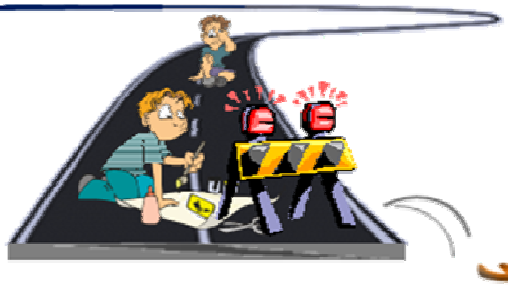
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD GENNAIO 2015

Am J Med Genet Part B Neuropsychiatr Genet. 2015;168:45-53.

INTERACTIONS BETWEEN MAOA AND SYP POLYMORPHISMS WERE ASSOCIATED WITH SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHINESE HAN SUBJECTS.

Gao Q, Liu L, Li H-M, et al.

As candidate genes of attention-deficit/hyperactivity disorder (ADHD), monoamine oxidase A (MAOA), and synaptophysin (SYP) are both on the X chromosome, and have been suggested to be associated with the predominantly inattentive subtype (ADHD-I). The present study is to investigate the potential gene-gene interaction (GnullG) between rs5905859 of MAOA and rs5906754 of SYP for ADHD in Chinese Han subjects. For family-based association study, 177 female trios were included. For case-control study, 1,462 probands and 807 normal controls were recruited. The ADHD Rating Scale-IV (ADHD-RS-IV) was used to evaluate ADHD symptoms. Pedigree-based generalized multifactor dimensionality reduction (PGMDR) for female ADHD trios indicated significant gene interaction effect of rs5905859 and rs5906754. Generalized multifactor dimensionality reduction (GMDR) indicated potential gene-gene interplay on ADHD RS-IV scores in female ADHD-I. No associations were observed in male subjects in case-control analysis. In conclusion, our findings suggested that the interaction of MAOA and SYP may be involved in the genetic mechanism of ADHD-I subtype and predict ADHD symptoms.

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Applied Psychophysiology and Biofeedback. 2014 Dec;39:193-202.

THE EFFECTS OF INDIVIDUAL UPPER ALPHA NEUROFEEDBACK IN ADHD: AN OPEN-LABEL PILOT STUDY.

Escolano C, Navarro-Gil M, Garcia-Campayo J, et al.

Standardized neurofeedback (NF) protocols have been extensively evaluated in attention-deficit/hyperactivity disorder (ADHD). However, such protocols do not account for the large EEG heterogeneity in ADHD. Thus, individualized approaches have been suggested to improve the clinical outcome. In this direction, an open-label pilot study was designed to evaluate a NF protocol of relative upper alpha power enhancement in fronto-central sites. Upper alpha band was individually determined using the alpha peak frequency as an anchor point. 20 ADHD children underwent 18 training sessions. Clinical and neurophysiological variables were measured pre- and post-training. EEG was recorded pre- and post-training, and pre- and post-training trials within each session, in both eyes closed resting state and eyes open task-related activity. A power EEG analysis assessed long-term and within-session effects, in the trained parameter and in all the sensors in the (1–30) Hz spectral range. Learning curves over sessions were assessed as well. Parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity. Neurophysiological tests showed an improvement in working memory, concentration and impulsivity (decreased number of commission errors in a continuous performance test). Relative and absolute upper alpha power showed long-term enhancement in task-related activity, and a positive learning curve over sessions. The analysis of within-session effects showed a power decrease (“rebound” effect) in task-related activity, with no significant effects during training trials. We conclude that the enhancement of the individual upper alpha power is effective in improving several measures of clinical outcome and cognitive performance in ADHD. This is the first NF study evaluating such a protocol in ADHD. A controlled evaluation seems warranted due to the positive results obtained in the current study.

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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.

Asia-Pacific Psychiatry. 2014;6:379-85.

NATIONWIDE RATE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER DIAGNOSIS AND PHARMACOTHERAPY IN KOREA IN 2008-2011.

Hong M, Kwack YS, Joung Y-S, et al.

Introduction: Using the National Health Insurance database in Korea, we examined the diagnostic and treatment incidence and comorbidity of attention-deficit hyperactivity disorder (ADHD).

Methods: During 2007-2011, we chose subjects aged 6-18 years, who had at least one medical claim containing an International Classification of Diseases, 10th Revision code for diagnosis of ADHD (F90.0) with no medication use in the previous 360 days. Then, we analyzed the data for 2008-2011 to determine the mean annual incidence and prevalence of newly diagnosed and medicated patients, as well as comorbidity.

Results: The average annual diagnostic incidence of ADHD was 0.357% (29,310.5/8,218,252), and the incidence of medication use for ADHD was 0.248% (20,340.3/8,218,252) during 2008-2011 with no significant annual difference. The transition rate from diagnosis to medication among newly diagnosed ADHD patients was 69%. The overall prevalence rate of ADHD diagnosis and medication during 2008-2011 was 0.799% (65,702/8,218,252) and 0.610% (50,127/8,218,252), respectively. Among newly diagnosed patients with ADHD, osmotic-controlled release oral delivery system methylphenidate was the most commonly used first medication, and depression was the most common comorbid psychiatric diagnosis.

Discussion: This is the first report of the nationwide data on the current diagnosis and pharmacotherapy of ADHD in the whole population aged 6-18 years. We need further investigation to find the factors of low diagnostic and treatment incidence compared with high prevalence of ADHD.

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Assessment. 2014 Dec;21:694-705.

PSYCHOMETRIC PROPERTIES OF THE PARENT AND TEACHER ADHD RATING SCALE (ADHD-RS): MEASUREMENT INVARIANCE ACROSS GENDER, AGE, AND INFORMANT.

Makransky G, Bilenberg N.

Attention deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in childhood and adolescence. Rating the severity of psychopathology and symptom load is essential in daily clinical practice and in research. The parent and teacher ADHD-Rating Scale (ADHD-RS) includes inattention and hyperactivity/impulsivity subscales and is one of the most frequently used scales in treatment evaluation of children with ADHD. An extended version, mADHD-RS, also includes an oppositional defiant disorder subscale. The partial credit Rasch model, which is based on item response theory, was used to test the psychometric properties of this scale in a sample of 566 Danish school children between 6 and 16 years of age. The results indicated that parents and teachers had different frames of reference when rating symptoms in the mADHD-RS. There was support for the unidimensionality of the three subscales when parent and teacher ratings were analyzed independently. Nonetheless, evidence for differential item functioning was found across gender and age for specific items within each of the subscales. The findings expand existing psychometric information about the mADHD-RS and support its use as a valid and reliable measure of symptom severity when used in age- and gender-stratified materials.

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Australian Journal of Guidance and Counselling. 2014 Dec;24:227-42.

ADHD AND ADAPTABILITY: THE ROLES OF COGNITIVE, BEHAVIOURAL, AND EMOTIONAL REGULATION.

Burns E, Martin AJ.

Adaptability has been recently proposed as cognitive, behavioural, and emotional regulation assisting individuals to effectively respond to change, uncertainty and novelty. Given students with attention-deficit/hyperactivity disorder (ADHD) have known impairments with regulatory functions, they may be at particular disadvantage as they seek to navigate change, uncertainty, and novelty in their academic lives. This discussion summarises current research of adaptability as relevant to students with ADHD, presents preliminary exploration of data that suggests evidence for the difficulties students with ADHD face with regards to adaptability (particularly in regards

to cognitive and behavioural regulation), and concludes with suggestions for counselling, psychological, and educational practices aimed at enhancing the adaptability of students with ADHD.

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Behav Brain Funct. 2014 Nov;10.

THE ROLE OF THE BRAIN-DERIVED NEUROTROPHIC FACTOR GENOTYPE AND PARENTING IN EARLY LIFE IN PREDICTING EXTERNALIZING AND INTERNALIZING SYMPTOMS IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Park S, Kim BN, Kim Jw, et al.

Background: We aimed to determine whether early parenting is associated with externalizing and internalizing symptoms in children with attention-deficit hyperactivity disorder (ADHD) and whether such an association is affected by the brain-derived neurotrophic factor (BDNF) val66met polymorphism.

Methods: The participants included 92 patients with ADHD aged 6–15 years. Measures of parenting in early life and externalizing and internalizing symptoms and the genotype of the BDNF Val66Met polymorphism were obtained.

Results: The degree to which the baby's autonomy was allowed was significantly and negatively correlated with the CDI scores in ADHD children ($r = -0.38$, $p = 0.005$). After adjusting for the child's gender, the child's age, the family's gross annual income, and the maternal education level, there was a significant interaction for the BDNF genotype and mother's positive feelings about caring in relation to the development of childhood anxiety/depression in ADHD children ($F = 2.51$, $p = 0.011$).

Conclusions: Our results provide evidence of an interaction between the BDNF met allele and early parenting on the development of depression/anxiety symptoms.

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BMC Psychiatry. 2014;304.

PATIENT CHARACTERISTICS ASSOCIATED WITH TREATMENT INITIATION AMONG PAEDIATRIC PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN A NATURALISTIC SETTING IN CENTRAL EUROPE AND EAST ASIA.

Hong J, Novick D, Treuer T, et al.

Background: Cultural views of Attention-Deficit/Hyperactivity Disorder (ADHD), differing healthcare systems and funding mechanisms, and the availability of mental health services can greatly influence the perceptions, diagnosis, and treatment of ADHD. There is, however, lack of information about treatment practice and the treatment decision-making process for ADHD, particularly in non-Western countries. Our study compared characteristics of paediatric patients newly diagnosed with ADHD symptoms who did and who did not initiate treatment, and also examined whether any differences varied by region in Central Europe and East Asia.

Methods: Data were taken from a 1-year prospective, observational study that included 1,068 paediatric patients newly diagnosed with ADHD symptoms. Clinical severity was measured using the Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) scale and the Child Symptom Inventory-4 (CSI-4) checklist. Logistic regression was used to explore patient characteristics associated with treatment initiation (pharmacotherapy and/or psychotherapy) at baseline for each region.

Results: A total of 74.3% of patients initiated treatment at baseline (78.3% in Central Europe and 69.9% in East Asia). Of these, 48.8% started with both pharmacotherapy and psychotherapy in Central Europe, and only 17.1% did so in East Asia. The level of clinical severity was highest in the combination treatment group in Central Europe, but was highest in the psychotherapy only group in East Asia. In East Asia, treatment initiation was associated with being older, being male, and having a higher CGI-ADHD-S score. In Central Europe, treatment initiation was associated with parental psychological distress, having a higher CSI-4 score, and not being involved in bullying.

Conclusions: Although factors associated with treatment initiation differed to some extent between Central Europe and East Asia, clinical severity appeared to be one of the most important determinants of treatment initiation in both regions. However, the choice between pharmacotherapy and psychotherapy, either alone or in combination, varied substantially across the regions.

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Brain and Behavior. 2014;4:602-14.

WITHHOLDING AND CANCELING A RESPONSE IN ADHD ADOLESCENTS.

Bhaijiwala M, Chevrier A, Schachar R.

Background: Deficient response inhibition in situations involving a trade-off between response execution and response stopping is a hallmark of attention deficit hyperactive disorder (ADHD). There are two key components of response inhibition; reactive inhibition where one attempts to cancel an ongoing response and prospective inhibition is when one withholds a response pending a signal to stop. Prospective inhibition comes into play prior to the presentation of the stop signal and reactive inhibition follows the presentation of a signal to stop a particular action. The aim of this study is to investigate the neural activity evoked by prospective and reactive inhibition in adolescents with and without ADHD.
Methods: Twelve adolescents with ADHD and 12 age-matched healthy controls (age range 9-18) were imaged while performing the stop signal task (SST).
Results: Reactive inhibition activated right inferior frontal gyrus (IFG) in both groups. ADHD subjects activated IFG bilaterally. In controls, prospective inhibition invoked preactivation of the same part of right IFG that activated during reactive inhibition. In ADHD subjects, prospective inhibition was associated with deactivation in this region. Controls also deactivated the medial prefrontal cortex (MPFC) during prospective inhibition, whereas ADHD subjects activated the same area.
Discussion: This pattern of activity changes in the same structures, but in opposite directions, was also evident across all phases of the task in various task-specific areas like the superior and middle temporal gyrus and other frontal areas.
Conclusion: Differences between ADHD and control participants in task-specific and default mode structures (IFG and MPFC) were evident during prospective, but not during reactive inhibition. We examined how neural activity evoked during prospective reactive inhibition varies in adolescents with and without attention deficit hyperactive disorder (ADHD).

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Child Adolesc Ment Health. 2014;19:251-58.

BEHAVIOURAL TREATMENT RECOMMENDATIONS IN CLINICAL PRACTICE GUIDELINES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SCOPING REVIEW.

Vallerand IA, Kalenchuk AL, McLennan JD.

Background: The extent of behavioural treatment recommendations described in attention-deficit/hyperactivity disorder (ADHD) practice guidelines has not been examined.
Method: A scoping review identified eight agency-based ADHD practice guidelines. Key components of behavioural treatment recommendations were summarized.
Results: All guidelines mentioned behavioural treatment as a consideration for managing ADHD, however, the extent to which they were detailed varied. Most guidelines provided lists of behavioural techniques but with minimal specifics regarding treatment delivery.
Conclusions: There is far less detailing of behavioural approaches compared to pharmacological treatments for ADHD. Greater detailing of evidence-based behavioural approaches may foster improved delivery of high-quality behaviour treatment.

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Child Adolesc Psychiatr Clin North Am. 2015 Jan;24:79-97.

PSYCHOSOCIAL INTERVENTIONS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: UPDATE.

Antshel KM.

Attention-deficit/hyperactivity disorder (ADHD) is the most common reason for referral to child and adolescent psychiatry clinics. Although stimulant medications represent an evidence-based approach to managing ADHD, psychosocial interventions for child/adolescent ADHD target functional impairments as the intervention goal, and rely heavily on behavioral therapy techniques and operant conditioning principles. Evidence-based psychosocial interventions for managing pediatric ADHD include behavioral parent training, school-based interventions relying on behavioral modification, teaching skills, and operant conditioning principles, and intensive summer treatment

programs. The use of conjoint psychosocial treatments with ADHD medications may enable lower doses of each form of treatment.

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Child Psychiatry Hum Dev. 2014 Dec;45:765-75.

ATTRIBUTIONS FOR PARENTS' BEHAVIOR BY BOYS WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Colalillo S, Williamson D, Johnston C.

Attributions for parents' behavior were examined in a sample of boys with and without Attention-Deficit/Hyperactivity Disorder (ADHD). Sixty-six boys (mean age = 9.75 years) rated attributions for their mothers' and their fathers' behavior, across positive and negative scenarios, and along four attribution dimensions (parent ability, parent effort, task difficulty, and child responsibility). Three-way interactions emerged among child ADHD status, parent gender, and attribution type, and among scenario valence, parent gender, and attribution type. All children rated attributions higher in the positive scenarios, and attributions of child responsibility higher for fathers than mothers. Children rated task-related attributions higher for mothers in negative scenarios, but higher for fathers in positive scenarios. Boys with ADHD rated child responsibility attributions higher than controls, across all scenarios. Results highlight important differences in children's perceptions of their parents' behavior that may have implications for understanding parent–child relationships in families of children with and without ADHD.

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Child Psychiatry Hum Dev. 2014 Dec;45:675-85.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DIMENSIONS AND SLUGGISH COGNITIVE TEMPO SYMPTOMS IN RELATION TO COLLEGE STUDENTS' SLEEP FUNCTIONING.

Becker SP, Luebbe AM, Langberg JM.

This study examined separate inattentive, hyperactive, and impulsive dimensions of attention-deficit/hyperactivity disorder (ADHD), as well as sluggish cognitive tempo (SCT) symptoms, in relation to college students' sleep functioning. Participants were 288 college students (ages 17–24; 65 % female; 90 % non-Hispanic White; 12 % self-reported having an ADHD diagnoses) who completed measures of ADHD/SCT symptoms and sleep functioning. Participants reported obtaining an average of 6.8 h of sleep per night (only 26 % reported obtaining =8 h of sleep) and having a sleep onset latency of 25 min. 63 % were classified as "poor sleepers," and poor sleepers had higher rates of ADHD and SCT symptoms than "good sleepers". Path analysis controlling for ADHD status and psychiatric medication use was used to determine associations between psychopathology and sleep functioning domains. Above and beyond covariates and other psychopathologies, hyperactivity (but not impulsivity) was significantly associated with poorer sleep quality, longer sleep latency, shorter sleep duration, and more use of sleep medications. SCT symptoms (but not inattention) were significantly associated with poorer sleep quality and increased nighttime sleep disturbance (e.g., having bad dreams, waking up in the middle of the night, feeling too cold or too hot). Both inattention and SCT were associated with greater daytime dysfunction. Regression analyses demonstrated that hyperactivity predicted sleep quality above and beyond the influence of daytime dysfunction, and inattention and SCT predicted daytime dysfunction above and beyond sleep quality. Further studies are needed to examine the interrelations of nighttime sleep functioning, ADHD/SCT, and daytime dysfunction, as well to elucidate mechanisms contributing to related functional impairments.

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Clin Pediatr. 2014;54:164-73.

DIFFERENTIAL RESPONSE PROFILES IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: TREATMENT WITH ATOMOXETINE.

Wietecha LA, Wang S, Saylor KE, et al.

Atomoxetine has been shown to be safe and effective in the treatment of attention-deficit/hyperactivity disorder (ADHD). The purpose of this post hoc analysis was to examine response trajectories of pediatric patients treated

with atomoxetine. Data were pooled from 7 atomoxetine double-blind, placebo-controlled clinical trials conducted in pediatric patients between November 1998 and June 2004. Growth mixture modeling was applied to the investigator-rated ADHD rating scale (ADHDRS-Inv) and Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scores in the randomized acute phase (6-9 weeks) to explore whether there were groups of patients who differed in their response to atomoxetine. Classification and regression tree analyses were performed to identify predictors that can help categorize subjects to different response profiles. Patients (N = 925) were mostly male (73%) and of the combined subtype (74%). Most patients had a response pattern characterized by gradual, modest improvement, while a smaller group experienced early, robust improvement.

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Current Opinion in Clinical Nutrition and Metabolic Care. 2015.

CURRENT EVIDENCE AND FUTURE DIRECTIONS FOR RESEARCH WITH OMEGA-3 FATTY ACIDS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gow RV, Hibbeln JR, Parletta N.

PURPOSE OF REVIEW: Nutritional insufficiencies of nutrients such as omega-3 highly unsaturated fatty acids (HUFAs), vitamins and minerals have been linked to suboptimal developmental outcomes including attention deficit hyperactivity disorder (ADHD). Although the predominant treatment is currently psychostimulant medications, randomized clinical trials with omega-3 HUFAs have reported small-to-modest effects in reducing symptoms of ADHD in children despite arguable individual methodological and design misgivings

RECENT FINDINGS: This review presents, discusses and critically evaluates data and findings from meta-analytic and systematic reviews and clinical trials published within the last 12 months. Recent trajectories of this research are discussed, such as comparing eicosapentaenoic acid and docosahexaenoic acid and testing the efficacy of omega-3 HUFAs as an adjunct to methylphenidate. Discussion includes highlighting limitations and potential future directions such as addressing variable findings by accounting for other nutritional deficiencies and behavioural food intolerances

SUMMARY: The authors conclude that given the current economic burden of ADHD, estimated in the region of $77 billion in the USA alone, in addition to the fact that a proportion of patients with ADHD are either treatment resistant, nonresponders or withdraw from medication because of adverse side-effects, the investigation of nonpharmacological interventions including omega-3 HUFAs in clinical practice warrants extrapolating.

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Drug Alcohol Depend. 2015;147:183-89.

ASSOCIATION OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND CONDUCT DISORDER WITH EARLY TOBACCO AND ALCOHOL USE.

Brinkman WB, Epstein JN, Auinger P, et al.

Background: The association of attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) with tobacco and alcohol use has not been assessed in a young adolescent sample representative of the U.S. population.

Methods: Data are from the 2000-2004 National Health and Nutrition Examination Survey, a cross-sectional sample representative of the U.S. population. Participants were age 12-15 years (N= 2517). Exposure variables included diagnosis of ADHD and CD, and counts of ADHD and CD symptoms based on caregiver responses to the Diagnostic Interview Schedule for Children. Primary outcomes were adolescent-report of any use of tobacco or alcohol and age of initiating use. Multivariate logistic regression and Cox proportional hazard models were conducted.

