NEWSLETTER

INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD maggio 2016

Acta Psychiatr Scand. 2016.

RESTING STATE DEFAULT MODE NETWORK CONNECTIVITY IN CHILDREN AND ADOLESCENTS WITH ADHD AFTER ACUTE TRYPTOPHAN DEPLETION.

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

Objective: Alterations of the default mode network (DMN) have been described in patients with neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD), and the neurotransmitter serotonin (5-HT) is known to modulate DMN activity. This study aimed to explore the role of 5-HT on the DMN and its functional connectivity (FC) in young patients with ADHD.

Methods: Young male patients with ADHD (n = 12) and healthy controls (n = 10) (both aged 12-17 years) were subjected to acute tryptophan depletion (ATD) and subsequently diminished brain 5-HT synthesis. Three hours after challenge intake (ATD or a balanced control condition, BAL), resting state fMRI scans were obtained.

Results: In patients, ATD led to attenuated FC of the right superior premotor cortex (BA 6) with the DMN, comparable to the extent found in controls after BAL administration. ATD lowered FC of the left somatosensory cortex (BA 3) with the DMN, independently of the factor group, but with stronger effects in controls.

Conclusions: Data reveal a serotonergic modulation of FC between BA 6 and 3, known to be relevant for motor planning and sensory perception, and the DMN, thereby possibly pointing toward ATD acting beneficially on neural planning of motor activity in patients with ADHD

……..

……

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.

ADHD Atten Deficit Hyperact Disord. 2016;1-10.

A COST-EFFECTIVENESS ANALYSIS OF OFF-LABEL ATYPICAL ANTIPSYCHOTIC TREATMENT IN CHILDREN AND ADOLESCENTS WITH ADHD WHO HAVE FAILED STIMULANT THERAPY.

Sohn M, Talbert J, Moga DC, et al.

The objectives of this study are: (1) to estimate the expected health outcomes of atypical antipsychotics (AAPs) and other non-stimulant attention-deficit/hyperactivity disorder (ADHD) medications and (2) to evaluate the cost-effectiveness of AAPs compared to other non-stimulant ADHD medications. We used decision analysis to compare three alternatives for treating children and adolescents with ADHD who failed initial stimulant treatment: (1) AAPs, (2) a selective norepinephrine reuptake inhibitor (atomoxetine), and (3) selective +¦2-adrenergic agonists (clonidine and guanfacine). Probability estimates and quality-adjusted life year (QALY) weights were derived from a literature review. Cost-effectiveness was estimated using the expected health outcomes derived from the decision analysis and expected costs from the literature. The study was conducted from the third-party payer perspective, and the study period was 1 year. One-way deterministic sensitivity analysis and a Monte Carlo simulation were performed. Over the course of 1 year of ADHD pharmacotherapy, the highest QALY was for clonidine/guanfacine (expected QALY = 0.95) followed by atomoxetine (expected QALY = 0.94). Atypical antipsychotics yielded the lowest health outcome with an expected QALY of 0.84. In the cost-effectiveness analysis, the AAP strategy was dominated as it was less effective and more costly than other two strategies. Compared to clonidine/guanfacine, AAPs provided lower QALYs (0.11 QALY lost) at an additional cost of $2186 on average. Compared to atomoxetine, AAPs resulted in 0.10 QALYs lost at an additional cost of $2186. In this decision analysis model, AAPs provide lower expected health outcomes than other ADHD medications in children and adolescents who failed prior stimulant therapy. Furthermore, AAPs were not a cost-effective option

……..

ADHD Atten Deficit Hyperact Disord. 2016;1-8.

INSECURE MATERNAL ATTACHMENT IS ASSOCIATED WITH DEPRESSION IN ADHD CHILDREN.

López Seco F, Mundo-Cid P, Aguado-Gracia J, et al.

The objective of this study was to analyze the possible association between maternal attachment style and comorbidity associated with childhood ADHD. We evaluated a total of 103 children with ADHD treated at a Child and Adolescent Mental Health Centre and their mothers. Comorbidity was evaluated using the MINI-KID interview. Maternal attachment was evaluated using the Adult Attachment Questionnaire. We considered child variables that could be associated with the clinical course of ADHD, such as symptom severity, age, gender, evolution time, academic level, and current pharmacological treatment; parental variables, such as the motherΓÇÖs psychiatric history, current psychopathology, marital status, academic level, income, and employment, were also considered. We found an association between maternal insecure attachment and comorbid depressive disorder in childhood ADHD. An insecure maternal attachment style must be considered in the assessment and treatment of childhood ADHD with comorbid depression

……..

Alcohol Clin Exp Res. 2016;40:969-78.

PROSPECTIVE MEMORY IMPAIRMENT IN CHILDREN WITH PRENATAL ALCOHOL EXPOSURE.

Lewis CE, Thomas KGF, Molteno CD, et al.

Background: Prenatal alcohol exposure (PAE) is linked to impaired performance on tests of retrospective memory, but prospective memory (PM; the ability to remember and act on delayed intentions) has not been examined in alcohol-exposed children. We investigated event-based PM in children with heavy PAE and the degree to which associations between PAE and PM are influenced by IQ, executive functioning (EF), retrospective memory, and attention deficit/hyperactivity disorder (ADHD).

Methods: We administered a computerized PM task to 89 children (Mage = 11.1 years) whose mothers were recruited prenatally: 29 with fetal alcohol syndrome (FAS) or partial FAS (PFAS), 32 nonsyndromal heavily

exposed (HE), and 28 Controls. We examined effects of diagnostic group, cue focality, and task difficulty on PM performance. The association between a continuous measure of alcohol exposure and PM performance was also examined after controlling for sociodemographic confounders. Mediation of alcohol effects on PM by IQ, EF, and retrospective memory scores was assessed as was the effect of ADHD on PM performance.
Results: Children with FAS/PFAS made more PM errors than either HE or Control children. PAE was negatively related to PM performance even after adjusting for sociodemographic confounders, EF, and retrospective memory. This relation was only partially mediated by IQ. PAE was related to ADHD, but ADHD was not related to PM performance.
Conclusions: Fetal alcohol-related impairment in event-based PM was seen in children with FAS/PFAS. The effect of PAE on PM was not attributable to impaired EF and retrospective memory and was not solely attributable to lower IQ. Consistent with previous studies, we found no effect of ADHD on event-based PM performance at this age. This is the first study documenting PM impairment in children with heavy PAE and identifies a new domain of impairment warranting attention in diagnosis and management of fetal alcohol spectrum disorders

……..

Arch Dis Child. 2016.

ASSOCIATION BETWEEN AUTISM SYMPTOMS AND FUNCTIONING IN CHILDREN WITH ADHD.

Green JL, Sciberras E, Anderson V, et al.

Objective To examine the association between autism spectrum disorder (ASD) symptoms and (a) social functioning, (b) mental health, (c) quality of life and (d) sleep in children with and without attention-deficit hyperactivity disorder (ADHD).
Methods Participants were 6-10-year-old children with ADHD (N=164) and without ADHD (N=198). ADHD was assessed via community-based screening (wave 1) and case confirmation using the Diagnostic Interview Schedule for Children IV (DISC-IV) (wave 2). ASD symptoms were identified using the Social Communication Questionnaire (SCQ). Outcome measures were social functioning (Strengths and Difficulties Questionnaire (SDQ)), mental health (DISC-IV, SDQ), quality of life (QoL, Pediatric Quality of Life Inventory 4.0) and sleep problem severity.
Results Greater ASD symptoms were associated with more parent and teacher-reported peer problems and emotional and conduct problems. For every SD increase in SCQ scores, internalising (OR 1.8, 95% CI 1.3 to 2.6, p=0.001) and externalising disorders (OR 1.5, 95% CI 1.1 to 2.1, p=0.02) increased, QoL decreased by 6.7 units (p<0.001), and moderate/severe sleep problems increased (OR 1.5, 95% CI 1.0 to 2.2, p=0.04). Most findings held in analyses adjusting for socio-demographic factors, ADHD symptom severity and comorbidities (when not the outcome), with the exception of externalising disorders and sleep problems.
Conclusions ASD symptoms are associated with poorer functioning in children with ADHD. It is important to identify and potentially manage ASD symptoms in children with ADHD given that they exacerbate functional impairments in this already vulnerable group

……..

Basic Clin Neurosci. 2016;7:167-71.

CASE REPORT: THE EFFECT OF NEUROFEEDBACK THERAPY ON REDUCING SYMPTOMS ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CASE SERIES STUDY.

Deilami M, Jahandideh A, Kazemnejad Y, et al.

Introduction: This study aimed to evaluate the effectiveness of neurofeedback on attention deficit hyperactivity disorder.
Methods: This is a quasi-experimental study without a control group. The study population included all children aged 5 to 12 years old affected with attention deficit hyperactivity disorders in Tehran, Iran who were referred to psychiatric clinics and given the diagnosis. The sample included 12 children with attention deficit hyperactivity disorder who were selected based on their availability (non-random sampling). They received

30 sessions of neurofeedback treatment, 2 times per week. Before and after neurofeedback training, the children were evaluated and compared with the use of cognitive assessment system test. Data were analyzed using dependent T-test.
Results: The total mean score for pretest was 88.81 while the total mean score for the post test was 82.23. The mean in pretest for attention hyperactivity disorder was higher than the mean in the post test. Moreover, The difference of pretest and post test scores of children affected with learning disorder associated with ADHD was calculated that showed significant (P=0.003).
Conclusion: Neurofeedback is effective in the improvement of attention deficit hyperactivity disorder

……..

Biol Psychol. 2016;118:25-34.
COGNITIVE ENDOPHENOTYPES OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND INTRA-SUBJECT VARIABILITY IN PATIENTS WITH AUTISM SPECTRUM DISORDER.
Biscaldi M, Bednorz N, Weissbrodt K, et al.
Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) have previously been studied mainly in isolation from each other. However the two conditions may be aetiologically related and thus show overlap in aetiologically relevant functions. In order to address this question of potential aetiological overlap between ADHD and ASD, the present study set out to investigate putative endophenotypes of ADHD in N = 33 typically developing (TD) children and N = 28 patients with ASD that were (ASD+) or were not (ASD-) co-morbid for ADHD. With regard to both the cognitive endophenotype candidates (working memory, inhibition, temporal processing) and intra-subject variability (ISV) the pattern of abnormalities was inconsistent. Furthermore, the overall profile of ASD-TD differences was extremely similar to the pattern of differences between the ASD+ and ASD- sub-groups, suggesting that any abnormalities found were due to the comorbid ASD subgroup. This held in particular for ISV, which did not show in patients with ASD the task-general increase that is common in ADHD samples. Altogether, the present results do not support the hypothesis of aetiological overlap between ASD and ADHD

……..

BMJ (Online). 2016;353.
ATTENTION DEFICIT IN CHILDREN IS LINKED TO EXPOSURE TO PHTHALATES IN MEDICAL TUBING.
Dyer O.

……..

Chemosphere. 2016;156:118-27.
PERFLUOROALKYL SUBSTANCES IN CORD BLOOD AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN SEVEN-YEAR-OLD CHILDREN.
Lien GW, Huang CC, Shiu JS, et al.
Objective: The effect of perfluoroalkyl substances (PFASs) on the development of neurotoxicity in children is still controversial. This study aimed to evaluate the association between in utero exposure to four PFASs and the development of neurobehavioral symptoms related to attention deficit hyperactivity disorder (ADHD) in early childhood.
Methods: Eligible study subjects were selected from the Taiwan Birth Panel Study and the Taiwan Early-Life Cohort, which enrolled a total of 1526 mother-infant pairs during 2004 and 2005. We collected umbilical cord blood and analyzed perfluorooctanoic acid (PFOA), perfluorooctanyl sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluoroundecanoic acid (PFUA) levels. When a child was 7 years old, to evaluate ADHD related neurobehavioral symptoms, their parents completed the Swanson, Nolan, and Pelham IV scale (SNAP-IV), the Child Behavior Checklist (CBCL), and the Strengths and Difficulties Questionnaire (SDQ)

questionnaires. We used linear regression models with inverse probability weighting to explore the association between prenatal exposure to four PFASs and ADHD rating scores.
Results: A total of 282 subjects have completed the PFASs analysis and questionnaire survey. After adjusted for potential confounders, we observed that PFNA is inversely associated with inattention and oppositional defiant disorder of SNAP-IV, and hyperactivity/inattention of SDQ. No association between PFOA, PFOS, or PFUA and ADHD symptoms was found.
Conclusions: Prenatal exposure to PFNA was found to associate with neurobehavioral symptoms related to ADHD among Asian seven-year-old children. Further studies are needed to elucidate the causal relationship

……..

Child Neuropsychol. 2016;1-17.

RAPID AUTOMATIZED NAMING (RAN) IN CHILDREN WITH ADHD: AN EX-GAUSSIAN ANALYSIS.

Ryan M, Jacobson LA, Hague C, et al.

Children with ADHD demonstrate increased frequent "lapses" in performance on tasks in which the stimulus presentation rate is externally controlled, leading to increased variability in response times. It is less clear whether these lapses are also evident during performance on self-paced tasks, e.g., rapid automatized naming (RAN), or whether RAN inter-item pause time variability uniquely predicts reading performance. A total of 80 children aged 9 to 14 years-45 children with attention-deficit/hyperactivity disorder (ADHD) and 35 typically developing (TD) children-completed RAN and reading fluency measures. RAN responses were digitally recorded for analyses. Inter-stimulus pause time distributions (excluding between-row pauses) were analyzed using traditional (mean, standard deviation [SD], coefficient of variation [CV]) and ex-Gaussian (mu, sigma, tau) methods. Children with ADHD were found to be significantly slower than TD children ($p < .05$) on RAN letter naming mean response time as well as on oral and silent reading fluency. RAN response time distributions were also significantly more variable (SD, tau) in children with ADHD. Hierarchical regression revealed that the exponential component (tau) of the letter-naming response time distribution uniquely predicted reading fluency in children with ADHD ($p < .001$, $\Delta R^2 = .16$), even after controlling for IQ, basic reading, ADHD symptom severity and age. The findings suggest that children with ADHD (without word-level reading difficulties) manifest slowed performance on tasks of reading fluency; however, this "slowing" may be due in part to lapses from ongoing performance that can be assessed directly using ex-Gaussian methods that capture excessively long response times

……..

Child Health Care. 2016;1-19.

THE MODERATING ROLE OF BODY DISSATISFACTION IN THE RELATIONSHIP BETWEEN ADHD SYMPTOMS AND DISORDERED EATING IN PEDIATRIC OVERWEIGHT AND OBESITY.

Gowey MA, Stromberg SE, Lim CS, et al.

Background: Identifying factors linked to disordered eating in overweight and obesity (OV/OB) may provide a better understanding of youth at risk for disordered eating. This project examined whether ADHD symptoms and body dissatisfaction were associated with disordered eating.
Methods: ADHD symptoms, disordered eating, and body dissatisfaction were assessed in 220 youth ages 7–12 who were OV/OB.
Results: Multiple linear regressions showed that body dissatisfaction and ADHD symptoms were associated with disordered eating.
Discussion: Children with ADHD symptoms and OV/OB may be at greater risk for disordered eating when highly dissatisfied with their bodies. Health care providers should assess body image and disordered eating in youth with comorbid OV/OB and ADHD

……..

Clinical Neuroradiology. 2016;1-7.

PILOT STUDY OF BRAIN MORPHOMETRY IN A SAMPLE OF BRAZILIAN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: INFLUENCE OF CLINICAL PRESENTATION.

Pastura G, Kubo TTA, Gasparetto EL, et al.

Purpose: Currently, the diagnosis of attention deficit hyperactivity disorder (ADHD) rests on clinical criteria. Nonetheless, neuroimaging studies have demonstrated that children with ADHD have different cortical thickness and volume measures to typically developing children (TDC). In general, studies do not evaluate the influence of clinical presentation in the brain morphometry of ADHD children. Our objective was to perform a pilot study in order to evaluate cortical thickness and brain volume in a sample of Brazilian ADHD children and compare these to those of TDC, taking into account the influence of clinical presentation.
Methods: We performed an analytic study comparing 17 drug-na+»ve ADHD children of both genders, aged between 7 and 10, and 16 TDC. ADHD subjects were first considered as one group and further separated based on clinical presentation.
Results: The brain volume did not differ between patients and TDC. Smaller cortical thicknesses were identified on the left superior, medium and inferior temporal cortex, as well as in the left inferior parietal cortex. When compared to TDC, combined and inattentive ADHD presentations depicted smaller cortical thickness with high significance and power. The same magnitude of results was not observed when comparing inattentive ADHD and TDC.
Conclusions: In this pilot study, ADHD is associated with abnormalities involving the cortical thickness of the posterior attentional system. The cortical thickness in the left superior, medium and inferior temporal cortex, as well as in the left inferior parietal cortex may differ according to ADHD presentations

……..

Clin Psychol Rev. 2016.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND CHILDREN'S EMOTION DYSREGULATION: A META-ANALYSIS.

Graziano PA, Garcia A.

