleus, thus uncovering new tools for mechanistic and therapeutic research in ADHD.

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Emot Behav Difficulties. 2016;21:83-100.

A SYSTEMATIC REVIEW AND SYNTHESIS OF QUALITATIVE RESEARCH: THE INFLUENCE OF SCHOOL CONTEXT ON SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gwernan-Jones R, Moore DA, Cooper P, et al.

This systematic review and synthesis of qualitative research explored contextual factors relevant to non-pharmacological interventions for attention deficit hyperactivity disorder (ADHD) in schools. We conducted meta-ethnography to synthesise 34 studies, using theories of stigma to further develop the synthesis. Studies suggested that the classroom context requiring pupils to sit still, be quiet and concentrate could trigger symptoms of ADHD, and that symptoms could then be exacerbated through informal/formal labelling and stigma, damaged self-perceptions and resulting poor relationships with staff and pupils. Influences of the school context on symptoms of ADHD were often invisible to teachers and pupils, with most attributions made to the individual pupil and/or the pupilΓÇÖs family. We theorise that this ΓÇÿinvisibilityΓÇÖ is at least partly an artefact of stigma, and that the potential for stigma for ADHD to seem ΓÇÿnatural and rightΓÇÖ in the context of schools needs to be taken into account when planning any intervention

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Epilepsy Behav. 2016.

REPLY TO "DOES THE ASSOCIATION BETWEEN ADHD AND PEDIATRIC EPILEPSY SIGNAL A TOLERANCE CONTINUUM TO HUMAN ENVIRONMENT EXPOSURE?

Salpekar JA, Mishra G.

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Epilepsy Behav. 2016;58:1-6.

PARTIAL VALIDATION OF A FRENCH VERSION OF THE ADHD-RATING SCALE IV ON A FRENCH POPULATION OF CHILDREN WITH ADHD AND EPILEPSY. FACTORIAL STRUCTURE, RELIABILITY, AND RESPONSIVENESS.

Mercier C, Roche S, Gaillard S, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is a well-known comorbidity in children with epilepsy. In English-speaking countries, the scores of the original ADHD-rating scale IV are currently used as main outcomes in various clinical trials in children with epilepsy. In French-speaking countries, several French versions are in use though none has been fully validated yet. We sought here for a partial validation of a French version of the ADHD-RS IV regarding construct validity, internal consistency (i.e., scale reliability), item reliability, and responsiveness in a group of French children with ADHD and epilepsy.

Method: The study involved 167 children aged 6-15 years in 10 French neuropediatric units. The factorial structure and item reliability were assessed with a confirmatory factorial analysis for ordered categorical variables. The dimensions' internal consistency was assessed with Guttman's lambda 6 coefficient. The responsiveness was assessed by the change in score under methylphenidate and in comparison with a control group.
Results: The results confirmed the original two-dimensional factorial structure (inattention, hyperactivity/impulsivity) and showed a satisfactory reliability of most items, a good dimension internal consistency, and a good responsiveness of the total score and the two subscores.
Conclusion: The studied French version of the ADHD-RS IV is thus validated regarding construct validity, reliability, and responsiveness. It can now be used in French-speaking countries in clinical trials of treatments involving children with ADHD and epilepsy. The full validation requires further investigations

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Epilepsy Behav. 2016.
DOES THE ASSOCIATION BETWEEN ADHD AND PEDIATRIC EPILEPSY SIGNAL A TOLERANCE CONTINUUM TO HUMAN ENVIRONMENTAL EXPOSURES? A REPLY TO SALPEKAR AND MISHRA (2014).
Fluegge K.

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Eur Arch Psychiatry Clin Neurosci. 2015;265:S105.
VISUAL ATTENTION DEFICITS IN 7-YEAR-OLD CHILDREN OF PARENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER: PART OF THE DANISH HIGH RISK AND RESILIENCE STUDY VIA 7.
Hemager N.
Objective: The aim of this substudy is to measure attentional functioning in children at genetic high risk for developing schizophrenia (SZ) or bipolar disorder (BD). We expected that children at genetic high risk for SZ would show more severe impairments than children at genetic high risk for BD and that the latter group would show more deficits in visual attention compared to children of parents without these disorders.
Methods: We are currently establishing a stratified cohort of 500 7-year-old children with either 0, 1, or 2 parents with SZ or BD. This substudy is focusing on visual attention in 133 subjects of this cohort (SZ: N = 56; BD: N = 32; Controls: N = 45). Based on Bundesen's Theory of Visual Attention (TVA) (Bundesen 1990), visual attention was assessed using the instrument TVA-based Whole Report. Three parameters of attention were calculated: The storage capacity of visual short-term memory (K), the speed of visual processing (C), and the threshold for conscious visual perception (t0).
Results: The children of parents with SZ showed significantly lower visual processing speed than the control group ($p<.001$). The children of parents with BD also showed lower processing speed than the control group ($p = .03$). The two high risk groups did not differ in processing speed ($p = 0.29$). In terms of visual short-term memory capacity, we found a lower capacity in children of parents with BD than in children of parents with SZ ($p = .05$) and the control group ($p = .02$), whereas the capacity of the children of parents with SZ and the control group did not differ ($p = .87$). There were no significant differences between any of the three groups in terms of perceptual threshold.
Conclusion: This finding supports the evidence suggesting that offspring of parents with SZ and offspring of parents with BD may share a neurocognitive profile of overall impairments but with distinct variations across the cognitive domains

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Eur Child Adolesc Psychiatry. 2016;25:273-82.

DECREASING ADHD PHENOTYPIC HETEROGENEITY: SEARCHING FOR NEUROBIOLOGICAL UNDERPINNINGS OF THE RESTRICTIVE INATTENTIVE PHENOTYPE.

Ercan ES, Suren S, Bacanl-¦ A, et al.

During the process of developing the DSM-5, a new phenotype of ADHD was proposedΓÇöthe ADHD restrictive inattentive presentation (ADHD-RI), describing subjects with high endorsement of inattentive symptoms and a low level of hyperactivity. However, this phenotype was not included in the DSM-5 because of the lack of robust neurobiological data. We aimed to assess the specific neurobiological underpinnings of individuals presenting ADHD-RI. We compared a sample of 301 subjects (101 ADHD-Combined; 50 ADHD-RI; 50 ADHD predominantly inattentive type and 100 typically developing subjects) aged 8ΓÇô15-áyears, using a complete neuropsychological battery, molecular genetic data (DRD4 and DAT1 most studied polymorphisms) and functional MRI during a Go-No/Go task. Subjects with ADHD-RI had a significantly different neuropsychological profile compared with the other groups, including lower psychomotor speeds, longer reaction times and the worst overall performance in the global neurocognitive index. The proportion of subjects with the presence of DRD4ΓÇô7 repeat allele was significantly higher in ADHD-RI. The fMRI data suggested that more attention-related posterior brain regions (especially temporo-occipital areas) are activated in ADHD-RI during both Go and No-Go cues compared to TD controls and ADHD predominantly inattentive type. ADHD-RI may represent a different phenotype than other types of ADHD. In addition, our results suggest that reducing the phenotypic heterogeneity may aid in the search for the neurobiological underpinnings of ADHD

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Eur Child Adolesc Psychiatry. 2016;1-9.

PREDICTORS OF PERSISTENCE OF ADHD INTO ADULTHOOD: A SYSTEMATIC REVIEW OF THE LITERATURE AND META-ANALYSIS.

Caye A, Spadini AV, Karam RG, et al.

Attention-deficit/hyperactivity disorder (ADHD) is traditionally conceptualized as a neurodevelopmental disorder that continues into adulthood in up to half of diagnosed cases. In light of current evidence, factors associated with the course of the disorder remain unknown. We performed a systematic review of the literature searching for risk markers from childhood that predicted the persistence of ADHD into adulthood. We reviewed 26,168 abstracts and selected 72 for full-text review. We identified data from 16 studies, comprising 6 population-based retrospective samples and 10 clinical follow-ups. We performed meta-analyses of factors evaluated by at least three studies. Severity of ADHD (OR 2.33, 95 % CI = 1.6ΓÇô3.39, p < 0.001), treatment for ADHD (OR 2.09, 95 % CI = 1.04ΓÇô4.18, p = 0.037), comorbid conduct disorder (OR 1.85, 95 % CI = 1.06ΓÇô3.24, p = 0.030), and comorbid major depressive disorder (OR 1.8, 95 % CI = 1.1ΓÇô2.95, p = 0.019) emerged as predictors already presented in childhood for ADHD persistence into adulthood. Further, we suggest that cohort studies should be designed to clarify such an important question for research and clinical practice

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Eur Child Adolesc Psychiatry. 2016;1-2.

IS THE EVIDENCE BASE OF METHYLPHENIDATE FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER FLAWED?

Hoekstra PJ, Buitelaar JK.

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Eur Neuropsychopharmacol. 2016;26:674-83.

STIMULANT TREATMENT HISTORY PREDICTS FRONTAL-STRIATAL STRUCTURAL CONNECTIVITY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schweren LJS, Hartman CA, Zwiers MP, et al.

Diffusion tensor imaging (DTI) has revealed white matter abnormalities in individuals with attention-deficit/hyperactivity disorder (ADHD). Stimulant treatment may affect such abnormalities. The current study investigated associations between long-term stimulant treatment and white matter integrity within the frontal-striatal and mesolimbic pathways, in a large sample of children, adolescents and young adults with ADHD. Participants with ADHD (N=172; mean age 17, range 9-26) underwent diffusion-weighted MRI scanning, along with an age- and gendermatched group of 96 control participants. Five study-specific white matter tract masks (orbitofrontal-striatal, orbitofrontal-amygdalar, amygdalar-striatal, dorsolateral-prefrontal-striatal and medialprefrontal- striatal) were created. First we analyzed case-control differences in fractional anisotropy (FA) and mean diffusivity (MD) within each tract. Second, FA and MD in each tract was predicted from cumulative stimulant intake within the ADHD group. After correction for multiple testing, participants with ADHD showed reduced FA in the orbitofrontal-striatal pathway (p=0.010, effect size=0.269). Within the ADHD group, higher cumulative stimulant intake was associated with lower MD in the same pathway (p=0.011, effect size=-0.164), but not with FA. The association between stimulant treatment and orbitofrontal-striatal MD was of modest effect size. It fell short of significance after adding ADHD severity or ADHD type to the model (p=0.036 and p=0.094, respectively), while the effect size changed little. Our findings are compatible with stimulant treatment enhancing orbitofrontal-striatal white matter connectivity, and emphasize the importance of the orbitofrontal cortex and its connections in ADHD. Longitudinal studies including a drug-na+»ve baseline assessment are needed to distinguish between-subject variability in ADHD severity from treatment effects

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Expert Rev Neurother. 2016;16:279-93.

AN UPDATE ON THE COMORBIDITY OF ADHD AND ASD: A FOCUS ON CLINICAL MANAGEMENT.

Antshel KM, Zhang-James Y, Wagner KE, et al.

Attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) commonly co-occur. With the DSM-5, clinicians are permitted to make an ASD diagnosis in the context of ADHD. In earlier versions of the DSM, this was not acceptable. Both ASD and ADHD are reported to have had substantial increases in prevalence within the past 10 years. As a function of both the increased prevalence of both disorders as well as the ability to make an ASD diagnosis in ADHD, there has been a significant amount of research focusing on the comorbidity between ADHD and ASD in the past few years. Here, we provide an update on the biological, cognitive and behavioral overlap/distinctiveness between the two neurodevelopmental disorders with a focus on data published in the last four years. Treatment strategies for the comorbid condition as well as future areas of research and clinical need are discussed

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Frontiers in Cellular Neuroscience. 2016;10.

IMPROVING INTERFERENCE CONTROL IN ADHD PATIENTS WITH TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS).

Breitling C, Zaehle T, Dannhauer M, et al.

The use of transcranial direct current stimulation (tDCS) in patients with attention deficit hyperactivity disorder (ADHD) has been suggested as a promising alternative to psychopharmacological treatment approaches due to its local and network effects on brain activation. In the current study, we investigated the impact of tDCS over the right inferior frontal gyrus (rIFG) on interference control in 21 male adolescents with ADHD and 21 age matched healthy controls aged 13ΓÇô17 years, who underwent three separate sessions of tDCS (anodal, cathodal, and sham) while completing a Flanker task. Even though anodal stimulation appeared to diminish commission errors in the ADHD group, the overall analysis revealed no significant effect of tDCS. Since participants showed a considerable learning effect from the first to the second session, performance

in the first session was separately analyzed. ADHD patients receiving sham stimulation in the first session showed impaired interference control compared to healthy control participants whereas ADHD patients who were exposed to anodal stimulation, showed comparable performance levels (commission errors, reaction time variability) to the control group. These results suggest that anodal tDCS of the right inferior frontal gyrus could improve interference control in patients with ADHD

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Frontiers in Psychology. 2016 Jan;7.

DIFFERENCES IN SPEECH RECOGNITION BETWEEN CHILDREN WITH ATTENTION DEFICITS AND TYPICALLY DEVELOPED CHILDREN DISAPPEAR WHEN EXPOSED TO 65 DB OF AUDITORY NOISE.

Söderlund GBW, Jobs EN.

The most common neuropsychiatric condition in the in children is attention deficit hyperactivity disorder (ADHD), affecting ~6–9% of the population. ADHD is distinguished by inattention and hyperactive, impulsive behaviors as well as poor performance in various cognitive tasks often leading to failures at school. Sensory and perceptual dysfunctions have also been noticed. Prior research has mainly focused on limitations in executive functioning where differences are often explained by deficits in pre-frontal cortex activation. Less notice has been given to sensory perception and subcortical functioning in ADHD. Recent research has shown that children with ADHD diagnosis have a deviant auditory brain stem response compared to healthy controls. The aim of the present study was to investigate if the speech recognition threshold differs between attentive and children with ADHD symptoms in two environmental sound conditions, with and without external noise. Previous research has namely shown that children with attention deficits can benefit from white noise exposure during cognitive tasks and here we investigate if noise benefit is present during an auditory perceptual task. For this purpose we used a modified Hagerman's speech recognition test where children with and without attention deficits performed a binaural speech recognition task to assess the speech recognition threshold in no noise and noise conditions (65 dB). Results showed that the inattentive group displayed a higher speech recognition threshold than typically developed children and that the difference in speech recognition threshold disappeared when exposed to noise at supra threshold level. From this we conclude that inattention can partly be explained by sensory perceptual limitations that can possibly be ameliorated through noise exposure.

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Gait Posture. 2016;44:245-49.

AGE-RELATED DECLINE OF GAIT VARIABILITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SUPPORT FOR THE MATURATIONAL DELAY HYPOTHESIS IN GAIT.

Manicolo O, Grob A, Lemola S, et al.

Background: Previous findings showed a tendency toward higher gait variability in children with attention-deficit/hyperactivity disorder (ADHD) compared to controls. This study examined whether gait variability in children with ADHD eventually approaches normality with increasing age (delay hypothesis) or whether these gait alterations represent a persistent deviation from typical development (deviation hypothesis).

Method: This cross-sectional study compared 30 children with ADHD (25 boys; Mage = 10 years 11 months, range 8-13 years; n = 21 off medication, n = 9 without medication) to 28 controls (25 boys; Mage = 10 years 10 months, range 8-13 years). Gait parameters (i.e. velocity and variability in stride length and stride time) were assessed using an electronic walkway system (GAITRite) while children walked at their own pace.

Results: Children with ADHD walked with significantly higher variability in stride time compared to controls. Age was negatively associated with gait variability in children with ADHD such that children with higher age walked with lower variability, whereas in controls there was no such association.

Conclusions: Children with ADHD displayed a less regular gait pattern than controls, indicated by their higher variability in stride time. The age-dependent decrease of gait variability in children with ADHD showed that gait performance became more regular with age and converged toward that of typically developing

children. These results may reflect a maturational delay rather than a persistent deviation of gait regularity among children with ADHD compared to typically developing children

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Health Informatics J. 2016 Mar 17. [Epub ahead of print]

THE IMPACT OF A MODEL-BASED CLINICAL REGIONAL REGISTRY FOR ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Zanetti M, Cartabia M, Didoni A, et al.

This article describes the development and clinical impact of the Italian Regional ADHD Registry, aimed at collecting and monitoring diagnostic and therapeutic pathways of care for attention-deficit hyperactivity disorder children and adolescents, launched by the Italian Lombardy Region in June 2011. In particular, the model-based software used to run the registry and manage clinical care data acquisition and monitoring, is described. This software was developed using the PROSAFE programme, which is already used for data collection in many Italian intensive care units, as a stand-alone interface case report form. The use of the attention-deficit hyperactivity disorder regional registry led to an increase in the appropriateness of the clinical management of all patients included in the registry, proving to be an important instrument in ensuring an appropriate healthcare strategy for children and adolescents with attention-deficit/hyperactivity disorder

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Huisarts en Wetenschap. 2014;57:595.

MORE CHILDREN WITH ADHD.

van Avendonk M, Stirbu-Wagner I, Korevaar J, et al.

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Int J Pediatr Otorhinolaryngol. 2016;85:5-7.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN WITH VOCAL FOLD NODULES.

Erdur O, Herguner A, Ozturk K, et al.

Objectives: The aim of this case-control study was to investigate the symptoms of attention-deficit/hyperactivity disorder (ADHD) in children with vocal fold nodules (VNs).

Methods: Study group (SG) included children between 4 and 12 years. As a control group (CG), children between 4 and 12 years without VNs were included in the study. Parents of the participants completed the Conners' Parent Rating Scale-Revised: Short Form (CPRS-RS) which was used to analyze the symptoms of ADHD.

Results: Forty-five children (30 boys and 15 girls) with VNs and 45 controls (30 boys and 15 girls) were enrolled in the study. Multivariate analysis of variance revealed that the CPRS-RS Hyperactivity and Oppositional Subscales were significantly higher in the SG than the CG ($p < .05$), after controlling the effects of age and gender.

Conclusions: Our findings suggest associations between VNs and hyperactivity and oppositional behaviors in children. Clinicians should be aware of ADHD symptoms in children with VNs

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Int J Psychiatry Med. 2015;50:238-47.

RELATIONSHIP BETWEEN SOLUBLE INTERCELLULAR ADHESION MOLECULES AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Alaşehirli B, Oguz E, Gokcen C, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common childhood- oneset psychiatric disease, characterized by excessive overactivity, inattention, and impulsiveness. In recent studies, it is emphasized that inflammation may have a role in ADHD. In this study, we aimed to investigate whether there

are associations between ADHD and serum levels of soluble intercellular adhesion molecules (s-ICAMs) which have important role in inflammatory diseases. We also measured the levels of these molecules after treatment with oros-methylphenidate.
Methods: Twenty-five patients diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria and 18 healthy volunteer controls were included in this study. The levels of sICAMs were measured in the serum of the patients and healthy volunteers by ELISA kit as described.
Results: The levels of sICAM-1 and sICAM-2 were significantly higher in patients compared with controls. The level of sICAM-2 was decreased significantly in group treated with oros-methylphenidate.
Conclusions: This is the first study pointing out the relationship between sICAMs and ADHD. The changes in sICAM-2 level may have a role in the effect mechanism of oros-methylphenidate, used for the treatment of ADHD

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Iran J Med Sci. 2016;41:186-90.

COMPARISON OF AUDITORY PERCEPTION IN COCHLEAR IMPLANTED CHILDREN WITH AND WITHOUT ADDITIONAL DISABILITIES.

Hashemi SB, Monshizadeh L.

Background: The number of children with cochlear implants who have other difficulties such as attention deficiency and cerebral palsy has increased dramatically. Despite the need for information on the results of cochlear implantation in this group, the available literature is extremely limited. We, therefore, sought to compare the levels of auditory perception in children with cochlear implants with and without additional disabilities.
Methods: A spondee test comprising 20 two-syllable words was performed. The data analysis was done using SPSS, version 19.
Results: Thirty-one children who had received cochlear implants 2 years previously and were at an average age of 7.5 years were compared via the spondee test. From the 31 children,15 had one or more additional disabilities. The data analysis indicated that the mean score of auditory perception in this group was approximately 30 scores below that of the children with cochlear implants who had no additional disabilities.
Conclusion: Although there was an improvement in the auditory perception of all the children with cochlear implants, there was a noticeable difference in the level of auditory perception between those with and without additional disabilities. Deafness and additional disabilities depended the children on lip reading alongside the auditory ways of communication. In addition, the level of auditory perception in the children with cochlear implants who had more than one additional disability was significantly less than that of the other children with cochlear implants who had one additional disability

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JCRPE J Clin Res Pediatr Endocrinol. 2016;8:61-66.

EVALUATION OF IODINE DEFICIENCY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Kanık Yüksek S, Aycan Z, Öner Ö.

OBJECTIVE: Evaluation of the incidence and effects on mental functions of iodine deficiency (ID) in lack of attention and disorders of comprehension, perception and learning were aimed. A prospectively review of children with attention-deficit/hyperactivity disorder (ADHD) from September 2009 to June 2010 was performed at Dr. Sami Ulus Maternity and Children's Training and Researh Hospital, in the central Turkey. Eighty-nine children diagnosed with ADHD were enrolled.
METHODS: A questionnaire to the parents, Conners' rating scales to the parents (CPRS) and teachers (CTRS), and revised Wechsler Intelligence Scale for Children (WISC-R) to the children were applied. Serum thyroid-stimulating hormone, free T3 and T4, thyroglobulin, anti-thyroid peroxidase, anti-thyroglobulin and urinary iodine levels of children were measured.
RESULTS: Median age of children was 9.41±1.95 years and 83.1% was male. The mean urinary iodine levels of children were 92.56 ± 22.25 µg/L. ID was observed in 71.9% and all of them were mild ID. There was no significant relationship between urinary iodine levels with WISC-R subtest scores and CPRS.

However, a significant association was obtained between urinary iodine levels and hyperactivity section of CTRS (p <0.05). Likewise, a significant relationship was found between learning-disorder/mental retardation diagnosis with freedom subtest of WISC-R (p <0,05).
CONCLUSION: This study is important to highlight the effects of ID on comprehension, perception, attention and learning, which are less known and less conspicuous signs of ID. However, the indicated results should be supported by new randomized controlled trials in order to contribute to clinical applications.

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J Abnorm Psychol. 2016;125:248-55.
COMMENTARY: RECENT LONGITUDINAL STUDIES OF CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: IMPORTANT THEMES AND QUESTIONS FOR FURTHER RESEARCH.
Barkley RA.

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J Child Adolesc Psychopharmacol. 2016;26:19-25.
IMPULSIVE AGGRESSION AS A COMORBIDITY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.
Saylor KE, Amann BH.
Objective: This article examines the characteristics of impulsive aggression (IA) as a comorbidity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD), focusing on its incidence, impact on ADHD outcomes, need for timely intervention, and limitations of current treatment practices.
Methods: Relevant literature was retrieved with electronic searches in PubMed and PsycINFO using the search strategy of "ADHD OR attention deficit hyperactivity disorder" AND "impulsive aggression OR reactive aggression OR hostile aggression OR overt aggression" AND "pediatric OR childhood OR children OR pre-adolescent OR adolescent" with separate searches using review OR clinical trial as search limits. Key articles published before the 2007 Expert Consensus Report on IA were identified using citation analysis.
Results: More than 50% of preadolescents with ADHD combined subtype reportedly display clinically significant aggression, with impulsive aggression being the predominant subtype. Impulsive aggression is strongly predictive of a highly unfavorable developmental trajectory characterized by the potential for persistent ADHD, increasing psychosocial burden, accumulating comorbidities, serious lifelong functional deficits across a broad range of domains, delinquency/criminality, and adult antisocial behavior. Impulsive aggression, which triggers peer rejection and a vicious cycle of escalating dysfunction, may be a key factor in unfavorable psychosocial outcomes attributed to ADHD. Because severe aggressive behavior does not remit in many children when treated with primary ADHD therapy (i.e., stimulants and behavioral therapy), a common practice is to add medication of a different class to specifically target aggressive behavior.
Conclusions: Impulsive aggression in children and adolescents with ADHD is a serious clinical and public health problem. Although adjunctive therapy with an aggression-targeted agent is widely recommended when aggressive behaviors do not remit with primary ADHD therapy, empirical evidence does not currently support the use of any specific agent. Randomized controlled trials are needed to identify aggression-targeted agents with favorable benefit-risk profiles

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J Child Adolesc Psychopharmacol. 2016;26:164-73.
PREVALENCE AND TREATMENT OUTCOMES OF PERSISTENT NEGATIVE MOOD AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AGGRESSIVE BEHAVIOR.
Blader JC, Pliszka SR, Kafantaris V, et al .
Objective: Diagnostic criteria for disruptive mood dysregulation disorder (DMDD) require 1) periodic rageful outbursts and 2) disturbed mood (anger or irritability) that persists most of the time in between outbursts. Stimulant monotherapy, methodically titrated, often culminates in remission of severe aggressive behavior, but it is unclear whether those with persistent mood symptoms benefit less.This study examined the

association between the presence of persistent mood disturbances and treatment outcomes among children with attention-deficit/hyperactivity disorder (ADHD) and periodic aggressive, rageful outbursts.
Methods: Within a cohort of children with ADHD and aggressive behavior (n = 156), the prevalence of persistent mood symptoms was evaluated at baseline and after completion of a treatment protocol that provided stimulant monotherapy and family-based behavioral treatment (duration mean [SD] = 70.04 [37.83] days). The relationship of persistent mood symptoms on posttreatment aggressive behavior was assessed, as well as changes in mood symptoms.
Results: Aggressive behavior and periodic rageful outbursts remitted among 51% of the participants. Persistent mood symptoms at baseline did not affect the odds that aggressive behavior would remit during treatment. Reductions in symptoms of sustained mood disturbance accompanied reductions in periodic outbursts. Children who at baseline had high irritability but low depression ratings showed elevated aggression scores at baseline and after treatment; however, they still displayed large reductions in aggression.
Conclusions: Among aggressive children with ADHD, aggressive behaviors are just as likely to decrease following stimulant monotherapy and behavioral treatment among those with sustained mood symptoms and those without. Improvements in mood problems are evident as well. Therefore, the abnormalities in persistent mood described by DMDD's criteria do not contraindicate stimulant therapy as initial treatment among those with comorbid ADHD. Rather, substantial improvements may be anticipated, and remission of both behavioral and mood symptoms seems achievable for a proportion of patients.
Trial Registration: ClinicalTrials.gov (U.S.); IDs: NCT00228046 and NCT00794625; www.clinicaltrials.gov

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J Child Adolesc Psychopharmacol. 2016;26:154-63.
THE EFFECTIVENESS AND TOLERABILITY OF CENTRAL NERVOUS SYSTEM STIMULANTS IN SCHOOL-AGE CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND DISRUPTIVE MOOD DYSREGULATION DISORDER ACROSS HOME AND SCHOOL.
Baweja R, Belin PJ, Humphrey HH, et al.
Objective: This study examines the effectiveness and tolerability of stimulants in children with attention-deficit/hyperactivity disorder (ADHD) and disruptive mood dysregulation disorder (DMDD).
Methods: To be eligible, participants had to meet Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV) criteria for the combined subtype of ADHD and National Institute of Mental Health (NIMH) severe mood dysregulation criteria. The Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V) DMDD criteria were retrospectively assessed after the study was completed. An open-label medication trial lasting up to 6 weeks was completed to optimize the central nervous system (CNS) stimulant dose. Measures of affective symptoms, ADHD symptoms and other disruptive behaviors, impairment, and structured side effect ratings were collected before and after the medication trial.
Results: Optimization of stimulant medication was associated with a significant decline in depressive symptoms on the Childhood Depression Rating Score-Revised Scale ($p<0.05$, Cohen's $d=0.61$) and Mood Severity Index score ($p<0.05$, Cohen's $d=0.55$), but not in manic-like symptoms on the Young Mania Rating Scale. There was a significant reduction in ADHD ($p<0.05$, Cohen's $d=0.95$), oppositional defiant disorder (ODD) ($p<0.05$, Cohen's $d=0.5$), and conduct disorder (CD) symptoms ($p<0.05$, Cohen's $d=0.65$) as rated by parents. There was also a significant reduction in teacher-rated ADHD ($p<0.05$, Cohen's $d=0.33$) but not in ODD symptoms. Medications were well tolerated and there was no increase in side effect ratings seen with dose optimization. Significant improvement in functioning was reported by clinicians and parents (all p's<0.05), but youth still manifested appreciable impairment at end-point.
Conclusions: CNS simulants were well tolerated by children with ADHD comorbid with a diagnosis of DMDD. CNS stimulants were associated with clinically significant reductions in externalizing symptoms, along with smaller improvements in mood. However, most participants still exhibited significant impairment, suggesting that additional treatments may be needed to optimize functioning

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J Child Neurol. 2016;31:584-88.

CLINICAL IMPACT OF EPILEPTIFORM DISCHARGE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Lee EH, Choi YS, Yoon HS, et al.