Results: Adolescents with ADHD + CD diagnoses had a 3- to 5-fold increased likelihood of using tobacco and alcohol and initiated use at a younger age compared to those with neither disorder. Having ADHD alone was associated with an increased likelihood of tobacco use but not alcohol use. Hyperactive-impulsive symptom counts were not independently associated with any outcome, while every one symptom increase in inattention increased the likelihood of tobacco and alcohol use by 8-10%. Although participants with a diagnosis of CD alone (compared to those without ADHD or CD) did not have a higher likelihood of tobacco or alcohol use, for every one symptom increase in CD symptoms the odds of tobacco use increased by 31%.

Conclusions: ADHD and CD diagnoses and symptomatology are linked to higher risk for a range of tobacco and alcohol use outcomes among young adolescents in the U.S.

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Drug Alcohol Depend. 2015.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND SMOKING TRAJECTORIES: RACE AND GENDER DIFFERENCES.

Lee C-T, Clark TT, Kollins SH, et al.

Purpose: This study examined the influence of Attention Deficit Hyperactivity Disorder (ADHD) symptoms severity and directionality (hyperactive-impulsive symptoms relative to inattentive symptoms) on trajectories of the probability of current (past month) smoking and the number of cigarettes smoked from age 13 to 32. Racial and gender differences in the relationship of ADHD symptoms and smoking trajectories were also assessed.
Methods: A subsample of 9719 youth (54.5% female) was drawn from the National Longitudinal Study of Adolescent to Adult Health (Add Health). Cohort sequential design and zero-inflated Poisson (ZIP) latent growth modeling were used to estimate the relationship between ADHD directionality and severity on smoking development.
Results: ADHD severity's effect on the likelihood of ever smoking cigarettes at the intercept (age 13) had a greater impact on White males than other groups. ADHD severity also had a stronger influence on the initial number of cigarettes smoked at age 13 among Hispanic participants. The relationships between ADHD directionality (hyperactive-impulsive symptoms relative to inattentive symptoms) and a higher number of cigarettes smoked at the intercept were stronger among Hispanic males than others. Gender differences manifested only among Whites.
Conclusion: ADHD severity and directionality had unique effects on smoking trajectories. Our results also highlight that the risk of ADHD symptoms may differ by race and gender.

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Front Human Neurosci. 2014;8.

DIFFERENTIAL EFFECTS OF THETA/BETA AND SMR NEUROFEEDBACK IN ADHD ON SLEEP ONSET LATENCY.

Arns M, Feddema I, Kenemans JL.

Recent studies suggest a role for sleep and sleep problems in the etiology of attention deficit hyperactivity disorder (ADHD) and a recent model about the working mechanism of sensori-motor rhythm (SMR) neurofeedback, proposed that this intervention normalizes sleep and thus improves ADHD symptoms such as inattention and hyperactivity/impulsivity. In this study we compared adult ADHD patients (N = 19) to a control group (N = 28) and investigated if differences existed in sleep parameters such as Sleep Onset Latency (SOL), Sleep Duration (DUR) and overall reported sleep problems (PSQI) and if there is an association between sleep-parameters and ADHD symptoms. Secondly, in 37 ADHD patients we investigated the effects of SMR and Theta/Beta (TBR) neurofeedback on ADHD symptoms and sleep parameters and if these sleep parameters may mediate treatment outcome to SMR and TBR neurofeedback. In this study we found a clear continuous relationship between self-reported sleep problems (PSQI) and inattention in adults with- and without-ADHD. TBR neurofeedback resulted in a small reduction of SOL, this change in SOL did not correlate with the change in ADHD symptoms and the reduction in SOL only happened in the last half of treatment, suggesting this is an effect of symptom improvement not specifically related to TBR neurofeedback. SMR neurofeedback specifically reduced the SOL and PSQI score, and the change in SOL and change in PSQI correlated strongly with the change in inattention, and the reduction in SOL was achieved in the first half of treatment, suggesting the reduction in SOL mediated treatment response to SMR neurofeedback. Clinically, TBR and SMR neurofeedback had similar effects on symptom reduction in ADHD (inattention and hyperactivity/impulsivity). These results suggest differential effects and different working mechanisms for TBR and SMR neurofeedback in the treatment of ADHD.

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Front Human Neurosci. 2015;8.

NEAR-INFRARED SPECTROSCOPY (NIRS) NEUROFEEDBACK AS A TREATMENT FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)NULLA PILOT STUDY.

Marx A-M, Ehlis A-C, Furdea A, et al.

In this pilot study near-infrared spectroscopy (NIRS) neurofeedback was investigated as a new method for the treatment of Attention Deficit-/Hyperactivity Disorder (ADHD). Oxygenated hemoglobin in the prefrontal cortex of children with ADHD was measured and fed back. 12 sessions of NIRS-neurofeedback were compared to the intermediate outcome after 12 sessions of EEG-neurofeedback (slow cortical potentials, SCP) and 12 sessions of EMG-feedback (muscular activity of left and right musculus supraspinatus). The task was either to increase or decrease hemodynamic activity in the prefrontal cortex (NIRS), to produce positive or negative shifts of SCP (EEG) or to increase or decrease muscular activity (EMG). In each group nine children with ADHD, aged 7null10 years, took part. Changes in parentsnull ratings of ADHD symptoms were assessed before and after the 12 sessions and compared within and between groups. For the NIRS-group additional teachersnull ratings of ADHD symptoms, parentsnull and teachersnull ratings of associated behavioral symptoms, childrensnull self reports on quality of life and a computer based attention task were conducted before, 4 weeks and 6 months after training. As primary outcome, ADHD symptoms decreased significantly 4 weeks and 6 months after the NIRS training, according to parentsnull ratings. In teachersnull ratings of ADHD symptoms there was a significant reduction 4 weeks after the training. The performance in the computer based attention test improved significantly. Within-group comparisons after 12 sessionsof NIRS-, EEGand EMG-training revealed a significant reduction in ADHD symptoms in the NIRS-group and a trend for EEG and EMG-groups. No significant differences for symptom reduction were found between the groups. Despite the limitations of small groups and the comparison of a completed with two uncompleted interventions, theresults of this pilot study are promising. NIRS-neurofeedback could be a time-effective treatment for ADHD and an interesting new option to consider in the treatment of ADHD.

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Front Human Neurosci. 2015;8.

DISSOCIATIONS BETWEEN DEVELOPMENTAL DYSLEXIAS AND ATTENTION DEFICITS.

Lukov L, Friedmann N, Shalev L, et al.

We examine whether attention deficits underlie developmental dyslexia, or certain types of dyslexia, by presenting double dissociations between the two. We took into account the existence of distinct types of dyslexia and of attention deficits, and focused on dyslexias that may be thought to have an attentional basis: letter position dyslexia (LPD), in which letters migrate within words, attentional dyslexia (AD), in which letters migrate between words, neglect dyslexia, in which letters on one side of the word are omitted or substituted, and surface dyslexia, in which words are read via the sublexical route. We tested 110 children and adults with developmental dyslexia and/or attention deficits, using extensive batteries of reading and attention. For each participant, the existence of dyslexia and the dyslexia type were tested using reading tests that included stimuli sensitive to the various dyslexia types. Attention deficit and its type was established through attention tasks assessing sustained, selective, orienting, and executive attention functioning. Using this procedure, we identified 55 participants who showed a double dissociation between reading and attention: 28 had dyslexia with normal attention and 27 had attention deficits with normal reading. Importantly, each dyslexia with suspected attentional basis dissociated from attention: we found 21 individuals with LPD, 13 AD, 2 neglect dyslexia, and 12 surface dyslexia without attention deficits. Other dyslexia types (vowel dyslexia, phonological dyslexia, visual dyslexia) also dissociated from attention deficits. Examination of 55 additional individuals with both a specific dyslexia and a certain attention deficit found no attention function that was consistently linked with any dyslexia type. Specifically, LPD and AD dissociated from selective attention, neglect dyslexia dissociated from orienting, and surface dyslexia dissociated from sustained and executive attention. These results indicate that visuospatial attention deficits do not underlie these dyslexias.

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Hum Brain Mapp. 2015 Jan;36:367-77.

COMT GENOTYPE AFFECTS BRAIN WHITE MATTER PATHWAYS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hong SB, Zalesky A, Park S, et al.

Increased dopamine availability may be associated with impaired structural maturation of brain white matter connectivity. This study aimed to derive a comprehensive, whole-brain characterization of large-scale axonal connectivity differences in attention-deficit/hyperactivity disorder (ADHD) associated with catechol-O-methyltransferase gene (COMT) Val158Met polymorphism. Using diffusion tensor imaging, whole-brain tractography, and an imaging connectomics approach, we characterized altered white matter connectivity in youth with ADHD who were COMT Val-homozygous (N = 29) compared with those who were Met-carriers (N = 29). Additionally, we examined whether dopamine transporter gene (DAT1) and dopamine D4 receptor gene (DRD4) polymorphisms were associated with white matter differences. Level of attention was assessed using the continuous performance test before and after an 8-week open-label trial of methylphenidate (MPH). A network of white matter connections linking 18 different brain regions was significantly weakened in youth with ADHD who were COMT Met-carriers compared to those who were Val-homozygous (P < 0.05, family-wise error-corrected). A measure of white matter integrity, fractional anisotropy, was correlated with impaired pretreatment performance in continuous performance test omission errors and response time variability, as well as with improvement in continuous performance test response time variability after MPH treatment. Altered white matter connectivity was exclusively based on COMT genotypes, and was not evident in DAT1 or DRD4. We demonstrated that white matter connectivity in youth with ADHD is associated with COMT Val158Met genotypes. The present findings suggest that different layers of dopamine-related genes and interindividual variability in the genetic polymorphisms should be taken into account when investigating the human connectome.

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Indian J Med Res. 2014;140:644-48.

USE OF COMPUTERIZED TESTS TO EVALUATE PSYCHOMOTOR PERFORMANCE IN CHILDREN WITH SPECIFIC LEARNING DISABILITIES IN COMPARISON TO NORMAL CHILDREN.

Taur S, Karande S, Saxena AA, et al.

Background & objectives: Children with specific learning disabilities (SpLD) have an unexplained difficulty in acquiring basic academic skills resulting in a significant discrepancy between their academic potential and achievements. This study was undertaken to compare the performance on a battery of six psychomotor tests of children with SpLD and those without any learning disabilities (controls) using computerized tests

Methods: In this study, 25 children with SpLD and 25 controls (matched for age, socio-economic status and medium of instruction) were given three training sessions over one week. Then children were asked to perform on the six computerized psychomotor tests. Results were compared between the two groups. Results: children with SpLD fared significantly worse on finger tapping test, choice reaction test, digit picture substitution test and card sorting test compared to the controls ($p<0.05$)

Interpretation & conclusions: Children with SpLD have impairment of psychomotor skills like attention, sensory-motor coordination and executive functioning. Further research is needed to evaluate if the remedial education plan results in improvement in psychomotor performance of children with SpLD on these selected tests.

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Indian J Psychiatry. 2014;56:405-06.

ASSOCIATION OF ATTENTION DEFICIT HYPERKINETIC DISORDER AND EPILEPSY: FURTHER EXPLORED.

Pratibha S, Subhas GT, Chandrashekar H.

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Int J Emerg Ment Health. 2014;16:322-25.

WHY ARE PSYCHIATRIC DISORDERS IN CHILDREN BECOMING MORE AND MORE COMMON?

Buchhorn R.

In the last decades, an increase of new paediatric problems requiring medical care like eating disorders, behavioural and attention problems has been observed. Based on the hypothesis that mental illness is accompanied by autonomic dysfunction, we compared measurements of heart rate variability (HRV) in Holter ECG's from children with attention deficit/hyperactivity disorder (ADHD) with those of healthy children and a historical control from 1997. METHOD: We analysed the HRV parameters SDNN, rMSSD and pNN50 from 24 hours Holter ECG from children (mean age 10.8 years) with ADHD before or during medical therapy with methylphenidate (MPH). These values were compared with aged matched healthy children. RESULTS: Compared to healthy controls ADHD children with and without MPH treatment showed significantly higher mean heart rates, lower pNN50 and lower RMSSD. pNN50 and RMSSD values of healthy children are lower compared to the historical control group from 1997. CONCLUSION: Compared to healthy children the peak of parasympathic activity measured by the HRV values pNN50 and RMSSD in early adolescence was reduced in children with ADHD. Compared to a historical control these values are also reduced in healthy children. A reduced vagal activity will--within the meaning of W. Porges polyvagal theory--have consequences on the social and emotional development of children. Moreover this observation may have consequences for an enhanced cardiovascular risk.

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Iran J Psychiatry. 2014;9:222-27.

COMPARING THE DRAWINGS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH NORMAL CHILDREN.

Haghighi M, Khaterizadeh M, Chalbianloo G, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is the most common behavioral problem during childhood and in school-aged children. Various projection drawings have been designed for assessing children's personality and psychological disorders including the tests of draw a person (DAP) and draw a family (DAF). We aimed to compare the differences between typically developing children and children with ADHD using these tests.

Methods: In this case-control study, all the 9-10 year-old boy students studying at the third and fourth grades were enrolled from schools in the 2nd educational district of Shiraz, south of Iran. Eighty students were then selected and enrolled into the ADHD group and the control group. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition- text Revised (DSM-IV-TR), and the Child Symptoms Inventory were used to diagnose the children with ADHD. We evaluated and analyzed impulsiveness, non-impulsiveness, emotional problems and incompatibility indices in the DAP and DAF tests in each group.

Results: A significant difference was found in the indices of incompatibility and emotional problems, impulsiveness, non-impulsiveness and DAF between typically developing children and those with ADHD. The mean ((plus or minus)SD) total scores of the above mentioned indices in the ADHD group were 19.79((plus or minus)2.94), 12.31((plus or minus)1.84), 5.26((plus or minus)2.29) and 5.89((plus or minus)2.13), respectively ($P < 0.001$). The corresponding figures for these indices in the normal group were 12.11((plus or minus)4.74), 5.63((plus or minus)2), 10.36(plus or minus) (2.33) and 2.88((plus or minus)2.13), respectively ($P < 0.001$).

Conclusion: Significant differences were obtained between the control group and children with ADHD using these two drawing tests. The rate of impulsivity and emotional problems indices in drawings of children with ADHD was markedly more common than those of the typically developing children. This suggests the need for further assessment to screen ADHD.

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Iran J Psychiatry. 2014;9:197-202.

NEUROCOGNITIVE PROFILE OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDERS (ADHD): A COMPARISON BETWEEN SUBTYPES.

Ahmadi N, Mohammadi MR, Araghi SM, et al.

Objective: The aim of this study was to examine the differences between ADHD subtypes in executive function tasks compared to themselves and normal controls.

Method: In this study, 45 school aged children with Attention Deficit Hyperactivity Disorder (ADHD) and 30 normal children who were matched based on age and IQ score in Wechsler Intelligence Scale for Children-Revised (WISC-R) were compared in terms of executive function. We used Wisconsin Sorting Card Test to assess executive function in both groups. We also used children's scores in Children Symptom Inventory-4 (CSI-4) for diagnosing ADHD and specifying ADHD subtypes. Data were entered in SPSS-17 and analyzed by T-test and ANOVA static tests to clarify the differences between ADHD and controls and between ADHD subtypes. Scheffe's test was also used to identify which groups were different from one another. The mean and standard divisions (SD) were used for descriptive analysis.

Results: ADHD subtypes are significantly different in terms of perseverative responses (p(less-than or equal to) 0/01) and perseverative errors (p(less-than or equal to)0/001). Based on Scheffe's test, Attention Deficit Hyperactivity Disorders-Hyperactive type (ADHD-H) is not that different from Attention Deficit Hyperactivity Disorders-Inattention type (ADHD-I) and Attention Deficit Hyperactivity Disorders-Combined type (ADHD-C), but there are significant responses and perseverative differences between ADHD-I and ADHD-C in terms of perseverative errors. ADHD-C shows more perseverative responses and perseverative errors than ADHD-I.

Conclusion: The findings of this study revealed that executive function patterns are different in children with ADHD compared to normal children. In this study it was also found that ADHD subtypes are also different in terms of perseveration and response inhibition domains; ADHD-C has more deficits in these domains.

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J Adolesc. 2015;40:24-33.

PARENTAL MONITORING IN LATE ADOLESCENCE: RELATIONS TO ADHD SYMPTOMS AND LONGITUDINAL PREDICTORS.

Salari R, Thorell LB.

In this study, we aimed to replicate Stattin and Kerr's (2000) study on parental monitoring and adolescents' deviant behavior, to extend their findings to ADHD symptoms, and to examine the longitudinal predictors (8-18 years) of parental knowledge and child disclosure. Results showed that conduct problems were primarily associated with parental knowledge and child disclosure, but not with parental solicitation and control. A similar pattern was observed for ADHD symptoms. However, while the relations for conduct problems were generally independent of ADHD symptoms, the relations for ADHD symptoms were primarily non-significant after controlling for conduct problems. Moreover, early behavior problems, but not insecure/disorganized attachment, were associated with parental knowledge and child disclosure in adolescence. In conclusion, child disclosure is primarily associated with deviant behavior rather than ADHD, and early child problem behavior is a more important predictor of child disclosure (implicating reciprocal relations between these two constructs) than is insecure/disorganized attachment.

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Journal of Attention Disorders. 2015 Jan;19:18-26.

ANXIETY IN YOUNG PEOPLE WITH ADHD: CLINICAL AND SELF-REPORT OUTCOMES.

Tsang TW, Kohn MR, Efron D, et al.

Objective: (a) To determine the prevalence of comorbid anxiety disorder in ADHD, defined by diagnostic criteria and (b) to compare anxiety as reported by parents and participants with clinician assessment.

Method: Children with ADHD were assessed for comorbid anxiety disorder using the Anxiety Disorder Interview Schedule for Children. Parent report (Conners' Parent Rating Scale–Revised: Long version) and self-report (State-Trait Anxiety Inventory and Brain Resource Inventory for Screening Cases–Child version) scales were used to assess anxiety. The ADHD–Rating Scale IV was used to measure ADHD symptoms.

Results: Of 134 participants (11.0 ± 2.6 years), 31.3% had comorbid anxiety disorder. Comorbid anxiety disorder was associated with greater severity of ADHD. Anxiety symptoms from parent reports (p < .05) but not from child/self-report (p > .05) correlated with clinician assessment.
Conclusion: Assessment for comorbid anxiety disorder and inclusion of parent rating in this assessment are important components of ADHD treatment in children and adolescents.

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Journal of Attention Disorders. 2015 Jan;19:35-43.

IMPACT OF ADHD IN ADULTS WITH NEUROFIBROMATOSIS TYPE 1: ASSOCIATED PSYCHOLOGICAL AND SOCIAL PROBLEMS.

Mautner VF, Granström S, Leark RA.

Objective: To analyze the psychological phenotype of ADHD, and the effect of ADHD on life satisfaction and personality in adults with neurofibromatosis type 1 (NF1).
Method: Adults with NF1 without (n = 26) and with ADHD (n = 22), and adults with ADHD only (n = 27) completed questionnaires on personality traits and life satisfaction. Differences between groups were analyzed.
Results: Participants with NF1 and ADHD present an emotionally instable psychological phenotype similar to adults with ADHD only, which differed significantly from that in adults with NF1 only. Participants with NF1 and ADHD had significantly lower overall life satisfaction than NF1 participants without such symptoms, affecting general health, self-satisfaction, sexuality, and family.
Conclusion: The authors' findings show that ADHD symptoms can persist through adulthood. These NF1 patients display problems similar to those of adults with ADHD only. This finding is highly relevant to understand the behavioral and psychological phenotype in adults with NF1 and to offer psychological and/or medical treatment.

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Journal of Attention Disorders. 2015 Jan;19:78-83.

QUANTIFYING THE RELATIONSHIP BETWEEN PERCEIVED CONSEQUENCES OF ADHD MEDICATION AND ITS USAGE.

Cox DJ, Davis MT, Cox BS, et al.

Objective: To address a major barrier of medication noncompliance for individuals with ADHD, the authors present the ADHD Medication Attitude Scale (AMAS) with initial psychometric analyses and discriminant validity data.
Method: The AMAS was posted on ADHD websites, along with questions about demographics and medication usage over a 6-month period. A total of 356 ADHD respondents qualified for data analysis (160 males, 196 females, mean age = 18.58, years range = 13-62 years, SD = 6.07).
Results: Factor analysis revealed two factors: one indicating positive and the other indicating negative attitude toward medication. The final refined 22-item scale demonstrated good reliability (a =.83). More positive and less negative attitude factor scores, as well as age (older than 19 years), independently predicted respondents' self-report of taking medication, ?² (1, N = 248) = 38.95, p < .001.
Conclusion: The AMAS is a psychometrically sound means of assessing attitudes toward ADHD medication, which significantly relate to self-reported medication usage.

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Journal of Attention Disorders. 2015 Jan;19:27-34.