While executive functioning deficits have been central to cognitive theories of Attention-Deficit Hyperactivity Disorder (ADHD), recent work has suggested that emotion dysregulation may also play a key role in understanding the impairments suffered by youth with ADHD. However, given the multiple processes involved in emotion dysregulation, the extent to which youth with ADHD are impaired across multiple domains of emotion dysregulation including: emotion recognition/understanding (ERU), emotion reactivity/negativity/lability (ERNL), emotion regulation (EREG), and empathy/callous-unemotional traits (ECUT) remains unclear. A meta-analysis of 77 studies (n = 32,044 youths) revealed that youth with ADHD have the greatest impairment on ERNL (weighted ES d = .95) followed by EREG (weighted ES d = .80). Significantly smaller effects were observed for ECUT (weighted ES d = .68) and ERU (weighted ES d = .64). Moderation analyses indicated that the association between ADHD and ERNL was stronger among studies that had a sample containing older youth (no other demographic factors were significant). Additionally, the association between ADHD and ECUT was significantly weaker among studies that controlled for co-occurring conduct problems. Co-occurring conduct problems did not moderate the link between ADHD and any other emotion dysregulation domain. Lastly, the association between ADHD and ERNL was significantly weaker when controlling for youth's cognitive functioning. Cognitive functioning did not moderate the link between ADHD and ERU, EREG, or ECUT, respectively. Theoretical/practical implications for the study of emotional dysregulation in youth with ADHD are discussed

……..

Cognitive Neuropsychiatry. 2016;1-15.

FACIAL AFFECT RECOGNITION IN AUTISM, ADHD AND TYPICAL DEVELOPMENT.

Berggren S, Engström AC, Bölte S.

INTRODUCTION: Autism spectrum disorder (ASD) and Attention-Deficit Hyperactivity Disorder (ADHD) have been associated with facial affect recognition (FAR) alterations.

METHODS: This study examined accuracy and response times for general and specific FAR in whole face and eye-region stimuli. FAR was assessed in matched samples of children and adolescents with ASD (n = 35), ADHD (n = 32), and typical development (TD) (n = 32) aged 8.6-15.9 years (M = 11.6; SD = 2.0).

RESULTS: Compared to TD, the ASD group performed less accurate and showed longer response times for general and specific FAR, mostly driven by problems in neutral and happy face identification. The ADHD group responded faster than the ASD group for global FAR. No differences between ADHD and TD were found. Attentional distractibility had a significant effect on FAR performance in ASD and ADHD.

CONCLUSIONS: Findings confirm FAR alterations in ASD, but not ADHD, and endorse effects of attentional distractibility on FAR in ASD and ADHD. FAR and attention function training is clinically meaningful in ASD. Future studies should include control for visual attention and facial configuration skills, use naturalistic FAR material and also investigate implicit FAR.

……..

Egypt J Med Hum Genet. 2016.

MAGNESIUM, ZINC AND COPPER ESTIMATION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Elbaz F, Zahra S, Hanafy H.

Background: Attention deficit hyperactivity disorder (ADHD) is a common neuro developmental disorder. Evidence for dietary/nutritional treatments for (ADHD) varies widely, however recommended daily allowance of minerals and essential fatty acids is an ADHD-specific intervention.

Aim of the work: To estimate magnesium, zinc and copper levels in the sera and hair of children with ADHD and compare them to normal children and also to correlate these levels with the disease symptoms.

Methods: This case-control study was conducted on 20 patients with ADHD and 20 age and sex matched healthy controls. All subjects were subjected to psychiatric evaluation according to DSMIV-R, magnesium, zinc and copper estimation in serum and hair follicles. ADHD children were further assessed by the Stanford Binnet intelligence scale for children, Conners' parent rating scale, and Wisconsin's card sorting test.

Results: Magnesium, zinc and copper deficiencies were found in 13 (65%), 14 (60%) and 12 (70%) of ADHD children respectively. Magnesium and zinc deficiencies were found to be correlated with hyperactivity, inattention and impulsivity. However, this correlation was not found in the copper deficient ADHD cases.

Conclusion: Children with ADHD have lower levels of zinc, copper and magnesium compared to both laboratory reference ranges and to normal controls in both hair and serum. These deficiencies are correlated with the core symptoms of ADHD

……..

Eur Child Adolesc Psychiatry. 2016;1-2.

THE EVIDENCE BASE OF METHYLPHENIDATE FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER IS IN FACT FLAWED.

Storebø OJ, Simonsen E, Gluud C.

……..

Eur Child Adolesc Psychiatry. 2016;1-12.

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

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

Autism spectrum disorder (ASD) symptoms are elevated in populations of children with attention-deficit/hyperactivity disorder (ADHD). This study examined cross-sectional associations between ASD symptoms and family functioning in children with and without ADHD. Participants were recruited to a longitudinal cohort study, aged 6ΓÇô10 years (164 ADHD; 198 controls). ADHD cases were ascertained using community-based screening and diagnostic confirmation from a diagnostic interview. ASD symptoms were measured using the Social Communication Questionnaire. Outcome variables were parent mental health, family quality of life (FQoL), couple conflict and support, and parenting behaviours. After adjustment for a range of child and family factors (including other mental health comorbidities), higher ASD symptoms were associated with poorer FQoL across all three domains; emotional impact (p = 0.008), family impact (p = 0.001) and time impact (p = 0.003). In adjusted analyses by subgroup, parents of children with ADHD+ASD had poorer parent self-efficacy (p = 0.01), poorer FQoL (p ΓëÑ 0.05), with weak evidence of an association for less couple support (p = 0.06), compared to parents of children with ADHD only. Inspection of covariates in the adjusted analyses indicated that the association between ASD symptoms and most family functioning measures was accounted forby child internalising and externalising disorders, ADHD severity, and socioeconomic status; however, ASD symptoms appear to be independently associated with poorer FQoL in children with ADHD. The presence of ASD symptoms in children with ADHD may signal the need for enhanced family support

……..

Eur Child Adolesc Psychiatry. 2016;1-2.

RESPONSE TO: THE EVIDENCE BASE OF METHYLPHENIDATE FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IS IN FACT FLAWED.

Hoekstra PJ, Buitelaar JK.

……..

Eur Child Adolesc Psychiatry. 2016;25:529-38.

BRAIN STRUCTURAL DEFICITS AND WORKING MEMORY FMRI DYSFUNCTION IN YOUNG ADULTS WHO WERE DIAGNOSED WITH ADHD IN ADOLESCENCE.

Roman-Urrestarazu A, Lindholm P, Moilanen I, et al.

When adolescents with ADHD enter adulthood, some no longer meet disorder diagnostic criteria but it is unknown if biological and cognitive abnormalities persist. We tested the hypothesis that people diagnosed with ADHD during adolescence present residual brain abnormalities both in brain structure and in working memory brain function. 83 young adults (aged 20ΓÇô24-áyears) from the Northern Finland 1986 Birth Cohort were classified as diagnosed with ADHD in adolescence (adolescence ADHD, n-á=-á49) or a control group (n-á=-á34). Only one patient had received medication for ADHD. T1-weighted brain scans were acquired and processed in a voxel-based analysis using permutation-based statistics. A sub-sample of both groups (ADHD, n-á=-á21; controls n-á=-á23) also performed a Sternberg working memory task whilst acquiring fMRI data. Areas of structural difference were used as a region of interest to evaluate the implications that structural abnormalities found in the ADHD group might have on working memory function. There was lower grey matter volume bilaterally in adolescence ADHD participants in the caudate (p-á< 0.05 FWE corrected across the whole brain) at age 20ΓÇô24. Working memory was poorer in adolescence ADHD participants, with associated failure to show normal load-dependent caudate activation. Young adults diagnosed with ADHD in adolescence have structural and functional deficits in the caudate associated with abnormal working memory function. These findings are not secondary to stimulant treatment, and emphasise the importance

of taking a wider perspective on ADHD outcomes than simply whether or not a particular patient meets diagnostic criteria at any given point in time

……..

Eur J Pediatr. 2016;1-10.

CARDIAC ARREST IN INFANTS, CHILDREN, AND ADOLESCENTS: LONG-TERM EMOTIONAL AND BEHAVIORAL FUNCTIONING.

van Zellem L, Utens EM, Madderom M, et al.

Very little is known about the psychological consequences of a cardiac arrest (CA) during childhood. Our aim was to assess long-term emotional and behavioral functioning, and its predictors, in survivors of CA in childhood. This long-term follow-up study involved all consecutive Very little is known about the psychological consequences of a cardiac arrest (CA) during childhood. Our aim was to assess long-term emotional and behavioral functioning, and its predictors, in survivors of CA in childhood. This long-term follow-up study involved all consecutive infants, children, and adolescents surviving CA in a tertiary-care university children's hospital between January 2002 and December 2011. Emotional and behavioral functioning was assessed with the Child Behavior Checklist (CBCL), Teacher's Report Form (TRF), and Youth Self-Report (YSR). Of the eligible 107 CA survivors, 52 patients, parents, and/or teachers filled out online questionnaires. Compared with normative data, parents and teachers reported significantly more attention and somatic problems (age range 6-18 years). Parents also reported more attention problems for age range 1.5-5 years. Twenty-eight percent of the children (n = 14) scored in the psychopathological range (i.e., for age range 1.5-18 years; $p < 0.001$) according to parent reports. Male gender, older age, and basic life support were significantly related to worse scores on the scales internalizing problems, externalizing problems, and total problems and subscale attention problems.

CONCLUSION: Long-term deficits in attention and somatic complaints were reported. Attention problems after childhood CA can interfere with school performance. Long-term follow-up with neuropsychological assessment should be organized.

WHAT IS KNOWN:

- Critical illness has a significant influence on the presence of long-term emotional and behavioral problems.
- Long-term emotional and behavioral problems have been described for various groups of critically ill children such as congenital heart disease, meningococcal septic shock, and neonatal asphyxia.

WHAT IS NEW:

- This is the first study that addresses long-term emotional and behavioral problems in a relatively large consecutive series of children and adolescents surviving cardiac arrest.
- Long-term deficits in attention and somatic complaints were reported.

……..

F1000Research. 2015;3.

"ADHD TRAINER": THE MOBILE APPLICATION THAT ENHANCES COGNITIVE SKILLS IN ADHD PATIENTS.

Tajima-Pozo K, Ruiz-Manrique G, Montañes-Rada F.

We report the case of a 10 year old patient diagnosed with attention deficit hyperactivity disorder (ADHD) and comorbid video game addiction, who was treated with medication combined with a novel cognitive training method based on video games called TCT method. A great risk of developing video game or internet addiction has been reported in children, especially in children with ADHD. Despite this risk, we hypothesize that the good use of these new technologies might be useful to develop new methods of cognitive training. The cognitive areas in which a greater improvement was observed through the use of video games were visuospatial working memory and fine motor skills. TCT method is a cognitive training method that enhances cognitive skills such as attention, working memory, processing speed, calculation ability, reasoning, and visuomotor coordination. The purpose of reviewing this case is to highlight that regular cognitive

computerized training in ADHD patients may improve some of their cognitive symptoms and might be helpful for treating video game addiction

……..

Hong Kong Med J. 2016;22:98-105.

PREVALENCE OF MOTOR PROBLEMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN HONG KONG.

Tsui KW, Lai KYC, Lee MMC, et al.

Introduction: Local data on the occurrence of motor problems in children with attention deficit hyperactivity disorder are not available but an understanding of this important issue may enable better planning of medical services. We aimed to determine the prevalence of motor problems in children with attention deficit hyperactivity disorder in a local population.

Methods: In this descriptive cross-sectional study, children aged 6 to 9 years diagnosed with attention deficit hyperactivity disorder over a period of 6 months from 1 July to 31 December 2011 were recruited from the Joint Paediatric and Child Psychiatric ADHD Program in New Territories East Cluster in Hong Kong. Movement Assessment Battery for Children and Developmental Coordination Disorder Questionnaire' Chinese version were used to determine the presence of motor problems.

Results: Data from 95 participants were included in the final analysis. The number of children who had no, borderline, or definite motor problems was 63, 15, and 17, respectively. It is estimated that up to one third of local children with attention deficit hyperactivity disorder might have developmental coordination disorder.

Conclusions: Motor problems are common in local children with attention deficit hyperactivity disorder and figures are comparable with those from other parts of the world. Despite the various limitations of this study, the magnitude of the problem should not be overlooked

……..

Hormone and Metabolic Research. 2016.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PEDIATRIC PATIENTS WITH PHEOCHROMOCYTOMA AND PARAGANGLIOMA.

Batsis M, Dagalakis U, Stratakis CA, et al.

The aim of the study is to evaluate if there is an association between attention deficit hyperactivity disorder (ADHD) and the diagnosis of pheochromocytoma/paraganglioma (PHEO/PGL) in pediatric patients. A case series study of 43 patients under the age of 18 with PHEO/PGL tumors who were evaluated at the National Institute of Health between January 2006 and May 2014 is reported. Prior diagnosis of ADHD and treatment course with stimulant medications was recorded. Patient symptoms, catecholamine and metanephrine levels, tumor characteristics, and genetic analyses for syndromes associated with PHEO/PGL were evaluated. A chi-squared test was used to assess the prevalence of ADHD in the PHEO/PGL patients compared to the general population. Nine out of 43 (21%) of patients diagnosed with PHEO/PGL had been diagnosed with ADHD prior to tumor identification. Four of the 9 patients had been treated with amphetamine, dextroamphetamine, and/or methylphenidate, potentially exacerbating an adrenergic crisis. In addition, 4 patients exhibited hypertension at the initial diagnosis of their PHEO/PGL. Three patients had resolution of their ADHD symptoms after successful surgical removal of PHEO/PGL. Our study found a prevalence of ADHD in 21% of our PHEO/PGL patients, significantly higher than 7.2% seen in the general pediatric population. Symptoms of anxiety and difficulty in concentration in these patients may have been related to their underlying PHEO/PGL and were not recognized as part of the constellation of symptoms in a child with PHEO/PGL. In pediatric patients with hypertension and ADHD symptomatology, an evaluation to rule out PHEO/PGL is warranted prior to treatment with stimulant medications

……..

Hum Brain Mapp. 2016.

UNIQUE WHITE MATTER MICROSTRUCTURAL PATTERNS IN ADHD PRESENTATIONS-A DIFFUSION TENSOR IMAGING STUDY.

Svatkova A, Nestrasil I, Rudser K, et al.

Attention-deficit/hyperactivity disorder predominantly inattentive (ADHD-PI) and combined (ADHD-C) presentations are likely distinct disorders that differ neuroanatomically, neurochemically, and neuropsychologically. However, to date, little is known about specific white matter (WM) regions differentiating ADHD presentations. This study examined differences in WM microstructure using diffusion tensor imaging (DTI) data from 20 ADHD-PI, 18 ADHD-C, and 27 typically developed children. Voxel-wise analysis of DTI measurements in major fiber bundles was carried out using tract-based spatial statistics (TBSS). Clusters showing diffusivity abnormalities were used as regions of interest for regression analysis between fractional anisotropy (FA) and neuropsychological outcomes. Compared to neurotypicals, ADHD-PI children showed higher FA in the anterior thalamic radiations (ATR), bilateral inferior longitudinal fasciculus (ILF), and in the left corticospinal tract (CST). In contrast, the ADHD-C group exhibited higher FA in the bilateral cingulum bundle (CB). In the ADHD-PI group, differences in FA in the left ILF and ATR were accompanied by axial diffusivity (AD) abnormalities. In addition, the ADHD-PI group exhibited atypical mean diffusivity in the forceps minor (FMi) and left ATR and AD differences in right CB compared to healthy subjects. Direct comparison between ADHD presentations demonstrated radial diffusivity differences in FMi. WM clusters with FA irregularities in ADHD were associated with neurobehavioral performance across groups. In conclusion, differences in WM microstructure in ADHD presentations strengthen the theory that ADHD-PI and ADHD-C are two distinct disorders. Regions with WM irregularity seen in both ADHD presentations might serve as predictors of executive and behavioral functioning across groups

……..

Int J Dev Neurosci. 2016;51:17-27.

ELECTROPHYSIOLOGICAL CORRELATES OF REINFORCEMENT LEARNING IN YOUNG PEOPLE WITH TOURETTE SYNDROME WITH AND WITHOUT CO-OCCURRING ADHD SYMPTOMS.

Shephard E, Jackson GM, Groom MJ.

Altered reinforcement learning is implicated in the causes of Tourette syndrome (TS) and attention-deficit/hyperactivity disorder (ADHD). TS and ADHD frequently co-occur but how this affects reinforcement learning has not been investigated. We examined the ability of young people with TS (n = 18), TS + ADHD (N = 17), ADHD (n = 13) and typically developing controls (n = 20) to learn and reverse stimulus-response (S-R) associations based on positive and negative reinforcement feedback. We used a 2 (TS-yes, TS-no) +ù 2 (ADHD-yes, ADHD-no) factorial design to assess the effects of TS, ADHD, and their interaction on behavioural (accuracy, RT) and event-related potential (stimulus-locked P3, feedback-locked P2, feedback-related negativity, FRN) indices of learning and reversing the S-R associations. TS was associated with intact learning and reversal performance and largely typical ERP amplitudes. ADHD was associated with lower accuracy during S-R learning and impaired reversal learning (significantly reduced accuracy and a trend for smaller P3 amplitude). The results indicate that co-occurring ADHD symptoms impair reversal learning in TS + ADHD. The implications of these findings for behavioural tic therapies are discussed

……..

Int J Psychiatry Clin Pract. 2016;20:77-82.

FACTORS RELATED TO DIAGNOSTIC PERSISTENCE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER IN TURKISH CHILDREN AND ADOLESCENTS.

Ayaz AB, Ayaz M, et al.