The aim of this study was to investigate the prevalence and clinical significance of epileptiform discharges in patients with attention-deficit/hyperactivity disorder (ADHD). The authors retrospectively reviewed 180 children who were diagnosed with ADHD and had an electroencephalography (EEG) recording. Epileptiform discharges were found in 29 (16.1%) of 180 patients with ADHD. Of these, 15 (8.3%) had generalized epileptiform discharges and 14 (7.7%) had focal epileptiform discharges. The focal epileptiform discharges were most prevalent from the frontal (5/14) and rolandic area (5/14). Among the 29 patients with epileptiform discharges and ADHD, 5 patients had previous history of epilepsy and 4 patients developed epilepsy later, whereas none of the normal EEG group developed epilepsy. The authors suggest that interictal epileptiform discharges appear to be associated with seizure occurrence in children with ADHD and might reflect maturational pathophysiology overlapping with epilepsy

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J Clin Exp Neuropsychol. 2016 Mar;38:361-69.

ELECTROENCEPHALOGRAM COMPLEXITY ANALYSIS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING A VISUAL COGNITIVE TASK.

Zarafshan H, Khaleghi A, Mohammadi MR, et al.

Objective: The aim of this study was to investigate electroencephalogram (EEG) dynamics using complexity analysis in children with attention-deficit/hyperactivity disorder (ADHD) compared with healthy control children when performing a cognitive task.

Method: Thirty 7–12-year-old children meeting Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition (DSM–5) criteria for ADHD and 30 healthy control children underwent an EEG evaluation during a cognitive task, and Lempel–Ziv complexity (LZC) values were computed. There were no significant differences between ADHD and control groups on age and gender.

Results: The mean LZC of the ADHD children was significantly larger than healthy children over the right anterior and right posterior regions during the cognitive performance. In the ADHD group, complexity of the right hemisphere was higher than that of the left hemisphere, but the complexity of the left hemisphere was higher than that of the right hemisphere in the normal group.

Conclusion: Although fronto-striatal dysfunction is considered conclusive evidence for the pathophysiology of ADHD, our arithmetic mental task has provided evidence of structural and functional changes in the posterior regions and probably cerebellum in ADHD.

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Journal of Clinical Child and Adolescent Psychology. 2016 Mar;45:176-87.

PREDICTIVE UTILITY OF FOUR METHODS OF INCORPORATING PARENT AND TEACHER SYMPTOM RATINGS OF ADHD FOR LONGITUDINAL OUTCOMES .

Shemmassian SK, Lee SS.

Despite robust evidence that parents and teachers provide incremental validity in the assessment of attention-deficit/hyperactivity disorder (ADHD), far less is known about the predictive utility of various strategies for incorporating these multi-informant data. Thus, we compared the 2-year predictive validity of four common assessment methods (i.e., algorithms) for ADHD symptoms—(a) parent only, (b) teacher only, (c) parent or teacher ("or rule"), and (d) parent and teacher ("and rule")—with respect to psychopathology and multidomain functional outcomes. At baseline, separate parent and teacher ratings of ADHD were obtained from an ethnically diverse (53% non-White) sample of 195 6- to 10-year-old children (30% female) to classify children according to the 4 algorithms. We then evaluated the predictive validity of each baseline ADHD algorithm with respect to its prediction of separate measures of internalizing and externalizing psychopathology, as well as normed ratings of academic and social impairment obtained at a 2-year follow-up. The "or rule" algorithm, based on symptoms being endorsed by either informant, optimally predicted

psychopathology and functional outcomes relative to the other algorithms. These findings converge with previous evidence that incorporating data from multiple informants, and more sensitive approaches in particular, provide incremental validity in the assessment of ADHD.

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Journal of Clinical Child and Adolescent Psychology. 2016 Mar;45:155-66.

PARENTING MEDIATES SYMPTOMS AND IMPAIRMENT IN CHILDREN WITH ADHD-INATTENTIVE TYPE.

Haack LM, Villodas MT, McBurnett K, et al.

The current study investigates potential pathways between inattentive symptom severity, positive and negative parenting practices, and functional impairment (i.e., academic, social, and home impairment) in a sample of children diagnosed with attention-deficit/hyperactivity disorder, Predominantly Inattentive Type (ADHD-I). Participants included 199 children and their parents and teachers enrolled in a randomized clinical trial investigating the efficacy of an integrated psychosocial intervention for children with ADHD-I. Boys constituted slightly more than half the sample; children averaged 8.6 years of age (range = 7–11) and were from varied ethnic/racial backgrounds. As part of the initial screening and assessment procedures, parents and teachers completed questionnaires assessing child behavior and parent/family functioning. Results supported both main effects of symptoms and parenting on impairment, as well as a mediational path between symptoms and impairment via parenting, as observed by parents in the home setting. Specifically, higher severity of inattention was associated with higher rates of homework, social, and home impairment. Negative parenting contributed to homework and home impairment, and positive and negative parenting contributed to social impairment, incrementally above and beyond the impact of inattention symptom severity alone. Negative parenting partially mediated the relationship between inattentive symptom severity and impairment, such that higher rates of inattention were associated with higher rates of negative parenting, which in turn was associated with higher rates of homework, social, and home impairment. Results provide support for underlying mechanisms for associations between symptoms and impairment in children with ADHD-I and identify potential intervention targets to improve impairment experienced by these children.

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J Clin Psychiatry. 2016;77:e155-e170.

PROLACTIN LEVELS DURING LONG-TERM RISPERIDONE TREATMENT IN CHILDREN AND ADOLESCENTS: A REANALYSIS OF DATA.

Findling RL, Daneman D.

To summarize, the results of our reanalysis support our statements in the manuscript. Of particular note, our finding that there was no direct correlation between prolactin elevation and SHAP is supported by the data in the reanalysis. In addition, our Conclusion section remains accurate

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J Neural Transm. 2016;1-11.

ENLARGED STRIATAL VOLUME IN ADULTS WITH ADHD CARRYING THE 9-6 HAPLOTYPE OF THE DOPAMINE TRANSPORTER GENE DAT1.

Onnink AMH, Franke B, van Hulzen K, et al.

The dopamine transporter gene, DAT1 (SLC6A3), has been studied extensively as a candidate gene for attention-deficit/hyperactivity disorder (ADHD). Different alleles of variable number of tandem repeats (VNTRs) in this gene have been associated with childhood ADHD (10/10 genotype and haplotype 10-6) and adult ADHD (haplotype 9-6). This suggests a differential association depending on age, and a role of DAT1 in modulating the ADHD phenotype over the lifespan. The DAT1 gene may mediate susceptibility to ADHD through effects on striatal volumes, where it is most highly expressed. In an attempt to clarify its mode of action, we examined the effect of three DAT1 alleles (10/10 genotype, and the haplotypes 10-6 and 9-6) on bilateral striatal volumes (nucleus accumbens, caudate nucleus, and putamen) derived from structural magnetic resonance imaging scans using automated tissue segmentation. Analyses were performed

separately in three cohorts with cross-sectional MRI data, a childhood/adolescent sample (NeuroIMAGE, 301 patients with ADHD and 186 healthy participants) and two adult samples (IMpACT, 118 patients with ADHD and 111 healthy participants; BIG, 1718 healthy participants). Regression analyses revealed that in the IMpACT cohort, and not in the other cohorts, carriers of the DAT1 adult ADHD risk haplotype 9-6 had 5.9 % larger striatum volume relative to participants not carrying this haplotype. This effect varied by diagnostic status, with the risk haplotype affecting striatal volumes only in patients with ADHD. An explorative analysis in the cohorts combined (N = 2434) showed a significant gene-by-diagnosis-by-age interaction suggesting that carriership of the 9-6 haplotype predisposes to a slower age-related decay of striatal volume specific to the patient group. This study emphasizes the need of a lifespan approach in genetic studies of ADHD

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J Pediatr. 2016.

INFLUENCE OF RELATIVE AGE ON DIAGNOSIS AND TREATMENT OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN TAIWANESE CHILDREN.

Chen MH, Lan WH, Bai YM, et al.

Objective: To determine the potential influence of relative age on the diagnosis and treatment of attention-deficit hyperactivity disorder (ADHD), especially in reference to an Asian country.

Study design: A total of 378 881 subjects aged 4-17 years during the study period (September 1, 1997 to August 31, 2011) were enrolled in our study from the Taiwan National Health Insurance Research Database. Logistic regression analysis was used to examine the likelihood of receiving ADHD diagnosis and treatment for those who were born in August (the youngest) compared with those who were born in September (the oldest).

Results: Both boys and girls born in August had a higher risk of being diagnosed with ADHD (OR 1.63, 95% CI 1.45-1.84; OR 1.71, 95% CI 1.36-2.15) and receiving ADHD medication (OR 1.76, 95% CI 1.53-2.02; OR 1.65, 95% CI 1.26-2.18) than those born in September. Sensitivity tests conducted over different periods revealed consistent findings.

Conclusions: Relative age, as an indicator of neurocognitive maturity, is crucial in the risk of being diagnosed with ADHD and receiving ADHD medication among children and adolescents. Our findings emphasize the importance of considering the age of a child within a grade when diagnosing ADHD and prescribing medication for treating ADHD

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J Psychiatr Res. 2016;76:121-27.

CHEMOSENSORY PROCESSING IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lorenzen A, Scholz-Hehn D, Wiesner CD, et al.

Background: In attention-deficit/hyperactivity disorder (ADHD) not only deficits in dopamine-related cognitive functioning have been found but also a lower dopamine-sensitive olfactory threshold. The aim of the present study was to proof that only olfactory but not trigeminal sensitivity is increased in ADHD. Structural magnetic resonance imaging (MRI) was used to show increased olfactory bulb (OB) volume- a structure which is strongly shaped by olfactory performance through the mechanism of neuroplasticity (e.g. synaptogenesis). To elucidate whether cortical mechanisms are involved in altered olfaction in ADHD, functional MRI (fMRI) was introduced.

Methods: A total of 18 boys with ADHD and 17 healthy controls (aged 7-12) were included in the study. Olfactory as well as trigeminal detection thresholds were examined. OB sizes were measured by means of structural MRI and an analysis of effective functional (fMRI) coupling of primary olfactory cortex was conducted. The frontal piriform cortex (fPIR) was chosen as seed region because of its importance in processing both trigeminal and olfactory stimuli as well as having profound influence on inner OB-signaling.

Results: Increased olfactory sensitivity as well as an increase in OB volume was found in ADHD. There were no group differences in sensitivity towards a trigeminal stimulus. Compared to healthy controls, the fPIR in ADHD was more positively coupled with structures belonging to the salience network during olfactory and, to a lesser extent, during trigeminal stimulation.

Conclusions: Olfactory functioning is superior in subjects with ADHD. The observed increase in OB volume may relate to higher olfactory sensitivity in terms of neuroplasticity. During the processing of chemosensory stimuli, the primary olfactory cortex in ADHD is differently coupled to higher cortical structures which might indicate an altered top-down influence on OB structure and function

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J Psychiatr Res. 2016;75:75-81.

NOS1 AND SNAP25 POLYMORPHISMS ARE ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN ADULTS BUT NOT IN CHILDREN.

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

Several investigations documented that Attention-Deficit/Hyperactivity Disorder (ADHD) is better conceptualized as a dimensional disorder. At the same time, the disorder seems to have different neurobiological underpinnings and phenotypic presentation in children compared to adults. Neurodevelopmental genes could explain, at least partly these differences. The aim of the present study was to examine possible associations between polymorphisms in SNAP25, MAP1B and NOS1 genes and ADHD symptoms in Brazilian samples of children/adolescents and adults with ADHD. The youth sample consisted of 301 patients whereas the adult sample comprises 485 individuals with ADHD. Diagnoses of ADHD and comorbidities were based on the Diagnostic and Statistical Manual of Mental Disorders-4th edition criteria. The Swanson, Nolan and Pelham Scale-Version IV (SNAP-IV) was applied by psychiatrists blinded to genotype. The total SNAP-IV scores were compared between genotypes. Impulsivity SNAP-IV scores were also compared according to NOS1 genotypes. Adult patients homozygous for the C allele at SNAP25 rs8636 showed significantly higher total SNAP-IV scores (F = 11.215; adjusted P-value = 0.004). Impulsivity SNAP-IV scores were also significantly different according to NOS1 rs478597 polymorphisms in adults with ADHD (F = 6.282; adjusted P-value = 0.026). These associations were not observed in children and adolescents with ADHD. These results suggest that SNAP25 and NOS1 genotypes influence ADHD symptoms only in adults with ADHD. Our study corroborates previous evidences for differences in the genetic contribution to adult ADHD compared with childhood ADHD

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J Psychiatry Neurosci. 2016;41:77-87.

REDUCED ERROR SIGNALLING IN MEDICATION-NAIVE CHILDREN WITH ADHD: ASSOCIATIONS WITH BEHAVIOURAL VARIABILITY AND POST-ERROR ADAPTATIONS.

Plessen KJ, Allen EA, Eichele H, et al.

We examined the blood-oxygen level-dependent (BOLD) activation in brain regions that signal errors and their association with intraindividual behavioural variability and adaptation to errors in children with attention-deficit/hyperactivity disorder (ADHD). Methods: We acquired functional MRI data during a Flanker task in medication-naive children with ADHD and healthy controls aged 8-12 years and analyzed the data using independent component analysis. For components corresponding to performance monitoring networks, we compared activations across groups and conditions and correlated them with reaction times (RT). Additionally, we analyzed post-error adaptations in behaviour and motor component activations. Results: We included 25 children with ADHD and 29 controls in our analysis. Children with ADHD displayed reduced activation to errors in cingulo-opercular regions and higher RT variability, but no differences of interference control. Larger BOLD amplitude to error trials significantly predicted reduced RT variability across all participants. Neither group showed evidence of post-error response slowing; however, post-error adaptation in motor networks was significantly reduced in children with ADHD. This adaptation was inversely related to activation of the right-lateralized ventral attention network (VAN) on error trials and to taskdriven connectivity between the cingulo-opercular system and the VAN. Limitations: Our study was limited by the modest sample size and imperfect matching across groups. Conclusion: Our findings show a deficit in cingulo-opercular activation in children with ADHD that could relate to reduced signalling for errors. Moreover, the reduced orienting of the VAN signal may mediate deficient post-error motor adaptions. Pinpointing general

performance monitoring problems to specific brain regions and operations in error processing may help to guide the targets of future treatments for ADHD

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Journal of the American Academy of Child & Adolescent Psychiatry. 2016 Mar;55:163-78.

THE INTERNAL, EXTERNAL, AND DIAGNOSTIC VALIDITY OF SLUGGISH COGNITIVE TEMPO: A META-ANALYSIS AND CRITICAL REVIEW.

Becker SP, Leopold DR, Burns GL, et al.

Objective: To conduct the first meta-analysis evaluating the internal and external validity of the sluggish cognitive tempo (SCT) construct as related to or distinct from attention-deficit/hyperactivity disorder (ADHD) and as associated with functional impairment and neuropsychological functioning.

Method: Electronic databases were searched through September 2015 for studies examining the factor structure and/or correlates of SCT in children or adults. The search procedures identified 73 papers. The core SCT behaviors included across studies, as well as factor loadings and reliability estimates, were reviewed to evaluate internal validity. Pooled correlation effect sizes using random effects models were used to evaluate SCT in relation to external validity domains (i.e., demographics, other psychopathologies, functional impairment, and neuropsychological functioning).

Results: Strong support was found for the internal validity of the SCT construct. Specifically, across factor analytic studies including more than 19,000 individuals, 13 SCT items loaded consistently on an SCT factor as opposed to an ADHD factor. Findings also support the reliability (i.e., internal consistency, test–retest reliability, interrater reliability) of SCT. In terms of external validity, there is some indication that SCT may increase with age (r = 0.11) and be associated with lower socioeconomic status (r = 0.10). Modest (potentially negligible) support was found for SCT symptoms being higher in males than females in children (r = 0.05) but not in adults. SCT is more strongly associated with ADHD inattention (r = 0.63 in children, r = 0.72 in adults) than with ADHD hyperactivity-impulsivity (r = 0.32 in children, r = 0.46 in adults), and it likewise appears that SCT is more strongly associated with internalizing symptoms than with externalizing symptoms. SCT is associated with significant global, social, and academic impairment (r = 0.38–0.44). Effects for neuropsychological functioning are mixed, although there is initial support for SCT being associated with processing speed, sustained attention, and metacognitive deficits.

Conclusion: This meta-analytic review provides strong support for the internal validity of SCT and preliminary support for the external validity of SCT. In terms of diagnostic validity, there is currently not enough evidence to describe SCT in diagnostic terms. Key directions for future research are discussed, including evaluating the conceptualization of SCT as a transdiagnostic construct and the need for longitudinal research.

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J Am Acad Child Adolesc Psychiatry. 2016;55:196-207.

A RANDOMIZED CLINICAL TRIAL OF AN INTEGRATIVE GROUP THERAPY FOR CHILDREN WITH SEVERE MOOD DYSREGULATION.

Waxmonsky JG, Waschbusch DA, Belin P, et al.

Objective Nonepisodic irritability is a common and impairing problem, leading to the development of the diagnoses severe mood dysregulation (SMD) and disruptive mood dysregulation disorder (DMDD). No psychosocial therapies have been formally evaluated for either, with medication being the most common treatment. This study examined the feasibility and efficacy of a joint parent-child intervention for SMD.

Method A total of 68 participants aged 7 to 12 years with attention-deficit/hyperactivity disorder (ADHD) and SMD were randomly assigned to the 11-week therapy or community-based psychosocial treatment. All participants were first stabilized on psychostimulant medication by study physicians. Of the participants, 56 still manifested impairing SMD symptoms and entered the therapy phase. Masked evaluators assessed participants at baseline, midpoint, and endpoint, with therapy participants reassessed 6 weeks later.

Results All but 2 therapy participants attended the majority of sessions (n = 29), with families reporting high levels of satisfaction. The primary outcome of change in mood symptoms using the Mood Severity Index

(MSI) did not reach significance except in the subset attending the majority of sessions (effect size = 0.53). Therapy was associated with significantly greater improvement in parent-rated irritability (effect size = 0.63). Treatment effects for irritability but not MSI diminished after therapy stopped. Little impact on ADHD symptoms was seen. Results may not be generalizable to youth with SMD and comorbidities different from those seen in this sample of children with ADHD, and are limited by the lack of a gold standard for measuring change in SMD symptoms.
Conclusion While failing to significantly improve mood symptoms versus community treatment, the integrative therapy was found to be a feasible and efficacious treatment for irritability in participants with SMD and ADHD. Clinical trial registration information - Group-Based Behavioral Therapy Combined With Stimulant Medication for Treating Children With Attention Deficit Hyperactivity Disorder and Impaired Mood; http://clinicaltrials.gov/; NCT00632619

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J Am Acad Child Adolesc Psychiatry. 2016;55:289-94.
RELATIONSHIP BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CARE AND MEDICATION CONTINUITY.
Brinkman WB, Baum R, Kelleher KJ, et al.
Objective To describe the relationships between attention-deficit/hyperactivity disorder (ADHD) care practices and subsequent medication use.
Method A retrospective cohort from a random sample of medical records in 50 pediatric practices with 188 providers, including 1,352 children who started ADHD medication, was studied. Independent variables included physician behaviors related to medication titration and monitoring of treatment response. Primary outcomes were number of days covered with ADHD medication during the first year of treatment and time from starting medicine to the first 30-day gap in medication supply. Multilevel modeling and Cox proportional hazards regression models were conducted.
Results Children had an average medication supply of 217 days in the first year. Half experienced a 30-day gap in medication supply in the first 3 months. Nearly three-fourths had a medication adjustment in the first year with the first adjustment usually being a dosage change. The average time to the first medication adjustment was over 3 months. Physician's first contact with parents occurred in the first month of treatment for less than half, with the average time being over 2 months. Little variation related to ADHD care quality was accounted for at the physician level. Early titration and early contact were related to greater medication supply and continuity of treatment.
Conclusion Earlier physician-delivered ADHD care (e.g., contact with parent after starting medication and medication adjustment) is related to greater medication supply and continuity. It remains to be determined whether interventions that improve the quality of titration and monitoring practices for children with ADHD would also improve medication continuity

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J Am Acad Child Adolesc Psychiatry. 2016;55:137-45.
MODE OF ANISOTROPY REVEALS GLOBAL DIFFUSION ALTERATIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Yoncheva YN, Somandepalli K, Reiss PT, et al.
Objective Diffusion tensor imaging (DTI) can identify structural connectivity alterations in attention-deficit/hyperactivity disorder (ADHD). Most ADHD DTI studies have concentrated on regional differences in fractional anisotropy (FA) despite its limited sensitivity to complex white matter architecture and increasing evidence of global brain differences in ADHD. Here, we examine multiple DTI metrics in separate samples of children and adults with and without ADHD with a principal focus on global between-group differences.
Method Two samples: adults with ADHD (n = 42) and without (n = 65) and children with ADHD (n = 82) and without (n = 80) were separately group matched for age, sex, and head motion. Five DTI metrics (FA, axial diffusivity, radial diffusivity, mean diffusivity, and mode of anisotropy) were analyzed via tract-based spatial statistics. Group analyses tested for diagnostic differences at the global (averaged across the entire white matter skeleton) and regional level for each metric.

Results Robust global group differences in diffusion indices were found in adults, with the largest effect size for mode of anisotropy (MA; Cohen's d = 1.45). Global MA also differed significantly between groups in the pediatric sample (d = 0.68). In both samples, global MA increased classification accuracy compared to the model with clinical Conners' ADHD ratings alone. Regional diagnostic differences did not survive familywise correction for multiple comparisons.
Conclusion Global DTI metrics, particularly the mode of anisotropy, which is sensitive to crossing fibers, capture connectivity abnormalities in ADHD across both pediatric and adult samples. These findings highlight potential diffuse white matter microarchitecture differences in ADHD

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Klin Psikofarmakol Bul. 2016;26:58-63.
INSIGNIFICANT EFFECTS OF ATOMOXETINE ON THYROID FUNCTIONS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN SHORT TERM.
Tanidir C, Tanidir IC, Bahali K, et al.
Objective: In this study, we aimed to explore the effects of atomoxetine on thyroid functions in children and adolescents with attention deficit hyperactivity disorder.
Methods: A retrospective chart review was done to evaluate the thyroid function tests of patients diagnosed with attention deficit hyperactivity disorder and treated with only atomoxetine. The thyroid function tests of 38 subjects, from both before atomoxetine was started and during an effective dose of atomoxetine treatment, were found from the patient charts and compared statistically.
Results: There were no statistically significant differences between the baselines levels of thyroidstimulating hormone (TSH), free T4, and free T3 values and those during an effective dose of atomoxetine treatment. In one subject, four weeks after atomoxetine was started and titrated to the effective dose, an insignificant increase in TSH was observed, which decreased to the normal range after the discontinuation of the atomoxetine treatment.
Conclusion: Therapeutic doses of atomoxetine do not seem to change thyroid functions in children and adolescents with attention deficit hyperactivity disorder

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Klin Psikofarmakol Bul. 2016;26:87-88.
EFFECT OF METHYLPHENIDATE ON IMPULSIVITY IN A CHILD WITH PICA AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Gunes H, Tanidir C, Adaletli H, et al.

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Med J Aust. 2016;204:139.
ADHD AND PSYCHOSTIMULANTS - OVERDIAGNOSIS AND OVERPRESCRIPTION.
Dunlop AJ, Newman LK.

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Med J Aust. 2016;204:154.
ADHD MEDICATION OVERDOSE AND MISUSE: THE NSW POISONS INFORMATION CENTRE EXPERIENCE, 2004-2014.
Cairns R, Daniels B, Wood DA, et al.
Objectives: To describe Australian trends in overdoses with medications used to treat attention deficit hyperactivity disorder (ADHD).
Design, setting and participants: This was a retrospective observational study of intentional exposures to methylphenidate, dexamphetamine, modafinil and atomoxetine reported to the New South Wales Poisons Information Centre (NSWPIC) from 1 January 2004 to 31 December 2014. The NSWPIC takes calls from

New South Wales, Tasmania and the Australian Capital Territory between 6am and midnight each day, and, as part of a national after-hours roster, from all Australian states between midnight and 6am on seven nights each fortnight. The target population included Australian residents aged 10-75 years.
Main outcome measures: Demographic characteristics of the patients, changes in numbers of exposures with time, co-ingestants, route of exposure, and disposition of patients. Results: During the 11-year study period, 1735 intentional exposures to the four medications were reported to NSWPIC. There was a 210% increase in intentional exposures to methylphenidate over this period, whereas the number of dexamphetamine exposures declined by 25%. Illicit use (defined as co-ingestion with alcohol or a street drug) increased by 429% across the study period. At least 93% of overdose patients required hospitalisation. Trends in exposures paralleled trends in the dispensing of these medications, as recorded in Pharmaceutical Benefits Scheme data.
Conclusions: NSWPIC data show a dramatic increase in intentional exposures to ADHD medications between 2004 and 2014, mainly to methylphenidate. Further, the data suggest that illicit use of these substances is increasing. The potential harm related to misuse of prescription stimulants and the close correlation between these exposures and the prescribing of these drugs causes concerns about their diversion, and highlights the importance of the quality use of medicines (ie, ensuring that they are used safely, appropriately and in an evidence-based manner, including considering non-medical or non-stimulant alternatives) and of risk assessment for misuse when prescribing ADHD drugs

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Mindfulness. 2016 Feb;7:68-75.

EFFECTS OF SAMATHA MEDITATION ON ACTIVE ACADEMIC ENGAGEMENT AND MATH PERFORMANCE OF STUDENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Singh NN, Lancioni GE, Karazsia BT, et al.

Students with attention deficit/hyperactivity disorder (ADHD) often do not actively engage in academic instruction because they have difficulty in attending to task demands in the classroom. Without adequate intervention, this may result in poor academic outcomes for these students. In a multiple baseline design study, we taught four 5th-grade students Samatha meditation and assessed active engagement in math instruction and the percentage of math problems correctly solved during baseline, meditation training, and meditation practice phases. Results showed the students had varying but low percentages of intervals of active engagement in math instruction during baseline, but evidenced statistically significant increases from baseline to the meditation practice phase. Similarly, their low but varying percentages of math problems solved correctly during baseline showed statistically significant increases from baseline to the meditation practice phase. These results suggest that Samatha meditation may enhance cognitive processes in students with ADHD at a level to benefit them academically.

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Minerva Pediatr. 2015;67:391-99.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND INFANTILE COLIC.

Kaymaz N, Uzun ME, Cevizci S, et al.

Aim. Attention deficit and hyperactivity disorder (ADHD) and infantile colic (IC) are heterogeneous diseases which's cause are unknown. Besides the different hypotheses in the etiology of both disorders maldevelopment in the metabolism of neurotransmitters in the central nervous system have been implicated. The goal of this study is to investigate the relationship between IC and ADHD due to possible common etiological factor as maldevelopment in neurochemical process.
Methods. A case-control study was carried out. The sample included 114 (77.2% male) children who were medically diagnosed with AD/HD and 149 (67.1% male) healthy children who were chosen from the same hospital's pediatric clinic as the control group. Parents and teachers completed the Conners Parent Rating Scale (CPRS), Conners Teacher Rating Scale (CTRS) and the patients were evaluated with The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The parents were asked questions on a survey form filled out. IC was defined according to Wessel's modified criteria.

Results. The mean age of AD/HD group was 10.14-¦2.48 years and 9.94-¦2.34 years in the non-AD/HD group. The rate of IC in AD/ HD and non-AD/HD groups were 50.0% and 30.2%, respectively and the difference was statistically significant between two groups (P=0.001). Duration of IC was similar in the groups (P=143).
Conclusion. IC may be a postnatal risk factor and marker for AD/HD during childhood. Both diseases may have a common mecha-nism. Such infants need to be examined and followed up more intensively

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Minerva Pediatr. 2015;67:427-36.

IMPACT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ON THE LIVES OF ITALIAN CHILDREN AND ADOLESCENTS: DATA FROM THE EUROPEAN LIFETIME IMPAIRMENT SURVEY.

Donfrancesco R, Loprieno U.

Aim. In Italy, attention-deficit/hyperactivity disorder (ADHD) remains under-diagnosed. The Lifetime Impairment Survey assessed impairments/symptoms of ADHD in children across six European countries. Results relating to the Italian sample are discussed here.
Methods. Parents/caregivers of children aged <20 years with ADHD (ADHD group) and without ADHD (control group) were invited to participate in an online survey. Participants answered questions relating to their eldest/only child. History of ADHD diagnosis was self-reported. Eight impairment and symptom scales and two summed scores were created to compare the ADHD and control groups; higher scores indicate greater impairment.
Results. In Italy, 104 parents/caregivers of children with ADHD and 105 parents/ caregivers of children without ADHD participated in the survey (N.=83 and N.=84, respectively, after exclusion of participants with implausible answers). The ADHD group had higher mean (standard deviation) scores than the control group for home impairment (2.1 [0.5]) vs. 1.9 [0.4]; P<0.001), school impairment (2.8 [0.6] vs. 2.1 [0.6]; P<0.001), relationship impairment (2.3 [0.8] vs. 1.9 [0.7]; P<0.001) and comorbid symptoms (3.3 [0.7] vs. 2.5 [0.7]; P<0.001). Impairment at home and at school were correlated with each other (r=0.478; P<0.001) and with ADHD symptoms (r=0.321; P<0.001 and r=0.462; P<0.001, respectively), comorbid symptoms (r=0.231; P<0.05 and r=0.420; P<0.001), school failure (r=0.208; P<0.02 and r=0.320; P<0.001) and relationship impairments (r=0.432; P<0.01 and r=0.645; P<0.001).
Conclusion. The daily lives of children with ADHD in Italy are significantly affected by impairments associated with ADHD. Children and adolescents with ADHD in Italy should receive prompt diagnosis and appropriate therapy

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Mol Psychiatry. 2016;21:419-25.