TEST-TAKING PERFORMANCE OF HIGH SCHOOL STUDENTS WITH ADHD.

Lewandowski L, Hendricks K, Gordon M.

Objective: The authors examined the test-taking performance of high school students with (n = 38) and without (n = 746) ADHD.
Method: Students were assessed via an online battery of tests (TestTracker) including reading speed, decoding, vocabulary, comprehension, effort, test anxiety, and time and strategy usage.

Results: Students with ADHD had poorer decoding scores, and lower comprehension and vocabulary accuracy. Groups performed similarly on reading speed, number of items attempted, perceived test anxiety, self-perception of testing skills, and strategy use.
Conclusion: Students with ADHD (all of whom were receiving test accommodations in school) made more errors on some reading tasks, yet performed similarly to typical students on indices of speed and amount of test items accessed. The finding of more errors but no time differences might argue for a different intervention beside extended time, unless the extra time is used to review and correct work.

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Journal of Attention Disorders. 2015 Jan;19:53-62.
ASSOCIATION BETWEEN STORY RECALL AND OTHER LANGUAGE ABILITIES IN SCHOOLCHILDREN WITH ADHD.
Papaeliou CF, Maniadaki K, Kakouros E.
Objective: The present study aimed to investigate the effect of working memory, vocabulary, and grammar on narrative comprehension in children with ADHD.
Method: Participants were 25 schoolchildren with ADHD and 25 typically developing (TD) children matched for chronological age and performance IQ. Children were assessed with the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), a verbal IQ test, and a story recall task.
Results: It was shown that children with ADHD recall less information from the stories than did TD children, while they are less sensitive to the importance of the information they recall. Moreover, it was found that children with ADHD experience problems in answering factual questions. Further analysis revealed that deficiencies in narrative comprehension may be accounted for by problems in working memory.
Conclusion: The discussion focuses on the role of working memory in narrative comprehension and the implications of these findings for intervention approaches.

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Journal of Child & Adolescent Substance Abuse. 2015 Jan;24:37-45.
THE ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND NICOTINE USE AMONG ADOLESCENTS AND YOUNG ADULTS.
Symmes A, Winters KC, Fahnhorst T, et al.
Previous research indicates that youths with attention deficit hyperactivity disorder (ADHD) are more susceptible to nicotine use compared to those without ADHD, and one explanation for this association is the self-medication theory. The present study examines nicotine use in a prospective sample derived from a community sampling procedure rather than a clinical setting. Nicotine use was measured through young adulthood (mean ages: 18, 20, and 22), and three groups were compared based on childhood status: ADHD only, ADHD externalizers, and control groups. Results indicated that at all three data points, individuals with childhood ADHD plus an externalizing disorder reported higher nicotine use on all variables compared to the ADHD group absent of an externalizing disorder and the comparison group of non-ADHD youths. The group differences were significant even after controlling for possible confounding variables (age, gender, and current treatment with psychostimulant medication). Study results are discussed in light of the self-medication hypothesis and of the importance of including nicotine prevention programs for adolescents and young adults with ADHD and externalizing problems.

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J Child Adolesc Psychopharmacol. 2014;24:590-93.
EMOTIONAL DYSREGULATION IN A CHILD WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ANXIETY: PSYCHOPHARMACOLOGICAL STATEGIES.
Srivastava A, Coffey B.

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J Child Adolesc Psychopharmacol. 2014;24:596-97.

PERSISTENT CAMPTOCORMIA ASSOCIATED WITH ATOMOXETINE IN A CHILD WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bhattacharya A, Praharaj SK, Sinha VK.

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J Child Adolesc Psychopharmacol. 2014 Dec;24:582-85.

A PILOT STUDY OF STIMULANT MEDICATION FOR ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) WHO ARE PARENTS OF ADOLESCENTS WITH ADHD: THE ACUTE EFFECTS OF STIMULANT MEDICATION ON OBSERVED PARENT-ADOLESCENT INTERACTIONS.

Babinski DE, Waxmonsky JG, Waschbusch DA, et al.

Objective: This study explores the use of stimulant-medication for parents with attention-deficit/hyperactivity disorder (ADHD) who also have adolescents with ADHD.

Methods: Five parents, diagnosed with ADHD, had their dose of lisdexamfetamine (LDX) titrated to optimal effect. Next, parents and their adolescents completed two interactions, once when parents were on placebo and once when parents were on optimal dose of LDX, to assess acute effects of parental medication on parenting during a neutral discussion (NeuDiss), a problem discussion (ProbDiss), and a homework task (HW).

Results: Parents demonstrated a significant decrease in the ratio of commands to total verbalizations during the NeuDiss on LDX compared with placebo. Although no other statistically significant effects emerged at the p < 0.05 level, moderate to large effects of medication on some aspects of parenting related to the amount and timing of speech (i.e., total verbalizations, total commands, ratio of commands to total verbalizations, and responsiveness) emerged and varied by task. Parental stimulant medication did not appear to impact the content of parents' speech (i.e., use of negative talk or praise).

Conclusions: These results add to a growing literature suggesting that treatment for parental ADHD may impact parenting performance, and suggest that attention to parental ADHD in treatment for adolescents with ADHD may possibly enhance family functioning.

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J Indian Assoc Child Adolesc Ment Health. 2015;11:56-79.

ASSESSMENT OF SLEEP DISTURBANCES IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Hazari N, Joseph A, Mehta M, et al.

Results: 60% of children with ADHD had at least one sleep problem as compared to 30% of controls. Significant differences were seen on bedtime resistance, night wakings,parasomnias, day time sleepiness. 40% children with ADHD were found to have restless legs symptoms compared to 15% of controls. On actigraphy, sleep onset latency was significantly greater with mean of 25 min as compared to 15 min in control group. Sleep efficiency was significantly lower in children with ADHD.

Conclusions: Sleep disturbances are common in ADHD children and hence, must be actively evaluated. Further studies using larger sample size and other objective measures like polysomnography can be used in future Indian studies.

Introduction: A high prevalence of sleep disturbances have been found in children with Attention deficit hyperactivity disorder (ADHD) and these impact daytime behavior and cognitive functioning. Previous studies have assessed these on subjective measures by parent and self report and by means of objective measures using actigraphy and polysomnography. This study aimed to find the subjective and objective impairments in sleep using parental report and actigraphy.

Methodology: 20 children attending the Child and Adolescent Psychiatry Clinic, AIIMS diagnosed as ADHD were assessed using Connersnull Parent Rating Scale-Revised (CPRS-R) and Connersnull Global Index-Parent (CGI-P) for ADHD and for sleep problems using Child Sleep Habits Questionnaire (CSHQ) and Pediatrics Sleep Questionnaire (PSQ). Actigraphy was carried out for objective assessment of sleep. The control group consisted of 20 age and gender matched normal children.

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J Neurodevelopmental Disord. 2014;6.

PRE-PULSE INHIBITION AND ANTISACCADE PERFORMANCE INDICATE IMPAIRED ATTENTION MODULATION OF COGNITIVE INHIBITION IN 22Q11.2 DELETION SYNDROME (22Q11DS).

McCabe KL, Atkinson RJ, Cooper G, et al.

Background: 22q11.2 deletion syndrome (22q11DS) is associated with a number of physical anomalies and neuropsychological deficits including impairments in executive and sensorimotor function. It is estimated that 25% of children with 22q11DS will develop schizophrenia and other psychotic disorders later in life. Evidence of genetic transmission of information processing deficits in schizophrenia suggests performance in 22q11DS individuals will enhance understanding of the neurobiological and genetic substrates associated with information processing. In this report, we examine information processing in 22q11DS using measures of startle eyeblink modification and antisaccade inhibition to explore similarities with schizophrenia and associations with neurocognitive performance.

Methods: Startle modification (passive and active tasks; 120- and 480-ms pre-pulse intervals) and antisaccade inhibition were measured in 25 individuals with genetically confirmed 22q11DS and 30 healthy control subjects.

Results: Individuals with 22q1 1DS exhibited increased antisaccade error as well as some evidence (trend-level effect) of impaired sensorimotor gating during the active condition, suggesting a dysfunction in controlled attentional processing, rather than a pre-attentive dysfunction using this paradigm.

Conclusions: The findings from the present study show similarities with previous studies in clinical populations associated with 22q11DS such as schizophrenia that may indicate shared dysfunction of inhibition pathways in these groups.

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J Neuroimmunol. 2015;278:212-22.

DETECTION OF AUTO-ANTIBODIES TO DAT IN THE SERUM: INTERACTIONS WITH DAT GENOTYPE AND PSYCHO-STIMULANT THERAPY FOR ADHD.

Giana G, Romano E, Porfirio MC, et al.

Interest is rising for auto-immune contribution in neuro-psychiatry. We evaluated the auto-antibodies against dopamine transporter (DAT aAbs) in 61 children (46 ADHD who met DSM-IV-TR criteria, 15 healthy controls). Methods: ADHD patients were assigned, according to severity, either to a non-pharmacological therapy (NPT, N. =. 32) or to a pharmacological treatment (PT, N. =. 14) with methylphenidate (MPH). In ADHD children, blood samples were withdrawn twice, at recruitment (T0 basal) and after 6. weeks (T1); following 16 excluded subjects, DAT genotype was characterized (9-repeat or 10-repeat alleles; N. =. 15 each). After 18. months of NPT or PT, some patients (carrying at least one 9-repeat allele) were blood sampled again (T2), for comparison with healthy controls (final n. =. 8). Results: Compared to NPT, basal DAT aAbs titers were higher within most severe patients (then assigned to PT), specifically if carrying a DAT 10/10 genotype. DAT aAbs levels of NPT group resulted highly correlated with distinct subscales of Conners' Parent/Teacher Scales (Rs. >. 0.34), especially within DAT 10/10 genotype (Rs. >. 0.53). While T1 titers were elevated over T0 baseline for NPT children, such an increase was not observed in PT patients carrying at least one 9-repeat allele, who also showed behavioral response to subchronic MPH. After 12-24 months of MPH exposure, DAT aAbs titers in PT subjects were comparable to those of healthy controls, while titers remained significantly elevated in NPT patients. Data warrant further research on serum DAT aAbs, which could be used to confirm ADHD diagnosis and/or to monitor therapeutic efficacy of MPH.

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J Neuropsychiatry Clin Neurosci. 2014;26:E6-E7.

MARKED EXACERBATION OF ADHD AFTER ONSET OF INHALANT USE: A CASE REPORT.

Gupta A, Mandal P, Bhargava R, et al.

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J Neuropsychiatry Clin Neurosci. 2014;26:335-43.

CONVENTIONAL SPECT VERSUS 3D THRESHOLDED SPECT IMAGING IN THE DIAGNOSIS OF ADHD: A RETROSPECTIVE STUDY.

Schneider H, Thornton JF, Freeman MA, et al.

Brain single photon emission CT (SPECT) scans indirectly show functional activity via measurement of regional cerebral blood flow. In conventional SPECT scans, the typical tomographic slices are produced. In threedimensional thresholded SPECT scans, pixels representing activity below a certain threshold are discarded. A retrospective analysis of 427 patients shows that three-dimensional thresholded SPECT scans yield a sensitivity for predicting clinical attention deficit hyperactivity disorder of 54% [95% confidence interval (CI), 46%null61%; specificity, 76%; 95% CI, 71%null 81%] compared with 4% sensitivity [95% CI, 2% null8%; specificity, 97%; 95% CI, 94%null98%] for conventional SPECT scans. For 170 of the patients originating from a general psychiatry practice, conventional SPECT showed 10% sensitivity (95% CI, 4%null23%) and 98% specificity (95% CI, 93%null99%), whereas threedimensional thresholded SPECT showed 83% sensitivity (95% CI, 68%null91%) and 77% specificity (95% CI, 69%null83%). These findings indicate that a much stronger signal is obtained when the three-dimensional thresholded SPECT scan is performed rather than the conventional SPECT scan in detecting attention deficit hyperactivity disorder and suggest similar results may be obtained for other psychiatric disorders.

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J Psychiatry Neurosci. 2015;40:46-57.

FUNCTIONAL DYSCONNECTIVITY OF CORTICOSTRIATAL CIRCUITRY AND DIFFERENTIAL RESPONSE TO METHYLPHENIDATE IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hong S-B, Harrison BJ, Fornito A, et al.

Background: Brain frontostriatal circuits have been implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD). However, effects of methylphenidate on circuit-level functional connectivity are as yet unclear. The aim of the present study was to comprehensively investigate the functional connectivity of major striatal subregions in children with ADHD, including subanalyses directed at mapping cognitive and treatment response characteristics.

Methods: Using a comprehensive seeding strategy, we examined resting-state functional connectivity of dorsal and ventral subdivisions of the caudate nucleus and putamen in children and adolescents with ADHD and in ageand sex-matched healthy controls.

Results: We enrolled 83 patients with ADHD and 22 controls in our study. Patients showed significantly reduced dorsal caudate functional connectivity with the superior and middle prefrontal cortices as well as reduced dorsal putamen connectivity with the parahippocampal cortex. These connectivity measures were correlated in opposite directions in patients and controls with attentional performance, as assessed using the Continuous Performance Test. Patients showing a good response to methylphenidate had significantly reduced ventral caudate/nucleus accumbens connectivity with the inferior frontal cortices compared with poor responders. Limitations: Possible confounding effects of age-related functional connectivity change were not excluded owing to the wide age range of participants.

Conclusion: We observed a region-specific effect of methylphenidate on resting-state functional connectivity, suggesting the pretreatment level of ventral frontostriatal functional connectivity as a possible methylphenidate response biomarker of ADHD.

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J Psychopharmacol. 2015 Jan;29:39-42.

SERVICES FOR YOUNG PEOPLE WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER TRANSITIONING FROM CHILD TO ADULT MENTAL HEALTH SERVICES: A NATIONAL SURVEY OF MENTAL HEALTH TRUSTS IN ENGLAND.

Hall CL, Newell K, Taylor J, et al.

Transition from child to adult mental health services is considered to be a difficult process, particularly for individuals with neurodevelopmental disorders such as attention deficit/hyperactivity disorder (ADHD). This article presents results from a national survey of 36 mental health National Health Service (NHS) trusts across

England, the findings indicate a lack of accurate data on the number of young people with ADHD transitioning to, and being seen by, adult services. Less than half of the trusts had a specialist adult ADHD service and in only a third of the trusts were there specific commissioning arrangements for adult ADHD. Half of the trusts reported that young people with ADHD were prematurely discharged from child and adolescent mental health services (CAMHS) because there were no suitable adult services. There was also a lack of written transition protocols, care pathways, commissioned services for adults with ADHD and inadequate information sharing between services. The findings advocate the need to provide a better transition service underpinned by clear, structured guidelines and protocols, routine data collection and information sharing across child and adult services. An increase in the commission of specialist adult ADHD clinics is needed to ensure individuals have access to appropriate support and care.

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J Sleep Res. 2014;23:295.

SYMPTOMS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) IN PEDIATRIC NARCOLEPSY.

Lecendreux M, Lavault S, Scholtz S, et al.

Background and objective: Retrospective reports in adults with narcolepsy have identified childhood symptoms of attention-deficit hyperactivity disorder (ADHD) as a significant area of difficulty. The aim of the current study was to evaluate the burden of ADHD symptoms in children with narcolepsy.

Methods: This was a cross-sectional, observational, non-randomized study. Children (n = 108, aged <18 years) presenting with narcolepsy with cataplexy (NC) or without cataplexy (NwoC) were seen in four french national reference centers and compared with age matched healthy controls (n = 67). Between-group statistical comparisons were conducted within a generalized linear models framework.

Results: ADHD symptoms were approximately 2-fold greater compared with controls, significant educational problems were evident compared with controls. For total ADHD symptoms, there was a 2- fold increase in the NwoC group vs. controls (P < 0.001) and a 1.8- fold increase in the NwC group vs. controls (P = 0.001). For inattention symptoms, there was a 2.2-fold increase in the NwoC group vs. controls (P < 0.001) and a 1.9-fold increase in the NwC group vs. controls (P < 0.001).

Conclusion: We confirm that ADHD symptoms represent a significant burden in children and adolescents with narcolepsy. Although there are some limitations to the study, these findings may have relevant clinical and therapeutic applications in the future.

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Journal of Sport and Health Science. 2014;3:320-25.

PARENTAL PERCEPTIONS OF THE EFFECTS OF EXERCISE ON BEHAVIOR IN CHILDREN AND ADOLESCENTS WITH ADHD.

Gapin JI, Etnier JL.

Background: Anecdotally, parents often report that children with attention deficit hyperactivity disorder (ADHD) who engage in regular physical activity (PA) experience positive behavioral changes. The purpose of this study was to examine this anecdotal relationship to provide preliminary evidence relevant to the potential benefits of PA on ADHD symptoms.

Methods: Parents (n=68) of children diagnosed with ADHD completed an Internet survey assessing perceptions of how PA influences their child's symptoms.

Results: A significantly greater percentage of parents reported that regular PA positively impacted symptoms. However, there were no uniform effects for all types of ADHD symptoms. The results indicate that there may be more positive benefits for symptoms of inattention and hyperactivity than for those of impulsivity.

Conclusion: This is the first study to empirically document parents' perceptions of how PA influences ADHD and suggests that PA can be a viable strategy for reducing symptoms. PA may have greater benefits for specific symptoms of ADHD, providing critical information for developing PA interventions for children and adolescents.

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J Int Neuropsychol Soc. 2014 Nov;20:971-81.

NEUROPSYCHOLOGICAL PERFORMANCE OF YOUTH WITH SECONDARY ATTENTION-DEFICIT/HYPERACTIVITY DISORDER 6- AND 12-MONTHS AFTER TRAUMATIC BRAIN INJURY.

Ornstein TJ, Sagar S, Schachar RJ, et al.

The present study compared executive dysfunction among children with attention-deficit/hyperactivity disorder (ADHD) after traumatic brain injury (TBI), also called secondary ADHD (S-ADHD), pre-injury ADHD and children with TBI only (i.e., no ADHD). Youth aged 6–16 years admitted for TBI to five trauma centers were enrolled (n = 177) and evaluated with a semi-structured psychiatric interview scheduled on three occasions (within 2 weeks of TBI, i.e., baseline assessment for pre-injury status; 6-months and 12-months post-TBI). This permitted the determination of 6- and 12-month post-injury classifications of membership in three mutually exclusive groups (S-ADHD; pre-injury ADHD; TBI-only). Several executive control measures were administered. Unremitted S-ADHD was present in 17/141 (12%) children at the 6-month assessment, and in 14/125 (11%) children at 12-months post-injury. The study found that children with S-ADHD exhibited deficient working memory, attention, and psychomotor speed as compared to children with pre-injury ADHD. Furthermore, the children with S-ADHD and the children with TBI-only were impaired compared to the children with pre-injury ADHD with regard to planning. No group differences related to response inhibition emerged. Age, but not injury severity, gender, or adaptive functioning was related to executive function outcome. Neuropsychological sequelae distinguish among children who develop S-ADHD following TBI and those with TBI only. Moreover, there appears to be a different pattern of executive control performance in those who develop S-ADHD than in children with pre-injury ADHD suggesting that differences exist in the underlying neural mechanisms that define each disorder, underscoring the need to identify targeted treatment interventions.

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Klin Psikofarmakol Bul. 2014;24:342-49.

OSMOTIC RELEASE ORAL SYSTEM METHYLPHENIDATE IS MORE EFFECTIVE THAN IMMEDIATE RELEASE METHYLPHENIDATE: A RETROSPECTIVE CHART REVIEW IN TURKISH CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ardic UA, Ercan ES, Ercan E, et al.

Objective: The aim of this study was to evaluate the efficacy and safety of osmotic release oral system methylphenidate (OROS-MPH) compared with immediate release methylphenidate (IR-MPH) in Turkish children with attention deficit hyperactivity disorder (ADHD).

Method: The medical records of primary school-aged children, who were first-time referrals to the outpatient clinic, were reviewed; 67 children receiving OROS-MPH and 47 children receiving IR-MPH were recruited for the study. A total of 114 children receiving treatment for ADHD were evaluated over 8 weeks.

Results: The total Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale scores from both the parent and teacher forms decreased significantly in both groups over 8 weeks ($p<0.001$). OROS-MPH was found to be superior to IR-MPH when comparing baseline-to-8th-week- mean inattention score changes on both the teacher ($p=0.007$) and parent ($p=0.015$) forms. OROS-MPH and IR-MPH were both well tolerated, with similar side- effect profiles.

Conclusion: OROS-MPH was found to be effective and safe in the treatment of ADHD symptoms in Turkish children.

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Klin Psikofarmakol Bul. 2014;24:333-41.