Objective: Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequently occurring mental disorders in children and adolescents. The purpose of this study was to determine diagnostic persistence

three years after the first clinical evaluation and to investigate the factors relating to diagnostic persistence in children and adolescents with ADHD.
Methods: The study included 183 children and adolescents who were evaluated in the first admission. Of 183 children and adolescents, 142 children and adolescents were evaluated in the second admission and only the data of 142 children and adolescents were analysed in the study. Diagnostic persistence was defined as having met the full criteria for ADHD on second evaluation. Symptom severity of ADHD was determined using the Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale-Parents Form (T-DSM-IV-S). Intelligence level was assessed through the Wechsler Intelligence Scale for Children-Revised.
Results: Of the children included in the study, 77.5% (n = 110) were determined to have ADHD diagnostic persistence. Low intelligence levels, younger age and higher T-DSM-IV-S inattention and conduct disorder scores were associated with diagnostic persistence. ADHD diagnosis in children and adolescents tends to continue at high rates.
Conclusions: Determination of the risks related to ADHD diagnostic persistence may contribute to improved treatment planning and interventions

……..

Int J Psychophysiol. 2016.
The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders .
Chiarenza GA, Chabot R, Isenhart R, et al.
Objective: The aim of our study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are responders and non-responders to long-term treatment with Atomoxetine at baseline and after 6 and 12. months of treatment. Patients with attention deficit hyperactivity disorder (ADHD) received atomoxetine titrated, over 7. days, from 0.5 to 1.2. mg/kg/day. QEEG and Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy.
Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked earlobes. Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values.
Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values.
Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta

……..

Iran J Psychiatr Behav Sci. 2016;10.
IRANIAN CHILDREN WITH ADHD AND MENTAL HEALTH OF THEIR MOTHERS: THE ROLE OF STRESS.
Babakhanian M, Sayar S, Babakhanian M, et al.
Background: Attention deficit/hyperactivity disorder (ADHD) is a psychiatric disorder that can result in stress for the mother, resulting in poor health.

Objectives: The current study, conducted in 2012, aims to assess stress among forty-six Iranian mothers of ADHD children (Group 1) who were admitted to a psychiatric center in Tehran with forty-six Iranian mothers of normal children (Group 2) in 2012.
Materials and Methods: The Child Symptom Inventory-4 (CSI-4), the child behavior checklist (CBCL) and the parental stress indexshort form (PSI/SF) were completed. Data was analyzed using the Levene test and the independent t-test in SPSS Version 18.
Results: With the exception of mood, ADHD children had more problems in attention compared with normal children. As a result, mothers of ADHD children had more stress compared with the controls.
Conclusions: ADHD can impair a mother's mental health by inducing stress. Specific diagnostic and treatment programs should be designed and tailored for the mothers of ADHD children in order to decrease stress

……..

J Am Med Assoc. 2016;315:1997-2008.

TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN ADOLESCENTS: A SYSTEMATIC REVIEW.

Chan E, Fogler JM, Hammerness PG.

Importance: Although attention-deficit/hyperactivity disorder (ADHD) is highly prevalent in adolescents and often persists into adulthood, most studies about treatment were performed in children. Less is known about ADHD treatment in adolescents.
Objective: To review the evidence for pharmacological and psychosocial treatment of ADHD in adolescents.
Evidence Review: The databases of CINAHL Plus, MEDLINE, PsycINFO, ERIC, and the Cochrane Database of Systematic Reviews were searched for articles published between January 1, 1999, and January 31, 2016, on ADHD treatment in adolescents. Additional studies were identified by hand-searching reference lists of retrieved articles. Study quality was rated using McMaster University Effective Public Health Practice Project criteria. The evidence level for treatment recommendations was based on Oxford Centre for Evidence-Based Medicine criteria.
Findings: Sixteen randomized clinical trials and 1meta-analysis, involving 2668 participants, of pharmacological and psychosocial treatments for ADHD in adolescents aged 12 years to 18 years were included. Evidence of efficacy was stronger for the extended-release methylphenidate and amphetamine class stimulant medications (level 1B based on Oxford Centre for Evidence-Based Medicine criteria) and atomoxetine than for the extended-release α2-adrenergic agonists guanfacine or clonidine (no studies). For the primary efficacy measure of total symptom score on the ADHD Rating Scale (score range, 0 [least symptomatic] to 54 [most symptomatic]), both stimulant and nonstimulant medications led to clinically significant reductions of 14.93 to 24.60 absolute points. The psychosocial treatments combining behavioral, cognitive behavioral, and skills training techniques demonstrated small- to medium-sized improvements (range for mean SD difference in Cohen d, 0.30-0.69) for parent-rated ADHD symptoms, co-occurring emotional or behavioral symptoms, and interpersonal functioning. Psychosocial treatments were associated with more robust (Cohen d range, 0.51-5.15) improvements in academic and organizational skills, such as homework completion and planner use.
Conclusions and Relevance: Evidence supports the use of extended-release methylphenidate and amphetamine formulations, atomoxetine, and extended-release guanfacine to improve symptoms of ADHD in adolescents. Psychosocial treatments incorporating behavior contingency management, motivational enhancement, and academic, organizational, and social skills training techniques were associated with inconsistent effects on ADHD symptoms and greater benefit for academic and organizational skills. Additional treatment studies in adolescents, including combined pharmacological and psychosocial treatments, are needed

……..

J Am Med Assoc. 2016;315:2009-10.
METHYLPHENIDATE FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.
Storebø O, Simonsen E, Gluud C.

……..

JAMA Pediatr. 2016;170:396-97.
CHANGES IN ACADEMIC DEMANDS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN YOUNG CHILDREN.
Brosco JP, Bona A.

……..

J Abnorm Child Psychol. 2016 May;44:771-85.
SLUGGISH COGNITIVE TEMPO AND ADHD INATTENTION AS PREDICTORS OF EXTERNALIZING, INTERNALIZING, AND IMPAIRMENT DOMAINS: A 2-YEAR LONGITUDINAL STUDY.
Bernad MdM, Servera M, Becker SP, et al.
Although sluggish cognitive tempo (SCT) is distinct from attention-deficit/hyperactivity disorder inattention (ADHD-IN), few studies have examined whether SCT longitudinally predicts other symptom or impairment dimensions. This study used 4 sources (mothers, fathers, primary teachers, and secondary teachers) and 3 occasions of measurement (first, second, and third grades) with 758 first grade (55 % boys), 718 second grade (54 % boys), and 585 third grade (53 % boys) children from Spain to determine SCT's and ADHD-IN's unique longitudinal relationships with psychopathology, academic impairment, and social impairment over the 1- and 2-year intervals (i.e., first to third grade, second to third grade). For 1- and 2-year intervals using both mothers' and fathers' ratings, higher levels of SCT uniquely predicted higher levels of anxiety, depression, academic impairment, and social impairment whereas higher levels of ADHD-IN uniquely predicted higher levels of ADHD-HI, ODD, and academic impairment. For 1- and 2-year intervals across different primary and secondary teachers (i.e., first/second and third grade ratings were provided by different teachers), higher scores on ADHD-IN uniquely predicted poorer outcomes across domains whereas higher scores on SCT uniquely predicted lower levels of ADHD-HI and ODD for both intervals in addition to higher levels of depression (for primary teachers only), academic impairment (for 1-year interval only), and peer rejection (2-year interval only for primary teachers). Overall, SCT was significantly associated with important outcomes independent of ADHD-IN over 1- and 2-year intervals and across four different raters. This study provides further evidence for distinguishing between SCT and ADHD-IN in home and school settings

……..

J Adolesc Health. 2016.
DIAGNOSIS AND TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER DURING ADOLESCENCE IN THE PRIMARY CARE SETTING: A CONCISE REVIEW.
Brahmbhatt K, Hilty DM, Hah M, et al.
Attention deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder with a worldwide prevalence of about 5% in school-age children. This review is intended to assist primary care providers (PCPs) in diagnosing and treating ADHD in adolescents. PubMed, PsychInfo, and Science Citation Index databases were searched from March 1990 to 2015 with the keywords: ADHD, primary care/pediatrics and children/adolescents, abstracts addressing diagnosis and/or treatment with 105 citations identified including supplementary treatment guidelines/books. Adolescent ADHD presents with significant disturbances in attention, academic performance, and family relationships with unique issues associated with this developmental period. Diagnostic challenges include the variable symptom presentation during adolescence, complex differential diagnosis, and limited training and time for PCPs to conduct thorough evaluations. The evidence base for treatments in adolescence in comparison to those in children or adults with ADHD is

relatively weak. Providers should be cognizant of prevention, early identification, and treatment of conditions associated with ADHD that emerge during adolescence as substance use disorders. Adolescent ADHD management for the PCP is complex, requires further research, and perhaps new primary care psychiatric models, to assist in determining the optimal care for patients at this critical period

……..

J Affective Disord. 2016;200:222-34.

THE CAREGIVER PERSPECTIVE ON PAEDIATRIC ADHD (CAPPA) SURVEY: UNDERSTANDING SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS, TREATMENT USE AND IMPACT OF ADHD IN EUROPE.

Flood E, Gajria K, Sikirica V, et al.

Background Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects the lives of patients and their families. The Caregiver Perspective on Paediatric ADHD (CAPPA) survey was conducted to evaluate the burden associated with ADHD in Europe and to identify unmet needs. Here, we describe sociodemographic and clinical characteristics, treatment use and impact of ADHD.

Methods The cross-sectional web-based CAPPA survey was fielded in 10 European countries among caregivers of children/adolescents (aged 6-17 years) with ADHD who were currently receiving or had received pharmacotherapy in the previous 6 months.

Results Data on 3688 completed CAPPA surveys were evaluated. Children/adolescents were diagnosed with ADHD at a mean age of 6.9 years; 80% were male. Most children/adolescents (56%) had undergone behavioural therapy. Overall, 78% of children/adolescents currently received ADHD pharmacotherapy; high rates of atypical antipsychotic use were reported in some countries. Overall, 23% of children/adolescents had repeated a school year and 4% had been expelled recently. Most caregivers (68-88%) reported difficulty with schoolwork, social interactions/activities and family relationships, even when the child/adolescent was receiving ADHD medication. Almost one third (31%) of caregivers felt the need to change employment status despite their child/adolescent receiving ADHD medication in 53% of these cases. Limitations Information was reported by caregivers recruited through market research panels; reporting, recall and selection biases may be present.

Conclusion Variation across Europe was observed in characteristics of caregivers and children/adolescents with ADHD, and treatment use. Even with medication, ADHD compromised or negatively impacted caregivers' work and children/adolescents' schoolwork, their social interactions and family relationships

……..

J Altern Complement Med. 2016;22:286-93.

CHANGES IN GAIT BALANCE AND BRAIN CONNECTIVITY IN RESPONSE TO EQUINE-ASSISTED ACTIVITY AND TRAINING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hyun GJ, Jung TW, Park JH, et al.

Objectives: Equine-assisted activity and training (EAAT) is thought to improve body balance and clinical symptoms in children with attention deficit hyperactivity disorder (ADHD). The study hypostheses were that EAAT would improve the clinical symptoms and gait balance in children with ADHD and that these improvements would be associated with increased brain connectivity within the balance circuit.

Methods: A total of 12 children with ADHD and 12 age- and sex-matched healthy control children were recruited. EAAT consisted of three training sessions, each 70 minutes long, once a week for 4 weeks. Brain functional connectivity was assessed by using functional magnetic resonance imaging.

Results: After 4 weeks of EAAT, children with ADHD showed improved scores on the Korean ADHD scale (K-ARS), while the K-ARS scores of healthy children did not change. During the 4 weeks, the plantar pressure difference between the left foot and right foot decreased in both the healthy control group and the ADHD group. After 4 weeks of EAAT, healthy controls showed increased brain connectivity from the cerebellum to the left occipital lingual gyrus, fusiform gyrus, right and left thalami, right caudate, right precentral gyrus, and right superior frontal gyrus. However, children with ADHD showed increased brain connectivity from the

cerebellum to the right insular cortex, right middle temporal gyrus, left superior temporal gyrus, and right precentral gyrus. In contrast, children with ADHD exhibited decreased brain connectivity from the cerebellum to the left inferior frontal gyrus.
Conclusion: EAAT may improve clinical symptoms, gait balance, and brain connectivity, the last of which controls gait balance, in children with ADHD. However, children with ADHD who have deficits in the fronto-cerebellar tract did not exhibit changes in brain connectivity as extensive as those in healthy children in response to EAAT

……..

Journal of Attention Disorders. 2016 May;20:400-13.
FEASIBILITY OF SCHOOL-BASED ADHD INTERVENTIONS: A MIXED-METHODS STUDY OF PERCEPTIONS OF ADOLESCENTS AND ADULTS.
Bussing R, Koro-Ljungberg M, Gagnon JC, et al.
Objective: Little is known about perceptions surrounding academic interventions for ADHD that determine intervention feasibility.
Method: As part of a longitudinal mixed-methods research project, representative school district samples of 148 adolescents (54.8%), 161 parents (59.4%), 122 teachers (50.0%), 46 health care providers (53.5%), and 92 school health professionals (65.7%) completed a cross-sectional survey. They also answered open-ended questions addressing undesirable intervention effects, which were analyzed using grounded theory methods.
Results: Adolescents expressed significantly lower receptivity toward academic interventions than adult respondents. Stigma emerged as a significant threat to ADHD intervention feasibility, as did perceptions that individualized interventions foster inequality.
Conclusion: Findings suggest that adolescents' viewpoints must be included in intervention development to enhance feasibility and avoid interventions acceptable to adults, but resisted by adolescents

……..

Journal of Attention Disorders. 2016 May;20:434-44.
TEACHER RATINGS OF THE ADHD-RS IV IN A COMMUNITY SAMPLE: RESULTS FROM THE CHIP-ARD STUDY.
Caci HM, Morin AJ, Tran A.
OBJECTIVE: Validated instruments to assess ADHD are still unavailable in many languages other than English for teachers, which constitutes a clear obstacle to screening, diagnosis, and treatment of ADHD in many European countries.
METHOD: Teachers rated 892 youths using the ADHD Rating Scale (ADHD-RS). We investigated the factor structure, reliability, and measurement invariance based on confirmatory factor analyses.
RESULTS: Results support a bifactor model, including one general ADHD factor and two specific Inattention and Hyperactivity-Impulsivity factors. But the latter is improperly defined calling into question the existence of a Predominantly Hyperactivity-Impulsivity subtype. The measurement invariance is fully supported across gender, age groups, and Gender × Age Groups.
CONCLUSION: Results support the multiple-pathways hypothesis and suggest that a total ADHD score is meaningful, reliable, and valid, as well as specific assessments of Inattention. Some youths-especially older ones-may present a profile of ADHD particularly marked by Inattention symptoms

……..

Journal of Attention Disorders. 2016 May;20:445-57.

DIFFERENCES BETWEEN JUVENILE OFFENDERS WITH AND WITHOUT AD(H)D IN RECIDIVISM RATES AND RISK AND PROTECTIVE FACTORS FOR RECIDIVISM.

van der Put CE, Asscher JJ, Stams GJ.

Objective: This study examined differences between juvenile offenders with AD(H)D (n = 1,348), with both AD(H)D and conduct problems (n = 933), and without AD(H)D or conduct problems (n = 2,180) in recidivism rates, prevalence of risk and protective factors, and strength of associations between risk/protective factors and recidivism.

Method: Existing data were used, collected with the Washington State Juvenile Court Assessment. ANOVA, Pearson correlations, and Fisher'sztests were calculated.

Results: Recidivism was highest in the AD(H)D-comorbid group, followed by the AD(H)D-only group and lowest in the comparison group. In offenders with AD(H)D, especially comorbid AD(H)D, the number of risk factors was considerably larger than the number of protective factors, whereas the number of risk and protective factors was the same in the comparison group.

Conclusion: Juvenile offenders with AD(H)D may benefit most from interventions that focus on risk and protective factors in multiple domains.

……..

Journal of Attention Disorders. 2016 May;20:414-23.

MATERNAL RATINGS OF THE ADHD SYMPTOMS: SUBTYPES VERSUS SEVERITY IN CLINIC-REFERRED CHILDREN AND ADOLESCENTS.

Gomez R, Vance A, Gomez RM.

Objective: This study used confirmatory factor analysis (CFA), latent class analysis (LCA), and factor mixture model (FMM) to ascertain the best model for ADHD symptoms, as presented in the Strengths and Weaknesses of ADHD-Symptoms and Normal Behavior Scale (SWAN).

Method: Mother ratings of the ADHD symptoms of 418 clinic-referred children and adolescents were obtained.

Results: The findings provided most support for an FMM with two classes (less severe inattention [IA] and hyperactivity/impulsivity [HI] symptoms and more severe IA/HI symptoms) and two factors (IA and HI) model. The more severe class had more individuals with the ADHD diagnosis, especially the combined type.

Conclusion: The findings are discussed in relation to dimensional and categorical views of ADHD

……..

Journal of Attention Disorders. 2016 May;20:424-33.

THE IMPACT OF COEXISTING EMOTIONAL AND CONDUCT PROBLEMS ON FAMILY FUNCTIONING AND QUALITY OF LIFE AMONG ADOLESCENTS WITH ADHD.

Schei J, Jozefiak T, et al.

Objective: The aim of this study was to assess the impact of self-reported emotional and conduct problems on family functioning and quality of life (QoL) among adolescents with ADHD.

Method: The ADHD group (N = 194) was divided into the following groups: without additional emotional or conduct problems, with emotional problems, with conduct problems, and with both problem types. The cross-sectional study included parent and adolescent reports.

Results: Adolescents with ADHD and both problem types reported significantly lower QoL and family functioning than all other ADHD groups. Parents reported better QoL for the ADHD group without additional problems, but similar family functioning for all groups.

Conclusion: A higher level of coexisting psychiatric problems had a significant impact on adolescents'

reports of family functioning and QoL. However, coexisting problems showed no association with parent reports of family functioning. Adolescents with ADHD might add important information in clinical assessment

……..