COMMON POLYGENIC RISK FOR AUTISM SPECTRUM DISORDER (ASD) IS ASSOCIATED WITH COGNITIVE ABILITY IN THE GENERAL POPULATION.

Clarke TK, Lupton MK, Fernandez-Pujals AM, et al.

Cognitive impairment is common among individuals diagnosed with autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). It has been suggested that some aspects of intelligence are preserved or even superior in people with ASD compared with controls, but consistent evidence is lacking. Few studies have examined the genetic overlap between cognitive ability and ASD/ADHD. The aim of this study was to examine the polygenic overlap between ASD/ADHD and cognitive ability in individuals from the general population. Polygenic risk for ADHD and ASD was calculated from genome-wide association studies of ASD and ADHD conducted by the Psychiatric Genetics Consortium. Risk scores were created in three independent cohorts: Generation Scotland Scottish Family Health Study (GS:SFHS) (n=9863), the Lothian Birth Cohorts 1936 and 1921 (n=1522), and the Brisbane Adolescent Twin Sample (BATS) (n=921). We report that polygenic risk for ASD is positively correlated with general cognitive ability (beta=0.07, P=6 +ù 10 -7, r 2 =0.003), logical memory and verbal intelligence in GS:SFHS. This was replicated in BATS as a positive association with full-scale intelligent quotient (IQ) (beta=0.07, P=0.03, r 2 =0.005). We did not find consistent evidence that polygenic risk for ADHD was associated with cognitive function; however, a negative

correlation with IQ at age 11 years (beta=-0.08, Z=-3.3, P=0.001) was observed in the Lothian Birth Cohorts. These findings are in individuals from the general population, suggesting that the relationship between genetic risk for ASD and intelligence is partly independent of clinical state. These data suggest that common genetic variation relevant for ASD influences general cognitive ability

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NeuroImage Clin. 2016;11:210-23.

ALPHA DESYNCHRONIZATION AND FRONTO-PARIETAL CONNECTIVITY DURING SPATIAL WORKING MEMORY ENCODING DEFICITS IN ADHD: A SIMULTANEOUS EEG-FMRI STUDY.

Lenartowicz A, Lu S, Rodriguez C, et al.

The underlying mechanisms of alpha band (8-12 Hz) neural oscillations are of importance to the functioning of attention control systems as well as to neuropsychiatric conditions that are characterized by deficits of that system, such as attention deficit hyperactivity disorder (ADHD). The objectives of the present study were to test if visual encoding-related alpha event-related desynchronization (ERD) correlates with fronto-parieto-occipital connectivity, and whether this is disrupted in ADHD during spatial working memory (SWM) performance. We acquired EEG concurrently with fMRI in thirty boys (12-16 yrs. old, 15 with ADHD), during SWM encoding. Psychophysiological connectivity analyses indicated that alpha ERD during SWM encoding was associated with both occipital activation and fronto-parieto-occipital functional connectivity, a finding that expands on prior associations between alpha ERD and occipital activation. This finding provides novel support for the interpretation of alpha ERD (and the associated changes in occipital activation) as a phenomenon that involves, and perhaps arises as a result of, top-down network interactions. Alpha ERD was associated less strongly with occipital activity, but associated more strongly with fronto-parieto-occipital connectivity in ADHD, consistent with a compensatory attentional response. Additionally, we illustrate that degradation of EEG data quality by MRI-amplified motion artifacts is robust to existing cleaning algorithms and is significantly correlated with hyperactivity symptoms and the ADHD Combined Type diagnosis. We conclude that persistent motion-related MR artifacts in EEG data can increase variance and introduce bias in interpretation of group differences in populations characterized by hypermobility - a clear limitation of current-state EEG-fMRI methodology

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Neurologia. 2016;31:83-88.

PILOT STUDY OF THE EFFICACY OF EMPOWERING PATIENTS THROUGH COACHING AS A COMPLEMENTARY THERAPY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

García Ron A, Serrano Grasa R, Blanco Lago R, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is the most frequent neurodevelopmental disorder and must be considered a public health priority because of its functional repercussions in school, family, and social settings. Health empowerment is an innovative model of care for patients with chronic diseases based on self-management education. Our goal is to evaluate the effectiveness of empowerment using coaching within a multimodal treatment plan in paediatric patients with ADHD.

Material and methods: Descriptive open prospective study. We included children between 6 and 12 years old belonging to patient association in a suburban area of the Region of Madrid. We evaluated the situation before and after 5 cost-free coaching sessions using the Conners Questionnaire, Dundee difficult times of day scale, and satisfaction scales.

Results: We included 49 patients (73.5% males) with an average age of 8.5 years. The ADHD hyperactive-impulsive subtype was present in 63.3% and 77.6% had some type of comorbidity. All were treated with methylphenidate and their clinical course was poor. Clinical improvements were observed in 79.6% with a 34.6% mean reduction in symptoms (SD 11.1), and improvements remained stable at 6 months follow-up after coaching. We reached a satisfaction level of 7.8 out of 10 (SD 1.7), and 95.9% of the participants recommended this treatment to other families.

Conclusions: Our results provide information on the potential benefits of coaching as complementary treatment for ADHD

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Neurosci Lett. 2016;617:166-72.

TEST-RETEST RELIABILITY OF ERP COMPONENTS: A SHORT-TERM REPLICATION OF A VISUAL GO/NOGO TASK IN ADHD SUBJECTS.

Kompatsiari K, Candrian G, Mueller A.

Event-related potentials (ERPs) have been widely used to investigate brain functioning in children with Attention Deficit Hyperactivity Disorder (ADHD) in both research and diagnostic settings. To ensure the efficiency of ERP techniques in ADHD diagnosis and in longitudinal observational studies, the test-retest reliability of the affected population must be validated. Thus, the present article assesses the short-term test-retest reliability of certain early and late ERPs (i.e., P1, N1, N2, P2, P3), as well as independent components (ICs) decomposed from the above mentioned ERPs (IC P3 Go, IC P3 NoGo early, IC P3 NoGo late) relevant to ADHD, through the Intraclass Correlation Coefficient (ICC). More specifically, we employ a cued visual Go/NoGo paradigm for recording ERPs from 22 children with ADHD (mean age 12.2), twice within 30 min. Amplitudes and latencies are calculated by the 'peak amplitude' method and by a variation of the fractional area. Results for amplitudes lie mostly within the 'good' and 'excellent' range for both measurement methods, while ICC for latencies is more variable ranging from 'poor' to 'excellent' results. Crucially, the ICs, which are associated with distinct functionally independent processes of the executive attentional system have shown a comparable test-retest reliability with the raw ERPs. Our results are consistent with other reliability studies of neurotypical population in the literature, and as such, consist initial evidence that ERPs could be reliable neurophysiological markers for the ADHD population

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Pediatrics. 2016;137.

DIAGNOSTIC ACCURACY OF RATING SCALES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A META-ANALYSIS.

Chang LY, Wang MY, Tsai PS.

CONTEXT: The Child Behavior Checklist-Attention Problem (CBCL-AP) scale and Conners Rating Scale-Revised (CRS-R) are commonly used behavioral rating scales for diagnosing attention-deficit/hyperactivity disorder (ADHD) in children and adolescents.

OBJECTIVE: To evaluate and compare the diagnostic performance of CBCL-AP and CRS-R in diagnosing ADHD in children and adolescents.

DATA SOURCES: PubMed, Ovid Medline, and other relevant electronic databases were searched for articles published up to May 2015.

STUDY SELECTION: We included studies evaluating the diagnostic performance of either CBCL-AP scale or CRS-R for diagnosing ADHD in pediatric populations in comparison with a defined reference standard.

DATA EXTRACTION: Bivariate random effects models were used for pooling and comparing diagnostic performance.

RESULTS: We identified and evaluated 14 and 11 articles on CBCL-AP and CRS-R, respectively. The results revealed pooled sensitivities of 0.77, 0.75, 0.72, and 0.83 and pooled specificities of 0.73, 0.75, 0.84, and 0.84 for CBCL-AP, Conners Parent Rating Scale-Revised, Conners Teacher Rating Scale-Revised, and Conners Abbreviated Symptom Questionnaire (ASQ), respectively. No difference was observed in the diagnostic performance of the various scales. Study location, age of participants, and percentage of female participants explained the heterogeneity in the specificity of the CBCL-AP.

CONCLUSIONS: CBCL-AP and CRS-R both yielded moderate sensitivity and specificity in diagnosing ADHD. According to the comparable diagnostic performance of all examined scales, ASQ may be the most effective diagnostic tool in assessing ADHD because of its brevity and high diagnostic accuracy. CBCL is recommended for more comprehensive assessments

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Pharmacopsychiatry. 2016;49:45-50.

RISK OF INJURY ACCORDING TO ATTENTION DEFICIT HYPERACTIVITY DISORDER, COMORBID MENTAL ILLNESS, AND MEDICATION THERAPY.

Merrill RM, Thygerson SM, Palmer CA.

Introduction: We identify the risk of selected types of injuries among patients with ADHD or ADHD and comorbid mental illness. We also assess whether selected medications used by patients with ADHD increase the risk of comorbid mental illness or influence the association between ADHD and injury.

Methods: A retrospective cohort study design was conducted using medical claims data from the Deseret Mutual Benefit Administrators (DMBA). ADHD diagnosis, injury, medication, and demographic data were extracted from claims files during 2001-2013. Rate ratios were adjusted for age, sex, and calendar year.

Results: Patients with ADHD were 7.9 (95% CI 7.6-8.2) times more likely to have psychosis, 5.5 (3.9-7.8) times more likely to have alcohol- or drug-induced psychosis, and 6.0 (5.9-6.2) times more likely to have neurotic or personality disorder. Therapy with amphetamine was positively associated with neurotic or personality disorder (rate ratio=1.08, 1.02-1.15); methylphenidate was negatively associated with neurotic or personality disorder (0.90, 0.84-0.97); and atomoxetine was positively associated with psychosis (1.33, 1.21-1.46), alcohol- or drug-induced psychosis (2.38, 1.04-5.43), and neurotic or personality disorder (2.38, 1.04-5.43). ADHD was associated with an increased risk of injury, with ADHD and comorbid mental illness having a stronger increased risk of injury. Psychostimulants ameliorated the increased risk of injury for patients with ADHD.

Conclusion: Patients with ADHD have an increased risk of injury, significantly more so for those with ADHD and comorbid mental illness. Psychostimulants can lower the risk of injury among patients with ADHD

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PLoS ONE. 2016;11.

QUALITATIVE TREATMENT-SUBGROUP INTERACTIONS IN A RANDOMIZED CLINICAL TRIAL OF TREATMENTS FOR ADOLESCENTS WITH ADHD: EXPLORING WHAT COGNITIVE-BEHAVIORAL TREATMENT WORKS FOR WHOM.

Boyer BE, Doove LL, Geurts HM, et al.

Objective: This study explored qualitative treatment-subgroup interactions within data of a RCT with two cognitive behavioral treatments (CBT) for adolescents with ADHD: a planning-focused (PML) and a solution-focused CBT (SFT). Qualitative interactions imply that which treatment is best differs across subgroups of patients, and are therefore most relevant for personalized medicine.

Methods: Adolescents with ADHD (N = 159) received either PML or SFT. Pre-, post- and three-month follow-up data were gathered on parent-rated ADHD symptoms and planning problems. Pretreatment characteristics were explored as potential qualitative moderators of pretest to follow-up treatment effects, using an innovative analyses technique (QUINT; Dusseldorp & Van Mechelen, 2014). In addition, qualitative treatment-subgroup interactions for the therapeutic changes from pre-to posttest and from post-to follow-up test were investigated.

Results: For the entire time span from pretest to follow-up only a quantitative interaction was found, while from posttest to follow-up qualitative interactions were found: Adolescents with less depressive symptoms but more anxiety symptoms showed more improvement when receiving PML than SFT, while for other adolescents the effects of PML and SFT were comparable.

Discussion: Whereas subgroups in both treatments followed different trajectories, no subgroup was found for which SFT outperformed PML in terms of the global change in symptoms from pretest to three months after treatment. This implies that, based on this exploratory study, there is no need for personalized treatment

allocation with regard to the CBTs under study for adolescents with ADHD. However, for a subgroup with comorbid anxiety symptoms but low depression PML clearly appears the treatment of preference

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PLoS ONE. 2016;11.

DESYNCHRONIZATION OF THETA-PHASE GAMMA- AMPLITUDE COUPLING DURING A MENTAL ARITHMETIC TASK IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Kim JW, Kim BN, Lee J, et al.

Introduction Theta-phase gamma-amplitude coupling (TGC)measurement has recently received attention as a feasible method of assessing brain functions such as neuronal interactions. The purpose of this electroencephalographic (EEG) study is to understand the mechanisms underlying the deficits in attentional control in children with attention deficit/hyperactivity disorder (ADHD) by comparing the power spectra and TGC at rest and during a mental arithmetic task.

Methods Nineteen-channel EEGs were recorded from 97 volunteers (including 53 subjects with ADHD) from a camp for hyperactive children under two conditions (rest and task performance). The EEG power spectra and the TGC data were analyzed. Correlation analyses between the Intermediate Visual and Auditory (IVA) continuous performance test (CPT) scores and EEG parameters were performed.

Results No significant difference in the power spectra was detected between the groups at rest and during task performance. However, TGC was reduced during the arithmetic task in the ADHD group compared with the normal group ($F = 16.70$, $p < 0.001$). The TGC values positively correlated with the IVA CPT scores but negatively correlated with theta power.

Conclusions Our findings suggest that desynchronization of TGC occurred during the arithmetic task in ADHD children. TGC in ADHD children is expected to serve as a promising neurophysiological marker of network deactivation during attention-demanding tasks

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PLoS ONE. 2016;11.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND URINARY NONYLPHENOL LEVELS: A CASE-CONTROL STUDY IN TAIWANESE CHILDREN.

Yu CJ, Du JC, Chiou HC, et al.

Objective: Nonylphenol (NP) belongs to the family of endocrine disruptors, and it is widely used in industrial applications and is ubiquitous in daily foods. Animal studies have suggested that NP exposure might promote motor hyperactivity, likely by causing deficits in dopaminergic neurons. However, research assessing NP exposure and epidemiology studies on human populations are limited. The aim of this study was to explore the association between child NP exposure and ADHD while considering particular covariants, such as lead levels and dopamine-related gene variations.

Methods: A case-control study was conducted on patients with clinically diagnosed ADHD; the Swan son, Nolan and Pelham, Fourth Revision (SNAP-IV) questionnaire was used to identify normal controls aged 4-15 years. Participants were examined for urinary NP concentrations, blood lead levels, and select single-nucleotide polymorphisms of two dopamine-related genes (D4 dopamine receptor, DRD4, and dopamine transporter, DAT1). Socio-demo-graphic variables, maternal lifestyle factors during pregnancy and family medical history were obtained using a questionnaire.

Results: A total of 97 children with doctor-diagnosed ADHD and 110 normal controls were enrolled. The blood lead levels in both groups were similar (1.57-¦0.73 vs. 1.73-¦0.77 pg/dL, $p = 0.15$). No significant difference in urinary NP concentration was found between the children with ADHD and the control subjects (4.52-3.22 pg/g cr. vs. 4.64-¦2.95 pg/g cr., $p = 0.43$). ADHD was significantly more prevalent among males in this study (male to female ratio: 5:1 for the ADHD group and 1.3:1 for the control group, $p<0.01$). The analysis was repeated after excluding the females, but this had no effect on the association between NP and ADHD. The regression model, including or excluding females, indicated no increased odds of having ADHD in the context of NP exposure after adjusting for covariants.

Conclusion: This study indicated that NP exposure might not promote ADHD in children, even though children in Taiwan had relatively high levels of NP compared to those reported previously and those in developed nations

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PLoS ONE. 2016;11.

NO TRYPTOPHAN, TYROSINE AND PHENYLALANINE ABNORMALITIES IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bergwerff CE, Luman M, Blom HJ, et al.

Background The aim of the current study was to explore the role of aromatic amino acids (AAAs) in blood in relation to attention-deficit/hyperactivity disorder (ADHD). Given their impact on the synthesis of serotonin and dopamine, decreased concentrations of the AAAs tryptophan, tyrosine and phenylalanine in blood may contribute to the expression of ADHD symptoms. Decreased AAA blood concentrations, in turn, may be related to lowered dietary protein intake or to abnormal AAA catabolism, as evidenced by increased urinary AAA concentrations.

Methods Eighty-Three children with ADHD (75% males) and 72 typically developing (TD) children (51% males), aged 6 to 13 years, participated in the study. AAA concentrations were assessed in blood spots and an 18-hour urinary sample. A nutritional diary was filled out by parents to calculate dietary protein intake. Parent and teacher questionnaires assessed symptoms of ADHD, oppositional defiant disorder, conduct disorder, and autism spectrum disorder.

Results Children with ADHD showed normal AAA concentrations in blood spots and urine, as well as normal protein intake compared to controls. No associations between AAA concentrations and symptoms of ADHD or comorbid psychiatric disorders were found.

Conclusions This study is the first to explore AAA metabolism in children with ADHD using a well-defined and relatively large sample. We found that AAA deficiencies are not related to ADHD. The results do not support treatment with AAA supplements in children with ADHD. Future studies regarding the cause of serotonin and dopamine alterations in ADHD should focus on other explanations, such as effects of altered transport of AAAs

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Prescriber. 2016;27:17-23.

MANAGEMENT OF ADHD IN CHILDREN AND ADOLESCENTS.

Pickett J.

Attention deficit hyperactivity disorder (ADHD) is a condition characterised by inattention, hyperactivity and impulsivity that is often diagnosed in early childhood and can interfere with school life and social functioning. This article discusses the assessment of children and adolescents with suspected ADHD, common co-morbidities and the properties of the drug treatment options available

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Psicothema. 2016 Feb;28:20-25.

MEDICATION AND CREATIVITY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Hernández GG-C, Selva JPS.

Background: The aim of this study was to determine the effect of methylphenidate (MPH) on creative potential in a group of children with attention deficit disorder with hyperactivity (ADHD).

Method: A randomized single blind crossover study was performed with 24 children with ADHD, aged between 8 and 12 years (M = 10.0, SD = 1.3), evaluating each child's creativity with and without MPH, using the Torrance Tests of Creative Thinking-Figural (TTCT).

Results: Children under treatment with MPH showed a lower global Creative Index and lower scores on Fluency, Originality and Creative Strengths, compared to when not under treatment. The capacities for

Elaboration, Abstractness of Titles, and Resistance to Closure did not differ whether on or off pharmacological treatment.
Conclusion: Our finding suggests that is important to take into account the impact that MPH might have on the creative potential of a child with ADHD to develop a more accurate evaluation and to develop better treatment plans.

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Psychiatr Invest. 2016;13:210-16.
ASSOCIATION BETWEEN RELN GENE POLYMORPHISMS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN KOREAN CHILDREN.
Kwon HJ, Jang WC, Lim MH.
OBJECTIVE: Attention deficit hyperactivity disorder (ADHD) is common disorder of the school-age population. ADHD is familial and genetic studies estimate heritability at 80-90%. The aim of the present study was to investigate the association between the genetic type and alleles for RELNgene (rs736707, rs2229864, rs362746, rs362726, rs362691, rs1062831, rs607755, and rs2072403) in Korean children with ADHD.
METHODS: The sample consisted of 180 ADHD children and 159 control children. We diagnosed ADHD according to DSM-IV. ADHD symptoms were evaluated with Conners' Parent Rating Scales and Dupaul Parent ADHD Rating Scales. Blood samples were taken from the 339 subjects, DNA was extracted from blood lymphocytes, and PCR was performed for RELN Polymorphism. Alleles and genotype frequencies were compared using the chi-square test. We compared the allele and genotype frequencies of RELN gene polymorphism in the ADHD and control groups.
RESULTS: This study showed that there was a significant correlation among the frequencies of the rs736707 (OR=1.40, 95% CI=1.03-1.90, p=0.031) of alleles of RELN, but the final conclusions are not definite.
CONCLUSION: Follow up studies with larger patient or pure subgroups are expected. These results suggested that RELN might be related to ADHD symptoms.

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Psychiatry Res. 2015;230:905-12.
CHILDHOOD PREDICTORS OF PERSISTENT ADHD IN EARLY ADULTHOOD: RESULTS FROM THE FIRST FOLLOW-UP STUDY IN CHINA.
Gao Q, Qian Y, He XX, et al.
It is known that childhood attention-deficit/hyperactivity disorder (ADHD) persists into adulthood. Previous studies have demonstrated that gender, ADHD symptoms, functional impairment severity, medication treatment, IQ, comorbid with oppositional defiant disorder, conduct disorder and follow-up periods were associated with ADHD persistence in longitudinal samples of western population. In this study, we attempted to widely investigate the predictors particularly in a Chinese Han ADHD cohort. 399 children who met DSM-IV ADHD criteria were followed up into early adulthood. Ordinal logistic regression combined with survival analysis were conducted to examine the association of retrospectively reported childhood factors with adult ADHD persistence based on both categorical indicators and quantitative traits. 46.37% of the participants still met ADHD criteria in adulthood. Logistic models and survival analyses indicated that ADHD combined type appeared as a significant risk factor for ADHD persistence while superior IQ played a protective role even after controlling for the other potential confounders. When quantitative traits were applied, a number of hyperactivity/impulsivity symptoms and IQ still made significant contributions. In conclusion, our results indicated the syndromic continuity of ADHD. Further, a number of hyperactivity/impulsivity symptoms were a risk factor while higher IQ was protective for ADHD persistence

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Psychiatry Res. 2016;237:138-46.
THE RELATIONSHIP BETWEEN TICS, OC, ADHD AND AUTISM SYMPTOMS: A CROSS- DISORDER SYMPTOM ANALYSIS IN GILLES DE LA TOURETTE SYNDROME PATIENTS AND FAMILY-MEMBERS.
Huisman-van Dijk HM, Schoot RVD, Rijkeboer MM, et al.

Gilles de la Tourette's syndrome (GTS) is a disorder in which obsessive-compulsive (OC), Attention Deficit Hyperactivity Disorder (ADHD) and autism symptoms occur in up to 60% of patients, suggesting shared etiology. We explored the phenotypic structure of tic, OC, ADHD, and autism symptoms as measured by the YGTSS,Y-BOCS,CAARS and AQ, in 225 GTS patients and 371 family members. First, Confirmatory Factor Analyses (CFA) were performed on the symptom structure of each separate symptom scale. Second, the symptom dimensions derived from each scale were combined in one model, and correlations between them were calculated. Using the correlation matrix, Exploratory Factor Analyses (EFA) were performed on the symptom dimensions across the scales. EFA revealed a five factor structure: tic/aggression/symmetry; OC symptoms/compulsive tics/ numbers and patterns; ADHD symptoms; autism symptoms; and hoarding/inattention symptoms. The results are partly in line with the traditional categorical boundaries of the symptom scales used, and partly reveal a symptom structure that cuts through the diagnostic categories. This phenotypic structure might more closely reflect underlying etiologies than a structure that classically describes GTS patients according to absence or presence of comorbid OCD, ADHD and autism, and might inform both future genetic and treatment studies

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Psychiatry Res. 2016;239:232-38.

GAMBLING BEHAVIORS AND PSYCHOPATHOLOGY RELATED TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN PROBLEM AND NON-PROBLEM ADULT GAMBLERS.

Fatseas M, Alexandre JM, V+®nisse JL, et al.

Previous studies showed that Pathological Gambling and Attention Deficit/Hyperactivity Disorder (ADHD) often co-occur. The aim of this study was to examine whether ADHD is associated with specific severity patterns in terms of gambling behavior, psychopathology and personality traits. 599 problem and non-problem-gamblers were recruited in addiction clinics and gambling places in France. Subjects were assessed with the Wender-Utah Rating Scale-Child, the Adult ADHD Self-Report Scale, the Mini International Neuropsychiatric Interview, the Temperament and Character Inventory, the South Oaks Gambling Screen and questionnaires assessing gambling related cognitive distortions and gambling habits. 20.7% (n=124) of gamblers were screened positive for lifetime or current ADHD. Results from the multivariate analysis showed that ADHD was associated with a higher severity of gambling-related problems and with more psychiatric comorbidity. Among problem gamblers, subjects with history of ADHD were also at higher risk for unemployment, psychiatric comorbidity and specific dysfunctional personality traits. This study supports the link between gambling related problems and ADHD in a large sample of problem and non-problem gamblers, including problem-gamblers not seeking treatment. This points out the necessity to consider this disorder in the prevention and in the treatment of pathological gambling

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Psychol Addict Behav. 2016 Mar;30:252-62.

THE RELATIONSHIP BETWEEN ADDICTIVE USE OF SOCIAL MEDIA AND VIDEO GAMES AND SYMPTOMS OF PSYCHIATRIC DISORDERS: A LARGE-SCALE CROSS-SECTIONAL STUDY.

Schou Andreassen C, Billieux J, Griffiths MD, et al.

Over the last decade, research into “addictive technological behaviors” has substantially increased. Research has also demonstrated strong associations between addictive use of technology and comorbid psychiatric disorders. In the present study, 23,533 adults (mean age 35.8 years, ranging from 16 to 88 years) participated in an online cross-sectional survey examining whether demographic variables, symptoms of attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and depression could explain variance in addictive use (i.e., compulsive and excessive use associated with negative outcomes) of two types of modern online technologies: social media and video games. Correlations between symptoms of addictive technology use and mental disorder symptoms were all positive and significant, including the weak interrelationship between the two addictive technological behaviors. Age appeared to be inversely related to the addictive use of these technologies. Being male was significantly associated with addictive use of video games, whereas being female was significantly associated with addictive use of social media. Being single

was positively related to both addictive social networking and video gaming. Hierarchical regression analyses showed that demographic factors explained between 11 and 12% of the variance in addictive technology use. The mental health variables explained between 7 and 15% of the variance. The study significantly adds to our understanding of mental health symptoms and their role in addictive use of modern technology, and suggests that the concept of Internet use disorder (i.e., “Internet addiction”) as a unified construct is not warranted

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Res Dev Disabil. 2016;53-54:296-304.

RISK-TAKING PROPENSITY AND SENSITIVITY TO PUNISHMENT IN ADOLESCENTS WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER SYMPTOMS AND/OR READING DISABILITY.

Poon K, Ho CSH.

Many studies reported that adolescents with ADHD/RD more frequently engage in risk-taking behaviors. Very few have examined their risk taking patterns and the impact of their comorbidity. The present study compared the risk-taking propensity, sensitivity to punishment and delinquency outcome in Chinese adolescents with ADHD symptoms (AS) and/or RD using a simulated risk task, the Balloon Analogous Risk Task (BART). Adolescents with AS (n = 37), RD (n = 35), AS + RD (n = 35), and control (n = 36) were recruited from local secondary schools. Results showed that adolescents with ADHD, despite their great risk-taking propensity, were sensitive to immediate punishment whereas adolescents with RD were found to display normal risk-taking propensity, yet showed a tendency of being less sensitive to punishment. The comorbidity ADHD + RD group had the highest delinquency score, and exhibited greatest risk taking and least sensitivity to punishment, which provided further support that comorbid condition might have stronger impact on risk taking or even delinquency than the pure groups. The present findings provides a useful picture of the risk taking pattern associated with different groups, allowing for effective matching for future prevention and intervention program

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Res Dev Disabil. 2016;53-54:258-66.

DEFICITS IN VISION AND VISUAL ATTENTION ASSOCIATED WITH MOTOR PERFORMANCE OF VERY PRETERM/VERY LOW BIRTH WEIGHT CHILDREN.

Geldof CJA, van Hus JWP, Jeukens-Visser M, et al.