AUTISTIC TRAITS AND FACTORS RELATED TO A CLINICAL DECISION TO USE RISPERIDONE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Guler AS, Yazgan Y, Pelin AU.

Methods: We retrospectively compared four treatment groups of children with a primary diagnosis of ADHD [no psychotropics group, NPG (n=73, mean age (in years)= 9.22(plus or minus)2.94); stimulant- only, S (n=184, mean age (in years)= 10.52(plus or minus)2.98); risperidone- only, R (n=51, mean age (in years)= 10.18(plus or minus)3.52); and stimulant plus risperidone, SR (n=30, mean age (in years)= 9.37(plus or minus)2.71] from a

private child and adolescent psychiatry clinic. Baseline assessments, in addition to a semistructured interview, included a sociodemographic information form, the parent-rated Child Behavior Checklist for ages 6 to 18 (CBCL-6-18) and the parent and teacher-rated SNAP-IV scale (Swanson, Nolan and Pelham).
Results: There were significant between-group differences on CBCL T scores for total problems, externalizing problems, social problems, thought problems, attention problems, and aggression (all p<0.05) and on the parent SNAP inattention and combined scores (one-way ANOVA). The SR group had significantly higher scores (i) on the mentioned subscales of the CBCL when compared with the NPG and S groups, (ii) on the CBCL social problems subscale when compared with the R group, (iii) on the parent SNAP inattention scale when compared with the NPG and R groups and (iv) on the parent-rated SNAP total score when compared with the other 3 groups (Tukey post hoc test). Sixty-four children above the CBCL-AT cutoff had higher scores than those of children below the cutoff on parent and teacher-rated individual ADHD symptoms. In the logistic regression analysis, the cliniciannulls decision to use risperidone (either alone or in combination with stimulants) was significantly related to higher scores on the CBCL social problems (p=0.025) and thought problems (p=0.039) subscales. The presence of AT as a category, however, did not predict treatment assignment.
Conclusion: In this clinical sample, parent-rated social problems and thought problems were associated with the cliniciannulls decision to use risperidone in the treatment of ADHD cases (alone or in combination with stimulants). ADHD children with AT had more severe symptoms of ADHD and displayed more learning disability. However, AT profile as a category was not significantly associated with the use of risperidone. The better characterization of non-ADHD symptoms of ADHD children (social and emotional symptoms) may help to develop more individualized clinical interventions, such as nonpharmacological interventions for social development, which may result in a reduction in the use of medications targeting these symptoms in this group of children.
Objective: Our aim was to investigate the factors associated with a clinical decision to use risperidone in children and adolescents with a primary diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) and to investigate autistic traits (ATs) and their influence on treatment decisions in this population.

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Klin Psikofarmakol Bul. 2014;24:384-86.
LONG-ACTING METHYLPHENIDATE TOXICITY: A CASE REPORT.
Eryilmaz G, Gul IG, Yorbik O, et al.
Methylphenidate is a psychostimulant that is used in the treatment of attention deficit hyperactivity disorder and behavior disorders. Neuropsychiatric symptoms like loss of consciousness, lethargy, seizures and psychotic symptoms, and cardiovascular side effects like tachycardia, hypertension and hyperthermia have been reported in methylphenidate toxicity. In this case report, the clinical manifestations of an adolescent having taken 486 mg methylphenidate in a suicide attempt are discussed.

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NeuroImage Clin. 2015;7:325-35.
ALTERED NEURAL CONNECTIVITY DURING RESPONSE INHIBITION IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THEIR UNAFFECTED SIBLINGS.
Van RD, Hartman CA, Mennes M, et al.
Introduction Response inhibition is one of the executive functions impaired in attention-deficit/hyperactivity disorder (ADHD). Increasing evidence indicates that altered functional and structural neural connectivity are part of the neurobiological basis of ADHD. Here, we investigated if adolescents with ADHD show altered functional connectivity during response inhibition compared to their unaffected siblings and healthy controls.
Methods Response inhibition was assessed using the stop signal paradigm. Functional connectivity was assessed using psycho-physiological interaction analyses applied to BOLD time courses from seed regions within inferior- and superior frontal nodes of the response inhibition network. Resulting networks were compared between adolescents with ADHD (N = 185), their unaffected siblings (N = 111), and controls (N = 125).
Results Control subjects showed stronger functional connectivity than the other two groups within the response inhibition network, while subjects with ADHD showed relatively stronger connectivity between default mode

network (DMN) nodes. Stronger connectivity within the response inhibition network was correlated with lower ADHD severity, while stronger connectivity with the DMN was correlated with increased ADHD severity. Siblings showed connectivity patterns similar to controls during successful inhibition and to ADHD subjects during failed inhibition. Additionally, siblings showed decreased connectivity with the primary motor areas as compared to both participants with ADHD and controls.
Discussion Subjects with ADHD fail to integrate activation within the response inhibition network and to inhibit connectivity with task-irrelevant regions. Unaffected siblings show similar alterations only during failed stop trials, as well as unique suppression of motor areas, suggesting compensatory strategies. These findings support the role of altered functional connectivity in understanding the neurobiology and familial transmission of ADHD.

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Neuropsychopharmacology. 2014;39:S52.
USING GRAPH THEORY TO INFORM HETEROGENEITY IN TYPICAL DEVELOPMENT AND IN ADHD.
Fair D.
Background: Research in psychiatry often relies on the assumption that the diagnostic categories identified in the DSM represent homogeneous syndromes. However, the mechanistic heterogeneity that potentially underlies the existing classification scheme might limit discovery of etiology.
Methods: In our current work we expand on previous brain imaging methods and use graph theory, specifically community detection, to clarifying behavioral and functional heterogeneity in children with and without ADHD.
Results: Using behavioral assays we have been able to identify several unique subgroups of children with ADHD, and importantly, in some cases, in control populations as well. Just as notably, characterizing these unique data driven sub-populations has revealed unique patterns of dysfunction in the children with ADHD. We also show in this longitudinal ADHD sample that this refined nosology is capable of improving our predictive capacity of longterm outcomes relative to current DSM-based nosology. Last, we demonstrate similar phenomena in the form of distinct sub-classifications based on patterns of functional connectivity MRI. As with the behavioral indices, the subgroups yield unique atypical connectivity patterns in the clinical population and shed light on the underlying functional patterns that may contribute to heterogeneity in ADHD.
Conclusions: These findings suggest several principles that have the potential to advance our understanding of typical and atypical developmental trajectories. The first tenet suggests that both children with and without ADHD can be classified into distinct subgroups based on psychometrics or neuroimaging. The second tenet proposes that the information in these data driven neurotypes can assist in predicting future outcomes. We argue that illumination of such phenomena will have significant practical importance for understanding typical development and to identifying the etiologic underpinnings of atypical developmental trajectories.

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Neuropsychopharmacology. 2014;39:S234.
GRAY MATTER VOLUME IN PEDIATRIC ANXIETY AND MOOD DISORDERS: REGIONAL PREFRONTAL CORTEX VOLUME DIFFERENCES IN ANXIETY, BIPOLAR DISORDER, SEVERE MOOD DYSREGULATION, AND ADHD.
Gold A, Lever SN, Adleman NE, et al .
Background: Prior pediatric and adult research links anxiety and mood disorders to structural brain abnormalities, particularly in the prefrontal cortex (PFC). Compared to healthy volunteers (HV), gray matter (GM) volume differences have been linked to anxiety disorders, bipolar disorder, severe mood dysregulation (SMD), and attention-deficit hyperactivity disorder (ADHD) in children and adolescents. However, virtually all of these findings accrue from separate studies comparing HV to one patient group. The current study directly compares GM volumes among children and adolescents with anxiety disorders, bipolar disorders, SMD, ADHD, and HVs.
Methods: Voxel-based morphometry (VBM) analysis was conducted on T1-weighted structural MRI scans acquired on a 3-Tesla scanner from 177 youths (36 anxious, 19 bipolar disorder, 52 SMD, 17 ADHD, and 53 HV). The five groups were matched on age, sex, and IQ (all ps> .1). We created a custom template, given the pediatric sample, and used standard procedures in the VBM8 toolbox in SPM8, including high-dimensional DARTEL normalization. Segmented GM images were modulated for nonlinear effects, resulting in relative GM volume images. One-way ANOVA tested the main effect of diagnosis on GM volume using a whole-brain voxel-

wise height threshold of p<.001 uncorrected, cluster extentZ200 voxels. Post-hoc pairwise comparisons were conducted on the mean GM volume values extracted from significant clusters (using Tukey's Honestly Significant Difference [HSD] correction).
Results: Diagnosis was significantly associated with GM volume in medial and lateral PFC as predicted, including clusters in ventromedial PFC (vmPFC), dorsomedial PFC (dmPFC), and dorsolateral PFC (dlPFC). Post-hoc tests revealed that, depending on the region, differences between HVs and patients were (1) specific to bipolar disorder, (2) common among multiple disorders, or (3) specific to anxiety disorders. First, decreased GM volume compared to HVs was specific to the bipolar group in the vmPFC (peak MNI coordinates: -16, 54, -8), dmPFC (-8, 62, 21), left superior frontal gyrus (-28, 41, 34), and left precental gyrus (-46, -16, 37). Second, decreased GM volume compared to HVs was common among bipolar disorder, SMD, and ADHD in the right superior frontal gyrus (26, 27, 58). Third, decreased GM volume compared to HVs was specific to the anxiety groups in the left middle frontal gyrus (-42, 33, 22) and right parahippocampal gyrus extending to lingual gyrus (22, -51, -2).
Conclusions: GM volume differences in pediatric disorders were found. Some were specific to anxiety disorders; others specific to bipolar disorder; and a third group shared among bipolar, SMD, and ADHD. Further research should test for specificity in larger samples with more diagnostic groups. Developmental research mapping the commonalities and differences of structural brain abnormalities among pediatric disorders is needed to inform functional neuroanatomical models and developmental risk trajectories.

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Neuropsychopharmacology. 2014;39:S224-S225.

SEROTONERGIC MODULATION OF DEFAULT MODE NETWORK FUNCTIONAL CONNECTIVITY WITH SUPERIOR PREMOTOR AND SOMATOSENSORY CORTICAL AREAS IN CHILDREN AND ADOLESCENTS WITH ADHD AND HEALTHY CONTROLS.

Biskup C, Helmbold K, Baurmann D, et al.

Background: The default mode network (DMN) as assessed via functional magnetic resonance imaging (fMRI) describes an interaction of brain regions that are active during random episodic silent thought (REST) in healthy humans, and that are less active during task performance ("task deactivation"). Alterations of the DMN have been described in patients with different neuropsychiatric disorders including psychotic disorders, depressive disorders and attention deficit hyperactivity disorder (ADHD). The neurotransmitter serotonin (5-HT) in particular has been suggested to influence the DMN. However, the effect of a reduced central nervous 5-HT synthesis on DMN connectivity with different brain regions in young patients with ADHD has not yet been investigated. Acute tryptophan depletion (ATD) is a neurodietary method of challenging the central nervous 5-HT system by ingesting a mixture of amino acids (AAs) lacking tryptophan (TRP), the physiological precursor AA of 5-HT. The administered AAs compete with endogenous TRP on the uptake into the central nervous system at the blood-brain-barrier, thus leading to decreased substrate availability for central nervous 5-HT synthesis, which in turn is diminished for a short period. The present work aimed to study the effects of a short-term reduction in central nervous 5-HT synthesis by means of ATD on fMRI-based resting state functional connectivity (FC) between the DMN and different brain regions in children and adolescents with ADHD and healthy controls of the same age group.
Methods: Young male patients (aged 12-17 years) with ADHD (N=12) and healthy controls (N=10) of the same age group were subjected to an ATD challenge and subsequently diminished central nervous 5-HT synthesis and a balanced amino acid load (BAL) serving as a control condition using a randomized double-blind within-subject repeated measures crossover-design. Approximately three hours after challenge intake (ATD/BAL) resting state fMRI scans were obtained (3 Tesla).
Results: In healthy controls, after ATD administration FC of the right superior premotor cortex (Brodmann area 6) with the DMN was increased, and this relationship was the opposite in patients with ADHD as indexed by a highly significant group-by-challenge interaction. Moreover, there was a highly significant main effect of challenge administration on FC of the left superior somatosensory cortex (Brodmann area 3) with the DMN as well as a highly significant group-by-challenge interaction. The main effect of challenge administration was driven by lowered z-values after ATD intake in both groups, but was more pronounced in controls. After BAL administration in the patient group lower FC of the left superior somatosensory cortex with the DMN was detected when compared to controls.

Conclusions: Increased FC of the right superior premotor cortex with the DMN after administration of the ATD challenge was found in healthy subjects, suggesting a serotonergic modulation of this particular area relevant for motor planning function with regard to the DMN. However, in patients with ADHD the ATD challenge led to attenuated FC of the right superior premotor cortex with the DMN, which could be relevant regarding changes in neural planning capacity for motor activity in these particular patients. ATD lowered FC of the left superior somatosensory cortex with the DMN independently of the factor group but with stronger effects in controls. Overall, with patients with ADHD showing lower FC of the left superior somatosensory cortex with the DMN after BAL administration the present pilot data could point towards an altered serotonergic modulation of FC of the DMN with this particular brain area in patients with ADHD. These results are in line with altered sensory perception in patients with ADHD as described by previous clinical research, and could hint towards an altered serotonergic modulation in these patients.

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Neuropsychopharmacology. 2014;39:S434-S435.

GENETIC MODERATORS OF CARDIOVASCULAR SIDE EFFECTS OF ADHD TREATMENT.

Nurmi E, McGough J, Mallya K, et al.

Background: Common side effects of standard attentiondeficit hyperactivity disorder (ADHD) pharmacotherapy include changes in cardiovascular (CV) profiles, complicating treatment and representing a source of serious adverse events including rare mortality. A recent study of over 700,000 subjects in the Denmark health registry found that individuals exposed to stimulants had a higher risk of CV events (HR 1.83), especially children (HR 2.20). The ability to identify those at risk could help guide safe clinical treatment matching.

Methods: We hypothesized that genetic variation may contribute to the variability in CV side effects of ADHD medications. During both acute (8 weeks) and long-term (18 months) treatment phases with the stimulant dexmethylphenidate (d-MPH), the alpha-agonist guanfacine, and a combination of both medications, we collected regular CV measures in the NIMH Translational Research to Enhance Cognitive Control (TRECC) sample of 180 children and adolescents with ADHD. Blood pressure (BP) and heart rate (HR) were recorded at each of up to 24 visits, and serial EKGs were performed at 5 time points to assess medication-related cardiac changes, including QTc interval prolongation predisposing to cardiac arrhythmia. We tagged common genetic variation across drug targets and pathways involved in medication response and side effects, including monoaminergic, cholinergic, and glutamatergic transmitter systems, regulators of energy balance, and mediators of growth and plasticity. Genetic variation at 120 single nucleotide polymorphisms (SNPs) was examined for association with treatment-induced CV changes.

Results: All treatments were associated with short-term CV changes. As expected, stimulant treatment increased and guanfacine exposure decreased HR and BP, while combination treatment produced the least change in these measures. Over the course of long-term treatment with each of the three regimens, CV measures returned to baseline. The guanfacine group experienced lower tolerability and greater dropout than the d-MPH group. When guanfacine and d-MPH were administered concomitantly, the dropout rate was comparable to the d-MPH group. Despite clinical concerns regarding potential QTc prolongation with the combined use of guanfacine and d-MPH, combination treatment resulted in less QTc prolongation than d-MPH alone. No genetic influences on QTc prolongation were observed. Four alpha 7 cholinergic receptor markers (CHRNA7 rs8028396, rs7170028, rs2651417, rs12915695), one cannabinoid receptor 3'UTR SNP (CNR1 rs806368), and one functional promoter/5'UTR variant in the norepinephrine transporter (SLC6A2 rs2242446) were significantly associated with treatment-dependent changes in HR and BP in both the complete dataset and the Caucasian subset, minimizing confounding effects of ethnicity (Bonferroni corrected significance $p<0.0004$). A SLC6A2 promoter SNP in strong linkage disequilibrium (LD) with rs2242446 was similarly associated with HR in a prior report. Findings at CNR1 and CHRNA7 are novel. These three genes are biologically relevant candidates given their expression in cardiac and vascular tissue and role in hemodynamic regulation.

Conclusions: Medication-induced CV changes normalize over time with long-term treatment. Combination stimulant and alpha-agonist treatment may alleviate many of the CV side effects of d-MPH or guanfacine monotherapy. Three plausible genes emerged as moderators of medication effects on CV function. These results survive correction for multiple testing; however, replication in independent datasets is warranted.

Differential responses to treatment suggest that medication choice may be guided by genetic information in order to avoid serious adverse effects

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Norsk Epidemiologi. 2014;24:169-76.

CONVERGENT AND DISCRIMINANT VALIDITY OF PSYCHIATRIC SYMPTOMS REPORTED IN THE NORWEGIAN MOTHER AND CHILD COHORT STUDY AT AGE 3 YEARS WITH INDEPENDENT CLINICAL ASSESSMENT IN THE LONGITUDINAL ADHD COHORT STUDY.

Biele G, Zeiner P, Aase H.

Epidemiological studies often use parent questionnaires to assess children's development and mental health. To date, few studies have investigated the validity of parent questionnaires with standardized clinical assessments as criterion. The current study examines discriminant and convergent validity of parent questionnaires for symptoms of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiance Disorder (ODD), and Conduct Disorder (CD) as well as symptoms of Separation Anxiety employed in the Norwegian Mother and Child Cohort Study by using structured clinical interviews performed 5 months later in the Longitudinal ADHD Cohort Study as a criterion. The comparison of confirmatory factor analysis models and examination of factor correlations indicate convergent and discriminant validity of MoBa parent questionnaires for preschool children, especially for the assessment of ADHD and ODD/CD. Future research should attempt to further improve parent questionnaires, examine their validity in representative samples, and explicitly test their utility for screening.

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Pediatr Neurol. 2014;52:115-18.

DISRUPTION OF SOX6 IS ASSOCIATED WITH A RAPID-ONSET DOPA-RESPONSIVE MOVEMENT DISORDER, DELAYED DEVELOPMENT, AND DYSMORPHIC FEATURES.

Ebrahimi-Fakhari D, Maas B, Haneke C, et al.

Background Sox6 is a transcription factor that is crucial for the differentiation and development of cortical interneurons and dopaminergic neurons of the substantia nigra pars compact. Loss-of-function mutations might thus result in complex paroxysmal diseases such as epilepsy syndromes or movement disorders.

Patient We present a 15-year-old boy with delayed speech development and attention deficit hyperactivity disorder who presented with a rapid-onset generalized dopa-responsive dystonia.

Results Neurological examination revealed generalized dystonic and frequent athetoid movements of the arms, trunk, and neck. Gait was severely impaired secondary to frequent dystonic postures. Both a resting tremor and action tremors were observed in both hands. Speech was dysarthric but language comprehension was unimpaired. Testing for saccadic dysfunction revealed hypometric horizontal and vertical saccades. Physical examination was otherwise significant for a pectus carinatum and splenomegaly. Laboratory studies, brain magnetic resonance imaging, and electroencephalography were unremarkable. Treatment with levodopa/carbidopa led to a complete and sustained remission of neurological symptoms. Genetic testing revealed a mono-allelic de novo 84-kb deletion on chromosome 11p15.2 encompassing exons 14-16 of the SOX6 gene (chr11: 15944880-16029095, NCBI 37/hg19).

Conclusions This is the first report of a dopa-responsive movement disorder associated with SOX6 disruption. SOX6 mutations should be considered in the differential diagnosis of unexplained dopa-responsive dystonia syndromes.

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Prog Neuro-Psychopharmacol Biol Psychiatry. 2015;58:89-96.

A HAPLOTYPE OF THE NOREPINEPHRINE TRANSPORTER GENE (SLC6A2) IS ASSOCIATED WITH VISUAL MEMORY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shang C-Y, Chiang H-L, Gau SSF.

Attention-deficit/hyperactivity disorder (ADHD) is a common heritable childhood-onset psychiatric disorder with impaired visual memory. Based on the evidence from treatment effect of atomoxetine, which interacts directly

with the norepinephrine transporter, on visual memory in children with ADHD, this study examined the linkage disequilibrium structure of the norepinephrine transporter gene (SLC6A2) and the association between SLC6A2 and ADHD and visual memory, a promising endophenotype for ADHD. This family-based association sample consisted of 382 probands with DSM-IV ADHD and their family members (n = 1298 in total) of Han Chinese in Taiwan. Visual memory was assessed by the Pattern Recognition Memory (PRM) and Spatial Recognition Memory (SRM) tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB). We screened 21 polymorphisms across SLC6A2 and used the Family-Based Association Test (FBAT) to test the associations of SLC6A2 polymorphisms with ADHD and the PRM and SRM measures. In haplotype analyses, a haplotype rs36011 (T)/rs1566652 (G) was significantly associated with ADHD (minimal p= 0.045) after adjustment for multiple testing. In quantitative analyses, this TG haplotype also demonstrated significant associations with visual memory measures, including mean latency of correct responses in PRM (minimal p = 0.019), total correct responses in PRM (minimal p= 0.018), and total correct responses in SRM (minimal p= 0.015). Our novel finding of the haplotype rs36011 (T)/rs1566652 (G) as a novel genetic marker involved in both ADHD disease susceptibility and visual memory suggests that allelic variations in SLC6A2 could provide insight into the pathways leading from genotype to phenotype of ADHD.