Journal of Attention Disorders. 2016 May;20:390-99.

THE RELATIONSHIP BETWEEN LIFE SATISFACTION AND ADHD SYMPTOMS IN MIDDLE SCHOOL STUDENTS: USING A BIFACTOR MODEL.

Ogg JA, Bateman L, Dedrick RF, et al.

Objective: ADHD is associated with increased academic and social difficulties and comorbid psychopathology which may lead to decreased life satisfaction (LS).

Methods: The current study utilized a bifactor model of ADHD consisting of a general factor and two specific factors (inattention and hyperactivity-impulsivity) to determine if ADHD symptoms place middle school students (n = 183) at risk for diminished LS and if this relationship differed depending on whether teachers versus students reported ADHD symptoms.

Results: Confirmatory factor analyses indicated that the bifactor model provided very good fit to the ADHD symptoms reported by students (comparative fit index [CFI] = .995; root mean square error of approximation [RMSEA] = .028) and teachers (CFI = .997; RMSEA = .043). Results also demonstrated that when students rated ADHD symptoms, the general ADHD factor and inattention were negatively related to LS; however, when teachers rated ADHD symptoms, only inattention was negatively related to LS.

Conclusions: Implications and future directions related to these results are discussed

……..

Journal of Attention Disorders. 2016 May;20:383-89.

IS ADHD A RISK FACTOR FOR HIGH SCHOOL DROPOUT? A CONTROLLED STUDY.

Fried R, Petty C, Faraone SV, et al.

Objective: This study examined whether ADHD was an independent contributor to grade retention when adjusting for IQ, learning disorders, and social class.

Method: Outcome data was from participants in studies at Massachusetts General Hospital (n = 404 ADHD, n = 349 controls) who underwent psychiatric interviews, socioeconomic status measures, and IQ testing.

Results: 28% of individuals with ADHD repeated a grade compared with 7% of controls ($p < .001$). Among participants with ADHD, social class, and IQ were significant predictors of high school dropout or repeated grade. An interaction effect of ADHD and gender was also found with females with ADHD having a higher risk ratio for repeated grade/dropout compared with males with ADHD.

Conclusion: Participants with ADHD were significantly more likely to repeat a grade, adjusting for all other variables indicating the critical importance of early identification of ADHD to help mitigate adverse educational outcomes

……..

Journal of Attention Disorders. 2016 May;20:458-68.

MATERNAL ADHD, PARENTING, AND PSYCHOPATHOLOGY AMONG MOTHERS OF ADOLESCENTS WITH ADHD.

Babinski DE, Pelham WEJr, Molina BSG, et al.

Objective: This study describes the parenting and psychopathology of mothers with ADHD of adolescents with ADHD (MCA), non-ADHD mothers of adolescents with ADHD (CA), and non-ADHD mothers of adolescents without ADHD (COMP).

Method: Two sets of pairwise comparisons: (a) COMP versus CA and (b) CA versus MCA were conducted. We hypothesized that CA would experience greater distress in parenting and psychopathology compared with COMP and that MCA would experience even more impairment compared with CA.

Results: Few differences emerged in comparisons of CA and COMP, with the exception of CA reporting greater parent' adolescent conflict and internalizing problems. In contrast, differences consistently emerged in comparisons of MCA and CA showing more difficulty for MCA in parenting and psychopathology.
Conclusion: These findings underscore the need for treatments that address parental ADHD when adolescent ADHD is the intended target.

……..

Journal of Child and Family Studies. 2016 May;25:1656-71.
PERCEPTION OF PARENTING STYLE BY CHILDREN WITH ADHD AND ITS RELATION WITH INATTENTION, HYPERACTIVITY/IMPULSIVITY AND EXTERNALIZING SYMPTOMS.
Molina MaF, Musich FMn.
Children's perception of their parents' behavior is very important for their adjustment. Raising a child with Attention-Deficit/Hyperactivity Disorder (ADHD) can be particularly challenging. However, little is known about how children with ADHD perceive their parents' childrearing style. The main purpose of this paper is to study how children with ADHD perceive acceptance and control in parent' child relationships and this perception's relationship with inattention, hyperactivity/impulsivity, and externalizing behaviors. Participants were children between 7 and 13 years old with ADHD who were attending psychotherapy (ADHD), children without ADHD who were attending psychotherapy (APG), and children with unknown ADHD status who were not attending psychotherapy (NPG). Furthermore, one parent of each child participated in the study. An analysis of variance (ANOVA) showed that children with ADHD perceived higher levels of pathological control in their relationships with their mothers than did APG and NPG children. NPG children perceived higher extreme autonomy than ADHD and APG children. Linear regression analyses revealed that the perception of pathological parental control and extreme autonomy predicted externalizing symptoms in children with ADHD. The perception of maternal acceptance and pathological control predicted inattention in APG children. Also, perceived maternal pathological control and perceived paternal acceptance predicted externalizing symptoms in APG children. Thus, these results show the importance of taking into account children's perception of their relationships with their parents in addition to parental reports of their own behavior

……..

J Child Neurol. 2013;29:1383-89.
TOURETTE SYNDROME AND COMORBID CONDITIONS: A SPECTRUM OF DIFFERENT SEVERITIES AND COMPLEXITIES.
Rizzo R, Gulisano M, Pellico A, et al.
To investigate clinical correlates of Tourette syndrome and to identify the impact of comorbidities, we retrospectively recruited 92 young people affected by Tourette syndrome compared with 102 healthy controls. Neuropsychological assessment included: Youth Quality of Life-Research, Multidimensional Anxiety Scale for Children, Children's Depression Inventory, and Conner's and Child Behavior Checklist; moreover, Tourette syndrome patients completed the Yale Global Tic Severity Rating Scale and the Yale-Brown Obsessive Compulsive Scale. Four clinical subgroups were identified: pure Tourette syndrome (49.8%), Tourette syndrome plus attention-deficit hyperactivity disorder (ADHD) (22.2%), Tourette syndrome plus obsessive-compulsive disorder (21.5%), and Tourette syndrome plus ADHD plus obsessive-compulsive disorder (6.5%). Our findings suggested that emotional lability appeared in all Tourette syndrome subgroups, independently from comorbidities, representing a clinical feature of Tourette syndrome itself. Moreover, our data suggested that all 4 clinical subgroups had higher statistically significant behavioral problems compared with the healthy controls (P =.000), whereas affective and anxiety symptoms were overrepresented in Tourette syndrome plus comorbidities subgroups. Finally, Tourette syndrome patients had a lower quality of

life compared with the healthy controls. These differences were statistically significant between the pure Tourette syndrome subgroups and Tourette syndrome plus comorbidities subgroups, as well as Tourette syndrome plus comorbidities subgroups and healthy controls

……..

J Child Neurol. 2015;31:784-96.

NONINVASIVE BRAIN STIMULATION IN PEDIATRIC ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): A REVIEW.

Rubio B, Boes AD, Laganiere S, et al.

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in the pediatric population. The clinical management of ADHD is currently limited by a lack of reliable diagnostic biomarkers and inadequate therapy for a minority of patients who do not respond to standard pharmacotherapy. There is optimism that noninvasive brain stimulation may help to address these limitations. Transcranial magnetic stimulation and transcranial direct current stimulation are 2 methods of noninvasive brain stimulation that modulate cortical excitability and brain network activity. Transcranial magnetic stimulation can be used diagnostically to probe cortical neurophysiology, whereas daily use of repetitive transcranial magnetic stimulation or transcranial direct current stimulation can induce long-lasting and potentially therapeutic changes in targeted networks. In this review, we highlight research showing the potential diagnostic and therapeutic applications of transcranial magnetic stimulation and transcranial direct current stimulation in pediatric ADHD. We also discuss the safety and ethics of using these tools in the pediatric population

……..

J Child Neurol. 2015;31:750-60.

EFFECTS OF SMART-TABLET-BASED NEUROFEEDBACK TRAINING ON COGNITIVE FUNCTION IN CHILDREN WITH ATTENTION PROBLEMS.

Shin MS, Jeon H, Kim M, et al.

We sought to determine whether smart-tablet-based neurofeedback could improve executive function - including attention, working memory, and self-regulation - in children with attention problems. Forty children (10-12 years old) with attention problems, as determined by ratings on the Conners Parent Rating Scale, were assigned to either a neurofeedback group that received 16 sessions or a control group. A comprehensive test battery that assessed general intelligence, visual and auditory attention, attentional shifting, response inhibition and behavior rating scales were administered to both groups before neurofeedback training. Several neuropsychological tests were conducted at posttraining and follow-up assessment. Scores on several neuropsychological tests and parent behavior rating scales showed significant improvement in the training group but not in the controls. The improvements remained through the follow-up assessment. This study suggests that the smart-tablet-based neurofeedback training program might improve cognitive function in children with attention problems

……..

Journal of Child Psychology and Psychiatry. 2016 May;57:633-44.

A RANDOMIZED CONTROLLED TRIAL INTO THE EFFECTS OF NEUROFEEDBACK, METHYLPHENIDATE, AND PHYSICAL ACTIVITY ON EEG POWER SPECTRA IN CHILDREN WITH ADHD.

Janssen TWP, Bink M, et al.

BACKGROUND: The clinical and neurophysiological effects of neurofeedback (NF) as treatment for children with ADHD are still unclear. This randomized controlled trial (RCT) examined electroencephalogram (EEG) power spectra before and after NF compared to methylphenidate (MPH) treatment and physical activity (PA)

- as semi-active control group - during resting and active (effortful) task conditions to determine whether NF can induce sustained alterations in brain function.
METHODS: Using a multicentre three-way parallel group RCT design, 112 children with a DSM-IV diagnosis of ADHD, aged between 7 and 13 years, were initially included. NF training consisted of 30 sessions of theta/beta training at Cz over a 10-week period. PA training was a semi-active control group, matched in frequency and duration. Methylphenidate was titrated using a double-blind placebo controlled procedure in 6 weeks, followed by a stable dose for 4 weeks. EEG power spectra measures during eyes open (EO), eyes closed (EC) and task (effortful) conditions were available for 81 children at pre- and postintervention (n = 29 NF, n = 25 MPH, n = 27 PA).
CLINICAL TRIALS REGISTRATION: Train Your Brain? Exercise and Neurofeedback Intervention for ADHD, https://clinicaltrials.gov/show/;NCT01363544, Ref. No. NCT01363544.
RESULTS: Both NF and MPH resulted in comparable reductions in theta power from pre- to postintervention during the EO condition compared to PA (ηp (2) = .08 and .12). For NF, greater reductions in theta were related to greater reductions in ADHD symptoms. During the task condition, only MPH showed reductions in theta and alpha power compared to PA (ηp (2) = .10 and .12).
CONCLUSIONS: This study provides evidence for specific neurophysiological effects after theta/beta NF and MPH treatment in children with ADHD. However, for NF these effects did not generalize to an active task condition, potentially explaining reduced behavioural effects of NF in the classroom

……..

J Clin Diagn Res. 2016;10:LC25-LC28.
PREVALENCE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN STUDENTS AND NEEDS MODIFICATION OF MENTAL HEALTH SERVICES IN SHAHREKORD, IRAN IN 2013.
Safavi P, Ganji F, Bidad A.
Introduction and Objectives: In view of the complications of Attention-Deficit Hyperactivity Disorder (ADHD) and significance of its treatment, the present study was aimed to investigate the prevalence of ADHD among elementary school students of Shahrekord and to assess the obstacles preventing patients from accessing mental health services.
Materials and Methods: In this cross-sectional study, 631 eligible students were selected from elementary school students in Shahrekord County, Iran. Multi-stage stratified random sampling was adopted. Demographic data were gathered and Child Symptom Inventory-4 for parents and teachers was filled out for each student. The students with suspected ADHD were identified, and examined for the association among mental health help-seeking steps. Obstacles to mental health help-seeking were assessed.
Results: ADHD prevalence was derived 17.3% and higher among male students (p=0.025). ADHD prevalence was associated with parentsΓÇÖ education and occupation. The evaluation and diagnosis rates were significantly associated with gender (p=0.002 and 0.005, respectively). The most prevalent obstacles facing access to mental health services were those relevant to feeling no need (86%), negative expectations of treatment (78%) and mental health system (64%).
Conclusion: ADHD was highly prevalent among elementary school students. Identifying the patients and examining the existing obstacles of access to mental health system seems necessary

……..

J Clin Exp Neuropsychol. 2016 May;38:487-96.
CLINICAL CORRELATES OF WORKING MEMORY DEFICITS IN YOUTH WITH AND WITHOUT ADHD: A CONTROLLED STUDY.
Fried R, Chan J, Feinberg L, et al.
Objective: Both working memory (WM; a brain system that provides temporary storage and manipulation of the information) and attention-deficit/hyperactivity disorder (ADHD) have been associated with educational deficits. Since WM deficits are prevalent in children with ADHD, the main aim of the present study was to

examine whether educational deficits are driven by working memory deficits or driven by the effect of ADHD itself.
Method: Participants were referred youth with (N = 276) and without (N = 241) ADHD ascertained from pediatric and psychiatric sources. Assessment included measures of psychiatric, psychosocial, educational, and cognitive functioning. Education deficits were defined as grade retention or placement in special classes and were assessed using interviews and written rating scales. Working memory was assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R) Freedom from Distractibility (FFD) factor based on Digit Span, Arithmetic, and Coding.
Results: Significantly more youth with ADHD had WM deficits than controls (31.9% vs. 13.7%, $p < .05$). In ADHD children, WM deficits were significantly ($p < .01$) associated with an increased risk for grade retention and placement in special classes as well as lower scores on reading and math achievement tests than for ADHD children without WM deficits. In contrast, no other differences were noted in other areas of functioning. Although WM deficits also had some adverse impact on educational and cognitive correlates in non-ADHD controls, these differences failed to attain statistical significance.
Conclusion: WM deficits significantly and selectively increase the risk for academic deficits and cognitive dysfunction in children with ADHD beyond those conferred by ADHD. Screening for WM deficits may help identify children with ADHD at high risk for academic and cognitive dysfunction

……..

Journal of Clinical Child and Adolescent Psychology. 2016 May;45:305-19.
THE ROLE OF PARENTAL ADHD IN SUSTAINING THE EFFECTS OF A FAMILY-SCHOOL INTERVENTION FOR ADHD.
Dawson AE, Wymbs BT, Marshall SA, et al.
This study investigated the extent to which parental Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms impact child and parent outcomes following a multimodal family-school intervention, the Family School Success (FSS) program, when compared to an active-control condition (CARE). Participants were 139 children with ADHD (67% male; 91% non-Hispanic; 77% Caucasian; Grades 2-6) and their primary caretaker (91% female; ages 26-59) who participated in a randomized clinical trial evaluating the efficacy of FSS. Associations were examined between parent-reported ADHD symptoms at baseline and intervention outcomes reported by parents and teachers after treatment and at a 3-month follow-up, including child homework and classroom impairments, child ADHD and oppositional defiant disorder symptoms, parenting behaviors, and parent-teacher relationship quality. Across both treatment conditions, parental ADHD was not associated with parent or child outcomes at postassessment. However, differences emerged between the two treatment groups at follow-up for parents with ADHD, particularly when an empirically supported symptom cutoff was used to identify parents at risk for having ADHD. In FSS, but not in CARE, parental ADHD was associated with declines in treatment gains in the quality of the parent-teacher relationship and the child's homework performance. Parents at risk for ADHD had difficulty maintaining treatment effects for themselves and their child in the FSS intervention but not in CARE. The supportive and educational components central to the CARE intervention may be helpful in promoting the sustainability of psychosocial interventions for children with ADHD who have parents with elevated ADHD symptoms

……..

Journal of Clinical Child and Adolescent Psychology. 2016 May;45:348-60.
DOES 5HTTLPR GENOTYPE MODERATE THE ASSOCIATION OF FAMILY ENVIRONMENT WITH CHILD ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMATOLOGY?
Elmore AL, Nigg JT, Friderici KH, et al.
Problematic family dynamics are common among youth with attention-deficit hyperactivity disorder (ADHD). Multiple mechanisms, including diathesis-stress (vulnerability) and differential susceptibility Gene × Environment interaction effects (G × E), have been proposed to account for this association. G × E effects for ADHD were examined via interactions between a genetic marker hypothesized to influence sensitivity to

the environment (the promoter polymorphism of the serotonin transporter gene -5HTTLPR) and family conflict and cohesion in predicting ADHD symptoms. There were 498 youth ages 6-17 years (251 ADHD, 213 non-ADHD) and their parents who completed a multistage, multi-informant assessment (including parent and youth reports on the Family Environment Scale), and saliva sample collection for genotyping. Linear regression analyses examined interactions between 5HTTLPR genotype and the Family Environment Scale scales of conflict and cohesion reported by parent and child. Criteria laid out by Roisman et al. (2012) were applied to evaluate diathesis stress versus differential susceptibility G × E mechanisms. Results demonstrated interactions between 5HTTLPR genotype and both conflict and cohesion in predicting inattention but not hyperactivity-impulsivity. Both interactions were highly consistent with differential susceptibility models of G × E effects. 5HTTLPR genotype appeared to moderate the relationship between family conflict/cohesion and inattentive symptoms. Interactions highlight the role of 5HTTLPR genotype as a potential marker of environmental sensitivity and provide support for differential susceptibility models of G × E effects for ADHD

……..

J Dev Behav Pediatr. 2016 Apr;37:196-204.

ADOLESCENT PERCEPTIONS OF OUTGROWING CHILDHOOD ATTENTION-DEFICIT HYPERACTIVITY DISORDER: RELATIONSHIP TO SYMPTOMS AND QUALITY OF LIFE.