Aim: To extend understanding of impaired motor functioning of very preterm (VP)/very low birth weight (VLBW) children by investigating its relationship with visual attention, visual and visual-motor functioning.
Methods: Motor functioning (Movement Assessment Battery for Children, MABC-2; Manual Dexterity, Aiming & Catching, and Balance component), as well as visual attention (attention network and visual search tests), vision (oculomotor, visual sensory and perceptive functioning), visual-motor integration (Beery Visual Motor Integration), and neurological status (Touwen examination) were comprehensively assessed in a sample of 106 5.5-year-old VP/VLBW children. Stepwise linear regression analyses were conducted to investigate multivariate associations between deficits in visual attention, oculomotor, visual sensory, perceptive and visual-motor integration functioning, abnormal neurological status, neonatal risk factors, and MABC-2 scores.
Results: Abnormal MABC-2 Total or component scores occurred in 23-36% of VP/VLBW children. Visual and visual-motor functioning accounted for 9-11% of variance in MABC-2 Total, Manual Dexterity and Balance scores. Visual perceptive deficits only were associated with Aiming & Catching. Abnormal neurological status accounted for an additional 19-30% of variance in MABC-2 Total, Manual Dexterity and Balance scores, and 5% of variance in Aiming & Catching, and neonatal risk factors for 3-6% of variance in MABC-2 Total, Manual Dexterity and Balance scores.

Conclusion: Motor functioning is weakly associated with visual and visual-motor integration deficits and moderately associated with abnormal neurological status, indicating that motor performance reflects long term vulnerability following very preterm birth, and that visual deficits are of minor importance in understanding motor functioning of VP/VLBW children

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Rev Neurol. 2016;62:S99-S102.

ASSESSMENT OF ANXIETY IN AUTISM SPECTRUM DISORDERS AND IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Fortea-Sevilla MS, Escandell-Bermudez MO, Castro-Sanchez JJ, et al.

Introduction. The identification of factors that influence attention deficit hyperactivity disorder (ADHD) or autism spectrum disorders (ASD) will allow the development of intervention strategies that will benefit the personal and social adjustment of these individuals. It is well known that children with developmental disorders have a higher risk of presenting symptoms of anxiety than typically developing children.

Aim. To assess the perception of anxiety of a group of children and adolescents with ADHD or ASD and the anxiety their parents believe their children have, through the Screen for Child Anxiety Related Emotional Disorder (SCARED).

Subjects and methods. Participants were 107 children and adolescents, 73 diagnosed with ADHD and 34 with ASD, with ages ranging between 8 and 17 years (91 boys and 16 girls), and their respective fathers or mothers (53 fathers and 54 mothers). All participants completed the corresponding version of the SCARED in the presence of one of the researchers.

Results. The results show differences in anxiety factors. Usually, these differences indicate higher levels of anxiety-both in parents and in children-in children and adolescents diagnosed with ADHD versus those diagnosed with ASD.

Conclusions. There are significant differences between the levels of anxiety shown both by children and adolescents diagnosed with ADHD and those diagnosed with ASD, and in the levels of anxiety perceived by their parents

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Rev Neurol. 2016;62:S85-S91.

INTEGRATING MODEL OF THE SOCIAL ADAPTATION OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Rosello-Miranda B, Berenguer-Forner C, Baixauli-Fortea I, Miranda-Casas A

Introduction. Children with attention deficit hyperactivity disorder (ADHD) experience social difficulties affecting their personal and academic functioning.

Aim. To review the research addressing the influence of cognitive/affective abilities involved in their social adaptation, from the perspective of an integrative model that includes executive functioning, theory of mind and pragmatic language.

Development. Research shows an association between executive functioning (working memory, inhibition, planning), pragmatic abilities, performance in theory of mind tasks, and the social problems experienced by individuals with ADHD.

Conclusions. Although literature supports a relationship between these constructs, deficits observed in theory of mind tasks or language use, seem rather to reflect a procedural deficit than a conceptual impairment

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Rev Neurol. 2016;62:S103-S107.

THE EFFECT OF PASSIVE TACTILE STIMULATION IN THE BRAIN ACTIVITY OF CHILDREN WITH ATTENTION DEFICIT.

Soria-Claros M, Serrano-Marugan I, Quintero J, Ortiz T.

Introduction. The N200 and P300 evoked potentials have proved a useful tool in monitoring children with attention deficit disorder (ADD).

Aim. To assess brain information processing by the N200 and P300 in touch modality in children with ADD.

Subjects and methods. The P300 and N200 components to oddball tactile stimulation paradigm were recorded in an experimental group of 17 children with ADD at the beginning and the end of the daily training tactile stimulation, another 12 children with ADD and 21 control children without ADD who no received tactile stimulation. Three groups aged between 7 and 11 years.
Results. Results show a significant decrease in latency of N200 and P300 waves in the experimental group at the study end. N200 significant differences in the experimental group temporal parietal and occipital areas were found, while the differences in the P300 are located in postcentral and parietal areas.
Conclusion. Systematic, orderly and organized tactile stimulation in children with ADD can be effective to improve N200-P300 latencies providing greater parietal brain plasticity, associated to perceptive attention

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Rev Paul Pediatr. 2016;34:71-77.

FREQUENCY OF OVERWEIGHT AND OBESITY IN CHILDREN AND ADOLESCENTS WITH AUTISM AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Kummer A, Barbosa IG, Rodrigues DH, et al.

OBJECTIVE: To assess the frequency of overweight and obesity in children and adolescents with autism spectrum disorder (ASD) and with attention deficit/hyperactivity disorder (ADHD) and their parents, in comparison with children and adolescents without developmental disorders.
METHODS: Anthropometric measures were obtained in 69 outpatients with ASD (8.4±4.2 years old), 23 with ADHD (8.5±2.4) and 19 controls without developmental disorders (8.6±2.9) between August and November 2014. Parents of patients with ASD and ADHD also had their anthropometric parameters taken. Overweight was defined as a percentile ≥85; obesity as a percentile ≥95; and underweight as a percentile ≤5. For adults, overweight was defined as a BMI between 25 and 30kg/m(2) and obesity as a BMI higher than 30kg/m(2).
RESULTS: Children and adolescents with ASD and ADHD had higher BMI percentile ($p<0.01$) and z-score ($p<0.01$) than controls, and increased frequency of overweight and obesity ($p=0.04$). Patients with ASD and ADHD did not differ between them in these variables, nor regarding abdominal circumference. Parents of children with ASD and ADHD did not differ between themselves.
CONCLUSIONS: Children and adolescents with ASD and ADHD are at a higher risk of overweight and obesity than children without developmental problems in the community

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School Psychology Quarterly. 2016 Mar;31:58-75.

WHICH KINDERGARTEN CHILDREN ARE AT GREATEST RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY AND CONDUCT DISORDER SYMPTOMATOLOGY AS ADOLESCENTS?

Morgan PL, Li H, Cook M, et al.

We sought to identify which kindergarten children are simultaneously at risk of moderate or severe symptomatology in both attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) as adolescents. These risk factor estimates have not been previously available. We conducted multinomial logistic regression analyses of multiinformant ratings by the end of middle school of a population-based, longitudinal sample of children followed from kindergarten to eighth grade (N = 7,456). Kindergarten children from low SES households, those raised by mothers with depressive symptoms or experiencing emotional problems or substance abuse, or those who were punished by spanking were significantly more likely to later display severe levels of ADHD-CD symptomatology in eighth grade. Kindergarten children frequently engaging in ADHD-CD-type behaviors were more likely to later experience both moderate (covariate adjusted OR = 2.37) and severe (covariate adjusted OR = 3.63) ADHD-CD symptomatology. Low academic achievement uniquely increased the risk of both moderate and severe symptomatology (adjusted OR range = 1.7 to 2.24). The results should guide early screening and school-based intervention efforts for ADHD-CD. Reducing children's risk for adolescent ADHD-CD symptomatology may require remediating low behavioral

and academic functioning by the end of kindergarten. When these 2 modifiable factors occur together they increase kindergarten children's odds of experiencing severe ADHD-CD symptomatology in eighth grade by a multiplicative factor of 8.1

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Sleep Med. 2016.

THE LINK BETWEEN PARENT AND CHILD SLEEP DISTURBANCES IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Bar M, Efron M, Gothelf D, et al.

Objective: Although sleep problems are widely known to be a prominent feature of childhood attention deficit/hyperactivity disorder (ADHD), little is known about the link between these difficulties and parental sleep disturbances.

Methods: The design was cross-sectional assessing a clinical sample of 62 children, aged 7-17 years (mean age = 10.0 years) diagnosed with ADHD and their parents. All participants completed measures of ADHD symptoms, sleep, anxiety, and executive functioning.

Results: Regression analysis revealed that child's pre-sleep arousal significantly predicted parental sleep, and that medication status and children's anxiety significantly predicted children's sleep. Children with a clinical sleep score were more impaired in behavioral, emotional, and cognitive domains.

Conclusion: Parents of children with ADHD exhibit sleep disturbances that might be affected by their child's arousal prior to bedtime. The nature of the interaction between children with ADHD and their parents' sleep abnormalities is yet to be elucidated

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Sleep Med. 2016.

SLEEP HABITS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PREDOMINANTLY INATTENTIVE TYPE AND ASSOCIATIONS WITH COMORBID PSYCHOPATHOLOGY SYMPTOMS.

Becker SP, Pfiffner LJ, Stein MA, et al.

Objectives: Much of what is currently known about the sleep functioning of children with attention-deficit/hyperactivity disorder (ADHD) is based on samples of children with ADHD combined type, and no study to date has examined the association between sluggish cognitive tempo (SCT) and sleep functioning in children diagnosed with ADHD. Accordingly, the objectives of this study were to (1) describe the sleep habits of children diagnosed with ADHD predominantly inattentive type (ADHD-I) and (2) examine whether comorbid internalizing, oppositional, and/or SCT symptoms are associated with poorer sleep functioning in children with ADHD-I. This study extends the current literature by using a large, clinical sample of children with ADHD-I to examine the association between SCT and other psychopathology symptoms with children's sleep functioning.

Methods: Participants included 147 children (age: 6-11, 59% male, 55% White) diagnosed with ADHD-I using a semi-structured diagnostic interview. Parents completed measures assessing their child's sleep habits as well as comorbid anxiety, depression, oppositionality, and SCT symptoms.

Results: Fourteen percent of children with ADHD-I obtain less sleep than recommended and 31% have a sleep onset latency of greater than 20 minutes. The few children taking medication for ADHD had a longer sleep onset latency than those without medication. Twenty-seven percent of parents indicated that it is "difficult" to get their child out of bed on school days and 41% of parents indicated that their child needs to catch-up on sleep on the weekend "at least a little". Regression analyses found anxiety and SCT sleepy/tired symptoms to be the most consistent dimensions of psychopathology associated with sleep functioning, with little support for depression or oppositionality being associated with sleep.

Conclusions: A sizeable minority of children with ADHD-I experience impaired sleep. In addition to SCT sleepy/tired symptoms, comorbid anxiety was most consistently associated with poorer sleep functioning in children with ADHD-I. SCT daydreaming and working memory symptoms were unassociated with sleep functioning, and the size of the effects between SCT sleepy/tired and sleep functioning indicates that these are not overlapping constructs. Longitudinal studies are needed to evaluate the interrelations of sleep

problems and comorbid psychopathology symptoms and their impact on the daytime functioning of children with ADHD-I

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Sleep Med. 2016.

ASSOCIATION BETWEEN SLEEP PARAMETERS AND COGNITIVE FUNCTION IN DRUG-NAÏVE CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A POLYSOMNOGRAPHIC STUDY.

Um YH, Jeong JH, Hong SC, et al.

OBJECTIVE: Sleep problems are common among patients with attention-deficit hyperactivity disorder (ADHD), and are considered major causes of behavioral and cognitive dysfunction in ADHD patients. In the present study, we investigated the relationship between sleep parameters and cognitive function in drug-naïve children with ADHD.

METHODS: Twenty-eight patients were recruited to participate in the study, and a polysomnography was used to measure sleep parameters of the subjects. Cognitive measurements were collected, utilizing the Wechsler Intelligence Scale for Children-III (WISC-III), and the Matching Familiar Figure Test for Korean Children (MFFT-KC), while behavioral characteristics of the subjects were assessed using Conners' Global Index-Parent version (CGI-P). Descriptive statistics were calculated for demographic data, sleep parameters, and neurocognitive characteristics of ADHD patients. Spearman's correlation analyses were performed to determine the association between sleep parameters and neurocognitive measures. Moreover, multiple regression analyses were used to identify the best predictors of cognitive function among the various sleep parameters.

RESULTS: The regression analyses revealed several meaningful correlations, suggesting that slow wave sleep, stage 2 sleep, REM sleep, and limb movement index with arousals (LMAs) as predictors of cognitive function in ADHD patients.

CONCLUSION: Based on our study results, sleep parameters and cognitive function were closely associated in ADHD patients; further research should be directed at clarifying this crucial link

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Tijdschr Geneeskd. 2016;72:221-33.

SAFE USE OF STIMULANTS FOR ADHD: MONITORING AND TREATMENT OF SIDE EFFECTS IN CHILDREN AND YOUNGSTERS.

Uytterhoeven L, Danckaerts M.

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder in children and adolescents, who are already being treated with stimulants for decades. Given the significant increase in use for the last 20 years, great concern is expressed about the safety of this medication. A systematic literature search was performed in order to provide an overview of the safety, the adverse effects and the contraindications of stimulants. In addition, the safety considerations to be observed when treatment with stimulants is indicated, are discussed. Recommendations for monitoring are discussed as well. The most frequent side effects, such as sleeping problems and appetite inhibition, occur shortly after initiation of treatment and do not involve major risks. In addition, serious but rare side effects, eg. sudden death and suicidal behavior, were reported, although direct causality has not yet been demonstrated. Also a statistically significant impact on the growth in length has been demonstrated in studies. Stimulants have a protective effect on the development of substance abuse in adolescence. Long-term effects (50-60 years) have not yet been studied. Overall, stimulants have an acceptable safety profile. Still, it remains very important to thoroughly assess the child both before and after the start of medication and observe the safety considerations

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EMBO Molecular Medicine

Lack of kinase-independent activity of PI3Kγ in locus coeruleus induces ADHD symptoms through increased CREB signaling

Ivana D'Andrea[1,†], Valentina Fardella[1,†], Stefania Fardella[1], Fabio Pallante[1], Alessandra Ghigo[2], Roberta Iacobucci[1], Angelo Maffei[1], Emilio Hirsch[2], Giuseppe Lembo[1,3,*] & Daniela Carnevale[1,3,**]

Abstract

Although PI3Kγ has been extensively investigated in inflammatory and cardiovascular diseases, the exploration of its functions in the brain is just at dawning. It is known that PI3Kγ is present in neurons and that the lack of PI3Kγ in mice leads to impaired synaptic plasticity, suggestive of a role in behavioral flexibility. Several neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), involve an impairment of behavioral flexibility. Here, we found a previously unreported expression of PI3Kγ throughout the noradrenergic neurons of the locus coeruleus (LC) in the brainstem, serving as a mechanism that regulates its activity of control on attention, locomotion and sociality. In particular, we show an unprecedented phenotype of PI3Kγ KO mice resembling ADHD symptoms. PI3Kγ KO mice exhibit deficits in the attentive and mnemonic domains, typical hyperactivity, as well as social dysfunctions. Moreover, we demonstrate that the ADHD phenotype depends on a dysregulation of CREB signaling exerted by a kinase-independent PI3Kγ-PDE4D interaction in the noradrenergic neurons of the locus coeruleus, thus uncovering new tools for mechanistic and therapeutic research in ADHD.

Keywords catecholamine; CREB; mouse model; phosphodiesterases (PDEs); stereotactic surgery

Subject Category Neuroscience

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EMBO Mol Med (2015) 7: 904–917

See also: **E Darcq & BL Kieffer** (July 2015)

Introduction

Phosphoinositide 3-kinases (PI3Ks) are intracellular signaling enzymes activated by various cell-surface receptors, modulating important cellular functions, such as cell survival, proliferation, migration and adhesion (Toker & Cantley, 1997; Bondeva *et al*, 1998). PI3Ks are grouped into three classes on the basis of their structural and biochemical features, and among these, the class I, further divided into IA and IB, has been the most extensively studied. The class IB (PI3Kγ) is composed by the single p110γ catalytic subunit, which is linked to the regulation of G protein-coupled receptor signaling (Stoyanov *et al*, 1995; Patrucco *et al*, 2004) and acting with a dual mechanism involving both kinase-dependent and kinase-independent activities (Carnevale & Lembo, 2012). It has been well demonstrated that PI3Kγ is expressed in the immune and cardiovascular systems, and more recently in the brain (Toker & Cantley, 1997; Oudit *et al*, 2004; Viard *et al*, 2004; Kok *et al*, 2009). However, although PI3Kγ has been extensively investigated in inflammatory and cardiovascular diseases, the exploration of its functions in the brain is just at dawning. On this issue, many years ago, it has been shown that PI3Kγ is present in neurons and that its Akt/PKB signaling is required for the potentiation of L-type channels and for changes in neuronal excitability (Viard *et al*, 2004). More recently, it has been shown that the lack of PI3Kγ in mice leads to an impairment in synaptic plasticity, associated with alterations suggestive of a role in mediating behavioral flexibility (Kim *et al*, 2011).

Several neuropsychiatric disorders, among which schizophrenia, attention-deficit/hyperactivity disorder (ADHD) and behavior addictions are the most common, involve an impairment of behavioral flexibility (Laughlin *et al*, 2011), with related symptoms principally attributed to combined deficits in alerting executive control, involving the prefrontal cortex and the striatum. The resulting poor inhibitory control seems to depend on variations in the monoaminergic system dynamics and particularly on the reciprocal interactions between catecholamines, particularly dopamine (DA) and noradrenaline (NA) (Thapar *et al*, 2005).

Here, we found a previously unreported expression of PI3Kγ throughout the noradrenergic neurons of the locus coeruleus (LC) in the brainstem, serving as a mechanism that regulates its activity of control on attention, locomotion and sociality. Mice with genetic

1 Department of Angiocardioneurology and Translational Medicine, IRCCS Neuromed, Pozzilli (IS), Italy
2 Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Torino, Italy
3 Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy
*Corresponding author. Tel: +39 0865 929644; Fax: +39 0865 927575; E-mail: lembo@neuromed.it
**Corresponding author. Tel: +39 0865 929614; Fax: +39 0865 927575; E-mail: daniela.carnevale@neuromed.it
†These authors contributed equally to this work

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ablation of PI3Kγ exhibit an unprecedented phenotype that mimics the core symptoms of ADHD: They display deficits in attentive domain and are hyperactive, together with an unbalanced catecholaminergic activity in the fronto-striatal areas, receiving projections from the LC. Finally, we propose a novel molecular mechanism that regulates the LC function, mediated by PI3Kγ through a kinase-independent activity and controlling PDE4D to keep homeostatic levels of cAMP. Interestingly, it is conceivable that this mechanism may be relevant for other psychiatric conditions linked to a malfunctioning of the LC, such as chronic stress, opiate addiction and depression.

Results

PI3Kγ is expressed in the noradrenergic neurons of the LC

We observed a previously unreported strong expression of PI3Kγ throughout the locus coeruleus (LC) in the brainstem (Fig 1A). In particular, tyrosine hydroxylase (TH)- and dopamine-β-hydroxylase (DBH)-positive cells, characterizing noradrenergic neurons, express PI3Kγ (Fig 1A). The noradrenergic LC mediates a control function on attention, sociality, arousal and activity, which are behavioral states having also a profound impact on cognition, involving the prefrontal cortex (PFC) and the striatum (STR) (Biederman & Spencer, 1999; Berridge & Waterhouse, 2003). Thus, we aimed at assessing the role of PI3Kγ signaling on the behavioral states regulated by the LC and, in order to accomplish this issue, we performed a series of behavioral tests that engage this pathway (Supplementary Table S1).

PI3Kγ KO mice display poor ability in set-shifting attention

In the first place, we investigated the cognitive responses of PI3Kγ KO mice in the attentional domain, through attentional set-shifting (ASS) test. ASS, adapted to animal models from the original human version, requires attending to relevant stimuli while ignoring irrelevant ones and subsequently shifting the allocation of attention, either within 'dimensions' or between 'dimensions' (Supplementary Tables S2 and S3) (Colacicco *et al*, 2002). Accordingly, mice from all groups required a smaller number of trials to learn simple (SD) and compound (CD) discrimination, compared to other tasks (Fig 1B). Conversely, when both intra- and extra-dimensional shift tasks (respectively, IDS and EDS) were required, PI3Kγ KO mice needed a significantly higher number of trials to reach the criterion, as compared to WT, suggesting poorer ability in set-shifting attention (Fig 1B). This conclusion was also confirmed by the higher number of perseverative errors, considered as a measure of disengaging from an old rule to a new one (Fig 1C). Moreover, PI3Kγ KO required significantly more trials in all the reversal tasks (Fig 1B), thus suggesting an impaired behavioral flexibility.

PI3Kγ KO mice are hyperactive

Because the LC neurons that project to the PFC may influence spontaneous physical activity, we hypothesized that the presence of PI3Kγ in this brainstem region may also serve as a regulator of this behavioral state. When we tested PI3Kγ KO and WT mice in the open field (OF), PI3Kγ KO displayed significantly greater locomotor activity, manifesting a clear hyperactive phenotype, as shown by distance moved, crossing and vertical activity (Fig 1D–F). The increased activity was also evident in the movement trace patterns: While WT mice moved in a circular fashion following the arena diameter, PI3Kγ KO tended to move with many short stops, frequently changing direction (Fig 1G). No differences emerged in the anxiogenic thigmotaxis behavior (i.e. time spent close to the wall; Supplementary Fig S1).

Attention deficit and hyperactivity of PI3Kγ KO mice are rescued by MPH

These behavioral phenotypes of PI3Kγ KO mice mimic the core symptoms of ADHD, one of the most prevalent human psychiatric disorders, more recently attributed also to an impairment of LC function (Biederman & Spencer, 1999; Berridge & Waterhouse, 2003). Thus, we hypothesized that methylphenidate (MPH), the drug of choice for the symptomatic treatment of ADHD (Mehta *et al*, 2004) that rescues as well the corresponding behavior in animal models of ADHD (Gray *et al*, 2007; Cao *et al*, 2012) would normalize the phenotype of PI3Kγ KO mice. We found that MPH significantly improved the attention deficit of PI3Kγ KO mice, as evaluated in the ASS test (Fig 1B and C). In particular, PI3Kγ KO mice treated with MPH needed a reduced number of trials to reach the criterion

Figure 1. PI3Kγ KO mice show attention deficit and hyperactive behavior rescued by MPH.

A PI3Kγ (green) is constitutively expressed in TH (red)- and DBH (yellow)-positive noradrenergic neurons of the LC. Scale bar, 50 μm. Images are representative of 4 independent experiments.

B Number of trials to reach the criterion in ASS: CD Re **P* = 0.00057 (KO veh vs WT veh), **P* = 0.00012 (KO veh vs KO MPH), **P* = 0.0053 (KO veh vs WT MPH); IDS **P* = 0.0048 (KO veh vs WT veh), **P* = 0.00012 (KO veh vs KO MPH), **P* = 0.0011 (KO veh vs WT MPH); IDS Re **P* = 0.026 (KO veh vs WT veh), **P* = 0.0008 (KO veh vs KO MPH), **P* = 0.0043 (KO veh vs WT MPH); EDS and EDS Re **P* < 0.000001 (KO veh vs all other groups).

C Typology of errors during ASS. **P* < 0.000001 (KO veh vs all other groups).

D Distance moved in OF. **P* < 0.000001 (KO veh vs all other groups).

E Number of crossing in OF: 5-min blocks 1: **P* = 0.000001 (KO veh vs WT veh), **P* = 0.000004 (KO veh vs KO MPH), **P* = <0.000001 (KO veh vs WT MPH); 5-min blocks 2: ***P* = 0.000002 (KO veh vs WT veh), **P* = 0.00002 (KO veh vs KO MPH), **P* = 0.00003 (KO veh vs WT MPH); 5-min blocks 3: **P* = < 0.000001 (KO veh vs all other groups).

F Vertical activity in OF: 5-min blocks 1: **P* = 0.000002 (KO veh vs WT veh), **P* < 0.000001 (KO veh vs KO MPH), **P* < 0.000001 (KO veh vs WT MPH); 5-min blocks 2: **P* = 0.0034 (KO veh vs WT veh), **P* = 0.00013 (KO veh vs KO MPH), **P* = 0.00015 (KO veh vs WT MPH).

G Video tracking showing moving traces of a representative mouse for each group during OF.

Data information: Data were analyzed by ANOVA for repeated measures followed by Bonferroni's *post hoc* test, *n* = 8. Data are means ± SEM.

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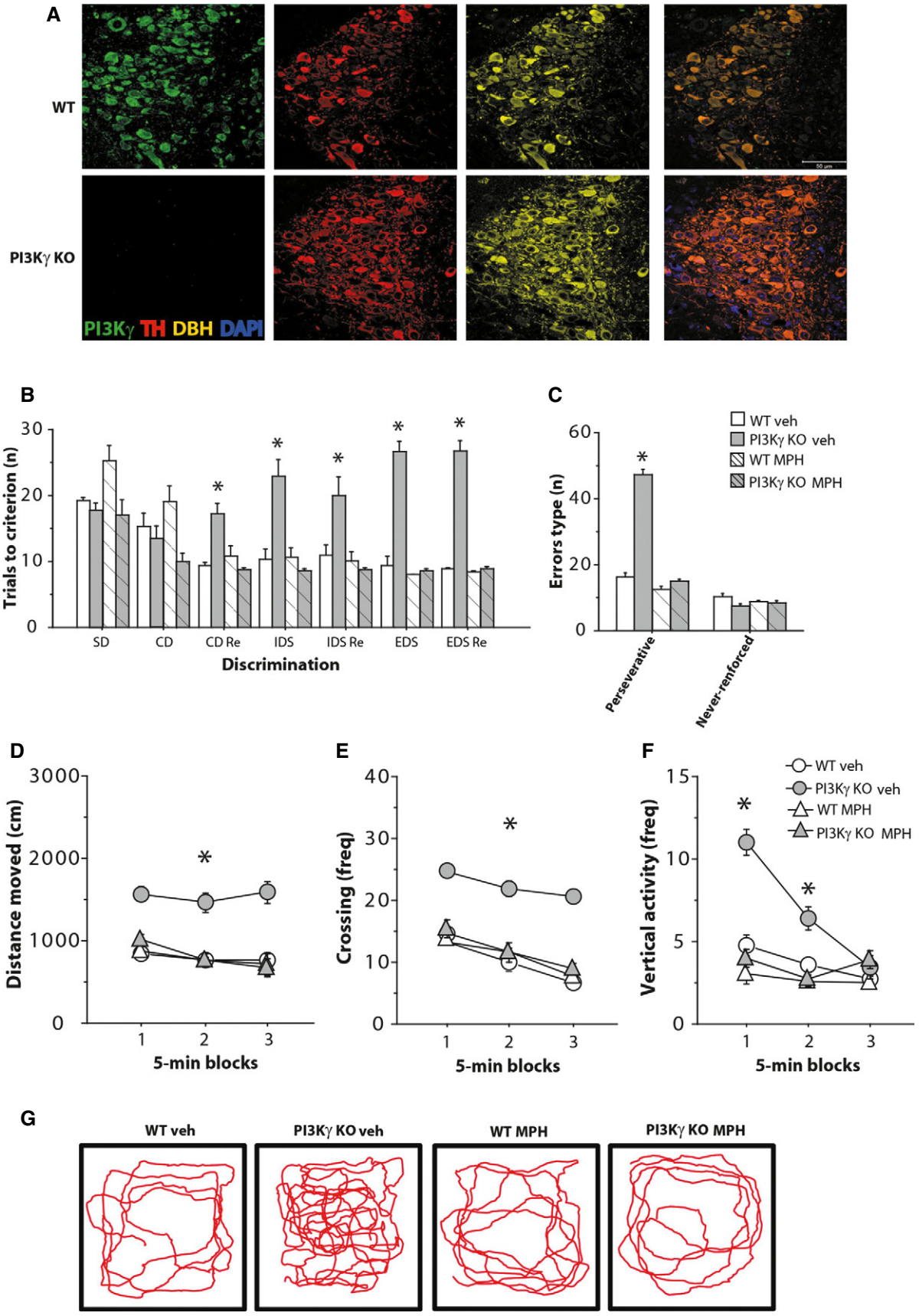

Figure 1.

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(Fig 1B), with less perseverative errors (Fig 1C). WT mice did not show significant alterations after MPH treatment, according to previous studies using similar chronic dosage (Koda *et al*, 2010). Moreover, the MPH treatment suppressed the hyperactivity of PI3Kγ KO, restoring locomotion to levels comparable to that of WT mice (Fig 1D–G).

Impaired memory in PI3Kγ KO mice

Attention-deficit/hyperactivity disorder patients usually show cognitive deficits in different behavioral patterns. Accordingly, mouse models of ADHD also display impaired memory (Won *et al*, 2011). When we evaluated PI3Kγ KO mice in the Morris water maze (MWM), which tests the spatial memory, we found that, during the acquisition phase, all mice significantly reduced the latency to find the platform (Fig 2A), indicating that PI3Kγ did not affect the normal processes of learning. However, in the probe phase, performed the day after the last acquisition trial, PI3Kγ KO spent significantly less time than WT mice in the quadrant where the platform was located before, indicating an impaired memory of platform location (Fig 2B). With regard to the other parameters considered in this analysis, PI3Kγ KO covered more distance and moved faster, as compared to WT mice (Supplementary Fig S2A and B), further supporting their hyperactive phenotype. During both the acquisition and the probe phases, no difference was found in the anxiogenic thigmotaxis behavior among the experimental groups (Supplementary Fig S2C and D).