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Psychiatr Genet. 2014 Dec;24:281-82.

LACK OF ASSOCIATION BETWEEN THE GRM7 GENE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

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

The aim of the present study was to investigate the possible association between these GRM7 gene polymorphisms and ADHD genetic susceptibility in Brazilian patients with ADHD.

The results reported here do not support a role for GRM7 in ADHD even though our sample has over 95% statistical power to detect differences of at least 10% on allele frequencies. These negative results confirm the need for replication in independent samples before any gene can be considered as an ADHD susceptibility gene. However, other members of the GRM family of receptors should be investigated to determine the role of glutamate in ADHD.

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Psychol Neurosci. 2014;7:461-73.

NEUROPHYSIOLOGICAL FACTORS ASSOCIATED WITH COGNITIVE DEFICITS IN CHILDREN WITH ADHD SYMPTOMS: EEG AND NEUROPSYCHOLOGICAL ANALYSIS.

Machinskaya RI, Semenova OA, Absatova KA, et al.

We neuropsychologically assessed cognitive deficits in 109 children with symptoms of attention-deficit/hyperactivity disorder (ADHD) and 51 children with typical development aged 7-8 years and 9-10 years and visually analyzed resting-state electroencephalography (EEG). The EEG recordings of children with ADHD more frequently contained EEG patterns of fronto-thalamic non-optimal functioning compared with controls, refected by groups of bilaterally synchronous frontal theta waves (FTWs) and right hemisphere local deviations of brain electrical activity. We found cognitive impairments associated with ADHD in children with different deviations of resting-state EEG. Children with FTWs in both age groups exhibited pronounced difficulties in programming, regulation and control (executive functions), and verbal performance. Children with right hemisphere local EEG abnormalities had executive dysfunction combined with difficulties in nonverbal performance. Executive performance in typically developing children significantly improved from 7-8 to 9-10 years of age. An analysis of neuropsychological scores in children with ADHD symptoms from age 7-8 to 9-10 with the same EEG abnormalities indicated specific age-related improvement of cognitive abilities. In children whose EEG showed patterns of fronto-thalamic involvement presented significant improvement in executive and verbal performance from 7-8 to 9-10 years of age. Overcoming the same age gap in children with right hemisphere local EEG deviations significantly improved only nonverbal performance, whereas improvements in executive function were not statistically significant.

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Psychol Neurosci. 2014;7:443-52.

SYNDROMIC ANALYSIS OF ADHD AT PRESCHOOL AGE ACCORDING TO A.R. LURIA CONCEPT.

Solovieva Y, Rojas LQ.

Different authors have studied attention-defcit/hyperactivity disorder (ADHD) in preschool children from different perspectives. Neuropsychological assessment can detect many kinds of cognitive diffculties, but the common syndromic picture has not yet been established. The idea of the existence of a specifc neuropsychological syndrome based on A.R. Lurianulls concept differs from syndromes that are established in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. The goal of the present study was to show qualitative parameters and features of cognitive activity in Mexican preschool children who receive a diagnosis of ADHD at preschool age. The proposal of such an analysis is for the whole syndrome. Neuropsychological assessment was applied to a group of Mexican preschool children with ADHD using the qualitative approach. Specifc diffculties were observed not only with regard to frontal cortical function but also with spatial processing and the tone of general brain activation. The qualitative analysis of the data obtained by neuropsychologically assessing ADHD at preschool age allowed us to establish a specifc complex of diffculties including functional weakness of the frontal and posterior associative cortical zones and general brain activation. New approaches to both assessment and remediation are urgently needed for preschool children in Latin America.

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Psychol Neurosci. 2014;7:453-60.

EXECUTIVE FUNCTION IN CHILDREN WITH ADHD.

Glozman JM, Shevchenko IA.

The study of executive function was one of the main topics of the work of A.R. Luria. Attention-defcit/hyperactivity disorder (ADHD) presents a good model of executive disorders, the experimental study of which reveals a complex structure of executive behavior including sustaining activity and attention, selectivity in decision making, shifting, planning, and prognostic ability. Cross-cultural (Russian/Italian) differences in executive function in children with ADHD are discussed. Comparisons of ADHD in preschool and primary school children are made in an attempt to prevent the aggravation of deficits and provide early remediation

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Psychopharmacology. 2014 Dec 24. [Epub ahead of print]

INVERSE FLUOXETINE EFFECTS ON INHIBITORY BRAIN ACTIVATION IN NON-COMORBID BOYS WITH ADHD AND WITH ASD.

Chantiluke K, Barrett N, Giampietro V, et al.

Rationale: Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are often comorbid and have both performance and brain dysfunctions during motor response inhibition. Serotonin agonists modulate motor response inhibition and have shown positive behavioural effects in both disorders.

Aims: We therefore used functional magnetic resonance imaging (fMRI) to investigate the so far unknown shared and disorder-specific inhibitory brain dysfunctions in these two disorders, as well as the effects of a single dose of the selective serotonin reuptake inhibitor fluoxetine.

Methods: Age-matched boys with ADHD (18), ASD (19) and healthy controls (25) were compared with fMRI during a stop task measuring motor inhibition. Patients were scanned twice, under either an acute dose of fluoxetine or placebo in a double-blind, placebo-controlled randomised design. Repeated measures analyses within patients assessed drug effects. To test for potential normalisation effects of brain dysfunctions, patients under each drug condition were compared to controls.

Results: Under placebo, relative to controls, ASD boys showed overactivation in left and right inferior frontal cortex (IFC), while ADHD boys showed disorder-specific underactivation in orbitofrontal cortex (OFC) and basal ganglia. Under fluoxetine, the prefrontal dysfunctions were no longer observed, due to inverse effects of fluoxetine on these activations: fluoxetine downregulated IFC and OFC activation in ASD but upregulated them in ADHD.

Conclusions: The findings show that fluoxetine normalises frontal lobe dysfunctions in both disorders via inverse effects, downregulating abnormally increased frontal activation in ASD and upregulating abnormally decreased frontal activation in ADHD, potentially reflecting inverse baseline serotonin levels in both disorders.

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Res Dev Disabil. 2015;38:7-17.

AN ANALYSIS OF CHALLENGING BEHAVIOR, COMORBID PSYCHOPATHOLOGY, AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN FRAGILE X SYNDROME.

Newman I, Leader G, Chen JL, et al.

The present study sought to investigate the relationship between challenging behavior, comorbid psychopathology, and Attention-Deficit/Hyperactivity Disorder (AD/HD) in Fragile X Syndrome (FRAX). Additionally, this study sought to examine how such disorders are predicted by gender, presence of autism spectrum disorder (ASD), and presence of intellectual disability (ID). A total of 47 children and adolescents with FRAX were assessed. Results revealed high levels of challenging behavior and AD/HD symptoms within the sample, with some participants exhibiting symptoms of comorbid psychopathology. Further analysis revealed that challenging behavior and comorbid psychopathology were positively correlated, with stereotypy correlating most strongly with comorbid psychopathology. In addition, ASD was found to predict challenging behavior, and gender was found to predict AD/HD symptoms. The implications of these findings are discussed.

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Res Dev Disabil. 2015 Jan;36:587-99.

ASSESSING EFFORTFUL CONTROL IN TYPICAL AND ATYPICAL DEVELOPMENT: ARE QUESTIONNAIRES AND NEUROPSYCHOLOGICAL MEASURES INTERCHANGEABLE? A LATENT-VARIABLE ANALYSIS .

Samyn V, Roeyers H, Bijttebier P, et al.

Objective: Effortful control (EC), the self-regulation component of temperament, is traditionally measured using questionnaires. Through the years, several neuropsychological measures originating from the cognitive psychology and the executive function (EF) literature have been introduced in the domain of temperament research to tap EC. Although this is not particularly surprising, given the conceptual overlap between EC and EF, it remains unclear whether EC questionnaires and neuropsychological EF tasks can really be used interchangeably when measuring EC. The current study addressed two important aspects in evaluating the interchangeability of both types of measures, that is: (a) do they measure the same construct? and (b) do they give the same results when comparing clinical populations?

Method: Three EC questionnaires, two inhibitory control tasks, and two attentional control tasks were administered in 148 typically developing children, 30 children with attention-deficit/hyperactivity disorder (ADHD), and 31 children with autism spectrum disorder (ASD). All children were between 10 and 15 years of age and had a full scale IQ of 80 or higher.

Results: Confirmatory factor analyses revealed that the questionnaires and EF tasks do not capture the same underlying latent variable(s). Groups could not be differentiated from each other based on their performance on EF tasks, whereas significant group differences were found for all EC-reports.

Conclusions: Overall, our findings show more differences than commonalities between the EC questionnaires and EF tasks and, consequently, suggest that both types of measures should not be used interchangeably.

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Res Dev Disabil. 2015;39:20-31.

ADHD AND AUTISTIC TRAITS, FAMILY FUNCTION, PARENTING STYLE, AND SOCIAL ADJUSTMENT FOR INTERNET ADDICTION AMONG CHILDREN AND ADOLESCENTS IN TAIWAN: A LONGITUDINAL STUDY.

Chen Y-L, Chen S-H, Gau SSF.

This longitudinal study investigated the prevalence, predictors, and related factors for Internet addiction among elementary and junior high school students in Taiwan. A convenient sample of grades 3, 5, and 8 students (n= 1153) was recruited from six elementary and one junior high schools. They were assessed during the beginning

and the end of the spring semester of 2013. Internet addiction was examined by the Chen Internet Addiction Scale (CIAS). Other factors were screened using the Chinese version of the Autism Spectrum Quotient (AQ) for autistic trait, the Parental Bonding Instrument (PBI) for parenting, the Family APGAR for family support, the Social Adjustment Inventory for Children and Adolescents for social function, and the Swanson, Nolan, and Pelham, version IV scale (SNAP-IV) for ADHD symptoms. The prevalence of Internet addiction decreased from 11.4% to 10.6%. Male, low family support, poor social adjustment, and high ADHD-related symptoms were related to Internet addiction. However, there was an inverse relationship between autistic traits and Internet addiction. Further, its predictivity could be accounted by poor academic performance, male, and protective parenting style. Internet addiction is not uncommon among youths in Taiwan. The predictors identified in this study could be the specific measures for the development of a prevention program for Internet addiction in the youth population.

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Res Dev Disabil. 2015;38:329-37.

READING COMPREHENSION IN ADOLESCENTS WITH ADHD: EXPLORING THE POOR COMPREHENDER PROFILE AND INDIVIDUAL DIFFERENCES IN VOCABULARY AND EXECUTIVE FUNCTIONS.

Martinussen R, Mackenzie G.

The overall objective of this study was to investigate reading comprehension in youth with and without a prior diagnosis of attention-deficit hyperactivity disorder (ADHD). The first goal was to determine whether youth with and without ADHD matched in word reading ability exhibited differences in reading comprehension proficiency. The next goal was to determine whether good and poor comprehenders within the ADHD subgroup differed from each other on language and academic achievement measures. The third objective was to examine whether word recognition or oral vocabulary knowledge mediated the effect of ADHD symptoms on reading comprehension performance. Youth with ADHD scored significantly lower than the comparison youth on a standardized measure of reading comprehension. Relative to good comprehenders with ADHD, poor comprehenders with ADHD exhibited weaknesses in expressive vocabulary, mathematical reasoning, written expression, and exhibited more executive function (EF) difficulties as reported by the teacher. Expressive vocabulary and word reading, but not teacher EF ratings, accounted for unique variance in reading comprehension performance and mediated the relationship between ADHD symptoms and reading comprehension. Implications for further research and educational practice are discussed.

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Res Dev Disabil. 2015;38:134-44.

VISUOSPATIAL WORKING MEMORY UNDERLIES CHOICE-IMPULSIVITY IN BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Patros CHG, Alderson RM, Lea SE, et al.

The present study examined the directional relationship between choice-impulsivity and separate indices of phonological and visuospatial working memory performance in boys (aged 8-12 years) with (n= 16) and without ADHD (n= 19). Results indicated that high ratings of overall ADHD, inattention, and hyperactivity were significantly associated with increased impulsivity and poorer phonological and visuospatial working memory performance. Further, results from bias-corrected bootstrapped mediation analyses revealed a significant indirect effect of visuospatial working memory performance, through choice-impulsivity, on overall ADHD, inattention, and hyperactivity/impulsivity. Collectively, the findings suggest that deficits of visuospatial working memory underlie choice-impulsivity, which in turn contributes to the ADHD phenotype. Moreover, these findings are consistent with a growing body of literature that identifies working memory as a central neurocognitive deficit of ADHD.

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School Mental Health. 2014 Dec;6:264-78.

PREVALENCE AND CHARACTERISTICS OF SCHOOL SERVICES FOR HIGH SCHOOL STUDENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Murray DW, Molina BSG, Glew K, et al.

This study examines the prevalence and characteristics of services reported by school staff for 543 high school students participating in the 8-year follow-up of the multi-site Multimodal Treatment study of ADHD (MTA). Overall, 51.6 % of students with a history of attention-deficit/hyperactivity disorder (ADHD) were receiving services through an individualized educational plan (IEP) or a 504 plan, a rate higher than expected for this age group. Less than 5 % of these had 504 plans; 35.5 % attended special education classes. Very few services (except tutoring) were provided outside of an IEP or 504 plan. Almost all students with services received some type of academic intervention, whereas only half received any behavioral support or learning strategy. Less than one-fourth of interventions appear to be evidence based. Students receiving services showed greater academic and behavioral needs than those not receiving services. Services varied based upon type of school, with the greatest number of interventions provided to students attending schools that only serve those with disabilities. Original MTA treatment randomization was unrelated to services, but cumulative stimulant medication and greater severity predicted more service receipt. Results highlight a need for accommodations with greater evidence of efficacy and for increased services for students who develop academic difficulties in high school.

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School Mental Health. 2014 Dec;6:251-63.

A STORY MAPPING INTERVENTION TO IMPROVE NARRATIVE COMPREHENSION DEFICITS IN ADOLESCENTS WITH ADHD.

Derefinko KJ, Hayden A, Sibley MH, et al.

The current study examined the effects of an 8-week story mapping intervention (SMI) to improve narrative comprehension in adolescents with attention-deficit hyperactivity disorder (ADHD). Thirty 12–16-year-old adolescents with ADHD who were participating in a summer treatment program for adolescents with ADHD received the SMI instruction ten times and completed SMI homework ten times in a structured environment with teacher feedback. Recall of fables and story creation were assessed before and after the SMI. At post-test, fable recalls included more of the most important events, were more coherent, and included a greater number of plausible inferences than pre-test fable recalls. SMI homework scores accounted for increases in recall of important events and plausible inferences, suggesting that consistent practice and feedback with story mapping could contribute to important recall gains. In contrast, the inclusion of goal-based events and the rated coherence of created stories did not improve, suggesting that more explicit instruction in applying story mapping to story creation may be required.

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Technol Eval Cent Assess Program Exec Summ. 2014 Oct;29:1-6.

QUANTITATIVE ELECTROENCEPHALOGRAPHY AS A DIAGNOSTIC AID FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Anon.

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The American Journal of Psychiatry. 2014 Dec;171:1310-19.

NEURAL AND COGNITIVE CORRELATES OF THE COMMON AND SPECIFIC VARIANCE ACROSS EXTERNALIZING PROBLEMS IN YOUNG ADOLESCENCE.

Castellanos-Ryan N, Struve M, Whelan R, et al.

Objective: The authors sought to model the unique and common variance across conduct disorder, substance misuse, and attention deficit hyperactivity disorder (ADHD) and to investigate the neurocognitive factors that relate generally or uniquely to externalizing problems in adolescence.

Method: Personality and behavioral measures and functional imaging responses to reward sensitivity and response inhibition tasks were assessed in 1,778 European adolescents at age 14 and, using structural equation

modeling, were related to the unique and common variance across externalizing problems assessed and modeled at ages 14 and 16.
Results: Externalizing problems best fit a general-specific model made up of a specific factor representing ADHD and conduct disorder symptoms, a specific factor representing substance misuse symptoms, and a common externalizing factor representing the variance shared among all symptoms. Common variance across externalizing problems was associated with high impulsivity and delay discounting as well as low blood-oxygen-level-dependent (BOLD) response in the substantia nigra and subthalamic nucleus but high BOLD response in the presupplementary motor area and precentral gyrus during successful inhibition. Unique variance for ADHD/conduct disorder was associated with impulsivity, poor response inhibition, and high delay discounting, as well as low BOLD response in frontal brain areas bilaterally during failed inhibition. In contrast, unique variance for substance misuse was associated with high sensation seeking and delay discounting, as well as differential brain response to reward anticipation: high BOLD response in the left orbitofrontal cortex but low BOLD response in the left inferior frontal gyrus.
Conclusions: Personality, behavioral, and fMRI findings suggest that abnormalities in response inhibition, error processing, and reward processing are differentially implicated in underlying vulnerability specific to ADHD/conduct disorder and substance misuse and general to externalizing problems.

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The Lancet Psychiatry. 2014;1:278-85.

CONTACT WITH THE JUVENILE JUSTICE SYSTEM IN CHILDREN TREATED WITH STIMULANT MEDICATION FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER: A POPULATION STUDY.

Silva D, Colvin L, Glauert R, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is the most frequent neurodevelopmental disorder in children and is sometimes noted retrospectively in young people and adults who are incarcerated. We aimed to investigate juvenile justice encounters in children with and without ADHD.
Methods: Between January, 1995, and December, 2010, we did a population-based cohort study in Western Australia. Anonymised linked population data were obtained from the Western Australia Midwives Notification System. 12831 non-Indigenous Australian children and young people aged 10-21 years, who were diagnosed and treated with stimulant drugs for ADHD and had a record in the Monitoring Drugs of Dependence System (ADHD cohort), were identified and frequency-matched by age, sex, and socioeconomic status to 29722 non-Indigenous Australian children and young people who had no record in the Monitoring Drugs of Dependence System (controls). Community correction records and incarceration records were retrieved for all participants from Total Offending Management Solutions. Our primary outcome was to compare justice outcomes between children with ADHD and those without this disorder. We compared cohorts by conditional logistic regression analysis.
Findings: 9939 boys and 2892 girls were diagnosed and treated for ADHD; 22875 boys and 6847 girls were frequency-matched controls. 792 (8%) boys and 75 (3%) girls with ADHD had a community correction record, compared with 822 (4%) boys and 75 (1%) girls without ADHD. 132 (1%) boys and 11 (<1%) girls with ADHD had an incarceration record, compared with 108 (<1%) boys and five (<1%) girls without ADHD. Compared with controls, boys with ADHD were two and half times more likely to have a community correction record (odds ratio 2(middle dot)48, 95% CI 2(middle dot)22-2(middle dot)76) or an incarceration record (2(middle dot)63, 2(middle dot)01-3(middle dot)44). Compared with their non-ADHD counterparts, girls with ADHD were nearly three times more likely to have a community correction record (odds ratio 2(middle dot)86, 95% CI 2(middle dot)03-4(middle dot)03) and seven times more likely to have an incarceration record (7(middle dot)27, 2(middle dot)29-23(middle dot)08). Boys with ADHD received their first community correction record at a younger age compared with controls (15(middle dot)9 vs 16(middle dot)3 years; p=0(middle dot)0005), but age at first community correction record was similar for girls (16(middle dot)5 vs 16(middle dot)4 years; p=0(middle dot)87). Burglaries and breaking and entering were the most common reason for a first justice record (total 659 [37%]), and this offence was twice as likely in children with ADHD (for boys, odds ratio 2(middle dot)24, 95% CI 1(middle dot)90-2(middle dot)64; for girls, 2(middle dot)19, 1(middle dot)40-3(middle dot)42).
Interpretation: Justice outcomes for boys and girls were more frequent among children and young people treated for ADHD compared with their non-ADHD counterparts. Unlike girls, boys were more likely to offend at a

younger age. Early diagnosis and management of children and young people with ADHD might reduce the over-representation of children with this disorder within the juvenile justice system.
Funding: National Health and Medical Research Council (Australia), Australian Research Council.