Anixt JS, Vaughn AJ, Powe NR, et al.

Objective: Parental and self-perceptions about outgrowing attention-deficit hyperactivity disorder (ADHD) likely impact treatment decisions; however, little is known about these perceptions. The aim of this study was to assess adolescent and parent perceptions of outgrowing childhood ADHD and evaluate how these perceptions relate to ADHD symptoms and quality of life (QoL).

Method: Cross-sectional survey of adolescents (13-18 years) with a childhood diagnosis of ADHD and their parents. Participants were contacted by mail and completed questionnaires about: perceptions of outgrowing ADHD, current ADHD symptoms (the Conners' Scales), and QoL (PedsQL). ANCOVAs were conducted to assess the relationship between the perception of outgrowing ADHD and: (1) current ADHD symptoms and (2) QoL, controlling for co-morbidities and medication use.

Results: 115 adolescent-parent dyads were enrolled. Mean age was 15.5 ± 1.7 years, 73% were male, and 63% were taking ADHD medication. Only 16% of adolescents and 9% of parents reported outgrowing ADHD, with little correlation between parent and adolescent responses (kappa 0.3). Adolescents who reported Yes or Don't Know to outgrowing ADHD, compared to those who reported No, had lower scores on the inattention (IA) and hyperactivity (H) scales of both parent report and adolescent self-report Conners' scales and higher scores on the adolescent self-report PedsQL.

Conclusion: A majority of adolescents do not endorse outgrowing their ADHD diagnosis, but those that do demonstrate fewer ADHD symptoms and better QoL than those who don't, suggesting that adolescents have insight about their level of impairment and should have a valued role in making treatment decisions

……..

J Dev Behav Pediatr. 2016 Apr;37:254-56.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, BEHAVIOR REGULATION AND VIRTUAL SCHOOL SUPPORT.

Wallace C, Ievers-Landis CE, Scherer C, et al.

CASE: Tony is a 6-year-old multiracial boy diagnosed as having attention-deficit/hyperactivity disorders combined type who is followed in your primary care practice and has started on a stimulant medication. Tony continues to have difficulty with emotion regulation and impulse control both at home and at school. He was asked to leave his private school soon after beginning first grade because of physical fighting, emotional outbursts, and arguing with teachers. His mother made the decision to enroll Tony in online virtual schooling for the remainder of the academic year, with the plan to transition back to traditional school for the next academic year. They have enrolled in a program that offers lessons online and sends materials to the home

for the child to use to complete certain types of assignments (e.g., science experiments). Virtual schools are different from traditional home schooling because children receive their instruction from teachers online with parental assistance as opposed to parents being responsible for teaching all material. Tony's mother comes to your practice requesting assistance with setting up an appropriate school environment for her son at home, where she can monitor and support his academic progress. Tony is a bright child, with an Intelligence Quotient in the superior range. He has advanced academic skills, but he becomes dysregulated if he is told he is wrong or that he has answered a question incorrectly. For example, if he answered a question incorrectly in class, he would become verbally abusive toward his teacher and often have temper tantrums. This challenging behavior occurred daily at school and was one of the factors leading to his expulsion. The behavior had predated the introduction of stimulant medication and had remained consistent after he began medication. Tony's parents are highly educated, and both parents hold professional jobs with steady income. His parents have good command of typical behavior management strategies such as the use of rewards, time out, and behavioral contingencies to target noncompliance and temper tantrums. However, Tony's difficulty identifying and regulating his emotions leads to emotional outbursts and shutdowns that have thus far been unresponsive to standard behavior management techniques. Tony continued to have outbursts even when the behavior was ignored. His mother is concerned not only about his learning during the coming year but also about his social relationships and the family dynamic. Tony's outbursts cause significant disruption in the home and are a source of tension among parents and siblings. His mother is asking for advice on how to support his behavior better at home now that he will be spending his entire day there. How might you assist this child and his mother by helping to integrate therapeutic goals into the academic environment?

……..

J Nerv Ment Dis. 2016 Apr;204:287-90.

RELIABILITY AND VALIDITY OF PROTOTYPE DIAGNOSIS FOR ADOLESCENT PSYCHOPATHOLOGY.

Haggerty G, Zodan J, Mehra A, et al.

The current study investigated the interrater reliability and validity of prototype ratings of 5 common adolescent psychiatric disorders: attention-deficit/hyperactivity disorder, conduct disorder, major depressive disorder, generalized anxiety disorder, and posttraumatic stress disorder. One hundred fifty-seven adolescent inpatient participants consented to participate in this study. We compared ratings from 2 inpatient clinicians, blinded to each other's ratings and patient measures, after their separate initial diagnostic interview to assess interrater reliability. Prototype ratings completed by clinicians after their initial diagnostic interview with adolescent inpatients and outpatients were compared with patient-reported behavior problems and parents' report of their child's behavioral problems. Prototype ratings demonstrated good interrater reliability. Clinicians' prototype ratings showed predicted relationships with patient-reported behavior problems and parent-reported behavior problems. Prototype matching seems to be a possible alternative for psychiatric diagnosis. Prototype ratings showed good interrater reliability based on clinicians unique experiences with the patient (as opposed to video-/audio-recorded material) with no training

……..

J Neural Transm. 2016;1-16.

TRANSCRANIAL DIRECT CURRENT STIMULATION IN CHILDREN AND ADOLESCENTS: A COMPREHENSIVE REVIEW.

Palm U, Segmiller FM, Epple AN, et al.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that has shown promising results in various neuropsychiatric disorders in adults. This review addresses the therapeutic use of tDCS in children and adolescents including safety, ethical, and legal considerations. There are several studies addressing the dosage of tDCS in children and adolescents by computational modeling of electric fields in the pediatric brain. Results suggest halving the amperage used in adults to obtain the same peak electric fields, however, there are some studies reporting on the safe application of tDCS with standard adult parameters in children (2 mA; 20-30 min). There are several randomized placebo controlled trials suggesting

beneficial effects of tDCS for the treatment of cerebral palsy. For dystonia there are mixed data. Some studies suggest efficacy of tDCS for the treatment of refractory epilepsy, and for the improvement of attention deficit/hyperactivity disorder and autism. Interestingly, there is a lack of data for the treatment of childhood and adolescent psychiatric disorders, i.e., childhood onset schizophrenia and affective disorders. Overall, tDCS seems to be safe in pediatric population. More studies are needed to confirm the preliminary encouraging results; however, ethical deliberation has to be weighed carefully for every single case

……..

J Neural Transm. 2016;1-10.

THE ROLE OF ASTN2 VARIANTS IN CHILDHOOD AND ADULT ADHD, COMORBID DISORDERS AND ASSOCIATED PERSONALITY TRAITS.

Freitag CM, Lempp T, Nguyen TT, et al.

Previous linkage and genome wide association (GWA) studies in ADHD indicated astrotactin 2 (ASTN2) as a candidate gene for attention-deficit/hyperactivity disorder (ADHD). ASTN2 plays a key role in glial-guided neuronal migration. To investigate whether common variants in ASTN2 contribute to ADHD disorder risk, we tested 63 SNPs spanning ASTN2 for association with ADHD and specific comorbid disorders in two samples: 171 families of children with ADHD and their parents (N = 592), and an adult sample comprising 604 adult ADHD cases and 974 controls. The C-allele of rs12376789 in ASTN2 nominally increased the risk for ADHD in the trio sample (p = 0.025). This was not observed in the adult case-control sample alone, but retained in the combined sample (nominal p = 0.030). Several other SNPs showed nominally significant association with comorbid disorders, especially anxiety disorder, in the childhood and adult ADHD samples. Some ASTN2 variants were nominally associated with personality traits in the adult ADHD sample and overlapped with risk alleles for comorbid disorders in childhood. None of the findings survived correction for multiple testing, thus, results do not support a major role of common variants in ASTN2 in the pathogenesis of ADHD, its comorbid disorders or ADHD associated personality traits

……..

J Paediatr Child Health. 2016;52:410-16.

THE DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN AUSTRALIAN CHILDREN: CURRENT PAEDIATRIC PRACTICE AND PARENT PERSPECTIVE.

Efron D, Sciberras E, Hiscock H, et al.

Aims In a sample of newly diagnosed children with attention-deficit/hyperactivity disorder (ADHD), the aims were to examine (1) paediatrician assessment and management practices; (2) previous assessments and interventions; (3) correspondence between parent-report and paediatrician identification of comorbidities; and (4) parent agreement with diagnosis of ADHD.

Methods Design: cross-sectional, multi-site practice audit with questionnaires completed by paediatricians and parents at the point of ADHD diagnosis.

Setting: private/public paediatric practices in Western Australia and Victoria, Australia.

Main outcome measures: **paediatricians**: elements of assessment and management were indicated on a study-designed data form.

Parents: ADHD symptoms and comorbidities were measured using the Conners 3 ADHD Index and Strengths and Difficulties Questionnaire, respectively. Sleep problems, previous assessments and interventions, and agreement with ADHD diagnosis were measured by questionnaire.

Results Twenty-four paediatricians participated, providing data on 137 patients (77% men, mean age 8.1 years). Parent and teacher questionnaires were used in 88% and 85% of assessments, respectively. Medication was prescribed in 75% of cases. Comorbidities were commonly diagnosed (70%); however, the proportion of patients identified by paediatricians with internalising problems (18%), externalising problems (15%) and sleep problems (4%) was less than by parent report (51%, 66% and 39%). One in seven parents did not agree with the diagnosis of ADHD.

Conclusions Australian paediatric practice in relation to ADHD assessment is generally consistent with best practice guidelines; however, improvements are needed in relation to the routine use of questionnaires and the identification of comorbidities. A proportion of parents do not agree with the diagnosis of ADHD made by their paediatrician

……..

J Am Acad Child Adolesc Psychiatry. 2016.

NEUROFEEDBACK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: META-ANALYSIS OF CLINICAL AND NEUROPSYCHOLOGICAL OUTCOMES FROM RANDOMIZED CONTROLLED TRIALS .

Cortese S, Ferrin M, Brandeis D, et al.

Objective: We performed meta-analyses of randomized controlled trials to examine the effects of neurofeedback on attention-deficit/hyperactivity disorder (ADHD) symptoms and neuropsychological deficits in children and adolescents with ADHD.

Method: We searched PubMed, Ovid, Web of Science, ERIC, and CINAHAL through August 30, 2015. Random-effects models were employed. Studies were evaluated with the Cochrane Risk of Bias tool.

Results: We included 13 trials (520 participants with ADHD). Significant effects were found on ADHD symptoms rated by assessors most proximal to the treatment setting, that is, the least blinded outcome measure (standardized mean difference [SMD]: ADHD total symptoms = 0.35, 95% CI = 0.11-0.59; inattention = 0.36, 95% CI = 0.09-0.63; hyperactivity/impulsivity = 0.26, 95% CI = 0.08-0.43). Effects were not significant when probably blinded ratings were the outcome or in trials with active/sham controls. Results were similar when only frequency band training trials, the most common neurofeedback approach, were analyzed separately. Effects on laboratory measures of inhibition (SMD = 0.30, 95% CI = -0.10 to 0.70) and attention (SMD = 0.13, 95% CI = -0.09 to 0.36) were not significant. Only 4 studies directly assessed whether learning occurred after neurofeedback training. The risk of bias was unclear for many Cochrane Risk of Bias domains in most studies.

Conclusion: Evidence from well-controlled trials with probably blinded outcomes currently fails to support neurofeedback as an effective treatment for ADHD. Future efforts should focus on implementing standard neurofeedback protocols, ensuring learning, and optimizing clinically relevant transfer

……..

Neuropsychiatr Dis Treat. 2016;12:969-81.

WHITE MATTER ALTERATIONS RELATED TO ATTENTION-DEFICIT HYPERACTIVITY DISORDER AND COMT VAL158MET POLYMORPHISM: CHILDREN WITH VALINE HOMOZYGOTE ATTENTION-DEFICIT HYPERACTIVITY DISORDER HAVE ALTERED WHITE MATTER CONNECTIVITY IN THE RIGHT CINGULUM (CINGULATE GYRUS).

Basay BK, Buber A, Basay O, et al.

Introduction: In this article, the COMT gene val158met polymorphism and attention-deficit hyperactivity disorder (ADHD)-related differences in diffusion-tensor-imaging-measured white matter (WM) structure in children with ADHD and controls were investigated.

Patients and methods: A total of 71 children diagnosed with ADHD and 24 controls aged 8ΓÇô15 years were recruited. Using diffusion tensor imaging, COMT polymorphism and ADHD-related WM alterations were investigated, and any interaction effect between the COMT polymorphism and ADHD was also examined. The effects of age, sex, and estimated total IQ were controlled by multivariate analysis of covariance (MANCOVA).

Results: First, an interaction between the COMT val158met polymorphism and ADHD in the right (R) cingulum (cingulate gyrus) (CGC) was found. According to this, valine (val) homozygote ADHD-diagnosed children had significantly lower fractional anisotropy (FA) and higher radial diffusivity (RD) in the R-CGC than ADHD-diagnosed methionine (met) carriers, and val homozygote controls had higher FA and lower RD in the R-CGC than val homozygote ADHD patients. Second, met carriers had higher FA and axial diffusivity in the left (L)-uncinate fasciculus and lower RD in the L-posterior corona radiata and L-posterior thalamic

radiation (include optic radiation) than the val homozygotes, independent of ADHD diagnosis. Third, children with ADHD had lower FA in the L-CGC and R-retrolenticular part of the internal capsule than the controls, independent of the COMT polymorphism.
Conclusion: Significant differences reported here may be evidence that the COMT gene val158met polymorphism variants, as well as ADHD, could affect brain development. ADHD and the COMT polymorphism might be interactively affecting WM development in the R-CGC to alter the WM connectivity in children with val homozygote ADHD

……..

Neuropsychiatr Dis Treat. 2016;12:1085-101.
GUANFACINE EXTENDED RELEASE FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: EFFICACY FOLLOWING PRIOR METHYLPHENIDATE TREATMENT.
Huss M, Sikirica V, Hervas A, et al.
Guanfacine extended release (GXR) and atomoxetine (ATX) are nonstimulant treatments for attention-deficit/hyperactivity disorder (ADHD). As nonstimulant treatments are often used after stimulants in ADHD, GXR was assessed relative to prior stimulant treatment in a randomized controlled trial (RCT), in which ATX was included as a reference arm, and in the open-label phase of a randomized-withdrawal study (RWS). Participants were 6-17 years old with ADHD Rating Scale version IV (ADHD-RS-IV) scores ≥32 and Clinical Global Impressions - Severity scores ≥4. RCT participants received dose-optimized GXR (1-7 mg/day), ATX (10-100 mg/day), or placebo for 10-13 weeks. RWS participants received dose-optimized GXR (1-7 mg/day) for 13 weeks. Participants' last stimulant medication prior to enrolment, and reasons for stopping this medication, were collected at baseline. Change from baseline ADHD-RS-IV score and the proportion of responders were assessed by prior stimulant exposure. Of 163 RCT and 296 RWS participants who had previously received stimulant treatment, 142 and 224, respectively, had received methylphenidate (MPH); due to the low number of participants and the heterogeneity of non-MPH treatments, we only report data for prior MPH treatment. The most frequent reasons for stopping MPH were lack of effectiveness or side effects. Placebo-adjusted ADHD-RS-IV changes from baseline were significant in participants receiving GXR (prior MPH, -9.8, P<0.001, effect size [ES] 0.85; stimulant-naïve, -7.6, P<0.001, ES 0.65). In ATX-treated participants, significant placebo-adjusted differences were seen in stimulant-naïve (-5.0, P=0.022, ES 0.43) but not prior MPH-treated (-1.8, P>0.05, ES 0.15) participants. More participants met responder criteria with GXR versus placebo, regardless of prior treatment. GXR response was unaffected by prior stimulant treatment; ATX produced improvement only in stimulant-naïve participants relative to placebo. These findings may be relevant to clinical decision-making regarding sequencing of ADHD treatments

……..

Psychiatry Clin Neurosci. 2016.
FUNCTIONAL CONSEQUENCES OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER ON CHILDREN AND THEIR FAMILIES.
Usami M.
Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with core symptoms that include hyperactivity, impulsiveness, and inattention, and it is the most common psychiatric disorder among children and adolescents. These core symptoms are continuously recognized throughout the day from childhood to adulthood. Furthermore, children with ADHD from childhood to adulthood might also have various comorbid psychiatric disorders. Recently, bipolar disorder and disruptive mood dysregulation disorder, a new clinical issue, have been discussed as comorbid disorders or differential disorders associated with ADHD. Furthermore, comorbid disorders of ADHD are related to quality of life and family burden. Children with ADHD have poorer long-term outcomes than controls with respect to: academic achievement and attainment, occupational rank and job performance, risky sexual practices and early unwanted pregnancies, substance use, relationship difficulties, marital problems, traffic violations, and car accidents. Irritability of children with ADHD has been a key symptom that clinicians and researchers have used to

evaluate the developmental condition of children with ADHD. ADHD is sometimes a chronic disorder that occurs over a long period, increasing the family burden of these children (including health-care costs), which will increase with aging for unremitted children with ADHD. Therefore, clinicians should evaluate not only the mental condition of the child but also the family burden. Children with ADHD should be treated during childhood to reduce their clinical symptoms and family burden

……..

Psychiatry Res Neuroimaging. 2016.

ALTERED STRUCTURAL CONNECTIVITY IS RELATED TO ATTENTION DEFICIT/HYPERACTIVITY SUBTYPES: A DTI STUDY.

Ercan ES, Suren S, Bacanli A, et al.