PI3Kγ KO mice show poor social skills with conspecifics

The ADHD psychopathology also unveils poor social adjustment, mainly as a consequence of stigmatization by peers. Thus, we investigated the spontaneous social behavior (SSB) in the home cage, in mice housed each one with a familiar cage mate, during two consecutive days exploiting a procedure known to challenge the social hierarchy (D'Andrea *et al*, 2007). As expected, WT mice modified their behavior according to the change in social hierarchy (Fig 2C and D; Supplementary Fig S3A and B). By contrast, PI3Kγ KO mice spent less time interacting with a conspecific (Fig 2C; Supplementary Fig S3A) and showed an abnormal aggressive grooming (Fig 2D; Supplementary Fig S3B), independently from the environmental challenge. Moreover, also in this test, PI3Kγ KO mice showed a significant increase in the locomotor activity, as compared to WT mice (Supplementary Fig S4A and B). Interestingly, when mice were tested in the elevated plus maze (EPM) test to specifically assess anxiety-like behavior, no difference emerged between two groups (Supplementary Fig S5), suggesting that the higher locomotion observed in PI3Kγ KO mice does not reflex an alteration in the emotional response, but is suggestive of a hyperactive phenotype.

ADHD-like behaviors of PI3Kγ KO mice depend on a kinase-independent mechanism

During the past years, PI3Kγ has been characterized as an enzyme that can act in a dual manner with kinase-dependent and

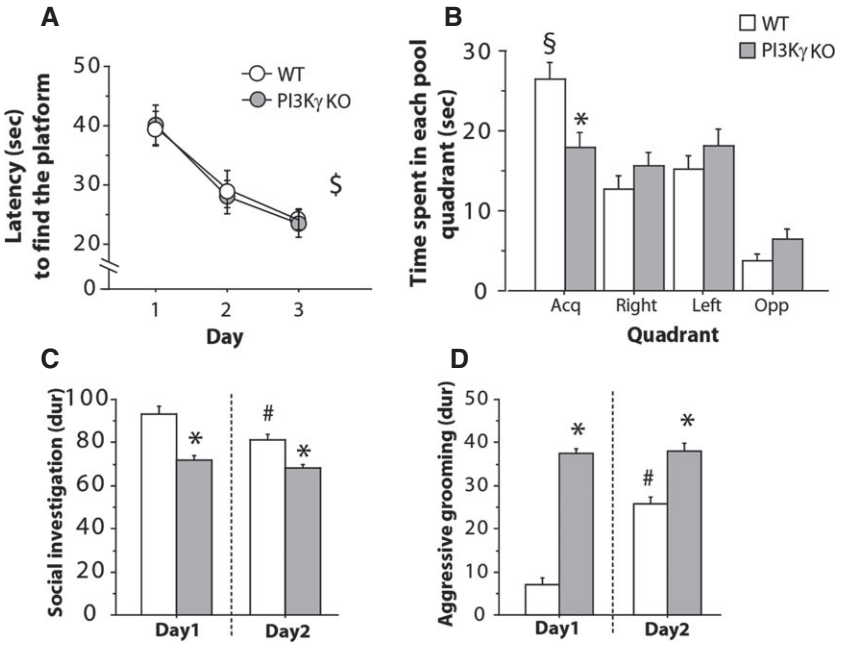

Figure 2. PI3Kγ KO mice display cognitive impairment and poor social skills.

A, B Learning curve in MWM (A) ($^{\$}P < 0.000001$ main effect of time) and probe test for memory retention of MWM test (B) ($^{*}P = 0.0029$, KO vs WT; $^{\S}P = 0.000052$ vs all other quadrants). ANOVA for repeated measures followed by Bonferroni's *post hoc* test, $n = 16$. Data are means ± SEM.

C, D Home cage spontaneous social behavior (SSB) showing duration of (C) social investigation, that is, sniffing and grooming the partner in all body regions indicative of affiliative behavior ($^{*}P = 0.00002$, 0.0011 KO vs WT at day 1 and day 2, respectively; $^{\#}P = 0.023$ day 2 vs day 1) and (D) aggressive grooming, that is, violent grooming of the animal on the back of the partner ($^{*}P < 0.000001$, 0.000009 KO vs WT at day 1 and day 2, respectively; $^{\#}P < 0.000001$ day 2 vs day 1). ANOVA for repeated measures followed by Bonferroni's *post hoc* test, $n = 10$. Data are means ± SEM.

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kinase-independent activities (Patrucco *et al*, 2004; Viard *et al*, 2004; Perino *et al*, 2014). The kinase activity of PI3Kγ is mainly linked to the generation of phosphoinositide (3,4,5)-trisphosphate (PIP3), whereas its kinase-independent actions principally affect cAMP levels through the modulation of specific phosphodiesterases (PDEs), the only means of degrading cAMP and maintaining its homeostasis (Patrucco *et al*, 2004; Damilano *et al*, 2011; Perino *et al*, 2011; Ghigo *et al*, 2012). In order to identify the contribution of kinase-dependent and kinase-independent activities of PI3Kγ, we tested the knock-in mouse model expressing a kinase-dead form of PI3Kγ (PI3Kγ KD) (Supplementary Fig S6). Interestingly, PI3Kγ KD exhibited no alterations of the behavioral phenotype both in the attention domain (Supplementary Fig S6A and B) and in the locomotor activity (Supplementary Fig S6C–E), which were clearly overlapping to that of WT mice, suggesting that the ADHD-like behaviors showed by PI3Kγ KO mice should be mediated by a kinase-independent mechanism.

PI3Kγ in the LC control PDE4D activity

Interestingly, cAMP levels are the main regulator of the LC function (Nestler & Aghajanian, 1997; Han *et al*, 2006). Since the lack of PI3Kγ, but not of its kinase activity, affects the brain domains organized and regulated by the noradrenergic LC, we reasoned that a mechanism affecting cAMP metabolism in the LC could be engaged in our model. Several isoforms of PDEs are known, but PDE4 is the cAMP-specific PDE that is prevalent in the brain (Kleppisch, 2009). Interestingly, PI3Kγ is also a critical activator of membrane-bound PDE4 in the myocardium (Ghigo *et al*, 2012). Thus, we examined whether PI3Kγ controls PDE4 in the LC. The major PDE4 isoenzymes of the mouse brain were immunoprecipitated from membrane and cytosolic fractions of PI3Kγ KO, KD and WT LC punches, and IP pellets were assayed for cAMP PDE activity (Fig 3A). The catalytic activity of particulate and soluble PDE4D was significantly lower in PI3Kγ KO than in WT tissues, whereas no difference was found in PI3Kγ KD as compared to WT (Fig 3A). PDE4A and PDE4B activities were unchanged in PI3Kγ KO (Fig 3A). Thus, the presence of PI3Kγ is required to selectively control PDE4D activity in both membrane and cytosolic compartments of the LC (Fig 3A). The finding that PDE4D physically interacts with PI3Kγ when we immunoprecipitated this latter from LC punches (Fig 3B) further strengthens the evidence that suggest that PI3Kγ signaling in the LC controls cAMP levels and homeostasis through PDE4D.

Lack of PI3Kγ turns into an increased CREB signaling in the LC and catecholaminergic activity in projection areas

The LC neuronal excitability is regulated by the activation status of the transcription factor cAMP response element binding protein (CREB) and its binding to the promoter of target genes (Nestler & Aghajanian, 1997; Han *et al*, 2006; Cao *et al*, 2010). Thus, we conceived that the reduced PDE4D activity observed in PI3Kγ KO could turn into dysregulated cAMP and increased CREB activation. Indeed, we found and increased pCREB/CREB in the LC of PI3Kγ KO (Fig 3C–E), suggestive of an increased activation of the noradrenergic activity of the LC, possibly determining an inhibitory effect on the dopaminergic transmission in the projecting brain areas. Accordingly, we measured NA and DA in PFC and STR, finding a significant increase in NA, with a concomitant reduction in DA (Fig 3F). Conversely, both NA and DA remained unchanged in the LC of PI3Kγ KO mice (Fig 3F). In order to exclude the possibility that the NA/DA balance in projecting areas could be due to other areas controlling the monoaminergic system, we evaluated the presence of PI3Kγ in the substantia nigra (SN) and in the ventral tegmental area (VTA), the major sources of dopaminergic neurons. As shown in Supplementary Fig S7A, we did not find expression of PI3Kγ in dopaminergic neurons of both SN and VTA (Supplementary Fig S7A).

Selective inhibition of CREB in the LC rescues the ADHD-like behavior of PI3Kγ KO mice

It has been reported that *in vivo* blockade of CREB activity in the LC prevents its neuronal hyperexcitability (Han *et al*, 2006). In order to better understand the role of the PI3Kγ-mediated regulation of cAMP–CREB signaling in the LC, we selectively injected the LC of PI3Kγ KO mice with an adeno-associated viral vector carrying dnCREB or GFP alone as a control, by bilateral stereotactic surgery (Fig 4A; Supplementary Fig S8). Three weeks later, we obtained an effective expression of the viral vector (Fig 4A). We found that, by antagonizing CREB in the LC, we were able to rescue the attention deficit (Fig 4B and C) and the hyperactivity (Fig 4D–F), displayed by PI3Kγ KO mice, while ameliorating their poor social skills (Fig 4G and H; Supplementary Fig S9). Moreover, we found a restoration of the NA/DA unbalance in the PFC and STR in PI3Kγ KO mice injected with AAVdnCREB, as compared to PI3Kγ KO AAVGFP control mice (Supplementary Fig S10).

Figure 3. Lack of PI3Kγ in the LC dysregulates PDE4D independently from kinase activity and consequent cAMP–CREB activation.

A Kinase-independent activity of PI3Kγ selectively regulates PDE4D activity in both membrane (mem) and cytosolic (cyt) compartments of LC (*P = 0.015 and *P = 0.046 in mem and cyt vs WT and $^{\#}P$ = 0.0037 and $^{\#}P$ = 0.030 in mem and cyt vs KO; ANOVA followed by Bonferroni's *post hoc* test, n = 5). Data are means ± SEM.

B PI3Kγ is constitutively associated with PDE4D, as shown by the co-IP of the two proteins in homogenates from bilateral LC punches (n = 5 for each experimental group).

C, D CREB (C, red) expression and pCREB (D, red) expression in TH (yellow)-positive noradrenergic neurons of the LC in PI3Kγ KO and WT mice (n = 5 for each experimental group). Scale bar, 50 μm.

E WB analysis of nuclear/cytosol extract from LC punches of PI3Kγ KO and WT mice, showing increased levels of pCREB in the nucleus of KO LC (n = 5 for each experimental group).

F Levels of NA and DA in LC and PFC/STR of PI3Kγ KO and WT mice (unpaired two-tailed Student's t-test, n = 8, *P = 0.033 NA in PFC and STR; *P = 0.029 DA in PFC and STR). Data are means ± SEM.

Source data are available online for this figure.

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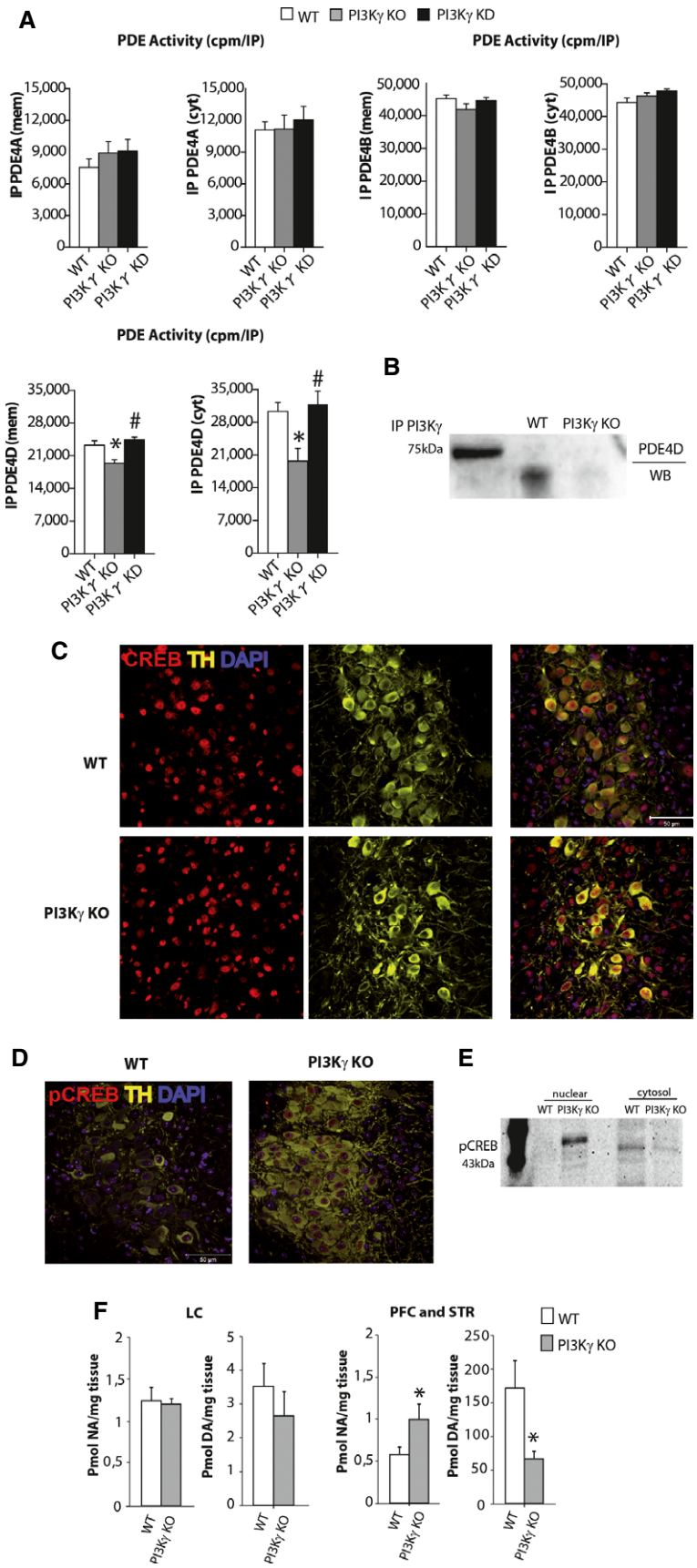

Figure 3.

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Constitutive activation of CREB in the LC of WT mice resembles ADHD-like phenotype

In order to assess further the relevance of the cAMP–CREB signaling in the behavioral alterations related to ADHD, we overexpressed a constitutively active CREB in the LC of WT mice, by an adeno-associated viral vector carrying caCREB (or GFP as a control), as described above. Interestingly, WT mice with AAVcaCREB induced behavioral alterations overlapping those observed in PI3Kγ KO mice. In particular, they needed more trials to reach the criterion (Fig 5A) and made more perseverative errors (Fig 5B) in the ASS compared to AAVGFP control mice. Moreover, AAVcaCREB mice were hyperactive (Fig 5C–E) and displayed poor social skills (Fig 5F and G; Supplementary Fig S11). Further supporting the ADHD-like phenotype, we found that the injection of AAVcaCREB in WT mice induced an alteration of NA and DA in the PFC and STR (Supplementary Fig S12) similar to that observed in PI3Kγ KO mice. Overall, these results clearly associate the ADHD phenotype, previously characterized in PI3Kγ KO mice, to a dysfunction of the cAMP–CREB pathway in LC.

Discussion

In the present work, we have identified that PI3Kγ in the brainstem is expressed in the LC and that its absence reproduces typical ADHD-like behaviors. In particular, PI3Kγ KO mice exhibit deficits in sustained attentional shifting capacity and are hyperactive. In addition, PI3Kγ KO mice show impaired spatial memory and social dysfunctions characterized by poor skills and competences with conspecifics. This behavioral phenotype is accompanied with neurochemical alterations, reflected by an unbalanced catecholaminergic activity in the PFC and STR, the brain areas receiving projections from the LC.

The diagnostic criteria in ADHD are currently based on behavioral symptoms rather than on molecular or neuroanatomical indicators. Thus, the development of mouse models recapitulating all the behavioral features of such disease is crucial to study the molecular bases underlying ADHD etiology. However, since ADHD is a heterogeneous disorder, suggested to result from combinations of genetic and environmental factors, we should be careful when translating behavioral data from animal models to humans. Murine models can mimic only certain aspect of the complex symptomatology of ADHD, but may still provide feasible hypotheses regarding the underlying causes of specific ADHD symptoms. Novel insights into disease mechanisms could be the only means for the design of targeted therapeutic treatments that indeed, so far, are mainly based on drugs that mildly relieve from some of the symptoms.

Catecholamines have an essential role in the emergence of ADHD. Despite several works focused on DA, it is known that also NE strongly affects cognitive abilities via postsynaptic α2A-adrenoreceptors (α2A-ARs) (Arnsten & Goldman-Rakic, 1985). Indeed, NA activation is known to profoundly affect the performance of attention, especially the maintenance of arousal, a cognitive function known to be poor in ADHD (Biederman & Spencer, 1999). In the present study, the molecular analysis of PI3Kγ KO mice revealed a main mechanism, involving LC-NA system leading to an increased NA transmission in fronto-striatal structures, predominantly regulated by NA neurons, able to exert an inhibitory control over DA transmission. This neurobiological perspective fits very well with the current neuropsychological, genetic, imaging and pharmacological data emerging in ADHD research, providing compelling support for a noradrenergic hypothesis of ADHD and demonstrating that very high levels of catecholamine release disrupt cognitive functions of the PFC (Arnsten & Goldman-Rakic, 1985; Franowicz *et al*, 2002). Our findings show that this mechanism is mediated by the constitutive presence of PI3Kγ in the LC where, through a kinase-independent mechanism, it controls PDE4D activity to keep homeostatic levels of cAMP. A balanced cAMP–CREB signaling pathway is well known to be needed for a proper working of the LC.

The ultimate goal of understanding the pathophysiology of the disorder is to develop therapeutic interventions, which would improve or restore physiological brain activity and, ultimately, lead to a rescue of the behavioral phenotype. Here, we have showed that a tonic upregulation of cAMP–CREB activity in the LC of PI3Kγ KO mice turns into a behavioral phenotype having face validity with ADHD symptoms. Interestingly, a selective genetic intervention obtained by a stereotaxis-driven inoculation of AAV carrying dnCREB in the LC rescued such behavioral alterations in PI3Kγ KO mice. Finally, the same stereotaxis manipulation, applied for inoculation of AAV overexpressing CREB in WT LC, reproduces the ADHD-like phenotype observed in PI3Kγ KO mice. These findings sustain the hypothesis whereby PI3Kγ controls NA transmission of the LC, by regulating the homeostasis of cAMP levels and the

Figure 4. Selective inhibition of CREB in the LC rescues the ADHD-like behaviors of PI3Kγ KO mice.

A Target sites of viral injection are shown in black in the section of brain atlas map comprising LC. GFP expression in the injected site of a representative animal shown at two different magnification scales.

B Number of trials to reach the criterion in ASS: CD Re $*P = 0.0028$ and 0.0021 vs WT AAVGFP and KO AAVdnCREB; EDS Re $*P = 0.000003$ and 0.000009 vs WT AAVGFP and KO AAVdnCREB; in the all other tasks: $*P < 0.000001$ (KO AAVGFP vs other two groups).

C Typology of errors in ASS test: $*P = < 0.000001$ vs other two groups.

D Distance moved in OF: 5-min blocks 1 and 2: $*P < 0.000001$ vs other two groups; 5-min blocks 3: $*P = 0.0032$, 0.000029 (KO AAVGFP vs WT AAVGFP and KO AAVdnCREB, respectively).

E Number of crossing in OF: $*P < 0.00001$ KO AAVGFP vs other groups.

F Vertical activity in OF: 5-min blocks 1: $*P = 0.000009$ (KO AAVGFP vs WT AAVGFP), 0.000057 (KO AAVGFP vs KO AAVdnCREB); 5-min blocks 2: $*P = 0.0014$ (KO AAVGFP vs WT AAVGFP) and 0.00035 (KO AAVGFP vs KO AAVdnCREB).

G, H SSB showing duration of (G) social investigation (day 1: $*P = 0.000044$ and 0.00010, KO AAVGFP vs WT AAVGFP and KO AAVdnCREB, respectively) and (H) aggressive grooming (day 1: $*P = 0.00020$ and 0.011, KO AAVGFP vs WT AAVGFP and KO AAVdnCREB, respectively; day 2: $*P = 0.00019$ and 0.00068, KO AAVGFP vs WT AAVGFP and KO AAVdnCREB, respectively; $^{\#}P = 0.0015$ day 2 vs day 1).

Data information: ANOVA for repeated measures followed by Bonferroni's *post hoc* test, $n = 10$. Data are means ± SEM.

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consequent activity of CREB transcription factor, the main regulator of LC neuronal excitability.

Overall, our results propose a novel molecular mechanism that regulates the LC function and is mediated by the constitutive presence of PI3Kγ through a kinase-independent activity that controls PDE4D to keep homeostatic levels of cAMP. Besides the relevance of this pathway in ADHD and the perspective to use PI3Kγ KO mice as a model of ADHD, our findings put perspective into a novel molecular pathway that balances the homeostasis of cAMP in the LC, allowing its relay activity, known to be important also in chronic perturbations, such as chronic stress, opiate addiction and depression (Nestler & Aghajanian, 1997; Mazei-Robison & Nestler, 2012).

Further supporting an essential role of PI3Kγ in the phenotypes related to behavioral flexibility, it has also been reported a genetic

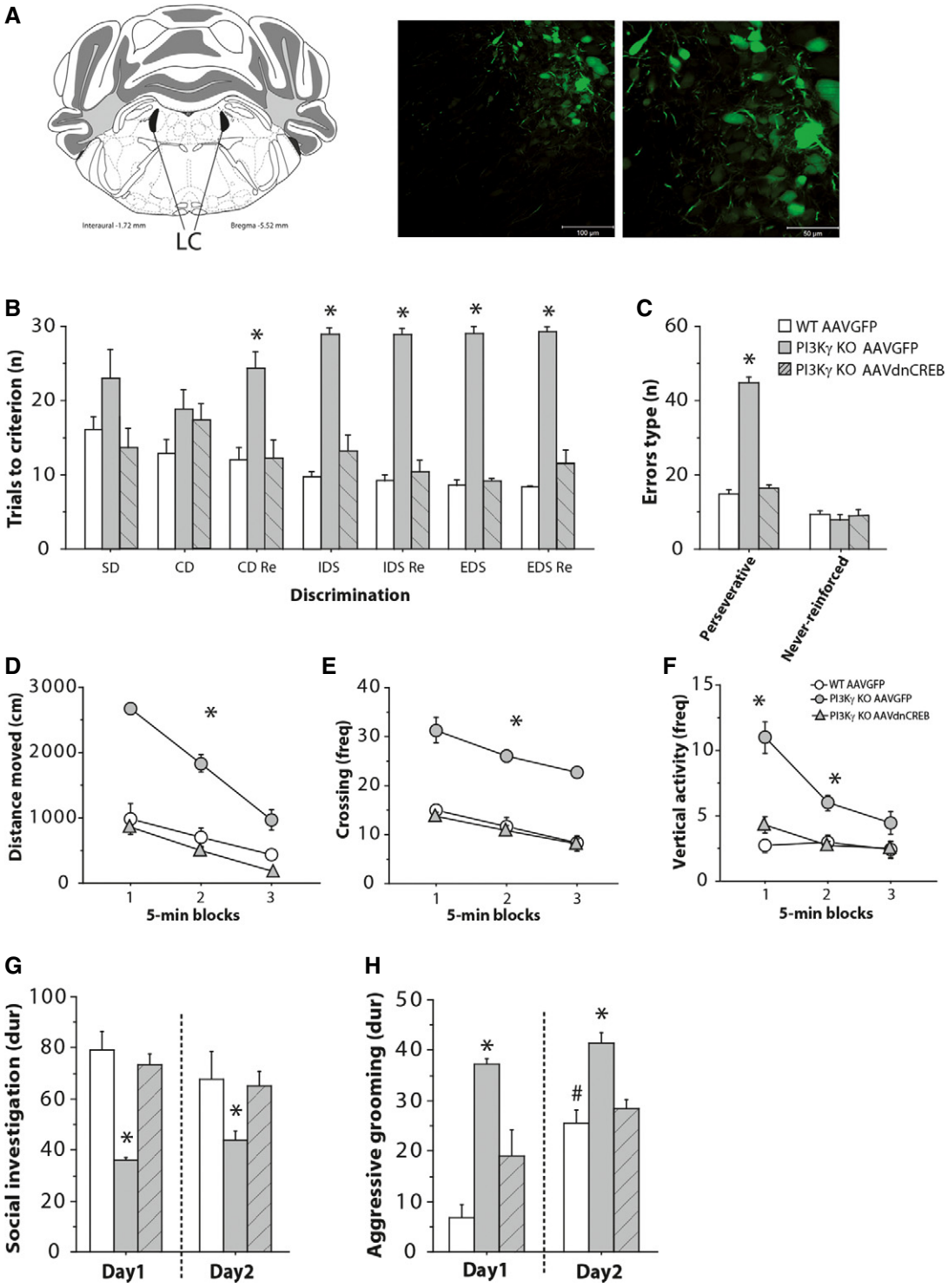

Figure 4.

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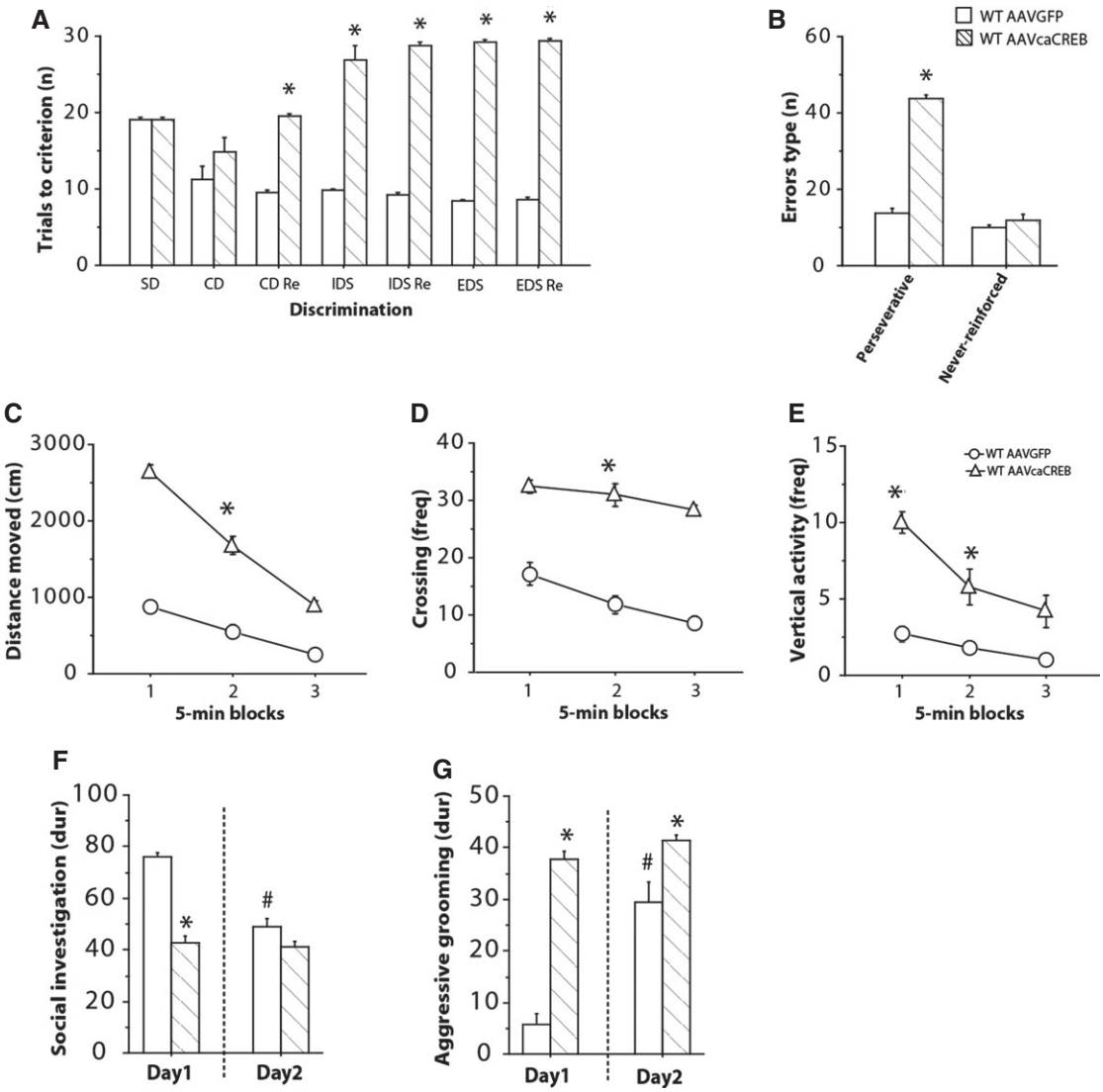

Figure 5. Selective overexpression of a constitutively active CREB in the LC induces ADHD-like behaviors in WT mice.