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The Lancet Psychiatry. 2014;1:118.
SCHOOL DAZE.
Sharpe K.

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WIREs Cognitive Science. 2015 Jan;6:39-52.
ATTENTION-DEFICIT HYPERACTIVITY DISORDER, MULTIMODAL TREATMENT, AND LONGITUDINAL OUTCOME: EVIDENCE, PARADOX, AND CHALLENGE.
Hinshaw SP, Arnold LE.
Given major increases in the diagnosis of attention-deficit hyperactivity disorder (ADHD) and in rates of medication for this condition, we carefully examine evidence for effects of single versus multimodal (i.e., combined medication and psychosocial/behavioral) interventions for ADHD. Our primary data source is the Multimodal Treatment Study of Children with ADHD (MTA), a 14-month, randomized clinical trial in which intensive behavioral, medication, and multimodal treatment arms were contrasted with one another and with community intervention (treatment-as-usual), regarding outcome domains of ADHD symptoms, comorbidities, and core functional impairments. Although initial reports emphasized the superiority of well-monitored medication for symptomatic improvement, reanalyses and reappraisals have highlighted (1) the superiority of combination treatment for composite outcomes and for domains of functional impairment (e.g., academic achievement, social skills, parenting practices); (2) the importance of considering moderator and mediator processes underlying differential patterns of outcome, including comorbid subgroups and improvements in family discipline style during the intervention period; (3) the emergence of side effects (e.g., mild growth suppression) in youth treated with long-term medication; and (4) the diminution of medication's initial superiority once the randomly assigned treatment phase turned into naturalistic follow-up. The key paradox is that while ADHD clearly responds to medication and behavioral treatment in the short term, evidence for long-term effectiveness remains elusive. We close with discussion of future directions and a call for greater understanding of relevant developmental processes in the attempt to promote optimal, generalized, and lasting treatments for this important and impairing neurodevelopmental disorder.

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Detection of auto-antibodies to DAT in the serum: Interactions with DAT genotype and psycho-stimulant therapy for ADHD

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ABSTRACT

Interest is rising for auto-immune contribution in neuro-psychiatry. We evaluated the auto-antibodies against dopamine transporter (DAT aAbs) in 61 children (46 ADHD who met DSM-IV-TR criteria, 15 healthy controls).
Methods: ADHD patients were assigned, according to severity, either to a non-pharmacological therapy (NPT, N = 32) or to a pharmacological treatment (PT, N = 14) with methylphenidate (MPH). In ADHD children, blood samples were withdrawn twice, at recruitment (T0 basal) and after 6 weeks (T1); following 16 excluded subjects, DAT genotype was characterized (9-repeat or 10-repeat alleles; N = 15 each). After 18 months of NPT or PT, some patients (carrying at least one 9-repeat allele) were blood sampled again (T2), for comparison with healthy controls (final n = 8)
Results: Compared to NPT, basal DAT aAbs titers were higher within most severe patients (then assigned to PT), specifically if carrying a DAT 10/10 genotype. DAT aAbs levels of NPT group resulted highly correlated with distinct subscales of Conners' Parent/Teacher Scales (Rs > 0.34), especially within DAT 10/10 genotype (Rs > 0.53). While T1 titers were elevated over T0 baseline for NPT children, such an increase was not observed in PT patients carrying at least one 9-repeat allele, who also showed behavioral response to subchronic MPH. After 12-24 months of MPH exposure, DAT aAbs titers in PT subjects were comparable to those of healthy controls, while titers remained significantly elevated in NPT patients. Data warrant further research on serum DAT aAbs, which could be used to confirm ADHD diagnosis and/or to monitor therapeutic efficacy of MPH.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) has been internationally recognized as a medical neuro-developmental condition (Curatolo et al., 2009; Davis et al., 2011; Purper-Ouakil et al., 2011; Cortese, 2012); global interest in long-term consequences of ADHD and of psycho-stimulant administration for ADHD is on the rise (Hinshaw et al., 2011). According to the current criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition – Text Revision (DSM IV-TR), ADHD prevalent symptoms include problems in maintaining attention, excessive motor activity, and impulsivity, which often lead to poor academic performance and impaired social interactions (American Psychiatric Association, 2000). These symptoms develop early in up to 5% of children (Polanczyk et al., 2007), and can persist into adolescence and adulthood (Biderman et al., 2006). Frequently comorbid with ADHD are other impulse-control disorders, like oppositional defiant disorder, conduct disorder, substance abuse and/or dependence problems (see Hollander et al., 2000, 2005 for pathological gambling), all of which may be conceptualized as part of the addictive disorder spectrum (Fontenelle et al., 2011).

Although the multi-factorial etiology of ADHD is still unclear, evidence suggests that the disorder is linked to imbalanced levels of dopamine neurotransmitter. Some accounts present ADHD as a motivational dysfunction (Sonuga-Barke, 2005), arising from altered processes within fronto-striatal circuits (Oades, 1998; Sagvolden and Sergeant, 1998; Chambers and Potenza, 2003). For this reason, one focus of ADHD research has converged on the brain dopamine transporter (DAT) in the clinics and in preclinical models. It has been proposed that specific ADHD symptoms may arise from a modification in DAT expression and function (Jucaite et al., 2005; Bannon, 2005; Berridge et al., 2007):

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0165-5728/

human DAT1 gene has a VNTR polymorphism of 40 bp (3–11 repeats) in the 3′ untranslated region, with 9- and 10-repeat variants being the most common in Caucasians. 10-repeat VNTR polymorphism of DAT has been associated with ADHD and with obsessive-compulsive disorder (Cook et al., 1995; Gill et al., 1997 Sharp et al., 2009; Scherk et al., 2009; Yang et al., 2007; Greenwood et al., 2013). DAT1 high-risk allele (i.e. the 10-repeat allele) can explain 1%–4% of the overall variance in ADHD symptoms; its relation with hyperactive–impulsive symptoms is stronger and more reliable than that with inattentive symptoms (Waldman et al., 1998).

However, although the presence of DAT1 high-risk alleles may influence the severity of the disorder and may explain why as many as 30% of ADHD children do not respond to psycho-stimulants (Madras et al., 2002), other non-genetic factors are crucial for the onset of ADHD symptoms. To account for a possible DAT alteration, a rising interest exists for auto-immune processes and psycho-immunological interactions (Shulman, 2009; Graus et al., 2010a,b). A breach in blood–brain barrier (BBB) integrity, due to conditions of stress (Kuang et al., 2004) or owing to a traumatic injury to the brain (like e.g. as complication of a difficult delivery, Ankeny and Popovich, 2010), could implicate the draining of CNS antigens to peripheral lymphoid organs, with subsequent auto-immune responses (Diamond et al., 2009; Levin et al., 2010). According to recent literature, anti-neuronal antibodies may target a wide range of CNS proteins, including neuro-receptors (Davies et al., 2007; Graus et al., 2008; Zuliani et al., 2012). Behavioral dysfunction might possibly stem from anti-neuronal auto-antibodies (aAbs) that would presumably compromise neural function (Granstrem et al., 2006). Circulating aAbs against neuro-receptors are reliable biomarkers for Systemic Lupus Erythematosus (Cohen-Solal and Diamond, 2011), intractable seizures (Rogers et al., 1994; Twyman et al., 1995), brain ischemic stroke (Dambinova et al., 2003), Hashimoto's encephalopathy (Chong et al., 2003) and Sydenham's chorea. Other two neurological conditions with a claimed role for aAbs and related neuro-psychiatric symptoms are the Limbic and the NMDAR-Ab encephalitis. While seizures are prominent with GABA-B receptor (GABAB-R) aAbs, there may be psychiatric features with AMPA receptor (AMPA-R) aAbs (Lai et al., 2009; Graus et al., 2010a,b; Lancaster et al., 2010; Zandi et al., 2010) and with NMDA receptor (NMDA-R) aAbs (Dalmau et al., 2011). Many of these patients are children who may initially seek for psychiatric wards for acute anxiety, behavioral change or psychosis. Interestingly, a role for auto-immunity in general and for aAbs in particular has been claimed for Tourette's (Hoekstra and Minderaa, 2005; Martino et al., 2009; Rizzo et al., 2010), for obsessive–compulsive disorder (Teixeira et al., 2014), and for ADHD as well (Passarelli et al., 2013; Hegvik et al., 2014).

Circulating aAbs to CNS antigens can be also detected in animal models (Dambinova et al., 1997, 1998; Vincent et al., 1999; Kowal et al., 2006; Knight et al., 2007; Capone et al., 2008; Colasanti et al., 2009), as well as in opiate-treated mice (Granstrem et al., 2006). In this line, we recently proposed (Adriani et al., 2012) that a DAT altered turnover/degradation ratio may lead to an over-production of neuro-receptor fragments, which might then overcome the BBB and spill into the blood, where they can generate an auto-immune reaction. This auto-immune challenge could in turn lead to an enduring and possibly detectable interference with the dopamine (DA) neurotransmission as well as to DA-related behavioral changes, like ADHD symptoms (i.e. impulsivity and hyperactivity). Thus, purpose of the present study was 1) to ascertain the presence in the blood of circulating auto-antibodies (aAbs) targeting some epitopes of the DAT protein, 2) to measure levels of such DAT aAbs, by means of an ELISA assay, as a function of therapy with or without pharmacological MPH treatment, 3) to correlate these DAT aAbs titers with clinical scores of ADHD symptoms, and 4) to further evaluate the above parameters as a function of the individual DAT genotype. We hypothesized that a more clear account of observed symptoms could be served by taking into consideration the interaction between genetic and auto-immune parameters.

2. Material and methods

2.1. Recruitment of patients and healthy controls

Participants included 61 children. We recruited 48 patients with a formal diagnosis of ADHD, with a female to male ratio of 1:5, referred to Child Psychiatry Unit of Tor Vergata University from April 2010 to March 2012. Two of these recruited ADHD children were dropped out, since they turned out to be non-responders to the recruitment commitments; we also recruited 15 healthy children (handled under the same routine conditions from April 2013 to March 2014, in the same period as the patients' re-sampling, see below) to act as controls. All subjects had a full Scale IQ over 84, as assessed by the Wechsler Intelligence Scale — III edition (Wechsler, 1991). They were evaluated by child neuro-psychiatrists who determined the diagnosis of ADHD, according to DSM IV-TR criteria (American Psychiatric Association, 2000); a medical work-up excluded any other neuro-genetic disease or immune disorder, as well as any psychiatric comorbidity (conduct disorder, obsessive–compulsive disorder, Tourette's, depression, bipolar disorder, psychosis), assessed by the Schedule for Affective Disorders and Schizophrenia for School Age Children — Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Post-recruitment exclusions were also made for coeliac or diabetic disease, and in case of recent fever or allergy, as resulting from standard blood screen.

The clinical sample was divided into two, based on therapeutic intervention decided at enrollment: children with milder symptoms, which did not need pharmacological treatment, underwent cognitive-behavioral therapy and/or periodic follow-up (unmedicated, NPT group; $N = 32$); severe children, with a significant impairment of adaptive functioning in different areas of life, were assigned to pharmacological treatment with MPH (PT group; $N = 14$).

The study was formally approved by ISS Ethical Committee (Prot. CE-ISS 09/270 of 15 July 2009, scientific responsible and PI: W.A.). Informed consent procedures included searching for consent from the child (using age-adequate approaches) and illustrating to parents the standard consent form; the parents gave their written informed consent for the child to participate in this study. All potential participants who decided not to participate in the study were not disadvantaged in any way by not participating. Also, we declare that collected biological materials were used solely to the purpose of this study; the responsible person for pediatric privacy is one of authors (M.C.P.). The rules set by the Code of Ethics of the World Medical Association (Declaration of Helsinki), which has been printed in the British Medical Journal (18 July 1964), were respected.

2.2. Clinical assessment

Each patient was evaluated by a staff of trained child neuro-psychiatrists at our "S. Alessandro" clinical Unit, according to the DSM-IV and ICD-10 criteria for ADHD. Information was gathered from the clinical interviews and questionnaires with the parents, teacher and from direct observations of the patients.

Parents completed *SNAP-IV* that elicits DSM-IV TR criteria for ADHD on a four-point scale of frequency (Swanson, 1983), also giving information about ADHD subtypes (inattentive, hyperactive–impulsive, combined type). ADHD symptoms were also determined using *Conners' Parent Rating Scale*; each item was scored according to the published measure from 0 (Not true at all) to 3 (Very much true) (Conners et al., 1998). The semi-structured *Schedule for Affective Disorders and Schizophrenia — Present and Lifetime version* (K-SADS/PL) and also the *Child Behavior Checklist/4–18* (CBCL; Achenbach, 1991) were used separately, to elicit parents' and patients' reports of signs and symptoms that might indicate possible co-morbidities.

The *Children's Global Assessment Scale* (CGAS) was used by clinicians to measure the overall severity of social and psychiatric functioning for children ages of 4–16 years (Shaffer et al., 1983). CGAS scores range between 1 and 100, with higher scores indicating better functioning.

The full clinical assessment was performed at time of recruitment, while both parents completed the Conners' Parent Rating Scale and clinicians completed the CGAS twice, at time T0 and T1. The patient's teacher completed (only once, at time of recruitment) the *Conners' Teacher Rating Scale*.

2.3. Biochemical and genetic assessment

After recruitment, in the 46 ADHD children we were able to collect two blood samplings. *Time T0*: basal withdrawal, at recruitment (early in the morning and/or without breakfast, i.e. when stomach was empty; also used for standard blood screen); *Time T1*: second withdrawal, taken either after 6 weeks from time T0 (for subjects who did not undergo pharmacological therapy, i.e. NPT group) or after 6 weeks from when MPH had reached the therapeutic dosage (for subjects which were assigned, at recruitment, under pharmacological treatment, i.e. PT group). Blood was withdrawn from patients using standard phlebotomy procedures: it was collected in a sterile 10-mL plain centrifuge tube and allowed to clot for 5–10 min, then centrifuged for 10 min at 1500 rpm in a standard centrifuge. The serum was stored at −80 °C until use.

Of 46 patients, 16 children were excluded a posteriori, due to recent fever/allergy before blood sampling, as altered values were detected in standard blood screen at T0. Ten children had higher lymphocytes count (41.0 ± 0.84%, up to 47.0%) and seven children had higher eosinophils count (4.0 ± 0.78%, up to 11.1%) than standard norm for healthy controls (four children had both); two children were classified as non-responders to MPH and switched to atomoxetine treatment; one child was also excluded since he was the only one not belonging to Caucasian ethnicity. In the remaining children (N = 30), we collected buccal samples using a Catch-all sample collection Swab (Epicentre, USA), in order to verify specifically the DAT1 gene VNTR polymorphism in the 3′ untranslated region (3′UTR), rs 28363170 (Vandenbergh et al., 1992; Sano et al., 1993). Of these, 15 had a DAT 10/10 genotype while 15 were carrying at least one 9-repeat allele.

We recruited 15 subjects as healthy controls. Of these, only 3 had a DAT 10/10 genotype (too few to be further assessed) while 12 were carrying at least one 9-repeat allele. After excluding 4 children with recent fever or allergy, we ended up with 8 healthy subjects. Hence, ADHD children with at least one 9-repeat allele were further contacted for re-sampling, after one-to-two years (average: 18 months) of exposure to MPH or to unmedicated conditions (PT or NPT, respectively). For the latter, we were able to involve just 4 patients (out of 11). We aimed to re-assess their DAT aAbs titers (*time T2*), to be compared with healthy controls; therefore, in addition to T0 baseline, blood samples were taken twice in these children, months apart, to improve reliability of findings. All these subjects were withdrawn blood samples in the same conditions as for time T0.

2.4. PCR methods

Genomic DNA was prepared from buccal swab samples by using the BuccalAmp™ DNA Extraction Kit, following the manufacturer's instructions (Epicentre, USA). Briefly, after collecting buccal cells, the swab end was placed into a tube containing QuickExtract DNA extraction solution and rotated a minimum of five times. The tube was vortex mixed for 10 s and incubated at 65 °C for 1 min. After vortex mix for 15 s, the tube was transferred to 98 °C and incubated for 2 min. After vortex mix for 15 s, the DNA was stored at −20 °C until processing. The yield of DNA is usually between 2 and 14 ng/μl.

The 3′-UTR repeated sequence of the DAT1 gene was amplified by the polymerase chain reaction (PCR). The primer sequences employed were 5′-TGT GGT GTA GGG AAC GGC CTG AG-3′ (DAT1-F) and 5′-CTT CCT GGA GGT CAC GGC TCA AGG-3′ (DAT1-R). The PCR amplification was carried out in a final volume of 50 μl containing 3 μl of genomic DNA prepared using the Buccal Amp DNA extraction kit, 1.5 mM of $MgCl_2$, 200 μM of dNTP, 50 mM of KCl, 10 mM of Tris–HCl (pH 8.3), 0.25 μM of each primer, and 1 U of Promega Taq DNA polymerase. The PCR amplification was performed for 35 cycles consisting of 94 °C for 45 s, 57 °C for 30 s, and 72 °C for 30 s. The genotype was estimated from the size of the PCR product analyzed by electrophoresis on 6% acrylamide gels stained with ethidium bromide.

2.5. ELISA methods

We used a novel and patented DAT-EIA-kit (patent holder: ISS, Italy), based on the ELISA method - most commonly used for determination in the serum of anti-neuronal auto-antibodies (aAbs) - exploiting peptide fragments of the human DAT sequence as antigens (see Adriani et al., 2012). Briefly, the concentration of DAT-aAbs is determined using modified synthetic peptides, corresponding to a fragment of DAT, as antigens. These peptide fragments were designed by selecting a 19-amino acid portion of the DAT sequence based on the most immuno-reactive portion (Granstrem et al. 10-AUG-2012 provisional patent; 10-AUG-2013 International Patent Application No. PCT/EP2013/066845), and custom synthesized by one of authors (O.G.).

The DAT-fragment antigen was affinely pre-adsorbed to the microplate (0.5 μg/well). In a first incubation step (1 h, 25 °C), the serum samples (diluted 1:100) are applied (80 μl per each well) on the immuno-plate (Costar, USA): antibodies react with the solid phase bound antigen. After intensive washing (PBS with 0.05% Tween 20, pH 7.4), the captured antibodies are detected using monoclonal murine antibodies (catalog number A8667; Sigma Aldrich, USA) to human IgG (diluted 5 mL/L in vehicle: albumine 0.5 g/L, PBS-Tween20 5 mL/L, thimerosal 0.02 g/L, sodium azide 0.05 g/L, distilled water; Sigma Aldrich, USA) conjugated with horseradish peroxidase (HP). This secondary antibody (diluted 1:20,000) is added (80 μl per each well) and incubated (1 h, 25 °C). Immuno-complex is semi-quantitatively determined by HRP/TMB-detection reaction: the substrate solution, TMB (catalog number 09743; Fluka, USA) is added (80 μl per each well). Stopping solution (2 N HCl) is then added converting the color to yellow. The plate is scanned at 450 nm on a Microplate reader 3550 (Bio-Rad, USA). The intensity of the yellow color is directly proportional to the concentration of DAT-aAbs in the serum sample.

2.6. Statistical analysis

The analyses of behavioral scales, of titers, and of correlations were run within all recruited ADHD patients (N = 46); after 16 were excluded a posteriori for recent fever/allergy, the analyses involved only genotyped ADHD children (N = 30). Subjects segregated into two DAT genotype groups (N = 15 each). Patients with DAT 9/9 genotype were too few to be reliably used for statistic purposes: henceforth, DAT 9/9 and 9/10 genotypes were pooled and referred to as "subjects with at least one 9-repeat DAT allele" (collectively termed 9/x).

First, we investigated the role of factors such as "group" (NPT vs. PT patients), "genotype" (DAT 10/10 vs. 9/x), and "time" (T0 vs. T1). The following variables were evaluated: 1) scores obtained in CGAS and in subscales of Conners' and 2) semi-quantitative anti-DAT titers, through the optical density values, obtained with the DAT-EIA-kit's ELISA assay.

Second, we run a full correlation analysis between anti-DAT titers, resulting from the DAT-EIA-kit's ELISA assay, and scores obtained by patients (in CGAS values assigned by clinicians; in Conners' Scales, compiled by parents and by teacher of the recruited children).

Third, we investigated the anti-DAT titers once again (time T2), after an 18-month period of exposure to MPH or to unmedicated conditions (NPT vs. PT patients, respectively), and compared them to the healthy controls (only DAT 9/x genotype, final n = 8).