This study aimed to provide novel insights into the white matter (WM) microstructural properties of Attention Deficit/Hyperactivity Disorder (ADHD) subtypes by recruiting a relatively large sample of stimulant-na+»ve children and adolescents who had no comorbidity other than Oppositional Defiant Disorder and were homogenous according to the DAT1 gene polymorphism. A sample of 72 ADHD subjects and 24 controls aged 8-15 years were enrolled in the study. We applied tract-based spatial statistics to the DTI measures for obtaining fractional anisotropy (FA) and axial, radial diffusivity (AD, RD) measures to explore ADHD type-related differences in WM for the whole brain. Comparing ADHD-Combined group (ADHD-C) with the ADHD predominantly inattentive group (ADHD-I) we detected increased RD in several bilateral brain area and increased AD mostly in left side of the brain, including the body and splenium of the corpus callosum; the anterior and posteriors limbs of the internal capsule; the superior, anterior and posterior corona radiata; the posterior thalamic radiation; and the superior longitudinal fasciculus. Likewise, mostly in the overlapping brain areas, the ADHD-C group presented increased AD values than ADHD-RI. Significant differences among ADHD types could be a preliminary evidence that they have distinct microstructural properties. There were no significant differences in diffusivity between controls and both the ADHD group as whole or any ADHD subgroups

……..

Psychol Med. 2016 Apr;46:1301-09.

CROSS-GENERATIONAL TRANSMISSION FROM DRUG ABUSE IN PARENTS TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Kendler KS, Ohlsson H, Sundquist K, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) predisposes to drug abuse (DA) and twin studies suggest shared genetic effects. We here seek to determine, using adoption and adoption-like samples, the magnitude of the cross-generational transmission from DA in parents to ADHD in their children and clarify the degree to which this arises from genetic v. rearing effects.

Method: We ascertained ADHD and DA from multiple Swedish registries. Statistical analysis was performed by Cox and path models.

Results: Risk for ADHD was significantly and similarly increased in the offspring of biological mothers and fathers with DA who did v. did not rear their offspring. Risk for ADHD was not elevated in the offspring of adoptive or step-parents with DA.

Conclusions: Cross-generational transmission was observed from DA in parents to ADHD in their children. An analysis of adoptive and adoptive-like parent' offspring relationships suggested that this transmission results from genetic and not from rearing effects

……..

Res Dev Disabil. 2016;55:268-78.

PSYCHOMETRIC PROPERTIES OF THE JAPANESE ADHD-RS IN PRESCHOOL CHILDREN.

Takayanagi N, Yoshida S, Yasuda S, et al.

Background: Children with ADHD show multiple difficulties in their lives. Its early detection is important to provide timely intervention.

Aims: To evaluate the psychometric properties of the Japanese version of the home and school form of the ADHD-Rating Scale-IV (P- and T-ADHD-RS) for screening five-year-olds with ADHD.

Methods: The parents and teachers of 838 children (452 boys, 386 girls; including 28 boys, 18 girls diagnosed ADHD) completed the ADHD-RS and the Strengths and Difficulties Questionnaire in a community health check-up.

Results: The P- and T-ADHD-RS confirmed the two-factor model (Inattention and Hyperactivity-Impulsivity) and internal consistencies (CFI=0.968, 980; RMSEA=0.049, 0.055; SRMR=0.030, 0.024; α=0.86-.93). Japanese boys and girls scored significantly lower in all scales of the P- and T-ADHD-RS (d=0.65-1.14, 0.36-0.59) than US children. The P-ADHD-RS showed higher accuracy in area under the curve (AUC), sensitivity, and positive predictive value (PPV) than the T-ADHD-RS (AUC=0.955, 0.692; sensitivity=89.13%, 30.23%; PPV=46.59%, 16.05%).

Implications: The P-ADHD-RS shows good reliability and validity for screening children with possible ADHD in a community. Longitudinal studies are needed to examine its predictive validity of adaptation in their lives at school

……..

Social Development. 2016 May;25:322-39.

REJECTION REACTIVITY, EXECUTIVE FUNCTION SKILLS, AND SOCIAL ADJUSTMENT PROBLEMS OF INATTENTIVE AND HYPERACTIVE KINDERGARTENERS.

Motamedi M, Bierman K, Huangâ€ Pollock CL.

This study examined emotional reactivity to rejection and executive function (EF) skills as potential mediators of the social behavior problems of inattentive and hyperactive kindergarteners. Participants included 171 children, including 107 with clinical levels of ADHD symptoms, 23 with sub-clinical levels of ADHD symptoms, and 41 typically-developing children (63% male; 73% Caucasian, 11% African American, 4% Latino/Hispanic, 1% Asian, and 11% multiracial; M_{age} = 5.2 years). Inattention (but not hyperactivity) was uniquely associated with poor EF, social withdrawal, and aggression. In structural equation models, EF skills mediated the associations between inattention and both aggression and social withdrawal. Hyperactivity (but not inattention) was uniquely associated with rejection reactivity and each contributed uniquely to aggression. Findings suggest that difficulties with emotion regulation may warrant more attention in early interventions planned for children with high levels of ADHD symptoms

……..

The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie. 2016 May;61:283-90.

APGAR SCORES ARE ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOM SEVERITY.

Grizenko N, Eberle ML, Fortier ME, et al.

OBJECTIVE: Adverse events during pregnancy and delivery have been linked to attention-deficit/hyperactivity disorder (ADHD). Previous studies have investigated Apgar scores, which assess the physical condition of newborns, in relation to the risk of developing ADHD. We propose to go one step further and examine if Apgar scores are associated with ADHD symptom severity in children already diagnosed with ADHD.

METHOD: ADHD symptoms severity, while off medication, was compared in 2 groups of children with ADHD: those with low (≤6, n = 52) and those with higher (≥7, n = 400) Apgar scores sequentially recruited from the ADHD clinic.

RESULTS: Children with low Apgar at 1 minute after birth had more severe symptoms as assessed by the externalizing scale of the Child Behaviour Checklist, the Conners' Global Index for Parents, and the DSM-IV hyperactivity symptoms count (P = 0.02, <0.01, <0.01, respectively).
CONCLUSION: Low 1-minute Apgar scores are associated with a significant increase in ADHD symptom severity. These findings underline the importance of appropriate pregnancy and perinatal care

……..

Transl Psychiatry. 2016;6.

ADOLESCENT BEHAVIORAL AND NEURAL REWARD SENSITIVITY: A TEST OF THE DIFFERENTIAL SUSCEPTIBILITY THEORY.

Richards JS, Arias V+ísquez A, Von Rhein D, et al.

Little is known about the causes of individual differences in reward sensitivity. We investigated gene-environment interactions (GxE) on behavioral and neural measures of reward sensitivity, in light of the differential susceptibility theory. This theory states that individuals carrying plasticity gene variants will be more disadvantaged in negative, but more advantaged in positive environments. Reward responses were assessed during a monetary incentive delay task in 178 participants with and 265 without attention-deficit/hyperactivity disorder (ADHD), from N=261 families. We examined interactions between variants in candidate plasticity genes (DAT1, 5-HTT and DRD4) and social environments (maternal expressed emotion and peer affiliation). HTTLPR short allele carriers showed the least reward speeding when exposed to high positive peer affiliation, but the most when faced with low positive peer affiliation or low maternal warmth. DAT1 10-repeat homozygotes displayed similar GxE patterns toward maternal warmth on general task performance. At the neural level, DRD4 7-repeat carriers showed the least striatal activation during reward anticipation when exposed to high maternal warmth, but the most when exposed to low warmth. Findings were independent of ADHD severity. Our results partially confirm the differential susceptibility theory and indicate the importance of positive social environments in reward sensitivity and general task performance for persons with specific genotypes

……..

World J Biol Psychiatry. 2016;1-14.

TESTING DIFFERENTIAL SUSCEPTIBILITY: PLASTICITY GENES, THE SOCIAL ENVIRONMENT, AND THEIR INTERPLAY IN ADOLESCENT RESPONSE INHIBITION.

Richards JS, Arias V+ísquez A, van Rooij D, et al.

OBJECTIVES: Impaired inhibitory control is a key feature of attention-deficit/hyperactivity disorder (ADHD). We investigated gene-environment interaction (GxE) as a possible contributing factor to response inhibition variation in context of the differential susceptibility theory. This states individuals carrying plasticity gene variants will be more disadvantaged in negative, but more advantaged in positive environments.
METHODS: Behavioural and neural measures of response inhibition were assessed during a Stop-signal task in participants with (N = 197) and without (N = 295) ADHD, from N = 278 families (age M = 17.18, SD =3.65). We examined GxE between candidate plasticity genes (DAT1, 5-HTT, DRD4) and social environments (maternal expressed emotion, peer affiliation).
RESULTS: A DRD4 × Positive peer affiliation interaction was found on the right fusiform gyrus (rFG) activation during successful inhibition. Further, 5-HTT short allele carriers showed increased rFG activation during failed inhibitions. Maternal warmth and positive peer affiliation were positively associated with right inferior frontal cortex activation during successful inhibition. Deviant peer affiliation was positively related to the error rate

CONCLUSIONS: While a pattern of differential genetic susceptibility was found, more clarity on the role of the FG during response inhibition is warranted before firm conclusions can be made. Positive and negative social environments were related to inhibitory control. This extends previous research emphasizing adverse environments

……..

Yeni Symp. 2015;53:2-8.

THE RELATION BETWEEN AGRESSION, EMPATHY AND 2D:4D RATIO IN MALE CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER.

Özdemir Demirci, Didem Behice Öztop.

Background: Although Attention-Deficit and Hyperactivity Disorder (ADHD) is known as a neurodevelopmental disorder with cognitive and executive disfunctons, social disfunctions are seen in children and adolescents with ADHD. Lower 2D: 4D finger ratio is associated with ADHD. In this study, we aimed to determinate the relationsihp between aggression, empathy and 2D:4D ratio, in male children and adolescents with ADHD.

Methods: This study was conducted in Department of Child and Adolescent Pscyhiatry. Study population consists of 40 ADHD patients without any other psychiatric disorder between 8-15 age interval. Control group was consist of 40 healthy, age matched, voluntarily children and adolescents. Patients and control groups filled Buss–Perry Aggression Questionnaire, KA-Sİ Empathic Tendency Scale for Children and Adolescents. 2D:4D ratios were measured in both of control and ADHD groups.

Results: In our study, when compared with control group, ADHD group aggression scores were significantly higher, empathy forms scores were statistically lower. ADHD group right hand 2D:4D ratios were statistically lower compared to controls and also lower 2D:4D ratios had association with high agression scores.

Conclusions: High agression and lower empathy skills which were effecting social disfunctions are seen in children and adolescents with ADHD. Also aggression is associated with low 2D:4D ratios. Further researchs with a large sample are needed in this field

……..

Z Kinder- Jugendpsychiatr Psychother. 2016;44:127-37.

WISC-IV PERFORMANCES OF YOUNG MALE SUBJECTS WITH AD(H)D, THE BENEFITS OF APPLYING COGNITIVE PROFILE ANALYSIS TO DIAGNOSTICS.

Walg M, Bowi U, El-Wahsch D.

Objective: Studies suggest that children and adolescents suffering from AD(H)D show a specific WISC-IV profile in comparison to subjects of the same age group without any mental disorder. The present study compares the cognitive profiles of male subjects with AD(H)D to those of a clinical control group. The benefits of applying an ADHD specific cognitive profile analysis to differential diagnostics are analyzed.

Method: The WISC-IV profiles of 50 male subjects with AD(H)D (8 to 15 years) were compared with the profiles of 54 male children and adolescents (7 to 16 years) with other mental disorders. In addition, subgroup differences within the AD(H)D group were investigated.

Results: Subjects with AD(H)D showed a significant lower processing speed than the control group. Within the AD(H)D group, patients with ADD showed the lowest speed index. There were no group differences in total IQ and other WISC-IV indexes.

Conclusions: A WISC-IV profile analysis is not a suitable instrument to certainly confirm or exclude an AD(H)D diagnosis. Nevertheless, the results of the present study speak for considering the WISC-IV profile in the diagnosis of AD(H)D as it increases the sensitivity of the clinical diagnostic process and provides useful indicators for differential diagnosis

……..

International Journal of Psychophysiology 104 (2016) 44–52

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders

Giuseppe Augusto Chiarenza [a,b,*,1], Robert Chabot [c], Robert Isenhart [c], Luciano Montaldi [a,b], Marco Paolo Chiarenza [b], Maria Grazia Lo Torto [a,b], Leslie S. Prichep [c]

[a] Child and Adolescent Neuropsychiatry Dept., Rho Hospital, Milan, Italy
[b] International Center Learning, Attention and Hyperactivity Disorders (CIDAAI), Milan, Italy
[c] Brain Research Laboratories, Dept. Psychiatry, New York University, NY, United States

ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form 18 April 2016
Accepted 19 April 2016
Available online 20 April 2016

Keywords:
ADHD
Atomoxetine
Responders
Non-responders
QEEG
VARETA

ABSTRACT

Objective: The aim of our study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are responders and non-responders to long-term treatment with Atomoxetine at baseline and after 6 and 12 months of treatment. Patients with attention deficit hyperactivity disorder (ADHD) received atomoxetine titrated, over 7 days, from 0.5 to 1.2 mg/kg/day. QEEG and Swanson, Nolan, and Pelham–IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy.
Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked ear-lobes. Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values.
Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values.
Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity that interferes with functioning or development and causes impairment in multiple settings: home, school and work. Population surveys suggest that in most cultures ADHD occurs in about 5% of children (Szatmari, 1992.) In general ADHD is more frequent in males than females, with an approximate 2:1 ratio in children. Its course is chronic in 30–50% of the affected children (American Psychiatry Association, DSM-V, 2013).

Extensive neuroimaging studies (QEEG, VARETA, ERPs, PET, fMRI) have demonstrated that during the execution of cognitive tasks, children with ADHD show a pattern of hypoactivation of the prefrontal lobes and of the striatal regions (di Michele et al., 2005; Lou et al., 1984, 1989; Rubia et al., 1999, 2001, 2011; Hastings and Barkley, 1978; Klorman, 1992; Taylor, 1986). Neuropsychological studies have also shown the impairment of several executive functions (sustained, focused and divided attention, working memory, response inhibition, time perception, flexibility, programming and delayed reward response). These executive functions are located in the frontal and prefrontal lobes and in particular in the dorso-lateral prefrontal cortex (Barkley, 1977a, 1997b; Barkley et al., 1992; Goodyear and Hynd, 1992). Neuropharmacological studies both in humans and animals have demonstrated that these executive functions are mediated by noradrenergic and dopaminergic neurotransmitters, adding more evidence of a probable deficit of these circuits in ADHD (Arnsten and Li, 2005; Hunt et al., 1988; Rapaport and Zametkin, 1988; Shaywitz

* Corresponding author at: CIDAAI, Centro Internazionale dei Disturbi di Apprendimento, Attenzione e Iperattività, via Edolo 46, 20163 Milano, Italy.
E-mail address: giuseppe.chiarenza@fastwebnet.it (G.A. Chiarenza).
[1] This research was partially supported by an unrestricted grant of Ely Lilly.

http://dx.doi.org/10.1016/j.ijpsycho.2016.04.004
0167-8760/

and Shaywitz, 1984; Shaywitz et al., 1983; Zametkin and Rapoport, 1986). Furthermore, Castellanos et al. (1994, 1996) have shown that in ADHD adults there is an evident reduction of the volume of some cerebral areas, including the right prefrontal areas, the nucleus caudatus, the globus pallidus and the cerebellum. It has been suggested that ADHD children show a maturational lag in the development of these cortical regions and their interconnections (Barry et al., 2003, 2009b). This maturational lag has been associated with elevated slow wave activity and deficiencies of fast wave. Elevated high amplitude theta with deficiencies of beta activity was associated with hypoarousal and excess beta activity was tentatively interpreted as hyperarousal. This profile has been found primarily in children with the combined type of ADHD (Chabot et al., 1999; Clarke et al., 2001d). All these studies used very restrictive ADHD inclusion criteria, with children with comorbidities being excluded (Clarke et al., 1998, 2001a, 2001c, 2001d). However, in line with recent works that links arousal abnormalities with global alpha activity (Barry et al., 2009b), the hyperarousal hypothesis as the underlying CNS abnormality was not confirmed (Clarke et al., 2011). On the other hand, Jaworska et al. (2013) examining QEEG relationships between anger and non-angry adults with ADHD noted increased beta 1 associated with anger and it was interpreted as modest resting cortical hyperarousal.

Recent evidence indicates that quantitative Electroencephalogram (QEEG) is a powerful tool in pharmaco-EEG applications. The identification of treatment responsive QEEG subtypes have been described in depression (Leuchter et al., 2009a, 2009b), obsessive compulsive disorder (Prichep et al., 1993; Hansen et al., 2003) and schizophrenia (John et al., 2007), suggesting that understanding of the underlying neurophysiology of the patient can contribute significantly to treatment optimization. QEEG has been shown to distinguish between ADHD responders (R) and non-responders (NR) to stimulant medication with sensitivity levels that fell between 68.7% and 81% with response to stimulants related to ADHD subtypes based upon QEEG profile differences (di Michele et al., 2005; Ogrim et al., 2014). Barry et al. (2007, 2009a) investigated the effects of a single dose of a selective inhibitor of norepinephrine transporters (SNRI), atomoxetine (ATX), on the electroencephalogram (EEG) and performance of children with ADHD. After 1 h ATX produced significant global increases in absolute and relative beta, with several topographic changes in other bands. This was accompanied by a significant reduction in omission errors on a Continuous Performance Task. The authors concluded that SNRIs can produce substantial normalization of the ADHD QEEG profile, together with behavioural performance improvements.