A Number of trials to reach the criterion in ASS: CD Re, IDS, IDS Re, EDS, EDS Re: $*P < 0.000001$, WT AAVcaCREB vs WT AAV-GFP.

B Typology of errors in ASS test: $*P < 0.000001$, WT AAVcaCREB vs WT AAV-GFP.

C Distance moved in OF: 5-min blocks 1 and 2: $*P < 0.000001$; 5-min blocks 3: $*P = 0.000078$, WT AAVcaCREB vs WT AAV-GFP.

D Number of crossing in OF: 5-min blocks 1: $*P = 0.000001$; 5-min blocks 2: $*P = 0.000001$; 5-min blocks 3: $*P = 0.000001$, WT AAVcaCREB vs WT AAVGFP.

E Vertical activity in OF: 5-min blocks 1: $*P = 0.000008$; 5-min blocks 2: $*P = 0.016$, WT AAVcaCREB vs WT AAVGFP.

F, G SSB showing duration of (F) social investigation ($*P = 0.000001$, WT AAVcaCREB vs WT AAVGFP; $^{\#}P = 0.000007$ day 2 vs day 1) and duration of (G) aggressive grooming ($*P < 0.000001$ and $*P = 0.017$, WT AAVcaCREB vs WT AAVGFP on day 1 and day 2 respectively; $^{\#}P = 0.000022$ day 2 vs day 1).

Data information: Data were analyzed by ANOVA for repeated measures followed by Bonferroni's *post hoc* test, $n = 5$. Data are means ± SEM.

link between PI3Kγ dysfunction and mental disorders, particularly autism. Indeed, the gene encoding PI3Kγ, *PI3KCG*, is located within the autism susceptibility locus *AUTS1* on chromosome 7q22 (Kratz *et al*, 2002; Serajee *et al*, 2003). On this issue, it is important to notice that, for long time, autism and, more in general, autism spectrum disorders (ASD) have been considered somewhat completely distinct from ADHD. However, this belief has been reevaluated when many observational data brought to light a frequent co-occurrence of the two conditions, opening the possibility that some symptoms found in ASD meet also the criteria of ADHD. With our findings that strongly suggest PI3Kγ as a crucial player of ADHD, we propose that the relationship between this psychiatric syndrome and ASD needs a more profound molecular and mechanistic investigation in mouse models, in order to open novel therapeutic perspectives.

Materials and Methods

Mice

PI3Kγ-deficient (PI3Kγ KO) mice used in all experiments were either in a 129Sv/Pas or in a C57Bl/6J background; knock-in with

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catalytically inactive PI3Kγ (PI3Kγ KD) mice was on C57Bl/6J background. PI3Kγ KO, PI3Kγ KD and their respectively wild-type (WT) control mice were generated as previously described (Patrucco *et al*, 2004; Kok *et al*, 2009; Perino *et al*, 2011; Carnevale & Lembo, 2012; Ghigo *et al*, 2012). The main phenotype of PI3Kγ KO mice, that is, ADHD, was present and comparable in both strains. Accordingly, we used PI3Kγ KO mice in the C57Bl/6J background as matched experimental group of PI3Kγ KD, whereas we carried out all the other experiments on 129Sv/Pas background.

The animals, aged 6–8 weeks, were housed in an air-conditioned room (temperature 21 ± 1°C, relative humidity 60 ± 10%) with lights on from 08.00 to 20.00 h, in same-sex groups of 4 individuals in 42 × 17 × 14 cm Plexiglas boxes with a metal top and sawdust as bedding, and with pellet food (Enriched standard diet, Riper, Vandoies, BZ, Italy) and tap water *ad libitum*. Regarding the number of mice used for each experimental setting, we referred to sample sizes commonly used for the same kind of studies. All animal handling and experimental procedures were performed according to the European Community guidelines (EC Council Directive 2010/63) and the Italian legislation on animal experimentation (Decreto L.vo 116/92). The protocol was approved by the Italian Ministry of Health (Permit number 58/2012-B). All efforts were made in order to minimize suffering. In particular, the principles of Replacement, Reduction and Refinement (i.e., the 'three Rs') have been applied to all experiments.

Behavioral tests

Ten mice per genotype were evaluated for each behavioral test. All tests were carried out between 09.30 and 16.30 h, by blinded investigators. Animals were transferred to the experimental room at least 45 min before the tests in order to let them acclimatize to the test environment. After testing each animal, each apparatus was thoroughly cleaned with cotton pads wetted with 30% ethanol. Behavior was videorecorded using a digital video camera (ICD-49E, Ikegami, Japan). The behavioral scoring was carried out using a computer-based video-tracking system Ethovision XT (Noldus, Wageningen, the Netherlands) and the commercial software Observer XT (Noldus). All scores were assigned from the same observer who was unaware of animal genotype and/or treatment.

Attentional set-shifting

We adopted the attentional set-shifting task, developed by Colacicco *et al* (2002). Apparatus and general procedure: The apparatus was an opaque PVC U-shaped box with a grid floor and a transparent Plexiglas lid (45 cm × 30 cm × 15 cm). Two identical choice compartments (15 cm × 15 cm) at one end of the apparatus could be accessed through sliding doors from a starting compartment (30 cm × 30 cm). A cylindrical food cup (40 mm diameter, 35 mm high) in each choice compartment could be baited with a small piece of cereal (30 mg; Honey Nut Loop, Kellogg's). The food was then covered with a layer of medium-scented digging (20 mm). The presence or absence of food reward in a cup was indicated by either tactile (type of digging medium) or olfactory stimuli (scent of the digging medium). The entire procedure took 5 days, a 1-day habituation period and a 4-day testing period. Habituation: On the day before testing, mice were given access to the apparatus for 30 min. Following this preliminary exposure, mice were trained to dig into food-baited bowls during a series of 9 consecutive trials. Testing: In order to avoid potential biases, the odor presentation was randomized across cage mates. A stage was considered complete when the mouse achieved a criterion of 8 correct trials out of 10. Trials were concluded after 5 min if no choice was made, and marked as incomplete. A session would continue until the animal ceased responding. However, one hour of responding resulted in an average of approximately 30 trials per day per subject. Briefly, a trial was initiated by raising the sliding wall to give the mouse access to the two digging bowls, only one of which was baited. Mice were required to dig into a rewarded bowl in order to obtain highly palatable food pellets. Digging bowls varied across two dimensions (digging medium and scent). During simple discrimination (SD), mice had to learn to discriminate between two different odors or digging media. After this stage, mice were required to perform a compound discrimination (CD), during which the baited stimulus of the previous stage was presented together with another, newly introduced, irrelevant stimulus of the other dimension. Despite the presence of the new stimulus, the correct and incorrect exemplars remained constant. At the end of this stage, mice had to perform CD reversal (CDR) learning. For the reversal, the exemplars and the relevant dimensions were unchanged: The mouse had to learn that the previously correct stimulus was now incorrect. For both intra-dimensional shift (IDS) and extra-dimensional shift (EDS), new exemplars of both dimensions were used. In the IDS, the relevant dimension is the same as before, whereas in the EDS, the mouse had to shift attention to the previous irrelevant dimension. The order of discriminations was always the same, but dimensions the pairs of exemplars were equally represented within groups and counterbalanced between groups as far as possible. Errors during testing were broken down into perseverative errors and never-reinforced errors. Perseverative errors were scored when a mouse continued to use the previously relevant but currently irrelevant rule. In 5 out of every 10 consecutive trials, the mouse was allowed to respond this way. Never-reinforced errors were scored when mice made incorrect choice using a rule that has never been rewarded previously.

Open field

Mice were individually placed in the center of a cubic arena (40 × 40 × 40 cm) made of black Plexiglas and allowed to freely explore for 15 min. The open field box was ideally divided into 25 squares and ideally partitioned into a central portion (26.4 × 26.4 cm) and a peripheral one (i.e., thigmotaxis—time spent near the walls), identified as the remaining parts of the arena. When data were analyzed, each session was subdivided in 3 5-min blocks and time spent in each portion of the arena, total distance moved as well as latency, frequency and duration of locomotion (crossings of squares, vertical activity, i.e., rearing and wall rearing), and self-directed behaviors (self-grooming) were scored.

Morris water maze

The water maze apparatus consisted of a white Plexiglas circular pool 88 cm in diameter and 33 cm in height, filled with water and kept at a temperature of 26 ± 1°C. A plastic transparent platform (8 cm in diameter) was placed 0.5 cm below the water surface and 10 cm from the edge of the pool. The ability of experimental subjects to identify and reach a visible platform was tested in one visual cued version of the task which preceded the 3 days of

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acquisition phase. Each day, mice underwent 3 trials during which they were allowed to freely swim for 60 s or until they found and climbed onto the platform; each trial was spaced from the other by a 40-min inter-trial interval. In the visual phase of the task, a visual cue was always located on the platform and the platform position was changed in each trial, whereas during the acquisition phase, the platform position remained fixed for all the trials in a 'target quadrant'. Platform finding was defined as staying for at least 3 s on it. During the acquisition phase, mice that did not find the platform were trained in locating it by placing them on the platform for 10 s at the end of the trial. On the last day (probe phase), each mouse was tested for memory retention in a 60-s probe trial during which the platform was removed from the pool and the time spent in the area of the maze where the platform was located was scored. For the acquisition phases, the variables recorded were latency to reach the platform, mean swimming speed, distance moved and thigmotaxis. For the probe phases, the variables recorded were time spent in each quadrant, mean swimming speed, distance moved and thigmotaxis.

Spontaneous social behavior

The spontaneous social behavior was recorded in the home cage according to the paradigm previously described (D'Andrea *et al*, 2007). Ten WT and 10 KO cages (two mice in each cage) were observed for a single 30-min session on two consecutive days. Since data collected concerning 20 mice per experimental group have been found to be dependent (significant effect of random cage factor in the mixed model ANOVA), only one mouse, randomly selected from each cage, has been considered in the analysis ($n = 10$). Seven days before the first day of observation, the cages were cleaned and one of the two experimental subjects was marked with a blue, scentless and nontoxic felt pen in order to discriminate the two animals during data collection. During the first day of observation, no manipulation was performed. On the second day, the cage sawdust was changed with clean sawdust just before the session of observation. This procedure is known to elicit aggressive behavior and to challenge social hierarchy. Social behavior was scored during a single 30-min session each day. The behavioral categories and elements scored for both frequency and duration were social investigation (sniffing and grooming the partner in all body regions indicative of affiliative behavior) and aggressive grooming (violent grooming of the animal on the back of the partner).

Elevated plus maze

The elevated plus maze comprised two open arms (30 cm × 5 cm × 0.25 cm) and two closed arms (30 cm × 5 cm × 15 cm) extended from a common central platform (5 cm × 5 cm). The apparatus was constructed from Plexiglas (black floor, transparent walls) and elevated to a height of 60 cm above the floor level on a central pedestal. Mice were individually placed on the center of the platform facing an open arm and allowed to explore freely the maze for 5 min. Behavioral parameters scored were time spent in open and closed arms and percentage of open time.

Drug administration

Mice were randomized to receive methylphenidate (3 mg/kg) or vehicle, daily administrated by gavage for 21 consecutive days.

PDE4 determination

Protein extraction

Total membranes and cytosolic fractions were prepared by homogenization of liquid nitrogen-frozen LC in 120 mmol/l NaCl, 50 mmol/l Tris–HCl (pH 8.0), protease inhibitor complete (Roche Applied Science, Indianapolis, IN) and phosphatase inhibitors (50 mmol/l sodium fluoride, 1 mmol/l sodium orthovanadate and 10 mmol/l sodium pyrophosphate). Lysates were incubated on ice for 30 min and then centrifuged at 1,500 *g* for 5 min at 4°C. Membrane and cytosolic fractions were then separated by centrifugation of supernatants at 38,000 rpm for 1 h at 4°C in a SW55Ti rotor (Beckman Coulter). Supernatants (cytosolic fraction) were collected, and pellets (membrane fraction) were solubilized in ice-cold lysis buffer, supplemented with 1% Triton X-100. Protein concentration was determined by the Bradford method, and extracts were used for immunoprecipitation and then assayed for PDE activity.

Immunoprecipitation

For immunoprecipitation assays, 150 μg of pre-cleared extracts was incubated with 20 μl of a 1:1 slurry of protein A- or G-Sepharose (Amersham Biosciences, Buckinghamshire, UK) and 1 μg of antibody/mg of protein for 2 h at 4°C. Immunocomplexes were then extensively washed with lysis buffer for PDE activity assay.

PDE assay

Phosphodiesterase activity in immunoprecipitates was measured according to the two-step method of Thompson and Appleman. In brief, immunoprecipitations were assayed in a total volume of 200 μl of reaction mixture containing 40 mmol/l Tris–HCl (pH 8.0), 1 mmol/l $MgCl_2$, 1.4 mmol/l 2-mercapto-ethanol, 1 μmol/l cAMP (Sigma-Aldrich, Saint Louis, MO) and 0.1 μCi of [3H]cAMP (Amersham Bioscience, Buckinghamshire, UK) for 45 min at 33°C. In order to stop the reaction, samples were boiled at 95°C for 3 min. The PDE reaction product 5′-AMP was then hydrolyzed by incubation of the assay mixture with 50 μg of Crotalus atrox snake venom for 15 min at 37°C (Sigma-Aldrich, Saint Louis, MO). The resulting adenosine was separated by anion exchange chromatography using 400 μl of a 30% (w/v) suspension of Dowex AG1-X8 resin (Bio-Rad, Segrate, Milano, Italy). The amount of radiolabelled adenosine in the supernatant was quantified by scintillation counting (Ultima Gold scintillation liquid from Perkin Elmer, Waltham, MA).

Antibodies

Anti-PDE4A, anti-PDE4B and anti-PDE4D antibodies used for immunoprecipitation were from Abcam (Cambridge, UK).

Immunofluorescence

Mice were anesthetized with farmotal and transcardially perfused with saline containing 4% paraformaldehyde. Brains were removed and immersed in fixative for six hours at 4°C and then cryoprotected in 20% sucrose overnight at 4°C. Thirty-micrometer-thick floating frozen section were cut using a cryostat (Leica) and then sequentially incubated with primary antibody: rabbit anti-Creb 1:1,600 (Cell Signaling), rabbit anti p-Creb 1:500 (Cell Signaling), mouse anti-PI3Kγ produced as previously described (Damilano *et al*, 2011; Perino *et al*,

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2011) 1:100 in MOM kit (Vector), goat anti-dopamine beta hydroxylase 1:800 (Abcam) and sheep anti-tyrosine hydroxylase 1:800 (Millipore). The secondary antibodies used were Alexa 488 1:200, Cy3 1:200 and Alexa 647 1:100 from Jackson Immunoresearch. Slides were cover-slipped with DAPI-containing medium (Vector).

Confocal microscopy analysis

All cover-slipped, mounted tissue sections were scanned using a Zeiss 780 confocal laser scanning microscope with a Zeiss ECPLAN-NEOFLUAR 20×/0.50 M27, ECPLAN-NEOFLUAR 5×/0.16 or ECPLAN-NEOFLUAR 40×/1.30 M27 oil immersion objective (Carl Zeiss Microimaging Inc.). We used a 405-nm diode laser to excite DAPI, a 488-nm argon laser to excite Alexa Fluor 488, a 543-nm HeNe laser to excite Cy3 and a 633-nm HeNe laser to excite Alexa Fluor-647. Z-stack projections and pseudo-coloring were performed using ZEN software (Carl Zeiss Microimaging, Inc.).

Western blot and immunoprecipitation

Mouse brains were rapidly removed and chilled in ice-cold buffer containing (in mM) 126 NaCl, 5 KCl, 1.25 NaH_2PO_4, 2 $CaCl_2$, 2 $MgCl_2$ and 10 D-glucose, pH 7.4. The LC was obtained from coronal brain slide of ~1 mm, cut with McIlwain tissue chopper. Bilateral punches of the LC from two slices of the same animals were homogenized by dunce homogenizer with NE-PER nuclear and cytoplasmatic extraction kit (Thermo Scientific). Protein content was determined by the BCA method. Fifty micrograms of proteins from each sample was separated by SDS–polyacrylamide gel electrophoresis using a Tris/Glycine/SDS buffer (Bio-Rad) and transferred to a PVDF membrane (Bio-Rad). Membranes were blocked using BSA (Sigma) and then incubated overnight at 4°C with primary antibody pCreb (ser133; Cell Signaling) 1:400 and secondary antibody goat anti-rabbit (Santa Cruz).

For immunoprecipitation, 250 μg of total proteins extracted from bilateral LC punches was incubated with 20 μl protein A/G agarose plus (Santa Cruz), 1 μg of anti-PI3kg antibody/mg of protein overnight at 4°C. Immunocomplexes were washed with lysis buffer and resolved by SDS–PAGE followed by Western blotting using the antibody PDE4D (Acris) 1:400.

Secondary antibodies were from Santa Cruz, and signal detection was performed with ECL Kit (Amersham) and analyzed with Chemidoc XRS Imaging System (Bio-Rad).

Noradrenaline and dopamine determination

Locus coeruleus was homogenized by sonication in lysis buffer 1 mM EDTA and 0.1 N HCl. Dopamine and Noradrenaline levels were measured with a high-sensitivity ELISA kit (IBL International), following the manufacturer's instructions.

Surgical procedure

Mice were anesthetized with an intraperitoneal injection of ketamine (90 mg/kg) and xylazine (10 mg/kg), and thermoregulation was provided through a thermostat-regulated heating pad (Harvard apparatus) and monitored through a rectal thermometer. The head was shaved and cleaned with iodine before incision. After making a skin incision of about 1 cm, mice were placed on the motorized stereotaxic apparatus (Stoelting). The point 0 (bregma) and subsequently the respective coordinates for injection into the LC (*x*-5.52 *y*-0.85 *z*-3.50) were established as described by Franklin and Paxinos (Franklin & Paxinos, 1996). Mice were randomized in experimental groups and injected with the following viral vectors: adeno-associated virus (AAV)-green fluorescent protein (GFP) as a control, AAV-dnCREB (a dominant-negative mutant of CREB) or AAV-caCREB (constitutively active mutant of CREB) as specified in each figure. Subsequently, skull and skin were closed with dental cement and a 6.0 (Ethicon) suture. After surgery, mice were monitored in an incubator at a controlled temperature and were treated with antibiotic for any post-operative infection.

Statistical analysis

Analyses were carried out using the SPSS 21.0 software (SPSS, Chicago, IL, USA). Unless otherwise indicated, results are presented as mean ± standard error of mean (SEM). All data normally distributed for more than two groups were examined by either one- or

The paper explained

Problem
PI3Ks are enzymes characterized by both lipid and protein kinase activity, which once activated modulate important cellular functions, affecting cell survival, proliferation, migration and adhesion. Among these, PI3Kγ, which is mainly linked to regulation of G protein-coupled receptor signaling, acts with a dual mechanism involving both kinase-dependent and kinase-independent activity, the first being mainly linked to regulation of intracellular levels of phosphoinositide (3,4,5)-trisphosphate (PIP3) and the second affecting cAMP levels through modulation of specific PDE isoforms activity. Although the role of PI3Kγ in inflammation and in cardiac function has been extensively investigated, the exploration of its CNS function is just at dawning. On this issue, it has been recently shown that the lack of PI3Kγ in mice leads to an impairment in synaptic plasticity associated with alterations suggestive of a role for PI3Kγ in mediating behavioral flexibility. Interestingly, among the neuropsychiatric disorders, the syndrome called ADHD (attention-deficit/hyperactivity disorder) involves difficulties in suppressing aggressive behaviors and displays many traits ascribable to behavioral inflexibility.

Results
Here, we show that the absence of PI3Kγ in mice reproduces the principal behavioral features observed in patients with ADHD. In particular, PI3Kγ KO mice exhibit deficits in the attentive and mnemonic domains, coupled with typical hyperactivity, as well as social dysfunctions. This behavioral phenotype is accompanied with neurochemical alterations, reflected by an unbalanced catecholaminergic activity in brain areas receiving projections from LC, where PI3Kγ is constitutively expressed. More importantly, we demonstrate, for the first time, that the observed behavioral phenotype, mediated by a kinase-independent mechanism, depends on a dysregulation of CREB signaling, exerted by PI3Kγ-PDE4D in LC, the largest cluster of noradrenergic neurons in the brain.

Impact
With our findings that strongly suggest PI3Kγ as a crucial player of ADHD, we propose an innovative molecular mechanism regulating behavioral flexibility in mouse models, which opens novel therapeutic perspectives and appropriate diagnostic strategies.

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two-way ANOVA with repeated measures followed by Bonferroni's *post hoc* test. Unpaired two-tailed Student's *t*-test was used in case two groups were compared.

Supplementary information for this article is available online: http://embomolmed.embopress.org

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Author contributions
ID performed behavioral phenotyping, analyzed and interpreted data, and drafted the manuscript. VF performed behavioral phenotyping, microsurgery and all the *in vivo* treatments. SF and RI performed molecular and histological analyses. FP performed microsurgery and all the *in vivo* treatments. AG and EH performed the analysis on PDE activity. AM performed statistical analysis. GL supervised the research, interpreted data, handled funding and critically read the manuscript. DC conceived the research, supervised experiments, analyzed and interpreted data, performed statistical analysis, handled funding and wrote the manuscript.

Conflict of interest
The authors declare that they have no conflict of interest.

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The impact of a model-based clinical regional registry for attention-deficit hyperactivity disorder

Michele Zanetti, Massimo Cartabia, Anna Didoni, Filomena Fortinguerra, Laura Reale, Matteo Mondini and Maurizio Bonati
IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Abstract
This article describes the development and clinical impact of the Italian Regional ADHD Registry, aimed at collecting and monitoring diagnostic and therapeutic pathways of care for attention-deficit hyperactivity disorder children and adolescents, launched by the Italian Lombardy Region in June 2011. In particular, the model-based software used to run the registry and manage clinical care data acquisition and monitoring, is described. This software was developed using the PROSAFE programme, which is already used for data collection in many Italian intensive care units, as a stand-alone interface case report form. The use of the attention-deficit hyperactivity disorder regional registry led to an increase in the appropriateness of the clinical management of all patients included in the registry, proving to be an important instrument in ensuring an appropriate healthcare strategy for children and adolescents with attention-deficit/hyperactivity disorder.

Keywords
adolescent, attention deficit disorder with hyperactivity, child, health information systems, registries

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by maladaptive, and inappropriate, levels of inattention and/or hyperactivity and impulsivity in early childhood that can persist through adolescence, pervade across settings and lead to notable impairments in adulthood.[1] Current evidence defines ADHD as a disorder resulting from complex interactions between genetic and environmental factors. ADHD is diagnosed by the severity and persistence of symptoms, which are associated with high levels of impairment in family and social relationships and with a higher risk of developing co-occurring psychiatric disorders during the lifetime, such as mood, conduct and substance abuse disorders.[2]

Corresponding author:
Michele Zanetti, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa, 19 – 20156 Milano, Italy.
Email: michele.zanetti@marionegri.it

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In recent years, there has been an increase in the clinical recognition of ADHD, with a corresponding increase in the number of children diagnosed and treated.[3] Worldwide, the prevalence of ADHD is estimated at 5.3 per cent, although there is wide variability between geographic locations.[4]

In the Italian Lombardy region (the most populated and economically important region in Italy), the estimated prevalence was 9.5 per 1000 children and adolescents aged between 6 and 17 years, and less than a quarter of them received drug therapy.[5]

Although there is growing evidence that stimulants for the treatment of ADHD both improve 'core' ADHD symptomatology and reduce the risk of developing psychiatric co-morbidities, psychosocial treatments such as psychoeducation, cognitive-behavioural therapy (CBT) and supportive training to help with organizing daily activities are also the first choice, alone or in combination with pharmacological therapy, according to clinical and environmental evaluation. Psychosocial treatments have been shown to be more effective than pharmacological therapy alone, in particular when both parents and teachers are involved.[6] According to the Italian guidelines on ADHD treatment (defined in 2003 through a consensus conference),[7] drug treatment should only be started after a child psychiatrist, who is an expert in ADHD, has thoroughly assessed the child or adolescent and confirmed the diagnosis. Moreover, once treatment has been initiated, the effectiveness and adverse effects need to be assessed carefully and regularly, and reported, by each reference centre's team of clinicians.

Because of the large concern about the safety and rational use of psychotropic drugs in children, a national initiative was launched in Italy in 2007 to monitor the prevalence and appropriateness of drug therapy in the ADHD paediatric population: the National ADHD Registry. The registry was set up under the auspices of the Italian Medicines Agency (AIFA) and coordinated by the Italian National Institute of Health, following the reintroduction of methylphenidate on the market (as immediate-release tablets) and the registration of atomoxetine. These are the only two drugs with a specific indication for ADHD available in Italy, and are registered for use only in children aged 6–17 years. The Italian registry is a unique tool internationally; it is able to ensure the monitoring and evaluation of the safety and tolerability of methylphenidate and atomoxetine in children and adolescents with ADHD.[8]

To create shared and feasible diagnostic and therapeutic pathways, however, an analysis of currently existing clinical and socio-anamnestic variables, such as type of ADHD or specific environmental life contexts, is a key step. This analysis then needs to be followed by a final evaluation of the process outcomes, including user satisfaction in relation to the health services provided and the quality of life of families. The data collected through the National ADHD Registry made it possible to clarify certain critical issues, but not to perform a finalized epidemiological analysis, nor to best plan effective strategies for improvement. In particular, few data concerning the families' anamnesis are collected and no information about ADHD patients receiving psychological treatment or other psychotropic agents are collected.

In this context, the need to create a new database to monitor the diagnostic and treatment pathways for all children and adolescents with ADHD, not only those already receiving drug treatment, was apparent. This article describes the development and clinical impact of the Italian Regional ADHD Registry, an initiative aimed at ensuring an appropriate management plan for children and adolescents with ADHD and set up as part of the project 'Sharing of diagnostic and therapeutic pathways for ADHD'.[9]

Methods

The new ADHD database, the 'Italian Regional ADHD Registry powered by PROSAFE', allowed, through a flexible interface, the collection of information relating to

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- Anamnestic data;
- Clinical assessment;
- Diagnosis;
- Therapeutic interventions, both pharmacological and non-pharmacological;
- Follow-up visits.

The information collected was analysed monthly, and the results were presented and discussed at regular meetings between the participating centres and the coordinating centre (IRCCS – Istituto di Ricerche Farmacologiche Mario Negri), in order to assess whether any improvements were achievable.[9] The coordinating centre published all results in a monthly summary report sent to each participating centre and posted it on the ADHD project website (adhd.marionegri.it).

Before the project started one of the 18 centres was selected as a pilot site to test the system and to resolve emerging technical problems. After a 3-month running period, a technical support service was established through a dedicated phone number and monthly meetings with all clinician participants were organized for feedback.

PROSAFE

The 'Italian Regional ADHD Registry powered by PROSAFE' originated from the development of an already-existing model-based software called 'PROSAFE', a programme used for data collection in many Italian intensive care units (ICUs).[10] The modular structure and features of the software have made it possible to create a stand-alone Case Report Form (CRF) interface to collect data on the Italian Regional ADHD Registry, while continuing to use the skills and technical characteristics that distinguish PROSAFE.

The software architecture used is PROSAFE CLIENT-SERVER, which allows more software to be installed on the same network, according to the needs of each individual centre. In addition, each centre may use and store data even offline without an internet connection – an option that would have been impossible with a web-based software. The software is free of charge for the ADHD centres.

Eligibility of centres and users

Italian healthcare is provided free or at a nominal charge through a network of 148 local health units (LHUs). Child and adolescent neuropsychiatric services (CANPS) are part of the LHU and provide care at the hospital and community level for children and adolescents with neurologic and/or psychiatric and/or neuropsychological disorders (including developmental disabilities and intellectual disabilities), and for their families. CANPS are multi-professional, comprehensive community services providing diagnosis, treatment, and rehabilitation. In order to prescribe methylphenidate or atomoxetine to ADHD patients, Italian regulatory rules require a strict clinical assessment for the diagnosis of the disorder and a systematic patient's monitoring during treatment. Since September 2007, local reference centres have been required to send patient information to the Italian National Registry dedicated to collecting data only on pharmacological treatment of ADHD patients aged less than 18 years. Regional health authorities are responsible for the accreditation of the reference centres in regional hospitals, which are linked to the CANPS located in the local communities. The reference centres are therefore the specialized hubs of the CANPS network on ADHD. In the Lombardy Region there are 18 ADHD reference centres and all participated in this project.