3. Results

As outlined in Material and methods, we enrolled 46 ADHD subjects and 15 healthy controls; we analyzed aAbs titers and psychometric scales of all ADHD subjects; after a posteriori exclusion, we came to

DAT genotype of 30 ADHD subjects (15 subjects per genotype), and eight healthy controls of DAT 9/x genotype. In general, the titer of DAT-aAbs was detectable (optical density around 0.81 in average) in all healthy controls and ADHD children, with a consistent elevation (optical density more than 1–1.1) in specific cases. As a whole, we report slightly but consistently elevated levels of DAT aAbs in the most severe ADHD patients; thus, determination of serum anti-DAT titers can be proposed as a suitable biomarker to help ADHD diagnosis.

3.1. Symptom scales: CGAS and Conners'

The average values of symptom scales (filled in by the mothers) and of CGAS values (assigned by the clinician) show, between time T0 and T1, a globally stable profile of ADHD symptoms in the group of children under non-pharmacological therapy (NPT, 32 subjects before the exclusion made a posteriori), as illustrated in Fig. 1 upper panel. The Student t-test analysis did not yield any significant results hence suggesting no improvement in the absence of medication.

In the group of children placed under pharmacological treatment (PT, 14 subjects before the exclusion made a posteriori), the average values of symptoms (scales filled in by their mothers and CGAS values assigned by the clinician) showed clearly more severe ADHD symptoms, compared to those subjects who did not need to take a pharmacological therapy. As expected, a period of 6 weeks under MPH treatment led to an important reduction of ADHD symptoms between T0 and T1: the reduction of symptoms was significant for CGAS ($t(26) = 3.67$), for the attention deficit sub-scale ($t(26) = 3.13$), and for the ADHD index ($t(26) = 3.27$), as the Student t-test analysis demonstrated (Fig. 1 lower panel).

The Student t-test analysis that compared Conners' scales and CGAS values between the two groups (NPT vs PT subjects) revealed, indeed:

- Time T0: a significant difference in score for CGAS values ($t(44) = 3.79$), for the attention deficit sub-scale ($t(44) = 2.92$) and for the ADHD index ($t(44) = 2.10$): this finding suggests that the subjects, later assigned to the MPH treatment group, were characterized indeed by more severe ADHD symptoms compared to subjects who did not need to take a pharmacological therapy.
- Time T1: no significant differences were evidenced. This indicates that, after 6 weeks of pharmacological treatment, these subjects showed an important reduction in symptoms, so that they could no longer be distinguished from subjects who did not take any pharmacological therapy. The recovery of symptoms by MPH did lead to children who appeared similar to unmedicated ones.

3.1.1. Role of DAT genotype

The group of subjects who did not take pharmacological therapy (9 were excluded for recent fever/allergy; 23 were genotyped out of 32 total) was split into two subgroups, namely in carriers of a DAT 10/10 (12 subjects) vs 9/x (11 subjects) genotype. It could be clearly observed that:

- Genotype 10/10 ($n = 12$): ADHD symptoms were unchanged from time T0 to T1 (Fig. 2 upper panel), suggesting no improvement at all following a non-pharmacological intervention.
- Genotype 9/x ($n = 11$): these subjects showed a more severe ADHD symptomatology at time T0, when compared to those carrying a 10/10 genotype ($t(21) = 2.39$). At time T1, these subjects showed a slight reduction of all symptoms (possibly, due to parent

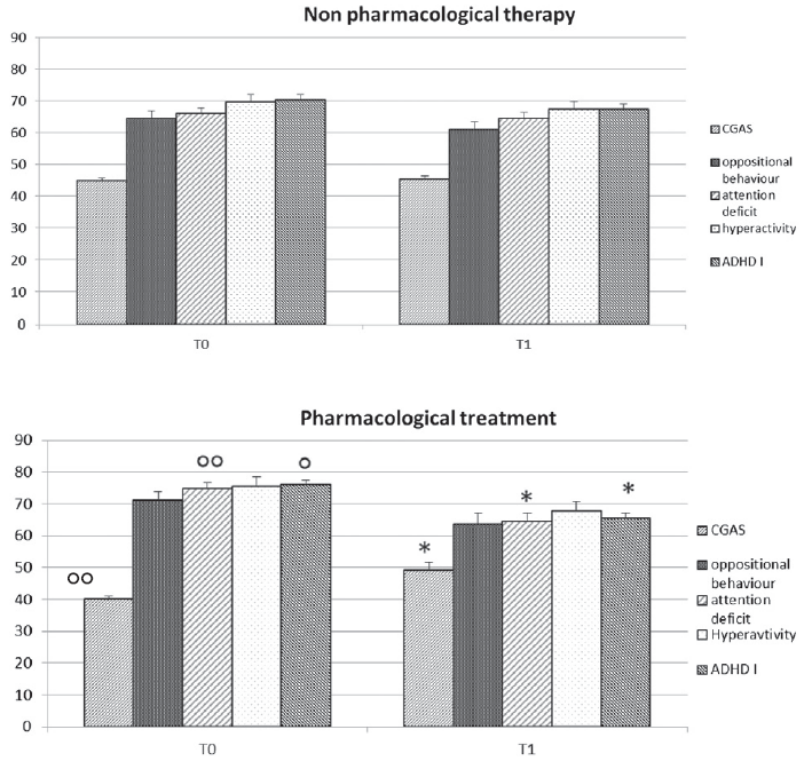

Fig. 1. (Upper panel) — Psychometric scales in recruited ADHD children not assigned to a pharmaco-therapy (NPT, N = 32). (Lower panel)—Psychometric scales in recruited ADHD children assigned to pharmacological treatment (PT, N = 14). Data include also ADHD children which were then not genotyped due to recent fever/allergy. ° denotes significance in comparing PT to NPT; * denotes significance in comparing T1 to T0.

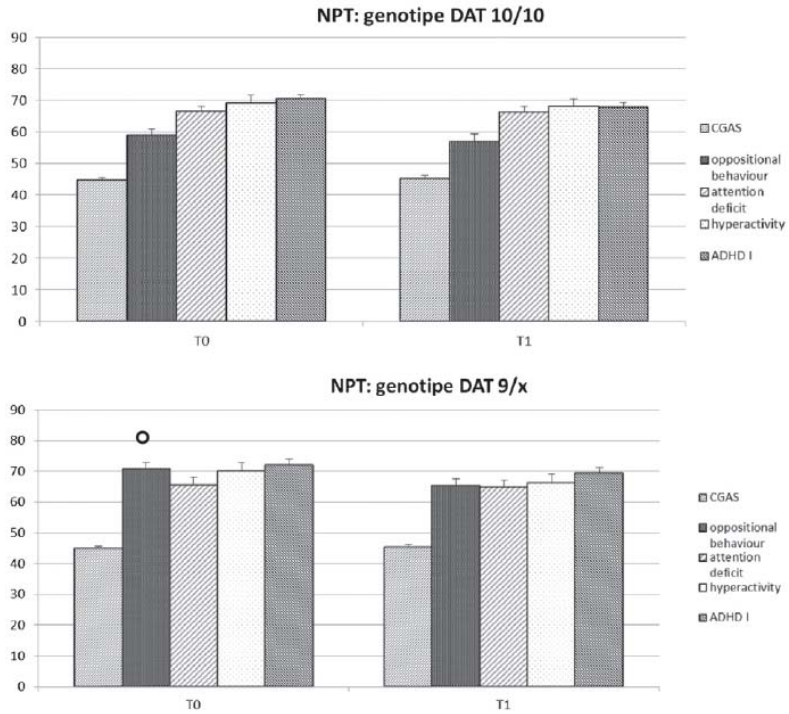

Fig. 2. (Upper panel)—Psychometric scales in genotype 10/10 children in NPT group (n = 12). (Lower panel)—Psychometric scales in genotype 9/x children of the NPT group (n = 11).

counseling and/or behavioral therapy); however, the oppositional behavior was still more severe compared to subjects carrying a 10/10 genotype (Fig. 2 lower panel). Compared to 10/10 patients, the DAT 9/x ones could be suggested to be more prone to recovery in general, even without medication.

Among subjects who needed to take pharmacological treatment, 7 were excluded and 7 were genotyped (out of 14 total). It is of note that (out of 7 excluded patients in the PT group) two were non-responder to MPH and switched to atomoxetine, while five had recent fever/allergy. Then, this group was split into two subgroups, namely, carriers of DAT 10/10 (3 subjects: Fig. 3 upper panel) vs DAT 9/x (4 subjects: Fig. 3 lower panel) genotype. We observed that:

- Genotype 10/10 (n = 3): subjects with both 10-repeat alleles showed just a trend towards a MPH-induced reduction of ADHD symptoms, according to CGAS and Conners' scales values, between T0 and T1; this reduction was however slight and did not reach statistical significance.
- Genotype 9/x (n = 4): subjects with at least a DAT 9-repeat allele showed symptoms of inattention, hyperactivity and ADHD Index which were slightly more severe than those found in subjects with a 10/10 genotype, at time T0. These subjects, however, showed a better therapeutical response to MPH: in fact, a significant reduction of CGAS ($t(6) = 2{,}80$) and of attention deficit Conners' sub-scale ($t(6) = 2{,}97$) was demonstrated by the Student t-test analysis.

3.2. Anti-DAT titer in plasma samples

The average aAbs titers in subjects who did not take pharmacological therapy showed a slight trend towards an increase in values from time T0 to T1 (Fig. 4 upper panel). This unexpected rise could represent a "physiological" phenomenon: at time T0, the sample was taken early in the morning (along with a routine blood screen), and could be therefore representative of the basal DAT aAbs titer; conversely, the sample withdrawn at time T1 could be used to estimate the "physiological" levels, reached in the late morning (and/or after having had a breakfast).

The average aAbs titer in subjects under pharmacological treatment showed, between time T0 and T1 time, a quite stable value (Fig. 4 lower panel). In these subjects, after 6 weeks of MPH treatment, we could not find an increasing titer, as we would have expected based on the findings from the non-pharmacological therapy (NPT group). Noteworthy, at T1 time, patients were not taking the morning dose of the drug, therefore any differences between PT and NPT subjects can be considered as indicative of subchronic (and not acute) drug effects.

When comparing the two groups (PT vs NPT), at time T0, we can observe that those subjects, later to be assigned to pharmacological treatment, presented higher basal anti-DAT titers compared to those subjects later assigned to a non-pharmacological therapy. These data allow us to hypothesize elevated basal anti-DAT titers in association with a more severe type of ADHD. Indeed, those PT patients were actually in need of a pharmacological approach. On the other hand, at time T1, this difference was no longer evident, because aAbs titers appeared to be similar in the two groups. Noteworthy, the analysis of behavioral profiles also evidenced very similar scores between the two groups (Fig. 1). Thus, a close relationship between changes in behavior and in the immune marker apparently emerges. Indeed, when PT and NPT subjects were detected with similar aAbs titers (at T1, i.e. after 6 weeks of MPH or unmedicated conditions, respectively), they also showed an indistinguishable behavioral profile. Notably, in the very same subjects, DAT aAbs titers did differ quite clearly when the symptoms also differed (i.e. at time T0). Thus, serum DAT aAbs titers could represent a valid and useful tool to monitor, among others, the efficacy of MPH.

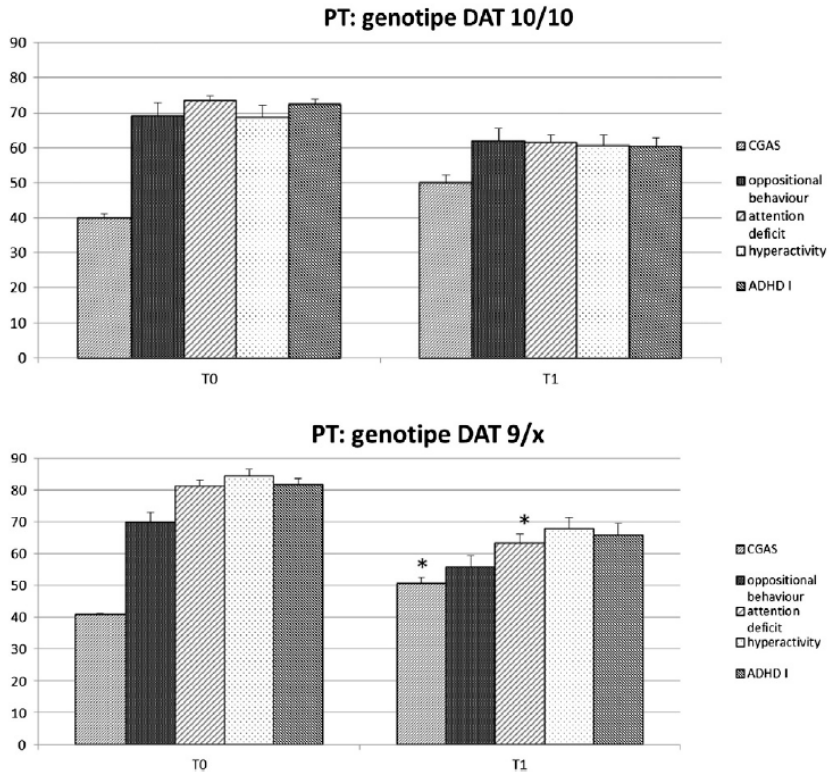

Fig. 3. (Upper panel)—Psychometric scales in genotype 10/10 children in PT group (n = 3). (Lower panel)—Psychometric scales in genotype 9/x children of the PT group (n = 4).

3.2.1. Role of DAT genotype

By splitting the group of milder ADHD subjects, who did not need to take pharmacological therapy (NPT), into the two different DAT genotypes, it could be observed that:

- Time T0: basal aAbs titers did not differ for subjects carrying a 10/10 genotype (Fig. 5a) when compared to 9/x subjects (Fig. 5b);
- Time T1: subjects carrying a 9/x genotype showed a significant elevation of anti-DAT titers from time T0 to T1 ($t(20) = 2.01$); however, at time T1, aAbs titers in subjects carrying a 9/x genotype didn't significantly differ from T1 titers in patients with a 10/10 genotype ($t(21) = 0.67$). As such, a slight trend to increase can be proposed for 10/10 patients as well.

By splitting the group of severe ADHD subjects, placed under MPH treatment (PT group), into the two different DAT genotypes, it can be observed that:

- Time T0: basal DAT aAbs titers of DAT 10/10 subjects (Fig. 5c) were almost double when compared to basal titers of 9/x subjects (Fig. 5d). It is interesting to note that all subjects, with severe symptoms and DAT 10/10 genotype, could be characterized by very high basal anti-DAT titers.
- Time T1: for the 10/10 genotype, the aAbs titer was significantly increased when compared to that of 9/x subjects ($t(5) = 2,59$). For the DAT 9/x genotype, there were no significant differences when the T1 titer was compared to the basal T0 titer. In conclusion, a high and drug-resistant titer (both basal and after treatment) may occur in DAT 10/10 people, i.e. the ones that also show a lower drug response as far as behavior is concerned (Fig. 3 upper panel). Conversely, while the titer should apparently rise from T0 to T1 (see e.g. in NPT patients), the aAbs titers are surprisingly not rising (i.e. T0 followed by no such an increase at T1) in the group under MPH treatment, carrying a DAT 9/x genotype.

3.3. Correlation between behavioral scales and DAT-aAbs

Anti-DAT titers and the behavioral scales filled in by the parents at T0 or T1 appeared significantly correlated in subjects under non-pharmacological therapy. A significant correlation was found between titers, both at time T1 and basal, and the values of inattention indicated in questionnaires compiled by fathers; also, a significant trend was found between basal titers and hyperactivity values indicated in questionnaires compiled by teachers. These correlation values are illustrated in Table 1. This profile of data seems to indicate that, when the inattention levels (indicated in questionnaires compiled by the fathers and/or the motor behavior suggested by the teachers) do increase, also the DAT-aAbs circulating in the blood show an increase.

When considering the role of genotype in the NPT group, the observed correlation between aAbs titers and the attention disorder (i.e. the score in questionnaires compiled by the father) disappears for the 9/x subgroup. On the other hand, for the 10/10 subgroup, the correlations were confirmed and extended. A statistically significant correlation emerged between titers (both basal and at time T1) and all the behavioral scales, indicated in questionnaires compiled by fathers. Moreover, it can be found a significant relationship between anti-DAT titers (both basal and at time T1) and the oppositional behavior indicated in questionnaires compiled by the teacher (Table 2).

Correlations between DAT-aAbs and behavioral scales for subjects under pharmacological treatment (PT group) did not show any statistically significant correlation (data not shown).

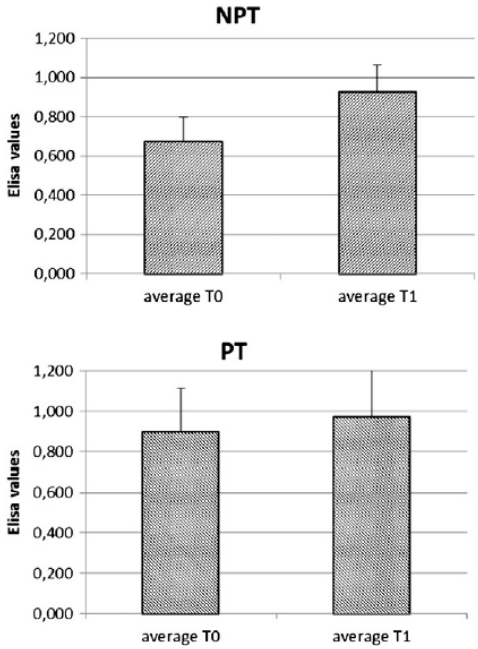

Fig. 4. (Upper panel)—hDAT aAbs titer in recruited ADHD children not assigned in a pharmaco-therapy (NPT, N = 32). (Lower panel)—hDAT aAbs titer in recruited ADHD children assigned to pharmacological treatment (PT, N = 14). Data include also ADHD children which were then not genotyped due to recent fever/allergy.

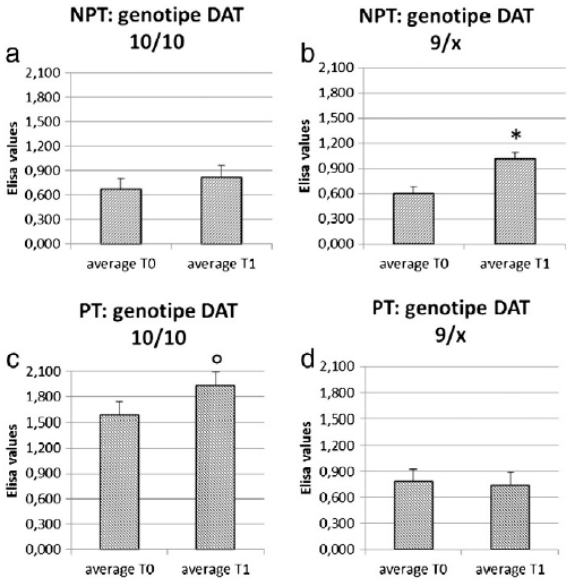

Fig. 5. (Panel a)—hDAT aAbs in children of NPT group, genotype DAT 10/10 (n = 12). (Panel b)—hDAT aAbs in children of NPT group, genotype DAT 9/x (n = 11). (Panel c)—hDAT aAbs in children in the PT group, genotype DAT 10/10 (n = 3). (Panel d)—hDAT aAbs in children in the PT group, genotype DAT 9/x (n = 4). ° denotes significance in comparing PT to NPT; * denotes significance in comparing T1 to T0.

3.4. Summary and comparison with control healthy subjects

Considering the role of genotype in the comparison between the two groups, we observe that:

1) Among 15 subjects carrying DAT 10/10 genotype, those three most severe cases, placed under a pharmacological treatment, turned out to show a doubled titer when compared to those 12 less severe cases, that were not in the need of a pharmacological therapy: this, both at time T0 (basal titer) and significantly at time T1 ($t(13) = 2.06$) after 6 weeks of therapy;
2) Subjects with a DAT 9/x genotype did not show any difference in basal titer (time T0) between the two PT and NPT groups; in the T1 serum sample, measure of aAbs titers revealed a significant "physiological" increase in the 11 NPT subjects (Fig. 5b). Notably, no such elevation was found in the 4 PT patients. Indeed, along with behavioral amelioration, a rise in titers was apparently prevented by a 6-week MPH treatment.

The recruitment of 15 healthy controls, carried out around 18 months after the main study (at the time of patients' re-sampling, time T2), provided reliable samples from 8 subjects, who were carrying at least one 9-repeat allele and not excluded a posteriori. These data were compared with eight 9/x patients, re-sampled (at the same time) after one-to-two years (time T2) of exposure to MPH or to the unmedicated condition (PT or NPT respectively). Interestingly, the control group presented a DAT aAbs titer of 0.838 ± 0.178 in average, a median of 0.601 and a third quartile of 1.027; the unmedicated ADHD children had a DAT aAbs titer of 1.673 ± 0.201 in average, with a median of 1.758 and a third quartile of 2.162; finally, the patients with 18-month long, daily exposure to MPH had a titer of 1.095 ± 0.188, with a median of 1.001 and a third quartile of 1.266.