It has been previously shown that atomoxetine increased extracellular concentrations of norepinephrine (NE) and dopamine (DA) in prefrontal cortex (Viggiano et al., 2004). Furthermore, chronic administration of atomoxetine for 21 days also increased NA and DA, but not 5-HT, levels in the prefrontal cortex. Acute and chronic atomoxetine increased the expression of c-Fos, a neuronal activity marker in the prefrontal cortex, but not in the striatum. These results suggest that acute and chronic administration of ATX selectively activate the prefrontal catecholamine systems in mice (Koda et al., 2010).

At the moment, in Italy, the drugs available and currently being used for the pharmacotherapy of ADHD are: methylphenidate (MPH) and atomoxetine. We are not aware of studies that measured the effect on the QEEG of long-term treatment of ATX in children with ADHD. In the light of personalized medicine and in order to reduce this gap, the aim of this study is to examine whether QEEG subtypes are related to treatment response to Atomoxetine in ADHD. We hypothesize: 1. at baseline both R and NR will have QEEG absolute power findings consistent with those reported in the literature to include increased power in delta, theta or alpha especially in frontal and anterior temporal regions (Chabot et al., 2001; Barry et al., 2003, 2009b); 2. absolute power increases at baseline will be greater in NR than in R especially in the delta and theta frequency bands; 3. increased absolute power findings in R will decrease as a function of treatment with atomoxetine, whereas, increased absolute power in NR will not change as a function of treatment with atomoxetine; 4. QEEG source localization using VARETA will reveal more widespread abnormal findings in NR than R when compared to the normal population of children; and 5. after 12 months of treatment with atomoxetine the R will show decreased abnormal activity, whereas, NR will remain at baseline levels.

2. Material and methods

This study was conducted by recruiting consecutive patients from the ADHD Centre of the Child and Adolescent Neuropsychiatry Department of Rho hospital. The following protocol was approved by the Ethical Committee of the hospital.

2.1. Clinical protocol

2.1.1. Inclusion criteria

Patients between 6 and 16 years of age were included in the study if they met all of the following criteria: patients met DSM-IV diagnostic criteria for ADHD (any subtype), scored at least 1.5 standard deviations above the age norm for their diagnostic subtype using published norms for the Swanson, Nolan, and Pelham–IV Questionnaire (SNAP-IV) (Swanson, 1992) subscale scores, and scored above one of the given cut-offs (T-score > 55) of the Conners subscale based on age and gender (Conners, 1997). Laboratory results, including serum chemistries, hematology, and urine analysis, showed no clinically significant abnormalities. An ECG was performed to exclude cardiac diseases at the baseline/screening visit.

2.1.2. Exclusion criteria

Patients were excluded from the study if they met any of the following criteria: presence of documented psychiatric disorders of the parents, weight <20 kg at baseline visit, a documented history of Bipolar type I or II disorder, history of psychosis or pervasive developmental disorder, seizure disorder, head injury with loss of consciousness or concussion, migraine, neurological/systemic medical disease (e.g.: lupus, diabetes) or with history of stroke or arterious-venus malformation or brain surgery. Comorbid non-psychotic psychiatric disorders (not more than two) were not an exclusion criteria but were documented. Functional comorbidities such as visual or auditory processing problems were not an exclusion criteria, but were documented with above IQ testing. Additional exclusion criteria were: serious suicidal risk as assessed by the investigator, history of alcohol or drug abuse within the past 3 months or currently using alcohol or drugs, current or past history of hypertension, narrow angle (Angle-Closure) glaucoma, uncontrolled hyperthyroidism or hypothyroidism, use of monoamine oxidase inhibitors, pregnant, breastfeeding young women and sexually active who do not use a medically acceptable method of contraception.

2.2. Phase 1 protocol

The study consisted of two phases. During phase 1 the screening and assessment were conducted according to the following protocol. Family history was obtained by clinical interviewing one or both parents. The patients were diagnosed as children or adolescents with ADHD according to the DSM-IV. At the first visit, after explaining to the patient and the parent/caretaker the purpose and the procedures of the study, informed consent was obtained from both parents, adolescents and children. Adequate time to consider the information was provided. In the assessment phase the following information was obtained: demographics, medical and psychiatric history, previous and concomitant medications, physical and neurological examination, laboratory samples, Electrocardiogram (ECG), QEEG, Amsterdam Neuropsychological Test (ANT, de Sonneville, 2014) a battery to test executive functions

and attention, SNAP-IV ADHD scale revised (SNAP IV - Swanson, 1992; Gaub and Carlson, 1997), Conners' rating scale-R for teachers (CTRS-S - Conners, 1997), Clinical Global Impressions–ADHD-Severity (CGI-ADHD-S, Guy, 1976). Children Depression Rating Scale, derived from the Hamilton Rating Scale for Depression (HAM-D), Paediatric Anxiety Rating Scale (PARS) were used to exclude mood and anxiety disorders. All patients were free of any medications according to the following guidelines for medications washouts: patients who were taking any medication that had a half-life >24 h had a washout equal to a minimum of 5 half-lives of the parent compound and any active metabolite of the parent compound prior to the second visit; patients who were taking any health food supplements that in the investigator's opinion had a central nervous system activity (for example, melatonin) had a washout equal to a minimum of 5 half-lives of that supplement prior to the second visit. If the half-life of the supplement was unknown, then the patients had a 28-day washout; no patient used monoamine oxidase inhibitors (MAOIs) during the 2 weeks (14 days) prior the first visit.

2.3. Phase 2 protocol

The second phase consisted of follow-up visits after the beginning of atomoxetine therapy, conducted at 3, 6 and 12 months. The tests administered in every subsequent visit were the SNAP-VI ADHD scale, CTRS-S, CGI, ANT and QEEG. We report only the QEEG and the SNAP results for brevity.

2.4. Atomoxetine treatment

The atomoxetine drug was titrated, in 7 days, from 0.5 mg/kg/day (dose ranging from 0.5 to 0.8 mg/kg/day) to the target dose of 1.2 mg/kg/day (range from 0.8 to 1.2 mg/kg/day). The total daily dose was administered once daily in the morning. If patients while taking atomoxetine at the target dose developed intolerable side effects, but were gaining a therapeutic benefit regarding their ADHD symptoms, the investigator administered atomoxetine in 2 divided doses (in the morning and in the evening). The dosing regimen was chosen on the basis of the research literature (Weiss et al., 2005; Kelsey et al., 2004; Michelson et al., 2002).

Safety assessment was monitored throughout the study by a qualified physician who reviewed every patient's safety data with the patient and/or parent at each visit. Adverse events were collected by open-ended discussion at all visits. Subject compliance was assessed at each visit by direct questioning. Patients were asked to return both used (including empty) and unused bottles distributed on the previous visit. No concomitant medications were present during ATX treatment.

2.5. Neurophysiologic assessment

2.5.1. EEG data acquisition

Twenty minutes of eyes closed resting EEG were recorded from 19 electrodes, using Electro-caps which place the sensors in accordance with the International 10/20 Electrode Placement System, referenced to linked earlobes. A differential eye channel (diagonally placed above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were below 5000 Ω. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points). All EEG data was collected on the same digital system compatible with the demands of the protocol in order to achieve amplifier equivalence. A standard calibration system was provided with the digital EEG machine. Data were sampled at a rate of 256 Hz with 12 bit resolution. In order to avoid drowsiness during EEG recordings and to have similar conditions throughout the different sessions, all the patients were recorded in the morning, instructed to keep their eyes closed and stay awake. Patients were monitored with a closed circuit television system, throughout EEG recording. EEG was recorded before therapy (baseline) and after 3, 6 and 12 months of therapy.

2.6. EEG data analysis

The raw EEG data were visually edited by trained EEG technologists, to identify and eliminate biological (e.g., muscle movement, EMG) and non-biological (e.g., electrical noise in the room) artifacts. This was augmented by a computerized artifact detection algorithm. Two minutes artifact-free data, collected from the beginning of the EEG recording were then submitted to frequency analysis (FFT) and features log transformed to obtain Gaussianity (John et al., 1980; Gasser et al., 1982). Absolute power values for each electrode position and for the delta (1.2–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25.0 Hz), frequency bands are reported in this paper. All absolute power values were Z-transformed relative to the difference between normative values and the values obtained from each individual child (John et al., 1983, 1988). Significant test re-test reliability for these measures has been demonstrated (John et al., 1983; Kondacs and Szabo, 1999).

2.7. QEEG source analysis

Two minutes of artifact-free EEG was also submitted for computation of source localization using Variable Resolution Electrical Tomography (VARETA) (Bosch-Bayard et al., 2001). With this method, very narrow band (VNB) spectra were computed using FFT with bins 0.39 Hz wide from 1.5–20 Hz, for every electrode derivation. Abnormalities in these data were identified using Z-spectra computed relative to normative values. The scalp electrode positions were placed in spatial distribution with a probabilistic MRI Brain Atlas (Evans et al., 1994). The mathematically most probable underlying sources of QEEG abnormalities recorded on the scalp were then superimposed upon MRI slices from that Atlas, and the values computed for each frequency in every voxel were encoded using a color palette with hues proportional to the standard- or Z-scores of deviations from expected normative values. The significance levels of the images take into consideration the large number of measurements made, using the correction introduced by Worsley et al. (1995). The anatomical accuracy of the functional QEEG source localization obtained by VARETA and other QEEG-based source localization methods has been repeatedly confirmed by co-registration with other brain imaging modalities e.g. functional magnetic resonance, fMRI (Mulert et al., 2004), positron emission tomography, PET (Zumsteg et al., 2005; Bolwig et al., 2007), and computerized tomography (Prichep et al., 2001).

2.8. Subjects

After screening and assessment, 61 children and adolescents, 52 male (85.25%) and 9 female (14.75%), 7–16 years of age (mean age 10.36 s.d. 2.85) with ADHD with or without co-morbidities, who meet DSM-IV criteria for ADHD, agreed to participate in the experiment. 41 (69.49%) belonged to ADHD combined type, 16 (27.12%) to the inattentive type and 2 (3.39%) to the hyperactive-impulsive type. The subjects were of normal intelligence with a total IQ of 101.09 s.d. 14.29, verbal IQ 101.27 s.d. 15.66, and performance IQ 99.17 s.d. 13.5 (WISC-III). Table 1 reports the presence of comorbidities of the total sample.

A total of 37 patients (60.6%), mean age 10.29 (s.d. 2.30) continued therapy for 6 and 12 months (33 M and 4 F). Of these 37 patients, 27 subjects belonged to ADHD_Combined type, 9 subjects to ADHD_inattentive type and 1 subject to ADHD_hyperactive type. 24 subjects (39.4%) discontinued ATX: 8 for side effects (tachyarrhythmia, increased blood pressure, syncope, allergic reaction, increased irritability) of which 2 were switched to MPH; 7 dropped out for low compliance of parents.; 8 for absence of positive outcome (2 subjects were switched to MPH); and 1 for “early” positive outcome.

Table 1
Reports the presence of comorbidities and percentage in the total sample of children with ADHD.

Comorbidity	Patients	%
Oppositional Defiant Disorder	23	37.70%
Specific learning disorder	15	24.59%
Anxiety disorder	4	6.56%
Conduct disorder	2	3.28%
Language disorder	2	3.28%
Generalized learning disorder	1	1.64%
Conduct disorder + anxiety disorder	1	1.64%
Language disorder + anxiety disorder	1	1.64%
Tics	1	1.64%
None	11	18.03%
Total	61	100.00%

2.9. Statistical analysis

Preliminary statistical analyses were conducted on those 37 patients for whom data was available 6 months after the initiation of therapy. These subjects were classified as responders (R), non-responders (NR) or partial responders (PR) based upon an increase/decrease of SNAP Z scores values between baseline and each of the time points (treatment). Subjects with a 30% increase or greater in SNAP scores were classified as responders. Subjects with a decrease of 30% or more in SNAP scores were called Non-Responders. All others were classified as partial responders. Age, SNAP-Inattentive, SNAP-Hyperactivity, SNAP-Combined and SNAP-Oppositional scores for R, NR, and PR patients at baseline, 3, 6 and 12 months were submitted to two way analysis of variance (ANOVA) with levels corresponding to response type (R, NR, and PR) and time (baseline, 3, 6, 12 months). In order to reduce the number of statistical comparisons and to simplify the QEEG findings all reported analyses included only the R and NR patient groups. The only QEEG variables used to compare responders and non-responders were Z-score absolute power from 19 monopolar regions for the delta, theta, alpha, and beta frequency bands. Separate ANOVAs were conducted for the differences between responders and non-responders for each electrode location and each frequency band. The $p < 0.005$ criteria were used to determine statistical significance in order to account for the use of multiple ANOVAs (19 electrodes by 4 frequency bands). The QEEG results are displayed as a set of maps color coded by the F values corresponding to the differences between the 2 groups.

The same type of analysis was conducted within each group only for R and NR, between BL and 3 months between BL and 6 months, BL and 12 months, separately. The results are displayed as a set of maps color coded by the F value of the significance of the differences between the 2 groups.

3. Results

3.1. Atomoxetine

Atomoxetine had a positive effect on 21 subjects (55.6%), of which 11 (27.8%) were classified as responders and 10 (27.8%) as partial responders. 16 subjects, (44.4%) were defined as non-responders according to the criteria defined above. Table 2 shows the distribution of the comorbidities of children with ADHD divided in R, PR and NR. As seen in the group of NR there is a higher rate of Oppositional Defiant Disorder (ODD) compared to the other 2 groups. The other more frequent comorbidity, specific learning disorder was nearly equally distributed in all the 3 groups.

3.2. Demographic and SNAP scores

The ages of the R, NR, and PR groups did not differ from one another ($F = 1.1$, $p = 0.34$). Changes in SNAP scores varied as a function of treatment interval across the R, NR, and PR groups (Table 3). At baseline there were no significant differences between the three groups for any SNAP score. Children in the NR group showed no changes for any SNAP score across treatment intervals. Children in the PR group showed decreased inattention scores after 3, 6, and 12 months of treatment although hyperactivity, combined, and oppositional SNAP scores remained at baseline levels across the 12 months of treatment. Children classified as responders showed decreased SNAP inattention, hyperactivity, combined, and oppositional SNAP scores after 3 months and these changes remained present after 6 and 12 months of treatment.

Table 2
Shows the distribution of the comorbidities of the 37 children with ADHD divided in responders (R), partial responders (PR) and non-responders (NR) for whom data was available after the third month of therapy.

Comorbidity	R	PR	NR
Oppositive Defiant Disorder	3	4	8
Specific learning disorder	4	3	2
Anxiety disorder	1	–	2
Conduct disorder	–	–	1
Language disorder	1	–	–
Generalized learning disorder	–	–	1
Conduct disorder + anxiety disorder	–	–	–
Language disorder + anxiety disorder	1	–	–
Tics + Oppositive Defiant Disorder	1	–	–
None	–	3	2
Total	11	10	16

3.3. QEEG

Fig. 1 presents color coded head maps of Z-absolute power (compared to database of normal children) separately for the R and NR groups at baseline, 6 months, and 12 months following treatment. At baseline responders showed increased frontal/anterior temporal alpha and elevated frontal/anterior temporal delta and theta in comparison to the normal population. Non-responders showed increased power across all frequency bands that were greatest in anterior and central regions. Across the 12 month treatment interval these increased absolute power values decreased in the responders (moved towards normal values), whereas, across these same time intervals the increased absolute power levels remained constant for the non-responders. Fig. 2 shows color coded head maps of the significance of the difference between R and NR children at each electrode location and each frequency band at baseline, 6 months and 12 months after treatment. It should

Table 3
Reports the Anova results at baseline (BL), 6 and 12 months for non-responders and responders of the SNAP-Combined (SNAP-C), SNAP-Hyperactivity (SNAP-H), SNAP-Inattention (SNAP-I) and SNAP-Opposition (SNAP-O) scores, respectively.