Children and adolescents aged 5–17 years who accessed any of the 18 local centres for a diagnosis of suspected ADHD were enrolled in the Regional ADHD Registry if (a) their first access to

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the service (first visit) was after 1 June 2011, regardless of the diagnosis or (b) they began their drug treatment after 1 June 2011 (if they were not already included in the national register).

Results

Access-history

The Italian Regional ADHD Register permitted an evaluation of the access to the ADHD reference centres by patients in the Lombardy Region, that is, the patients' requests and waiting times (time elapsed between the first request and the first survey).

Questions were also asked on the environment of the families and the patients (with whom they were living, if they had siblings, or if there were twins) and on the social situation of the parents, and their history, in order to better understand if there was a possible familiarity for ADHD and if there were any genetic hypotheses.

Assessment

The evaluation page contained a whole series of tests, interviews, and examinations that the patients underwent for the diagnosis of ADHD. These tests were agreed on by a specific sub-group of the regional project, formed by the operators from each participating centre, which had the task of sharing their own diagnostic methodologies (guidelines and tests) in order to allow a greater uniformity among all centres in the diagnostic phase.

Specifically, during the diagnostic evaluation the following tests/information required were as follows:

- Anamnestic data;
- Clinical interview;
- Neurological examination;
- Intelligence Quotient (IQ);
- Diagnostic Interviews: Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) or Development and Well-Being Assessment (DAWBA);
- Evaluation of parents: Conners' Parent Rating Scales (CPRS) and Child Behaviour Checklist (CBCL);
- Evaluation of teachers: Teachers' Parent Rating Scales (CTRS);
- Clinical Global Impressions-Severity (CIGS) or Children's Global Assessment Scale (CGAS).

Diagnosis

The diagnostic page contained questions on the patient's symptoms and behaviour. Based on the answers entered the programme then processed the data entered by the clinician and classified the diagnosis according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR), assigning one of four possible results:

1. Patient not diagnosed with ADHD;
2. Patient diagnosed with ADHD type I (inattention);
3. Patient diagnosed with ADHD type H (hyperactivity-impulsivity);
4. Patient diagnosed with ADHD type C (combined).

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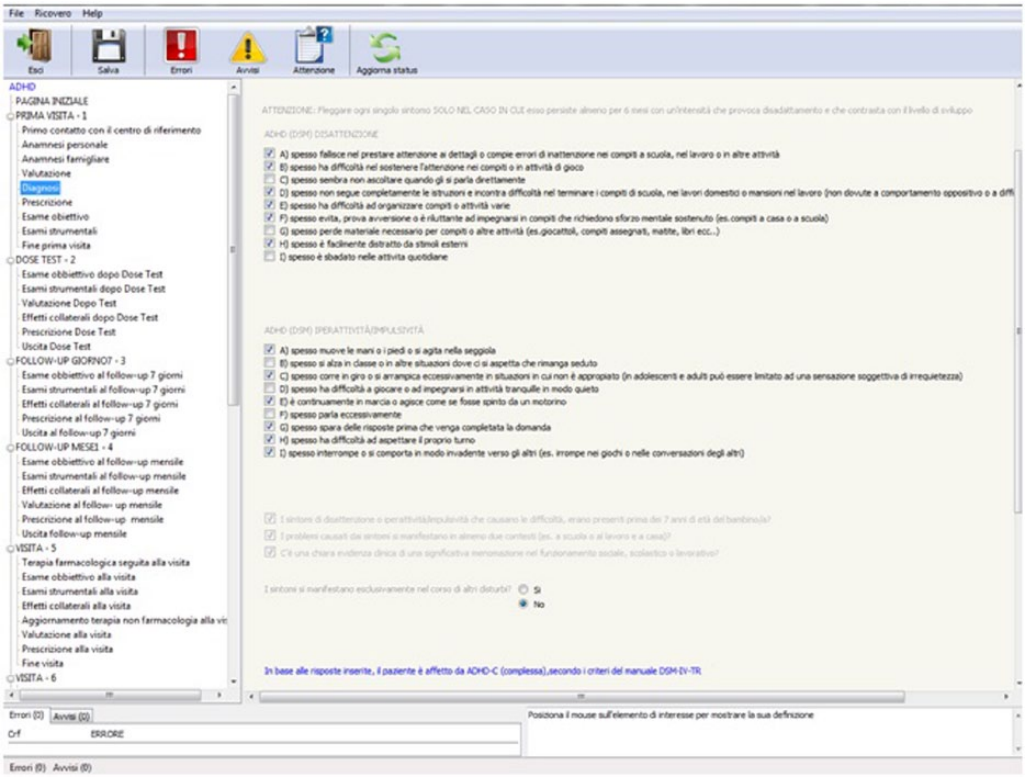

Figure 1. Data collection form in the diagnostic page.

Figure 1 shows an example of the data collection form.

In the case of an ADHD diagnosis, the centre's operator was requested to proceed with filling in the fields of the pages following the diagnosis section, according to the prescribed therapy.

In cases in which the patient was not diagnosed with ADHD the operator was sent to a page stating 'out of the registry', in which the following potential causes for the interruption of the visits were indicated: 'no ADHD', 'the patient does not show up at the visits', 'treatment interruption' or 'transfer to another ADHD centre'.

Therapy

According to the Italian Regional Registry the prescribed therapy was pharmacological, non-pharmacological, or both. The pharmacological treatment involved all the psychotropic drugs indicated for ADHD therapy: mainly methylphenidate or atomoxetine, and in a few cases other psychotropic agents.

Drug therapy was given in combination with non-pharmacological interventions, such as cognitive-behavioural therapy (CBT), child, parent, and teacher training, or counselling.

Once the therapy was prescribed the patient was seen for follow-up visits at given time periods, according to the type of prescribed therapy: in cases of methylphenidate or atomoxetine treatment, the patient was re-assessed after 7 days, while in cases of other psychotropic agents, after one month. This was different for non-pharmacological therapies, in which the type of prescribed ther-

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Table 1. Drug prescription on the first visit.

Methylphenidate	Atomoxetine	Other drug	First follow-up visit
YES	YES/NO	YES/NO	Dose test
NO	YES	YES/NO	7 days
NO	NO	YES	1 month
NO	NO	NO	3 months

apy did not influence the timing of the subsequent visit if associated with a pharmacological treatment, if not, the follow-up visit was provided after 3 months of the start of therapy.

Follow-up visits

Following the diagnosis of ADHD, the register was designed to provide several, differently structured types of follow-up visits, based on the prescribed therapy, in order to optimize the compilation of the CRF and to therefore have clean and correct data. In particular, the planned follow-up visits were as follows:

First visit. The set of requests for anamnestic data of patients and families, assessment and formulation of diagnosis and prescription of therapy.

Dose test. A visit performed only in cases in which the patient was treated with methylphenidate for the first time, and it was therefore necessary to ensure that there were no adverse drug reactions.

7 days. A visit following the dose test, whose aim was to provide further checks, or a visit for those patients prescribed atomoxetine for the first time.

1 month-visit. A visit following the '7 days' (for atomoxetine or methylphenidate), or a visit performed when an another psychotropic drug was prescribed.

3 month- and/or 6 month-visit. Control visits following the 1 month-visit to monitor all patients, whether or not on drug therapy.

Extra visit. An extraordinary (unplanned) visit performed due to the occurrence of side effects and/or adverse drug reactions, changes in therapeutic plan, or additional patient monitoring.

The order of the visits in the register was decided by the software, which followed an internal logic based on the drug therapy prescribed to the patient. The drug prescription on the first visit determined the first follow-up visit according to the written criteria indicated in the following Table 1.

The calculation of the follow-up visits took into consideration the following data:

- Type of previous follow-up visit;
- Drug therapy prescribed on the previous visit;
- Presence of extra visits not provided in the therapeutic plan;
- Type of current follow-up visit;
- Prescribed therapy in the current follow-up visit;
- Patient's compliance to the prescribed therapeutic plan.

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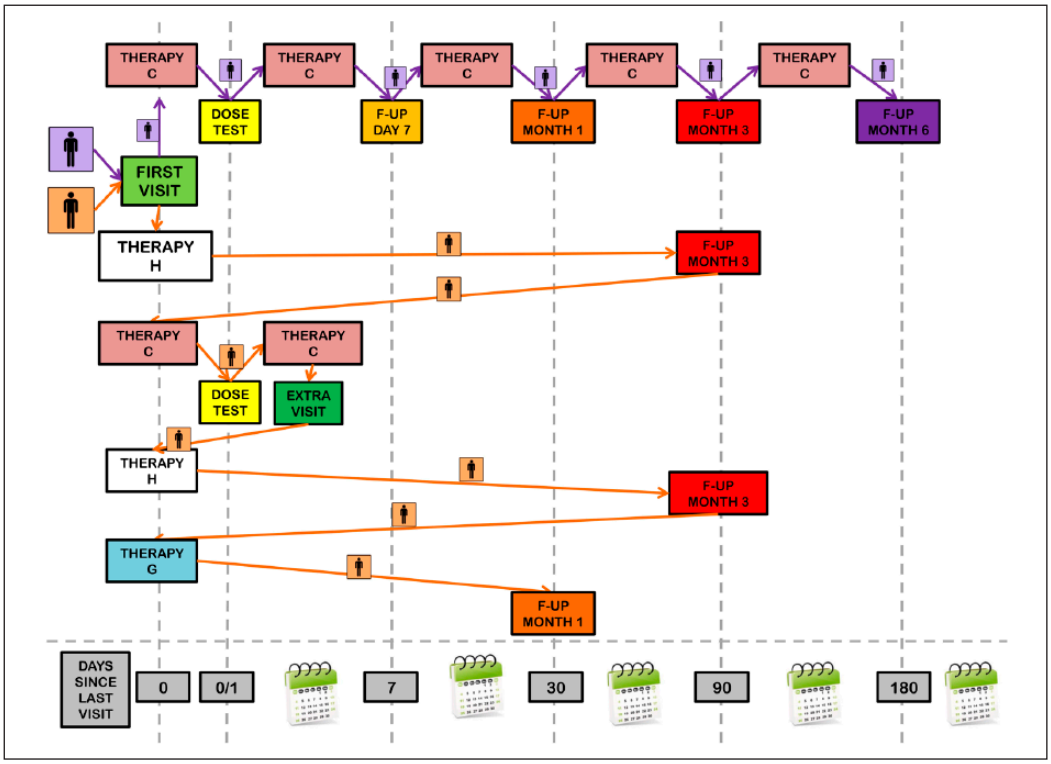

Figure 2. Follow-up visit logic.

Figure 2 shows the calculation of the follow-up visits, when the patient was in a normal situation without extra visits, and when the patient changed drug (or did not use it) and there was an extra visit.

The possible combination therapies in Figure 2 are outlined in Table 2 below.

Data collection

At the time of analysis, data from the Italian Regional ADHD Registry were collected and referred to the diagnostic and therapeutic pathways of 1338 children and adolescents. All of the 18 centres adopted the initiative and completed the patient records in the registry, with a range of 34–187 patients per centre (average 74). The number of patients per centre was related to the resident paediatric population.

Of the 1338 children and adolescents (86.7%), 1160 with suspected ADHD completed the diagnostic assessment, and 751 (64.7%) met criteria for ADHD. In all, 115 patients (15.3% of those diagnosed with ADHD) had been treated with at least one psychoactive drug: 107 with methylphenidate (5–60 mg daily), 19 with atomoxetine (10–80 mg daily) and 10 with other agents. A total of 63 adverse events were reported in 28 patients treated with drugs (rate: 24.3%), and headache, decreased appetite, asthenia and drowsiness were the leading events.

Of the children with ADHD who were treated, only 9 discontinued the drug prior to 1 year of treatment, none of whom because of adverse events. Although the medications for ADHD

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Table 2. Possible combination therapy.

Therapy	
Methylphenidate + atomoxetine + other drug	**A**
Methylphenidate + atomoxetine	**B**
Methylphenidate + other drug	**C**
Only methylphenidate	**D**
Atomoxetine + other drug	**E**
Only atomoxetine	**F**
Only other drug	**G**
No drug	**H**

are generally well tolerated, the Lombardy Region ADHD registry could be a useful tool to improve the rational use of drugs in children and adolescents by disseminating and monitoring evidence-based practices and by monitoring the safety and efficacy of treatments in both the short and long terms.[5]

Data processing and monitoring

The IRCSS – Mario Negri Institute for Pharmacological Research, as coordinating centre – monitored and processed the data entered in the Italian Regional ADHD Registry from all the centres and sent a monthly summary report to each participating centre (Figure 3).

The report contained a flow-chart illustrating the paths of the all patients enrolled in the registry, with the corresponding values achieved, and consisted of 3 sections:

1. General trend of all participating centres;
2. Trend of the each single centre, referring only to the patients of the centre receiving the report;
3. Inconsistent and/or missing data detected for the patients enrolled by each single centre. The centre receiving this indication was requested to correct its data.

Discussion

The differences between the centres (different management, structure, staff, etc.) led to many problems in drafting the CRF shared by all the centres. Consequently, it was necessary to create a series of software releases subsequent to the first one in order to standardize the data collection form. This was possible thanks to the programme's flexibility, because every single change could be made without affecting the normal compilation of the registry by the participating centres.

The use of diagnostic–therapeutic pathways and the follow-up visit logic controlled by the programme based on the data entered, as well as the parallel management of other resources supporting the software such as the monthly summary data report for each centre, the periodical newsletter sent to the centres and the website (adhd.marionegri.it) content update, led to an increase in the appropriateness of the clinical management of all patients included in the registry.

Initially, the use of the software by the ADHD centres was sporadic, mainly due to the lack of staff organization and capacity in filling out a computerized CRF. Continuous support activities performed by the coordinating centre, such as providing quick replies to the centres' queries by telephone or email and holding monthly meetings with the ADHD centres, led to a large

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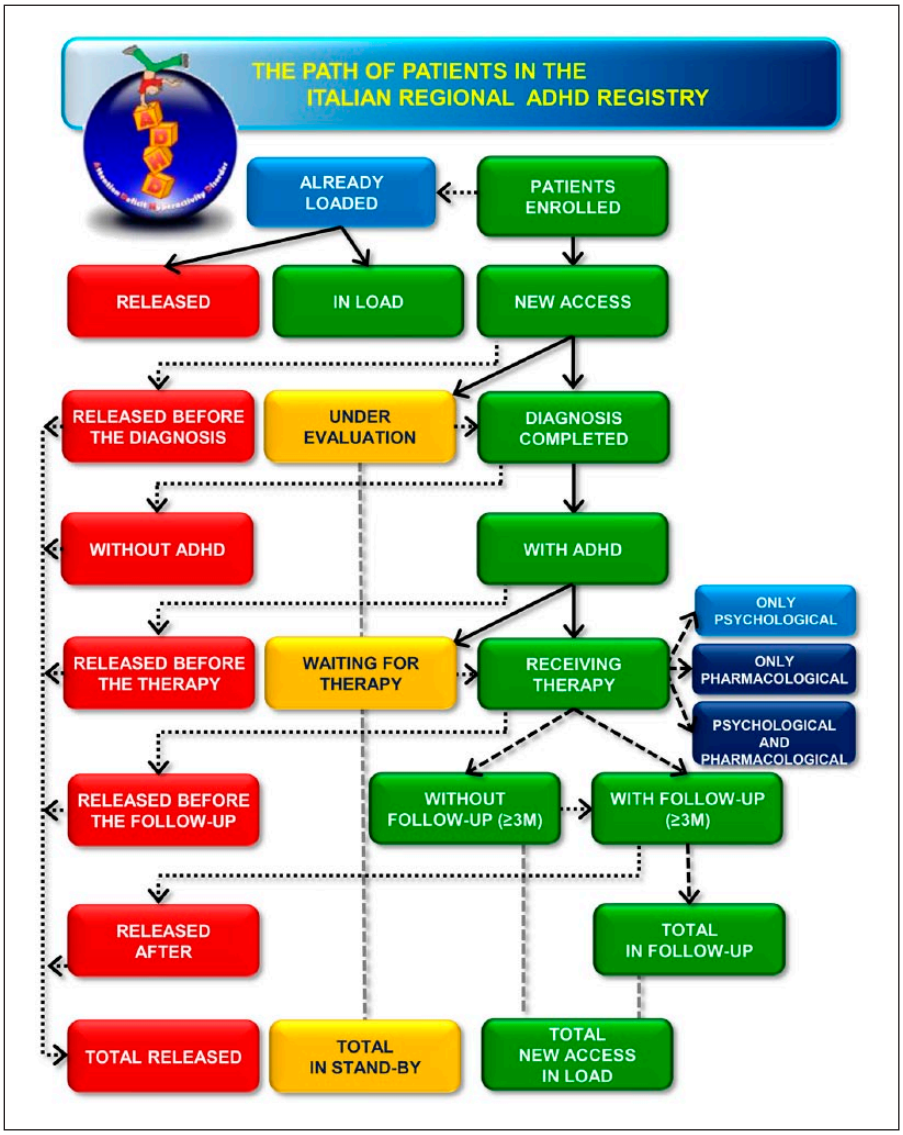

Figure 3. Report structure.

improvement, over a 1-year period, in the technical management of the programme and to a consequent improvement in the quality of data entered as well as to an increase in the frequency with which the centres connected to the programme.

The use of the software increased the centres' ability to use computer technology for clinical data collection, especially in centres that were not previously registering data systematically. Currently, most of the centres are connecting daily or weekly, with only a few centres connecting monthly. Finally, thanks to the ongoing development of the PROSAFE software, the registry can be continuously integrated and upgraded so as to bring constant improvements to the CRF and to the data collection in general, without causing any disturbance to users.

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The identification of centres and the software installation were carried out through a web portal, which monitored access and authentication by the different centres involved in the project. This project has demonstrated how the software has improved the appropriateness of diagnostic and therapeutic pathways for patients enrolled in the Regional ADHD Registry. Specifically, the software described allowed a greater ability to edit, check, and manage the diagnostic and therapeutic pathways, thanks to a flexible internal frame. In particular, the calculation of the follow-up visits was automatic, based on certain data values. The programme gave the centres access to the system for later follow-ups in a manner consistent with the diagnostic–therapeutic data entered previously.

Conclusion

The Italian Regional ADHD Registry is an efficient tool to estimate the prevalence and incidence of ADHD, to evaluate the patients' psychopathological profile and comorbid psychiatric conditions, and to monitor the clinical outcome of the prescribed therapy (psychological, pharmacological treatments or both) and potential adverse events and/or side effects of pharmacotherapy in the Lombardy Region's paediatric population. The software is free of charge and is potentially available for other regions and/or LHUs.

The Italian Regional ADHD Registry therefore represents a distinctive tool to promote a collaborative experience between several ADHD centres and the coordinating centre, that is unique in the international context and that assures the appropriate care and safety of drug use in ADHD children, according to recent evidence-based practices and guidelines.

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Impact of attention-deficit/hyperactivity disorder on the lives of Italian children and adolescents: data from the European Lifetime Impairment Survey

R. DONFRANCESCO [1], U. LOPRIENO [2]

[1]*Child Neuropsychiatry Department Sandro Pertini Hospital. Rome, Italy*
[2]*International Medical Affairs Shire, Florence, Italy*

Aim. **In Italy, attention-deficit/hyperactivity disorder (ADHD) remains under-diagnosed. The Lifetime Impairment Survey assessed impairments/symptoms of ADHD in children across six European countries. Results relating to the Italian sample are discussed here.**

Methods. **Parents/caregivers of children aged <20 years with ADHD (ADHD group) and without ADHD (control group) were invited to participate in an online survey. Participants answered questions relating to their eldest/only child. History of ADHD diagnosis was self-reported. Eight impairment and symptom scales and two summed scores were created to compare the ADHD and control groups; higher scores indicate greater impairment.**

Results. **In Italy, 104 parents/caregivers of children with ADHD and 105 parents/caregivers of children without ADHD participated in the survey (N.=83 and N.=84, respectively, after exclusion of participants with implausible answers). The ADHD group had higher mean (standard deviation) scores than the control group for home impairment (2.1 [0.5]) *vs.* 1.9 [0.4]; P<0.001), school impairment (2.8 [0.6] *vs.* 2.1 [0.6]; P<0.001), relationship impairment (2.3 [0.8] *vs.* 1.9 [0.7]; P<0.001) and comorbid symptoms (3.3 [0.7] *vs.* 2.5 [0.7]; P<0.001). Impairment at home and at school were correlated with each other (r=0.478; P<0.001) and with ADHD symptoms (r=0.321; P<0.001 and r=0.462; P<0.001, respectively), comorbid symptoms (r=0.231; P<0.05 and r=0.420; P<0.001), school failure (r=0.208; P<0.02 and r=0.320; P<0.001) and relationship impairments (r=0.432; P<0.01 and r=0.645; P<0.001).**

Conclusion. **The daily lives of children with ADHD in Italy are significantly affected by impairments associated with ADHD. Children and adolescents with ADHD in Italy should receive prompt diagnosis and appropriate therapy.**

KEY WORDS: Attention deficit hyperactivity disorder - Signs and symptoms - Diagnosis - Comorbidity.

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder in children and adolescents, which is highly prevalent worldwide.[1] It is characterised by the presence of at least six symptoms of frequent hyperactivity (hyperactive subtype), six of frequent inattention (inattentive subtype) or a combination of both of these conditions (combined subtype).[2] A vast body of literature exists relating to the neurobiological aspects of ADHD etiology.[3]

In Italy, rates of ADHD diagnosis are low and methylphenidate and atomoxetine have only been licensed since 2007.[4] Furthermore, rigorous studies on the preva-

Corresponding author: R. Donfrancesco, Child Neuropsychiatry Department, Sandro Pertini Hospital, Asl RM B, via dei Monti Tiburtini 385, 00157 Rome, Italy.
E-mail: renato.donfrancesco@yahoo.it

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lence of ADHD are limited. The Lombardy ADHD registry estimated 0.95% prevalence in children aged 6–17 years referred to hospitals and health services;[5] however, higher prevalence has been reported in other studies. For example, in one study, symptoms compatible with ADHD (DSM-III-R criteria) were observed in 3.9% of Italian children in fourth grade,[6] while a prevalence of 7.1% (DSM-IV criteria) at the end of the first year of primary school was reported in another study.[7] An ADHD prevalence of 5.6% was reported in a school-age (6–11 years) sample of 1000 children [8] and recently, a study utilising the ADHD rating scale for teachers (Scala per i Disturbi di Attenzione/Iperattività per Insegnanti [SDAI]), followed by a clinical confirmation of diagnosis, reported a prevalence of 3% in 6183 school-age children (5-15 years).[9] These results are similar to those published by researchers in other countries, where the prevalence of ADHD is approximately 5%.[1, 10]

Symptoms of inattention and hyperactivity have a clear socio-environmental impact on children as young as preschool age,[11] which continues in subsequent years.[12] The negative effects of ADHD include more time required to perform school and homework assignments, significant difficulties with carrying out routine family activities and wariness of, or even refusal to socialise with, peers.[13] Another aspect is frequent and early criminal behaviour, as evidenced by the psychopathological characteristics of individuals placed under arrest during adolescence and preadolescence.[14] Understanding the impact of ADHD is very important for informing decisions about institutional commitment to healthcare resources. The persistence of impairments associated with ADHD is also linked to poor outcomes in adulthood, and with the subsequent onset of psychiatric disorders.[13-18]

Common methods for measuring the impact of psychiatric disorders in children and adolescents include the Strengths and Difficulties Questionnaire (SDQ) [19] and the Children's Global Assessment Scale (C-GAS).[20] Although useful from the clinical point of view, results from these scales can be generic and may provide little ADHD-specific information.

The objective of the Lifetime Impairment Survey (LIS), conducted across six European countries, was to assess the impact of ADHD on the lives of patients with the disorder and evaluate how patients/caregivers perceive ADHD diagnosis and available treatments. This research allows a detailed description of the impact of ADHD on various aspects of daily life not addressed by the SDQ and C-GAS. These relate to comorbidities, relationships with family members, impairment at school and school failure. The study also addresses relationships with friends, self-esteem, life at home and other information relating to the parents' perception of the child; the hypothesis being that ADHD would be associated with a greater functional impairment, both at home and at school, relative to the control groups. European data from the survey, for all six countries, have previously been presented.[21] The purpose of this paper is to present the results obtained from the LIS for the Italian sample.

Materials and methods

Study design

The LIS was an online surveycarried out between 5 May and 23 June 2010 in France, Germany, Italy, Spain, the Netherlands and the United Kingdom. The study was developed and implemented by an independent market research organisation (GfK Healthcare, London, UK), under the direction of a steering committee of psychiatrists and psychologists specialising in the diagnosis and treatment of ADHD, representatives of each country in the study and representatives of the industry sponsor (Shire). The LIS was based on a previously published survey performed in adults with ADHD in the USA.[22]

The research was conducted in accordance with industry guidelines from the Market Research Society, World Association of Research Professionals, European Pharma-

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ceutical Market Research Association and British Healthcare Business Intelligence Association. As the survey was performed as market research, ethics committee approval was not required.

The survey was written in English and subsequently translated into local languages, taking care to adapt it to make it appropriate for the various participating countries. The survey included two sections from which the results are reported here. The first related to screening and classification (*e.g.*, age of the subject responding to the interview, sex, level of education achieved, relationship status, employment and earnings). A second section dealt with the social and personal impact of ADHD during childhood and adolescence and with wellbeing in general, *e.g.* the impact of ADHD at school and on relationships, and the presence of behavioural problems and comorbidities. The survey also included sections on impairment in adulthood and ADHD diagnosis and treatment; however, these data will not be discussed here. Parents/caregivers were asked for information regarding their eldest (or only) child and data were collected by computer-assisted web interviewing. Completion of the online survey took approximately 10 minutes for the control group and a maximum of 20 minutes for the ADHD group.

Subjects

Subjects who took part in the research were recruited by e-mail invitation from the GfK Global Online Panel (GfK Healthcare), a database of 487,533 individuals who had previously responded to advertisements on websites and search engines asking for volunteers to take part in market research. Those who responded positively to the invitation were informed of their rights and responsibilities regarding survey participation and completed a questionnaire defining their demographic profile. To maintain a level of confidentiality, personal identification details were not held in the database and participants were free to withdraw from the survey at any time. Subjects participating in the LIS were asked to nominate a charity to receive a donation after completion of the survey and were invited to enter into a prize draw.

Parents/caregivers of children and adolescents aged <20 years (born between 1991 and 2010, inclusive) were identified during the demographic profiling survey by a question regarding whether any of their children had ever been diagnosed with ADHD by a doctor or other healthcare provider. Allocation to the ADHD group was confirmed by a screening question during the LIS regarding whether a doctor had ever diagnosed their child with ADHD, attention-deficit disorder or hyperkinetic disorder. No formal sample size was calculated; however, a quota of 100 subjects per country per study group was considered representative. To reach the quota for the ADHD group in Italy, customised recruitment by referral from a healthcare provider was required (12%; 12/104).

Development of childhood impairment and symptom scales

The LIS Steering Committee developed eight scales and two sets of scores from preselected items for the comparison of impairment and symptoms between the ADHD and control groups. The majority of the individual items included in the scales were adapted from Biederman *et al.*[22] Principle components analysis was used to confirm item selection for each scale and internal consistency was assessed with Cronbach's alpha (Table I).

Children aged <6 years were excluded from scales that related to school experiences. Children aged <13 years were excluded from scales that referred to conduct disturbances because the conduct problem scale comprised items such as: "consumed too many alcoholic beverages or becoming intoxicated on a relatively frequent basis"; "recreationally used drugs which may or may not be illegal"; "been addicted to tobacco or smoking"; "been arrested"; and "often got into fights". It was therefore agreed by

TABLE I.—*Internal consistency (Cronbach's alpha) of ADHD impairment and symptom scale.*

Scale/score	Number of items per scale	Cronbach's alpha[a]	Mean (SD) score	
			ADHD group	Control group
ADHD symptom scale*[b]	8	0.87	3.9 (0.7) [c]	2.7 (0.8) [d]
Comorbid symptom scale*[b]	8	0.84	3.4 (0.7) [c]	2.5 (0.8) [d]
Conduct problems score*[e]	5	0.66	0.7 (1.1) [f]	0.3 (0.7) [g]
General impairment scale*	4	0.90	2.7 (1.2) [h]	1.8 (1.0) [i]
School impairment scale*[b]	9	0.84	2.7 (0.7) [c]	2.1 (0.7) [d]
School failure score*[b]	2	0.52	1.5 (1.3) [c]	0.5 (0.8) [d]
Home impairment scale*	7	0.79	2.1 (0.5) [h]	1.9 (0.4) [i]
Relationship impairment scale*	7	0.89	2.5 (0.9) [h]	1.9 (0.8) [i]
Perceived impact scale (ADHD only)	7	0.94	3.3 (1.3) [h]	
Perceived impairment scale (ADHD only)	10	0.87	3.5 (0.8) [h]	

ADHD: attention-deficit/hyperactivity disorder; SD: standard deviation. [a]Measure of internal consistency: Cronbach's alpha was calculated using the full European dataset (including data for all six countries), excluding respondents with impossible answers. Mean (SD) scale scores for the European are provided for information; [b]≥6 years old; [c]N.=489; [d] N.=365; [e]≥13 years old; [f] N.=243; [g] N.=231; [h] N.=531; [i] N.=515. *P<0.001 between groups.

the Steering Committee that this scale was not applicable to children <13 years. High scores represent greater impairment and vice versa.