The sample of unmedicated, 9/x ADHD children showed elevated titers compared to controls ($t(14)$; $p = 0.004$); conversely, the 9/x ADHD children under MPH treatment showed significantly reduced DAT aAbs titers ($t(14)$; $p = 0.029$), which were hardly distinguishable from those of controls. This latter finding, collected from eight re-sampled patients, can be compared with findings already collected from the very same 9/x children at T1: indeed, a 6-week MPH exposure (PT group, see Fig. 5d) was already found to prevent the rise of T1 titers, otherwise shown by the unmedicated subjects (NPT group, see Fig. 5b). As a whole, a main suggestion seems to emerge from these data: the majority of recruited ADHD children showed DAT aAbs titers (between 0.4 and 0.9) which were fully comparable to those of healthy subjects, carrying a 9/x genotype.

Interestingly, specific profiles emerged as a function of the genotype. The 10/10 ADHD children, in the three most severe cases needing drug treatment, showed an elevated titer (almost doubled, and much more than 1–1.1); also, in 12 less severe cases, the titer turned out to correlate quite well with symptoms' severity. Their DAT aAbs titer resulted, however, not sensitive to MPH exposure, and these subjects also did not show reliable relief of behavioral symptoms. The 9/x ADHD children showed – conversely – a quite interesting similarity between serum titers and behavioral symptoms, in that both appeared sensitive to MPH. Noteworthy, the 4 most severe cases showed relief of symptoms after just 6 weeks of therapy and, furthermore, the elevation of titers (expected based on all NPT-group findings) was prevented if subjects were medicated; this, both after 6 weeks (time T1) and following a longer, 1-to-2 year period (time T2). However, the aAbs titer did not correlate with individual symptoms' severity, neither before nor after medication.

4. Discussion

Nowadays, the diagnosis of ADHD is mainly based on structured interviews, questionnaires, and physicians' own judgment following clinical observation. Nevertheless, the diagnosis of ADHD is not unequivocal; indeed, the behavioral nature of these criteria renders ADHD diagnosis yet a debated question, at least in borderline conditions. There is currently

Table 1
Values of Pearson's R in correlations run between behavioral scores (obtained in CGAS and in various Conners' subscales compiled by parents and teachers, see Columns) and the DAT-aAbs titers, for children assigned to the non-pharmacology therapy (NPT) group. Data include also ADHD children which were then not genotyped due to recent fever/allergy (N = 32). First line: behavioral scores at recruitment correlated to baseline titers (at T0); Second line: behavioral scores at 6-week follow-up correlated to corresponding titers (at T1); Third line: behavioral scores at recruitment (c To) correlated to 6-week follow-up titers (Ab at T1). The few cases where correlation is significant are marked in bold for R > 0.34 (N = 32).

	NPT												
	CGAS	Conners' mother				Conners' father				Conners' teacher			
		Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index	Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index	Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index
Mean T0	0.091	−0.056	0.158	−0.122	−0.007	0.106	**0.514**	0.133	0.269	0.151	0.253	0.329	0.295
Mean T1	0.057	0.102	0.047	0.013	0.048	0.078	0.010	−0.042	0.021				
c T0 vs Ab T1	0.032	0.005	0.123	−0.004	0.016	0.176	**0.419**	0.202	0.274	0.093	0.123	0.246	0.185

much interest in the search for new biological and measurable markers, possibly detectable via a simple biochemical tool and with non-invasive, peripheral approaches (Scassellati et al., 2012).

The clinical-assessment data from subjects in the NPT group have shown a globally stable profile of ADHD symptoms over time (i.e. between recruitment and follow-up, at 6 weeks after recruitment). This stable profile was particularly evident for patients with DAT 10/10 genotype. On the other hand, subjects later assigned to a pharmacological treatment (PT) showed, at time of recruitment, more severe ADHD symptoms compared to NPT subjects, confirming that PT patients were actually in the need to take a pharmacological therapy. Furthermore, after 6 weeks under MPH treatment, some subjects showed an important and significant reduction in ADHD symptoms. By considering DAT genotype, we found that a reduction of ADHD symptoms over time (between recruitment and follow-up, 6 weeks after MPH reached the therapeutic dosage) was marked (and statistically significant) only in the subgroup of subjects with a DAT 9/x genotype. This confirms a greater efficacy of pharmacological treatment, in reducing ADHD symptoms, for patients bearing at least one 9-repeat DAT allele.

Our primary aim was to measure the blood levels of auto-antibodies (aAbs) targeting epitopes of the DAT protein. Interestingly, all children (including healthy controls) revealed measurable levels of DAT-directed aAbs. Notably, among patients, specific subjects showed an elevated titer. Moreover, as a function of genotype, titers apparently depended on behavioral symptoms and/or on MPH exposure. A first notion is that *severe* ADHD subjects – which were assigned to MPH pharmacological treatment – presented, at recruitment (time T0), higher anti-DAT titers compared to the *mild* ADHD group — which was assigned to a non-pharmacological therapy. These data suggest an association between elevated basal anti-DAT titers and a more severe profile of ADHD symptoms, therefore identifying the need of a pharmacological approach.

A second notion is that levels of these aAbs were not stable in unmedicated conditions. Subjects who entered a non-pharmacological therapy showed increasing titers from time T0 to T1, and further elevation when re-sampled 1-to-2 years later. This unexpected rise could represent, possibly, a "patho-physiological" phenomenon. It should be noted that NPT children were left in unmedicated conditions between T1 and T2, leaving room for the hypothesis that anti-DAT titers may indicate a progressively deteriorating immunological condition. We cannot however exclude the existence of a circadian physiological fluctuation in the aAbs titer, with increasing levels of circulating aAbs in the late morning and/or after food intake.

After 6 weeks from recruitment, overlapping behavioral profiles and similar aAbs titers were observed between subjects exposed to unmedicated conditions vs MPH treatment. Noteworthy, these two groups were *different* at the time of recruitment (i.e. PT patients showed elevated aAbs titer and more severe symptoms' profile). After 6 weeks from recruitment, children placed under pharmacological treatment did not show the rise in T1 aAbs titer over T0 baseline, conversely observed for NPT patients. In the PT subjects, the subchronic exposure to MPH treatment was apparently preventing the increase in anti-DAT titer.

Table 2
Same as in Table 1, but divided for genotype DAT 10/10 (Panel a, n = 12) vs. DAT 9/x (Panel b, n = 11). Teachers' evaluation was collected only at recruitment and not at 6-week follow-up. Interestingly, in DAT 10/10 patients at risk for ADHD, higher DAT-aAbs titers are related with poorer assessment by Conners' scales. Correlation is significant when marked in bold, for R > 0.53 (n = 12).

Panel a

	NPT: genotype 10/10												
	CGAS	Conners' mother				Conners' father				Conners' teacher			
		Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index	Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index	Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index
Mean T0	−0.349	0.237	0.374	−0.150	−0.212	**0.610**	**0.740**	**0.545**	**0.543**	**0.578**	0.302	0.400	0.399
Mean T1	−0.002	0.184	−0.157	−0.243	−0.338	0.193	−0.157	−0.243	−0.355				
c T0 vs Ab T1	−0.263	0.112	0.103	−0.131	−0.404	0.434	**0.543**	0.457	0.325	0.503	0.324	0.448	0.419

Panel b

	NPT: genotype 9/x												
	CGAS	Conners' mother				Conners' father				Conners' teacher			
		Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index	Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index	Oppositive behavior.	Impaired attention.	Hyperactivity	ADHD index
Mean T0	0.179	−0.300	0.233	−0.261	0.090	−0.428	0.267	−0.117	0.020	−0.154	**0.895**	0.070	0.351
Mean T1	−0.225	0.103	0.315	0.261	0.286	−0.129	0.120	0.033	0.082				
c T0 vs Ab T1	−0.155	−0.154	0.230	0.173	0.188	−0.084	0.232	0.171	0.233	−0.533	0.490	−0.270	−0.097

This information can lead us to propose, therefore, that anti-DAT titers could be used to monitor the efficacy of MPH.

4.1. Role of DAT genotype

By splitting the whole PT and NPT subjects into two subgroups, according to DAT genotype, we could observe that subjects carrying a 9/x genotype (and under non-pharmacological therapy, NPT) showed indeed the aforementioned, statistically significant increase of anti-DAT titers from T0 baseline to time T1. In other words, in the sample withdrawn at time T1, the titers revealed a significant and possibly "patho-physiological" increase over T0 baseline. This profile, however, was only evident in the group of NPT subjects, and notably no such an increase was found due to a 6-week MPH treatment. We suggest that, in DAT 9/x subjects placed under pharmacological treatment, a sub-chronic exposure to MPH prevented the increase of aAbs titers between T0 and T1, otherwise observed for subjects carrying a DAT 9/x genotype but not placed under pharmacological therapy. It is tempting to speculate that therapeutic effects of MPH might be accompanied by a specific modulation (i.e. preventing the spontaneous increase) of DAT aAbs titers.

In the group that needed to undergo MPH treatment, subjects with a DAT 10/10 genotype showed a very high levels of DAT-aAbs: the anti-DAT titers were almost double when compared both to those of DAT 9/x subjects, and to those of less severe DAT 10/10 patients, not placed under MPH. Anti-DAT levels were higher at baseline and further elevated after a 6-week pharmacological treatment, accompanied by the very slight and not significant reduction in symptoms' severity, reported by the clinician and parents. This suggests that subjects with a DAT 10/10 genotype could be characterized by a lower therapeutic response to MPH treatment (Madras et al., 2002). It is tempting to speculate that reduced drug efficacy comes along with lack of any effect over the very high (and rising) anti-DAT titer. This may suggests that, in case of ADHD subjects who are homozygous for DAT 10-repeat alleles, high and drug-resistant DAT aAbs titers can identify those patients in need of alternative, non-psychostimulant drug treatment (like e.g. atomoxetine).

4.2. Behavioral scales/anti-DAT titer correlations

The analysis of correlations was run between behavioral scales (filled in by the clinician, the parents and the teacher) and DAT aAbs titers. A profile of correlation was found in subjects under a non-pharmacological therapy. A significant correlation was found between basal aAbs titers and the values of inattention indicated by fathers; also, a significant trend was found between basal aAbs titers and hyperactivity values as indicated by patient's teacher. This means that, when inattention levels suggested by fathers and/or the motor behavior suggested by teachers is increased, the circulating DAT-aAbs may turn out to be elevated.

By splitting NPT patients into two subgroups, according to DAT genotype, the above correlations were confirmed and further extended for the DAT 10/10 subgroup. A statistically significant correlation emerged between titers (both basal and at time T1) and *all* the behavioral scales suggested by fathers. Moreover, we could find a significant relationship between titers (both basal and at time T1) and oppositional behavior indicated by the teacher. Therefore, in homozygous subjects carrying the DAT 10-repeat allele, the highest levels of DAT-aAbs came along with the more problematic behavior of children. Consistently, the most severe ADHD cases, in need of drug treatment (PT group), showed almost doubled DAT aAbs titers (see above). On the other hand, the correlation between scales and titers completely disappeared for DAT 9/x subgroup.

4.3. Patho-physiological remarks and perspectives

Abnormal dopamine levels and deregulation of dopaminergic components, expressed in immune cells, are associated with some auto-immune disorders (Pacheco et al., 2014). Dopamine can probably activate T-cell function indirectly, by suppressing T-regulatory cell (Treg) (Kipnis et al., 2004; Cosentino et al., 2007; Levite, 2008). Treg is involved in auto-immunity, and secretes IL-10 and TGF-b: because of its inhibitory properties, reduced activity of Treg (due to abnormal dopamine) could lead to uncontrolled activation and function of effector T-cells and to auto-immunity (Pacheco et al., 2010). Furthermore, dendritic-cell derived dopamine promotes IL-23 production and, thereby, enhances Th17 responses with inflammation (Pacheco et al., 2014). These findings suggest that dopamine can mediate communication between immune cells, and the cross-talk between the immune and nervous systems (Cosentino et al., 2007; Nakano et al., 2009; Sarkar et al., 2010; Buttarelli et al., 2011; Pacheco et al., 2014).

Thus, over-expression of DAT in lymphocytes of ADHD children could imply dysregulation of immune and neuro-immune systems. A reduced level of dopamine is typical of auto-immune pathologies (Buttarelli et al., 2011). Blockade of DAT by MPH may normalize the dopamine levels, which in turn may act on the lymphocytes. It was reported, consistently, that MPH may induce (i) a hyperactivity of the immune system and a heightened tendency to respond to antigenic or immunogenic stimuli, (ii) hyper-gamma-globulinemia, and (iii) reduction of T-helper/inducer cells (Auci et al., 1997). The issue of a role for neuro-immune components in ADHD and other developmental, neuro-psychiatric conditions deserves however further investigation.

4.4. Conclusion

Replication of our findings is needed: it will be necessary to investigate the selectivity of epitopes (i.e. to ascertain that aAbs recognize epitopes of DAT over other proteins), as well as their specificity (i.e. how do these DAT aAbs vary in other mental or immunological conditions which are not related to ADHD). For validation of DAT aAbs as a tool for diagnosis and/or therapy monitoring in subjects with ADHD, we would need to clarify the etiological implications: namely, the nature of the correlation between anti-DAT titers, on one hand, and clinical features of ADHD-like behavioral symptoms, on the other hand.

Present data do indicate for the first time that detectable levels of a DAT-directed, circulating auto-antibody can be evidenced in a pediatric population, including children with ADHD diagnosis. In addition, we propose that anti-DAT titers and DAT genotyping might possibly be used together, to determine a priority for drug intervention based on severity of child's symptoms. In other words, the elevation of serum anti-DAT titers and restoration of basal levels by few weeks of MPH can be proposed as bio-markers, to support diagnosed ADHD and its drug therapy. These biological indices could turn out to be useful: 1) to provide or verify diagnostic criteria, 2) to predict the evolution of symptoms over time, and 3) to monitor the efficacy of MPH treatment.

In the end, further study is warranted to deepen the knowledge about ADHD neurobiology, by exploring the relationship between this neuro-psychiatric disorder and the immune system. The presence of elevated circulating aAbs directed against DAT in ADHD subjects may well open new avenues of (pre)clinical research, as neuro-immune modulations are increasingly worthy of being explored.

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L'ESPERIENZA DEL PRIMO REGISTRO REGIONALE DI MONITORAGGIO DEI PAZIENTI

La Lombardia setaccia il «mito» Adhd

DI MAURIZIO BONATI *

Prevalenza: -15% sui dati generali

Coinvolte famiglie, scuola e operatori

L'Adhd (acronimo per l'inglese Attention deficit hyperactivity disorder) è un disturbo neurobiologico dell'età evolutiva, le cui manifestazioni cliniche nucleari sono la difficoltà a prestare attenzione, comportamenti impulsivi e un livello di attività motoria accentuato che si manifestano più frequentemente e in maniera più intensa che in altri bambini della stessa età o livello di sviluppo. I sintomi sono solitamente evidenti in età scolare, più frequentemente nei maschi e possono persistere nell'età adulta. La prevalenza media mondiale dell'Adhd nei bambini e negli adolescenti è del 5,3%, sebbene le stime varino molto tra aree geografiche, anche all'interno di una stessa Nazione. In Italia, la prevalenza sinora riportata varia dall'1 al 7% in relazione alla popolazione considerata, al contesto osservato, ma soprattutto alla modalità di valutazione diagnostica utilizzata nel singolo studio (e nella pratica clinica). Così come eterogenee sono le risposte terapeutiche, per tipo e modalità, sia tra i servizi di cura che tra gli operatori.

Le linee guida italiane, in accordo con le indicazioni europee, indicano che la terapia per l'Adhd si basa su un approccio multimodale che combini interventi psicologici con terapie mediche. Ogni intervento va adattato alle caratteristiche del soggetto in base all'età, alla gravità dei sintomi, ai disturbi secondari, alle risorse cognitive, alla situazione familiare e sociale. I trattamenti psicologici includono interventi psicoeducativi rivolti ai genitori e agli insegnanti e di tipo cognitivo-comportamentale per il paziente. Mentre l'intervento farmacologico sulla base delle evidenze scientifiche prevede l'uso degli psicostimolanti (il metilfenidato in particolare) come farmaci di prima scelta e parte di un piano multimodale di trattamento per i bambini con sintomatologia tale da compromettere gravemente il loro funzionamento in vari contesti di vita, o per coloro che non hanno avuto beneficio dai soli interventi psicologici. Per garantire questi percorsi di cura a tutti i pazienti su tutto il territorio nazionale le Uonpia (Unità operativa di Neuropsichiatria dell'infanzia e dell'adolescenza) necessiterebbero di risorse adeguate, non solo per rispondere alle richieste per l'Adhd, ma per tutti i disturbi neuropsichiatrici dell'età evolutiva che interessano circa il 10% della popolazione pediatrica e adolescenziale.

In tale contesto nel 2011 in Regione Lombardia è stato attivato un Registro per garantire un'adeguata valutazione dell'Adhd a ogni bambino e adolescente fin dal momento in cui il disturbo è sospettato o segnalato. Il Registro regionale è stato quindi concepito come registro di malattia raccogliendo informazioni relative non solo ai pazienti con diagnosi di Adhd in trattamento farmacologico (come previsto dal Registro nazionale attivato nel 2007 presso l'Istituto superiore di Sanità), ma a tutti i pazienti che afferiscono ai Centri di riferimento per sospetto Adhd.

L'iniziativa è parte di un progetto più articolato sostenuto dalla Direzione generale Salute con l'obiettivo principale di stimare la prevalenza del disturbo, definire e garantire percorsi diagnostico-terapeutici appropriati e condivisi attraverso l'applicazione di un protocollo condiviso di valutazione e monitoraggio del disturbo, intensificare la formazione e l'aggiornamento degli operatori e informare i cittadini. Un progetto ambizioso, a tutt'oggi unico non solo nel panorama nazionale.

Nel periodo 2012-2013, 1.150 nuovi pazienti hanno completato la valutazione diagnostica presso i 18 Centri di riferimento lombardi: avevano un'età mediana di 9 anni (5-17 anni); l'85% erano maschi; il 65% ha soddisfatto i criteri diagnostici del Dsm-IV-TR per Adhd. In base a questi dati, i pazienti Adhd di età compresa tra i 5 e i 17 anni che vivono in Regione Lombardia sarebbero circa 4.200 con una prevalenza del 3,5‰: circa quindici volte inferiore rispetto a quanto precedentemente osservato a livello nazionale

è internazionale.

Parte di queste differenze (sottostime) può essere attribuita alla rigorosa valutazione diagnostica concordata e condivisa dagli operatori dei Centri di riferimento partecipanti allo studio e al fatto che i pazienti che accedono ai Centri di riferimento sono principalmente quelli "complessi" che necessitano di una terapia farmacologica o di interventi multimodali che non tutte le Uonpia territoriali possono garantire. Le caratteristiche anamnestiche che si associano significativamente con la diagnosi di Adhd sono: una più bassa età alla diagnosi, essere figlio unico o adottato, avere una familiarità per Adhd e un ritardo del linguaggio. Nei pazienti con Adhd rispetto ai casi sospetti è più frequente la presenza di altri disturbi psichiatrici (in particolare il disturbo oppositivo-provocatorio e i disturbi del sonno). Sia i fattori di rischio che le comorbilità osservate rappresentano conferme di quanto conosciuto e quindi atteso. L'85% dei pazienti con Adhd ha ricevuto un trattamento psicologico, in particolare il parent training (seguito dal child e dal teacher training), mentre il trattamento farmacologico, nella quasi totalità in associazione a quello psicologico, è stato prescritto a quei pazienti con Adhd di maggiore gravità clinica. La percezione e i giudizi sia dei genitori che degli insegnanti sulla presenza del disturbo espressi sono risultati in buon accordo con la diagnosi clinica fatta dai neuropsichiatri: di buon auspicio per una gestione partecipata anche della terapia.

Questo studio rappresenta la prima valutazione sistematica dei percorsi di diagnosi e cura dei pazienti con Adhd in Italia in un'ampia popolazione che accede ai Centri di riferimento regionali.

Un risultato importante di un progetto che ha coinvolto i pazienti, le famiglie, gli insegnanti e gli operatori (neuropsichiatri, psicologi, pediatri di famiglia), da implementare e migliorare, non solo per la cura dell'Adhd, ma anche per gli altri disturbi neuropsichiatrici dell'età evolutiva.

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Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 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)
Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"*Percorsi diagnostico-terapeutici per l'ADHD*".

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