Statistical analyses

Subjects with ADHD were compared with controls using *t*-tests for continuous data and chi-squared tests for categorical data. Where possible, responses were combined, for example, "I agree" and "I strongly agree" for some individual scale items. The results were analysed based on the various types of responses per subject. Participants were not required to answer all the questions and no data imputation was used. For the symptom and impairment scales, mean scale scores were calculated for all participants who answered at least half of the questions on a particular scale; participants with scores on all applicable scales were included in scale-related analyses. Correlations between the scores obtained on the various impact and symptom scales were investigated using Spearman's correlation.

Results

Study population

In total, 1291 parents/caregivers from six European countries participated in the survey; 56 participants gave implausible answers (such as an age at diagnosis that exceeded the declared age of the child) and were removed from the database. Thus, the total number of parents included in the European analyses was 1235, of whom 583 were parents of children with ADHD (ADHD group) and 652 were parents of children without ADHD (control group).

The total numbers of participants in Italy were 104 in the ADHD group and 105 in the control group. After exclusion of individuals with implausible answers, 83 (ADHD group) and 84 (control group) participants were included in the analysis. The mean (standard deviation [SD]) age of the participants was 41.5 (8.2) years in the ADHD group and 46.0 (14.3) years in the control group (P<0.05). There were 58 women (69.9%) in the ADHD group and 40 women (47.6%) in the control group. The mean (SD) age of the children reported on was 11.3 (3.9) years in the ADHD group and 12.5 (4.4) years in the control group. Table II shows the age, employment history and personal income of participants, child's age and number of school days the child missed.

Table III shows the marital status and educational level of participants, for the two groups, and Table IV shows the urban and non-urban location of the participants.

Self-reported psychiatric disorders affecting the parents/caregivers themselves are provided in Table V. There was a wide

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TABLE II.—*Age, number of jobs and personal income of parents/caregivers interviewed, and age and number of missed school days of children reported on.*

	ADHD group			Control group			t-test		
	N.	Mean (SD)	Median	N.	Mean (SD)	Median		df	P value
Parent age	83	41.5 (8.2)	42.0	84	46.0 (14.3)	46.0	2.5	132	<0.05
Number of jobs in past 10 years[a]	68	2.4 (1.8)	2.0	60	2.8 (5.8)	1.0	0.5	126	ns
Personal income (€ 1000)	69	25.6 (26.1)	20.0	63	23.6 (19.1)	20.0	-0.5	130	ns
Age of child reporting on	83	11.3 (3.9)	12.0	84	12.5 (4.4)	13.0	1.8	165	ns
Days of school missed	76	20.7 (30.5)	12.5	75	14.3 (15.3)	10.0	-1.6	149	ns

ADHD: attention-deficit/hyperactivity disorder; df: degrees of freedom; ns: not significant; SD: standard deviation. [a]Employed participants only.

TABLE III.—*Marital status and education of participants in ADHD and control groups.*

Marital status	ADHD group N.=82		Control group N.=83		Chi-squared	df	P value
	N.	%	N.	%			
Divorced	5	6.1	7	8.4	6.7	4	ns
Separated (separated from a marriage and living apart but not divorced)	4	4.9	6	7.2			
Widowed			2	2.4			
In a serious relationship but not married	27	32.9	15	18.1			
None of the above	46	56.1	53	63.9			
Education	N.=82		N.=84				
Medium	51	62.2	58	69.0	0.9		ns
High	31	37.8	26	31.0			

ADHD: attention-deficit/hyperactivity disorder; df: degrees of freedom; ns: not significant.

TABLE IV.—*Description of community inhabited by participants in the ADHD and control groups.*

Community	ADHD group N.=83		Control group N.=81		Chi-squared	df	P value
	N.	%	N.	%			
Urban (within a city)	42	50.6	35	43.2	4.0	2	ns
Suburban (in the suburbs of a city or in a town)	26	31.3	37	45.7			
Rural (in the country)	15	18.1	9	11.1			

ADHD: attention-deficit/hyperactivity disorder; df: degrees of freedom; ns: not significant.

TABLE V.—*Psychiatric disorders diagnosed by a doctor or other healthcare professional in parents/caregivers of children/adolescents with and without ADHD.*

Parent/caregiver diagnosed with:	ADHD group N.=83		Control group N.=84		Chi-squared	df	P value
	N.	%	N.	%			
ADHD, ADD or HD	28	33.7			34.0		<0.001
Depression	30	36.1	12	14.3	10.6		<0.001
Bipolar disorder	16	19.3			17.9		<0.001
Anxiety disorder(s)	27	32.5	13	15.5	6.7		<0.01
Insomnia or other sleep disorders	37	44.6	14	16.7	15.3		<0.001
Conduct disorder	16	19.3	2	2.4	12.4		<0.001
Oppositional defiant disorder	15	18.1	1	1.2	13.7		<0.001
Alcohol or drug abuse or dependence	13	15.7	3	3.6	7.0		<0.01
Personality disorder	15	18.1	1	1.2	13.7		<0.001
None of these	28	33.7	57	67.9	19.5		<0.001
Decline to answer			4	4.8	4.0		<0.05

ADHD: attention-deficit/hyperactivity disorder; ADD: attention deficit disorder; df: degrees of freedom; HD: hyperkinetic disorder.

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range of psychiatric disorders diagnosed in the parents of the ADHD group that are significantly higher than in the control group, including ADHD, insomnia, depression, bipolar disorder, anxiety disorders, oppositional defiant disorder (ODD) and conduct disorder (CD).

Survey results

Parents in the ADHD group tended to think that their child's experiences in childhood or in adolescence negatively influenced their child more than the parents in the control group (39% *vs.* 14.3%; P<0.001). Approximately one third (34.9%) of participants in the ADHD group compared with 8.4% in the control group (P<0.001) felt that bad memories of childhood and adolescence would bother their child in later life. Childhood and adolescence were felt to be stages of life that would have a negative impact on the future achievements of the individual with ADHD (36.1% *vs.* 9.6%; P<0.001) and be worse than that experienced by most of their peers (42.7% *vs.* 9.6%; P<0.001). Children with ADHD were described as being unable to pay attention to schoolwork for long periods of time (78.7% *vs.* 44%; P<0.001) and finding it difficult to concentrate (78.9% *vs.* 38.7%; P<0.001). The negative impact on the lives of children with ADHD is demonstrated by their mood, with those in the ADHD group more often reported than those in the control group to be angry (45.9% *vs.* 18.7%; P<0.01) or sad (31.6% *vs.* 17.3%; P<0.05). This can lead to more errors in social situations (57.9% *vs.* 17.3%; P<0.001). Such errors are also generated by a certain degree of impulsiveness in children with ADHD, who acted more frequently without thinking than the control group (74.7% *vs.* 35.1%; P<0.001). Thus, while 53.5% of parents in the control group thought that their child had a bright outlook on their future, only 34.2% of parents in the ADHD group considered the same for their child (P<0.05). This may also be influenced by the fact that he/she was described as less inclined to recognise good opportunities (33.3% *vs.* 50%; P<0.05). A lower percentage of parents in the ADHD group reported that their child was satisfied with him/herself than in the control group (48% *vs.* 74.7%; P<0.001), whereas a higher percentage reported that their child was more easily frustrated (55.4% *vs.* 23%; P<0.001) and irritable at school (50.7% *vs.* 23.6%; P<0.001). Children with ADHD were described as procrastinators, leaving tasks to the last minute (70.7% *vs.* 54.1%; P<0.05), meaning they are completed outside the allotted time (66.7% *vs.* 32.4%, P<0.001). Table VI shows other school-related data.

Outside school, children with ADHD were less able to make friends than children without ADHD (65.9% *vs.* 86.6%; P<0.01), and were less able to get along with their parents (67.1% *vs.* 81%; P<0.05) and relatives in general (59.4% *vs.* 77.5%; P<0.05). However, there was no significant difference between the ADHD and control groups with regard

TABLE VI.— *Performance at school in children with and without ADHD, as reported by parents.*

	ADHD group		Control group		Chi-squared	df	P value
	N.	%	N.	%			
Position in class	N.=67		N.=63				
Top	28	41.8	29	46.0	0.3	2	ns
Middle	27	40.3	24	38.1			
Bottom	12	17.9	10	15.9			
Ever experienced	N.=76		N.=75				
Had a tutor to help him/her with schoolwork	37	48 7	5	6.7	33.2		<0.001
Taken a special class to get extra help with schoolwork	11	14.5	4	5.3	3.5		ns
Repeated a grade	22	28.9	5	6 7	12.8		<0.001
Been expelled or suspended	22	28.9	4	5.3	14.8		<0.001
None of these	20	26.3	65	86.7	55.9		<0.001

ADHD: attention-deficit/hyperactivity disorder; df: degrees of freedom; ns: not significant.

TABLE VII.—*Conditions diagnosed by a doctor or other healthcare professional in children/adolescents with and without ADHD.*

	ADHD group N.=83		Control group N.=84		Chi-squared	df	P value
	N.	%	N.	%			
Child been diagnosed with:							
ADHD, ADD or HD	83	100.0			167.0		<0.001
Depression	12	14.5	3	3.6	6.1		<0.05
Bipolar disorder	13	15.7	1	1.2	11.4		<0.001
Anxiety disorder(s)	17	20.5	3	3.6	11.3		<0.001
Insomnia or other sleep disorders	14	16.9	4	4.8	6.4		<0.05
Conduct disorder	19	22.9	4	4.8	11.6		<0.001
Oppositional defiant disorder	15	18.1			16.7		<0.001
Alcohol or drug abuse or dependence	10	12.0	1	1.2	8.0		<0.01
Personality disorder	16	19.3	2	2.4	12.4		<0.001
None of these			70	83.3	119.1		<0.001
Decline to answer			2	2.4	2.0		ns

ADHD: attention-deficit/hyperactivity disorder; ADD: attention deficit disorder; df: degrees of freedom; HD: hyperkinetic disorder; ns: not significant.

to whether parents thought their child was liked by adults (64.5% *vs.* 71.8%).

Furthermore, children with ADHD were less likely to be invited to parties by their peers than those without ADHD (57.3% *vs.* 73.8%; P<0.05) and parents felt that their child's friendships were less important to them (62.7% *vs.* 78.6%; P<0.05).

With regard to psychiatric comorbidities, numerous differences were observed between the two groups. A summary of diagnosed comorbidities (for the ADHD group) and pathologies (for the control group), as reported by parents, is shown in Table VII. While significantly more adolescents with than without ADHD had been diagnosed with alcohol or drug abuse disorders (12% *vs.* 1.2%; P<0.01), there was no difference between the two groups with regard to the consumption of alcohol or drugs in teenagers aged 13 years and older. However, teenagers with ADHD appeared more prone to eating disorders than those without ADHD (36.4% *vs.* 12%; P<0.01).

Impairment and symptom scale results

Table I shows the internal consistency of the scales used to assess both the symptoms and their impact on the children in both groups using Cronbach's alpha. Figure 1 summarises results from these assessment scales for symptoms and impairments; significantly greater impairments (P<0.001) were observed in the the ADHD group versus the control group for general impairment, school impairment, school failure, relationship impairment, home impairment, ADHD symptoms and comorbid symptoms.

Additional information of interest can be obtained by studying the correlations (Spearman's r) between the scores obtained on the various impairment and symptom scales. In children with ADHD, the home impairment scale appears to correlate with the ADHD symptom scale (r=0.321; P<0.001), the comorbid symptoms scale (r=0.231; P<0.05), the school impairment scale (r=0.478; P<0.001), the school failure scale (r=0.208; P<0.02) and the scale that assesses difficulties regarding relationships with others (r=0.432; P<0.01). The school impairment scale correlates with the home impairment scale (above), as well as with the ADHD (r=0.465; P<0.001) and comorbid (r=0.420; P<0.001) symptom scales, and with the school failure scale (r=0.345; P<0.001) and the scale relating to relationship difficulties (r=0.647; P<0.001). Lastly, on the scale for relationship difficulties correlates with the home impairment scale (above), the ADHD symptom scale (r=0.180; P<0.03), comorbid symptoms scale (r=0.386; P<0.001), and the school impairment (above) and school failure (r=0.320; P<0.001) scales.

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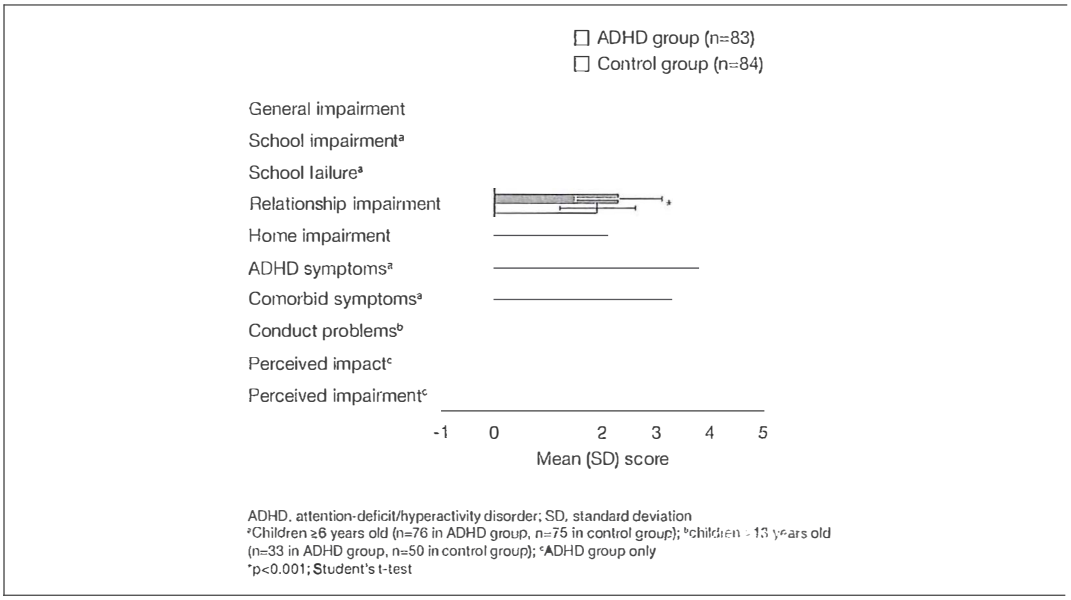

Figure 1.—ADHD impairment and symptom scale scores. ADHD: attention-deficit/hyperactivity disorder; SD: standard deviation. [a]Children ≥6 years old (N.=76 in ADHD group, N.=75 in control group); [b]children ≥13 years old (N.=33 in ADHD group, N.=50 in control group); [c]ADHD group only. *P<0.001: Student's *t* test.

Discussion

This paper assessed the impact of ADHD on the lives of Italian children. The results show that ADHD interfered substantially with the wellbeing of children both at home and at school. It should be noted that there is a greater prevalence of psychiatric disorders among the parents of children with than without ADHD.

Responses to survey questions showed that more parents of children in the ADHD group than those in the control group felt that their child would have unpleasant memories of their childhood/adolescence. Contrary to expectations, relationships with adults in general were not found to be overly negative for children with ADHD and did not differ from non-ADHD peers. However, there appears to be a critical difference between the two groups in their relationships with authority, specifically parents and teachers. For these two categories of adults, there was a marked difficulty in the relationships and behaviours for the group of children with ADHD. The general perception of the child was one of ineffectiveness, a child who makes trouble, with inappropriate behaviour for the context, and who has a less than bright future. This feeling was reinforced by failure at school, the more common need in the ADHD group than the control group for private lessons at home to help with schoolwork, and an understandable feeling of frustration and, not infrequently, dissatisfaction with oneself and depressed mood. Children with ADHD were frequently described as procrastinators, putting off tasks until the last minute and often missing deadlines. Parents of children with ADHD felt that they were not readily accepted, and friends tended to associate with them less, and to invite them to parties less frequently, compared with parents of children in the control group.

Overall, these results agree with previous studies conducted in other countries,[12, 23-27] and with the overall European data obtained in the LIS.[21] It is likely that the impact on the social and school lives of children with ADHD described here is also due to the existence of other behavioural problems, such as ODD and CD; this is confirmed by recent Italian studies carried out on clinical

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samples of children with ADHD.[28] Other disorders reported for children with ADHD are those already described in the literature, including generalised anxiety, greater tendency to alcoholism and bipolar disorder.[29] The impairment and symptom scales generally confirm this finding (good Cronbach alpha scores). Naturally there is a greater frequency of ADHD and psychiatric comorbidity symptoms in the ADHD group compared with the control group, confirming that the choice of study sample was correct. Furthermore, the scales support the general difficulties faced by children with ADHD arising from the impact of the disorder, as well as, in particular, impairment at school, leading to school failure and problems in the home environment.

The impairment and symptom scales highlighted difficulties in relationships with others and a perceived impairment that was considerably higher in the ADHD group than the control group. Correlation of these scales also showed that the greater the ADHD symptomatology, the more marked the impact of the disorder on the child in the home, at school and in relationships with others. Impairments at school, at home and in relationships were also correlated with level of comorbidity. Accumulative impairment from both ADHD and comorbidities will increase the difficulty in achieving good outcomes in these settings. In addition, school failure correlates with impairment at school and in relationships with others.

Limitations of the study

One limitation of this study related to the age of the participants, which was significantly lower in the parents of children with ADHD than in the control group. As other socio-demographic variables did not differ significantly between groups, this factor should not substantially affect the results of the survey. Of greater importance were the limitations of the data collection technique and the sample studied could have been improved. Overall survey response rate was unknown, the effect relating to the sex of the child could not be assessed, children in the ADHD group were not questioned directly, and the diagnosis of ADHD was not confirmed by a healthcare professional. Furthermore, in the control group, the absence of ADHD was assumed based on the absence of a medical diagnosis; therefore, some children with ADHD may have gone unrecognised. Although some respondents were excluded based on implausible answers, other potential data entry errors could not be controlled for. The study may also be affected by the fact that the participants were recruited on the basis of market research and interviewed online, not in person. Therefore, participants represented a select, well-educated, IT-literate population willing to participate in the survey and who may have greater awareness of the disorder, its symptoms and impairments. Customised recruitment through healthcare providers in Italy may have also impacted the ADHD sample in this country.

Overall, the data confirm those obtained in other studies of children with ADHD, some of which were performed in Italy, such as those exploring comorbidity with bipolar disorder and CD.[28, 29]

Conclusions

To our knowledge, this is the first study carried out in Italy on the impact of ADHD in the child and adolescent population. The results clearly indicate that Italian children are markedly affected by the impairment in their daily lives caused by the disorder. There is clear impairment both at home and at school that affects the child's self-esteem and capabilities. It is important, therefore, that children and adolescents with ADHD in Italy receive adequate assistance, prompt diagnosis and pharmacological or non-pharmacological therapies that are satisfactory and appropriate.

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Similar analyses of these data were presented at the 69th National Congress of the Italian Society of Pediatrics (*Società Italiana di Pediatria*, SIP), Bologna, Italy, 8-10 May 2013: Urania Loprieno and Renato Donfrancesco, *Impatto del disturbo da deficit di attenzione e iperattività sulla vita dei bambini e degli adolescenti italiani: risultati dello studio europeo 'lifetime impairment survey'.*

Conflicts of Interest.—RD has received consulting income from Shire and Novartis, and financial support from Shire and Eli Lilly for participation in congresses. UL is an employee of Shire Pharmaceuticals, Italy. Shire develops and manufactures treatments for psychiatric disorders including ADHD.

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Metilfenidato e ADHD

Ole Jacob Storeb et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane review with meta-analyses and trail sequential analyses of randomized clinical trails. BMJ 2015;351:h5203 doi: 10.1136/bmj.h5203

Obiettivo

Valutare i benefici e gli effetti avversi del Metilfenidato nel trattamento di bambini e adolescenti con ADHD mediante revisione sistematica della letteraura e metanalisi

Popolazione	Sono stati ricercati tutti gli RCT a gruppi paralleli o crossover pubblicati in qualsiasi lingua sul Cochrane Central Register of Controlled Trials, Medline, Embase, CINHAL, PsycINFO e registro dei trails clinici. La diagnosi di ADHD doveva essere in accordo con la definizione del DSM (terza, quarta o quinta edizione) o ICD9 o ICD 10; almeno il 75% dei partecipanti dovevano avere meno di 19 anni e un QI >70.
Intervento	Metilfenidato comparato con placebo o con nessun altra terapia
Oucomes/Esiti	PRIMARI: i sintomi di ADHD (disattenzione, iperattività e impulsività) sia a breve (entro sei mesi) che a lungo termine (oltre 6 mesi); effetti avversi definiti gravi (morte, rischio di morte, ospedalizzazione, aumento della disabilità). SECONDARI: tutti gli eventi avversi definiti come non gravi (alterazioni della crescita, problemi cardiologici, neurologici, gastroenterologici e disturbi del sonno e dell'appetito), comportamento generale e qualità di vita. Tutti gli studi considerati sono stati valutati e classificati ad alto, incerto o basso rischio di bias secondo le linee guida Cochrane
Tempo	tutti gli articoli pubblicati entro Febbraio 2015

Risultati principali

Sono stati selezionati 185 RCT di cui 38 RCT con gruppi paralleli (n=5111, durata media del trattamento 49 giorni) e 147 crossover RCT (n=7134, durata media del trattamento di 14 giorni). L'età media in tutti gli studi era di 9.7 anni.
L'analisi suggerisce un effetto positivo del metilfenidato sull'attenzione scolastica in 19 studi a gruppi paralleli (differenza media standardizzata -0.77, IC95% tra -0.90 e –0.64, n=1698), corrispondenti a una differenza media di -9.6 punti sulla scala di valutazione dell'ADHD (punteggio scala 0-100 con differenza minima significativa fissato, 6.6 punti).
Negli studi a lungo termine l'effetto sembra essere minore (DMS -0.47, IC95% da -0,72 a -0,4, uno studio 253 partecipanti) rispetto a quelli a breve termine (-0,81, IC95% da -0.94 a -0.68, 18 studi con 1445).
Non ci sono evidenze che il metilfenidato sia associato a un aumento di eventi avversi gravi (RR 0.98, nove studi, n=1532), TSA effetto intervento aggiustato RR 0.91.
Il metilfenidato è stato associato con un rischio di effetti avversi non gravi aumentato (1.29 in 21 studi n=3123; TSA aggiustato RR 1.29): i più comuni sono risultati la perdita d appetito e i disturbi del sonno.
Il comportamento generale sembrava migliorare con il metilfenidato (SMD -0.87, 5 studi, n=668).
Nella meta-analisi effettuata su tre studi n=514, il punteggio del questionario sanitario pediatrico a cui rispondevano i genitori mostrava una differenza di -8 punti (scala 0-100) con un miglioramento della qualità di vita.
Il 96.8% degli studi risultava ad alto rischio di errori rispetto alle linee guida Cochrane.
Tutti i risultati sono stati valutati di bassa qualità.

Conclusioni

I risultati suggeriscono che nei bambini e negli adolescenti con ADHD l'utilizzo del Metilfenidato può migliorare

l'attenzione scolastica, il comportamento generale e la qualità di vita riportata dai genitori. Tuttavia considerando l'alto rischio di bias presentato dagli studi ce la bassissima qualità dei risultati l'entità degli effetti è incerta.
Il metilfenidato è associato con un aumentato rischio di effetti avversi non gravi ma non di quelli gravi.

Altri studi sull'argomento

Il Metifenidato è un farmaco che viene utilizzato già da lungo tempo nella terapia dell'ADHD. In passato diverse revisioni e meta-analisi hanno descritto i miglioramenti che ess determina, soprattutto nel breve periodo, sulla sintomatologia che presentano i bambini e adolescenti affetti da ADHD. Queste revisioni presentano degli evidenti limiti metodologici, mancanza di ricerca esaustiva degli studi, non utilizzo di scale validate per misurare effetti ed eterogeneità degli outcomes considerati, mancanza di analisi dei risultati nei diversi sottotipi di ADHD e comorbilità associate. Inoltre la qualità dei lavori selezionati e la forza dei risultati ottenuti non viene correttamente valutata ed esplicitata.

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Che cosa aggiunge questo studio

Rispetto alle precedenti revisioni e meta-analisi pubblicate sugli effetti del metilfenidato, quest'ultimo lavoro utilizza una metodologia molto più rigorosa sia nella ricerca degli RCT che nella valutazione della qualità dei risultati ottenuti. Pur confermando il significativo beneficio clinico ottenuto sulla sintomatologia, qualità di vita e comportamento generale, la forza di questa evidenza appare debole e meritevole di nuovi lavori di maggiore qualità e con follow-up di lunga durata, in particolare per verificare eventuali effetti avversi gravi.

Commento

Validità interna

Disegno dello studio: gli autori hanno progettato e sviluppato questa revisione seguendo il manuale delle revisioni sistematiche della Cochrane, hanno ricercato in maniera esaustiva tutti gli RCT (anche quelli non pubblicati); le uniche banche dati non consultate sono state quelle della FDA e dell'EMA.
I criteri di inclusioni e gli outcomes primari e secondari sono stati definiti in modo chiaro, rispettosi della significatività clinica, utilizzando per la misurazione degli esiti delle scale di valutazione validate e definendo a priori la differenza minima significativa.
L'estrazione dei dati è stata effettuata da revisori indipendenti.
La qualità degli studi selezionati è stata valutata in accordo con le linee guida Cochrane; la forza delle evidenze ottenute è stato stabilito mediante GRADE.

Esiti: purtroppo il 96,8% degli RCT considerati sono risultati essere ad alto rischio di bias; solo 6 dei 185 studi sono risultati a basso rischio di bias. Le cause principali sono da riferire alla presenza di conflitti si interesse, alla mancanza di cecità sia dei partecipanti che dei valutatori, alla presenza di bias sia nella selezione dei partecipanti che nella selezione dei dati.
Un altro limite è rappresentato dal troppo breve periodo di follow-up (durata media è risultata di 2 mesi), con pochi studi con più di sei mesi di durata. In particolare la rilevazione degli eventi avversi gravi necessita di tempi di follow-up di lungo termine; anche gli effetti sul rendimento scolastico necessitano di dati più robusti nel trattamento prolungato nel tempo.

Trasferibilità

Dal giugno 2011 è attivo in Lombardia, come in ogni regione d'Italia, il registro regionale per l'ADHD che raccoglie i dati dei 18 centri specialistici che si occupano del percorso diagnostico-terapeutico dei bambini e adolescenti che soffrono di questo disturbo. I dati finora raccolti mostrano che i bambini segnalati e successivamente diagnosticati (3,5 per mille) sono ampiamente inferiori rispetto alla prevalenza attesa dell'ADHD (2-5%) e che di questi solamente il 15% viene sottoposto a una terapia farmacologica. Anche se i risultati di questa revisione non hanno raggiunto livelli di forte evidenza e anche se sono necessari ulteriori studi con follow-up di lungo periodo, sembra ragionevole considerare

il metilfenidato come uno dei possibili trattamenti per migliorare la vita di questi soggetti. La situazione italiana, che permette il suo utilizzo solo nei centri specialistici dopo un iter diagnostico molto rigoroso e accompagnato da interventi psicoeducativi, ci protegge da un uso non corretto e generalizzato.

Scheda redatta da Riccardo Cazzaniga e Gian Piero Del Bono e commentata da:
V. Casotti, R. Cazzaniga, G.P. Del Bono, V. Decimi, M. Gozzi, A. Lazzerotti, G. Lietti, L. Martelli, M.L. Melzi, M. Pelagatti, A. Pirola, F. Ragazzon, P. Rogari, C. Ronconi, E. Sala, F. Sala, M.T. Tartero, F. Zanetto.
(gruppo di lettura ACP Lombardia)

WebCenter

Questionario per la valutazione della Newsletter ADHD

Gent.mi lettori,

questo è un invito alla compilazione del questionario on-line sulla Newsletter ADHD.

Tale operazione Vi impegnerà per 2 minuti al massimo accedendo al seguente link:

http://www.adhd.marionegri.it/index.php/newsletter/valutazione-newsletter

Si confida nella Vs preziosa collaborazione.

Per ricevere la newsletter iscriversi al seguente indirizzo:
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*".

IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI
DIPARTIMENTO DI SALUTE PUBBLICA
Laboratorio per la Salute Materno Infantile
Via Giuseppe La Masa, 19 - 20156 Milano MI - Italia - www.marionegri.it tel
+39 02 39014.511 - fax +39 02 3550924 - mother_child@marionegri.i