	Non-responders		Responders			
	Mean	SD	Mean	SD	F-value	p-Value
SNAP-C						
BL	2.17	0.74	2.51	1.2	0.64	0.43
6 months	2.46	0.54	1.21	0.76	17.9	0.0003
12 months	2.32	1.02	1.20	1.1	3.41	0.08
SNAP-H						
BL	2.15	0.90	2.19	1.5	0.01	0.94
6 months	2.55	0.75	1.04	0.8	22.1	0.0001
12 months	2.10	1.2	0.71	0.9	6.8	0.02
SNAP-I						
BL	2.05	0.40	2.54	1.0	1.4	0.25
6 months	2.50	0.50	1.20	0.8	6.9	0.01
12 months	2.21	0.99	1.51	1.3	1.9	0.32
SNAP-O						
BL	1.56	0.43	1.42	0.54	0.35	0.56
6 months	1.52	0.37	1.07	0.37	7.7	0.01
12 months	2.10	0.29	0.99	0.41	25.0	0.0001

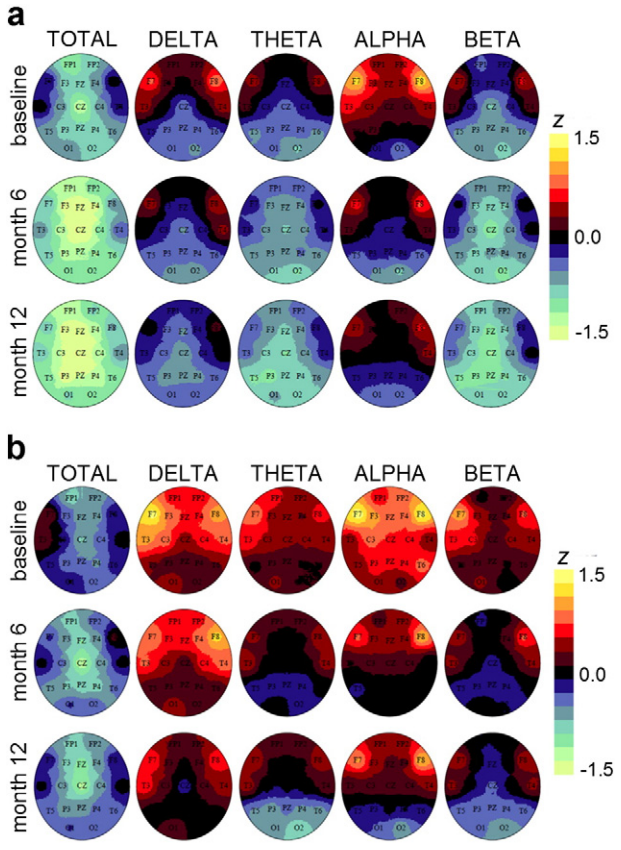


Fig. 1. Shows the average Z-score maps of absolute power for the delta, theta, alpha, and beta frequency bands of the responders and non-responders at baseline, 6 months and 12 months. Z-scores are relative to the normal population with statistical significance at the $p < 0.01$ level equal to a Z-score of 1.96/Square root of N.

be noted that at baseline significant R vs. NR differences involved mainly posterior regions but that by 6 and 12 months were generalized across all locations. Fig. 3 shows color coded head maps of the significance of the difference between baseline and 6 and 12 months after treatment separately for responders and non-responders. Responders showed significant decreases in power for all frequency bands at 6 and 12 months that was greatest in anterior, central, and temporal regions (regions where baseline abnormal findings were present) with no changes in posterior regions. Non-responders showed no changes in

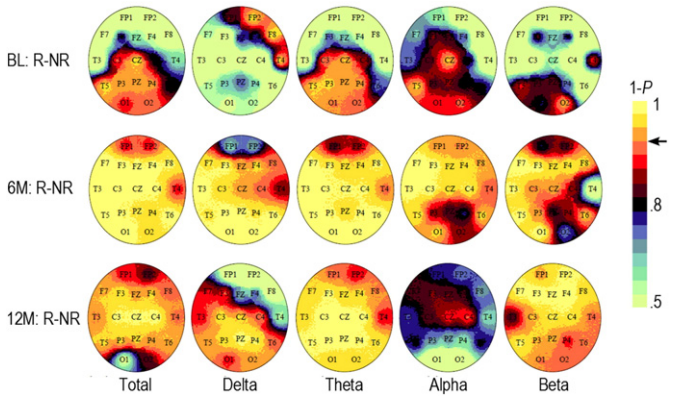


Fig. 2. Shows color coded head maps of the significance of absolute power difference between responders and non-responders at baseline (BL), 6 months (6 M) and 12 months (12 M). The black arrow indicates significance at the $p < 0.005$ level.

absolute power levels after 6 and 12 months of treatment compared to baseline values. Thus, treatment with ATX reduced the frontal QEEG abnormality present in the responders and had no effect upon the QEEG of the non-responders.

3.4. VARETA

Fig. 4a presents VARETA images for the responders at an average single Hertz frequency band of 11.7 Hz, the frequency band with the highest average Z-score relative to the normal population (1.5 to 30 Hz in 0.39 Hz steps). The responders at baseline showed increased activation relative to the normal population in the right middle, superior, and inferior temporal gyrus, in the right insular, in the pre and post central gyrus, in the supramarginal gyrus, in the mid frontal gyrus, in the posterior cingulate region, in the angular gyrus, in the medial frontal gyrus, and the superior parietal lobule. Fig. 4b shows the same VARETA images 12 months after treatment. Abnormal activation has decreased dramatically with significant findings seen only in the lateral, medial, and fronto-orbital gyrus, in the medial frontal gyrus, and the anterior cingulate region. Fig. 5a presents VARETA images at BL for the NR's at 15.2 Hz the frequency value with the greatest average increased Z-score relative to the normal population. Increased activity can be seen in right medial, inferior, and superior temporal gyrus, in the pre and post central gyrus, in the left inferior frontal gyrus, the supramarginal gyrus, in the left medial frontal gyrus, and in the angular gyrus. Decreased activation is present in the latero-medial fronto-orbital gyrus, superior and medial frontal gyrus the anterior cingulate region, the occipito-temporal gyrus and the cerebellum. Fig. 5b shows the same VARETA images 12 months after treatment. It can be seen that increased activity remains present in all areas that showed abnormal activation at baseline. The reduced activation is still present in the occipito-temporal gyrus and the cerebellum.

4. Discussion

In our study Atomoxetine had a positive effect on 21 subjects (55.6%), of which 11 (27.8%) were classified as responders and 10 (27.8%) showed a partial remission of ADHD symptoms (Partial Responders). Responders showed remission of all SNAP symptoms, whereas, the partial responders only showed a decrease in SNAP inattention. These results are in agreement with previous studies reporting that the effect size for atomoxetine treatment in ADHD patients ranges from 0.63 to 0.71 and the response to atomoxetine treatment ranges from 59.5% to 69% while remission ranges from 27% to 28.6% (Weiss et al., 2005; Kelsey et al., 2004; Michelson et al., 2002). 16 subjects, (44.4%) were defined as non-responders with SNAP-C, SNAP-I, and SNAP-O scores increasing and SNAP-I scores remaining at baseline levels.

An expanding literature has demonstrated a relationship between baseline profiles of quantitative Electroencephalogram (QEEG) or differences between baseline, retest profiles and ultimate clinical/treatment outcome (Prichep et al., 1993; Hansen et al., 2003; Pizzagalli et al., 2001; Leuchter et al., 2009a, 2009b). Saletu et al. (2002, 2005) suggested a “key and lock” model where the medication of choice is that which causes changes in brain electrical activity which is opposite to abnormalities seen in the baseline QEEG. Suffin and Emory (1995) conducted a prospective, randomized, multiply blinded, controlled pilot study to test clinical efficacy of the QEEG model, and found that pretreatment QEEG data predicted medication response with high accuracy in treatment resistant child and adolescent depression. In our sample responders to ATX had baseline QEEG alpha excess localized to frontal and anterior temporal regions and these abnormal findings decreased after 6 and 12 months of treatment. Non-responders showed QEEG abnormalities across all frequency bands and across frontal and central regions. These QEEG

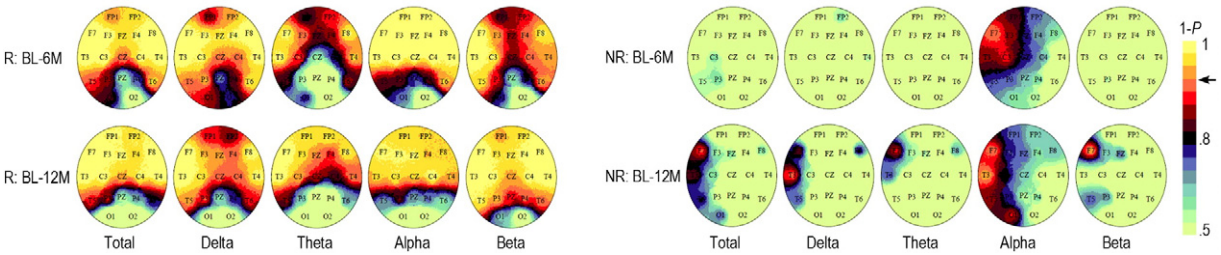


Fig. 3. Shows color coded head maps of the significance of absolute power difference between baseline (BL) and 6 months and 12 months after treatment separately for responders (left panel) and non-responders (right panel). The black arrow indicates significance at the $p < 0.005$ level.

abnormal findings remained constant after 6 and 12 months of treatment.

Many independent laboratories have reported that there are at least 5 different neurophysiological clusters (subtypes) that describe ADHD children. Furthermore, it has been demonstrated that each neurophysiological subtype shows abnormalities in all frequency bands, in terms of absolute, relative power and coherence in prefrontal and frontal areas and there may be a relationship between QEEG subtypes and treatment response. The QEEG profiles shown by the responders and non-responders in this study are consistent with those reported to characterize QEEG subtypes of children with ADHD (Clarke et al., 1998, 2001a, 2001b, 2001c, 2001d, 2002a, 2003a, 2006a; Barry et al., 2003, 2009a; Chabot and Serfontein, 1996; Chabot et al., 1996, 1999, 2001). As described above the responders and non-responders may represent two different QEEG subtypes of ADHD.

QEEG has been shown to have sensitivity and specificity levels varying from 90% to 98% in discriminating normal subjects from those with ADHD and ADHD children from LD children (di Michele et al., 2005; Monastra et al., 1999, 2001; Monastra, 2005). QEEG was also proved useful in the management of treatment response to stimulant medication. A number of studies have investigated changes in the EEG due to stimulant medications with the majority of studies finding that the stimulants result in some normalization of the EEG. Swartwood et al. (1998) and Lubar et al. (1999) failed to find changes in EEG power due to stimulant medication but Chabot et al. (1999) found that 56.9% of a group of children with ADHD showed normalization of the EEG after the administration of a stimulant, while 33.8% remained unchanged and 9.3% showed an increase in EEG abnormality. Loo et al. (1999) found that after the administration of methylphenidate, good responders had decreased theta and alpha but increased beta activity in the frontal regions, while poor responders showed the opposite EEG changes. Clarke et al. (2002b, 2003a, 2003b, 2007) found that stimulant medications resulted in normalization of the EEG with a reduction in theta activity and an increase in beta activity. These results were interpreted as indicating that stimulants acted at a cortical level by increasing arousal although complete normalization was not found in the entire sample.

However, the effects of non-stimulants on the EEG of children with ADHD have not been widely investigated. Clarke et al. (2006b, 2008) examined the EEG characteristics of responders to imipramine hydrochloride (Tofranil®) treatment. The authors reported that the responders to Tofranil© had significantly more absolute and relative theta with deficiencies of relative alpha across all sites compared to controls. Leuchter et al. (2014) used the theta cordance index in predicting atomoxetine treatment response in adult ADHD. Left temporo-parietal cordance in the theta frequency band after one week of treatment was associated with ADHD symptom improvement and quality of life measured at 12 weeks in atomoxetine-treated subjects, but not in those treated with placebo. In the scientific literature there is only one study that investigated the acute treatment effect of 20 mg of atomoxetine in children and adolescents with ADHD (Barry et al., 2007, 2009a). The EEG was recorded after 1 h of ATX administration. Acute atomoxetine administration produced a significant decrease of posterior absolute theta and an increase of absolute beta (especially in right and midline anterior regions). Relative delta was increased, particularly in central regions, and relative beta was globally increased. There were no significant medication effects on absolute alpha activity. However, this study has minimal implications on the long term effects of ATX on QEEG changes. In the present study ATX lead to a normalization of the QEEG's of the responders but had no effect upon the QEEG's of the non-responders.

Our study confirms that children with ADHD at baseline show QEEG abnormalities as reported in the literature and adds new data about the chronic effects of ATX on the QEEG of ADHD children. The effects of therapy are clearly visible at 6 months when R is compared with NR. Differences between R and NR were seen at baseline: the R show greater activity in the right prefrontal and frontal regions compared to the NR in the delta band. Theta activity is greater in the NR in the left temporal and parietal areas. The NR had greater alpha absolute power in central and left temporo-parietal and occipital regions bilaterally. Absolute power in the beta band especially in the posterior regions is higher in

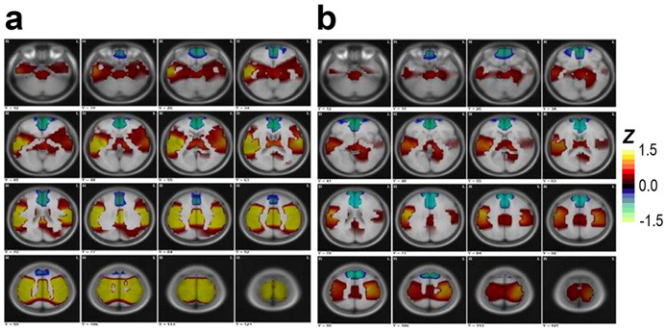


Fig. 4. a: Presents VARETA images at baseline for the responders at an average single Hertz frequency band of 11.7 Hz, the frequency band with the highest average Z-score relative to the normal population. b: Shows the same VARETA images 12 months after treatment.

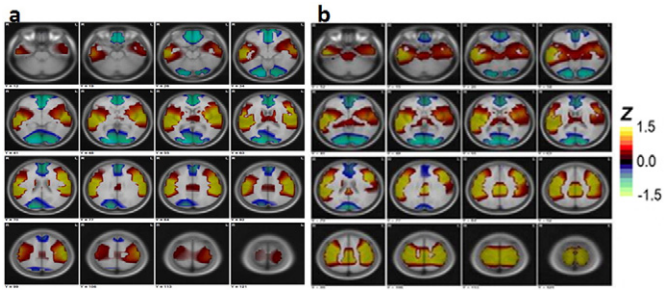


Fig. 5. a: Presents VARETA images at baseline for the non-responders at an average single Hertz frequency band of 15.2 Hz, the frequency range with the greatest average increased Z-score relative to the normal population. b: Shows the same VARETA images 12 months after treatment.

the NR. At 12 months of therapy the R show a normalization of absolute power in all frequency bands while the NR maintain the excess of activity in all frequency bands except the alpha band. The differences between R and NR at 12 months were highly significant especially in the delta band posteriorly, the theta band centrally and the beta band anteriorly.

VARETA source localization proved useful in the current study by indicating the cortical structures which show abnormal function in ADHD children. In a recent paper (Chabot et al., 2015) it was noted that groups of ADHD children and autistic children could be sub-typed based upon the mean frequency bands showing the greatest deviation from normal population. VARETA images calculated at these different frequency values showed consistent anatomical differences from normal that were similar across each subtype of autism and ADHD but that differences persisted between the autistic and ADHD at all frequency levels. ATX responders showed increased activation in right middle, superior, and inferior temporal gyrus, in the right insula, in the pre and post central gyrus, in the supramarginal gyrus, in the mid frontal gyrus, in the posterior cingulate region, in the angular gyrus, in the medial frontal gyrus, and the superior parietal lobe. This increased activation decreased after 6 and 12 months of ATX. Non-responders to ATX showed increased activation in right medial, inferior, and superior temporal gyrus, in the pre and post central gyrus, in the left inferior frontal gyrus, the supramarginal gyrus, in the left medial frontal gyrus, and in the angular gyrus with this increased activation remaining constant despite 12 months of treatment with ATZ. The reduced activation remained the same in the occipito-temporal gyrus and the cerebellum. Similar findings have been reported with different techniques supporting the evidence that these cerebral areas are involved in the pathophysiology of ADHD (Barkley, 2006).

The analysis of sources localization shows that at baseline the brain regions that show an excess of beta activity are the same in R and in NR. This might suggest that subjects with ADHD_C both R and NR share the same structural organization, but what distinguishes the R from NR is the functional organization as it appears by absolute power spectra. The NR continued to have an excess of beta activity and an excess of delta and theta activity.

One of the possible factors of the lack of response to ATX could be the presence of a greater number of ADHD subjects with Oppositional Defiant Disorders (ODD). Recently Chiarenza et al. (2014) reported that subjects with ADHD_C + ODD show abnormal EEG activity in the right anterior cingulate, in the right lateral and medial orbito frontal gyrus, in the alpha and beta bands in comparison to a group of subjects with ADHD_C.

Cortese et al. (2012) recently performed a comprehensive meta-analysis of 55 task-based functional MRI studies of attention deficit hyperactivity disorder. In children, hypoactivation in ADHD relative to comparison subjects was observed mostly in systems involved in executive function (fronto-parietal network) and attention (ventral attentional network). The authors provide evidence that ADHD is a result of dysfunction in multiple neuronal systems involved in higher-level cognitive functions and in sensorimotor processes, including the visual system and the default network. Our VARETA source localization method applied to QEEG, even if recorded with eyes closed and in quiet state, fully confirms these observations and contributes to the understanding of ADHD pathophysiology. It should be noted that the interpretation of VARETA has some pros/cons: it is statistically more robust, diminishes the effect of outliers and increases the chances of regions to become biomarkers. However if the region is big and few voxels are significant, the average can mask those significant voxels activities.

To date there are no studies that demonstrate a clear relationship between clinical profile of subjects with ADHD at “baseline” and response to treatment. Further, a limitation of most studies which have investigated the efficacy of stimulants or SNRI is that response measurements involve subjective teacher and parent ratings (Efron et al., 1997, 2002; Elia et al., 1991) and/or continuous performance tests (CPT) (Efron et al., 1997) without including objective and physiological measurements. Therefore, the questions related to aetiology, pathophysiology, diagnosis and therapy that ADHD imposes remain unresolved. There is a need for more precise and objective formulation of the diagnosis of ADHD, leading the way to more optimal treatment and increase the diagnostic sensitivity to ADHD. Increased understanding of neurophysiological profiles of children with ADHD could offer a refined definition of the pathology and a proper selection of subjects that may take some advantages from treatment optimization selection.

4.1. Study limitation

It should be remembered that the ATX selective inhibition of norepinephrine transporters action mechanism is still largely unknown. Therefore further studies are needed to draw a consistent action profile. Another limitation regards the use of multiple comparisons in analyzing the QEEG absolute power variables. Despite setting the significance level at 0.005 the changes observed in the different EEG frequency bands must be taken with caution although if significance was set at $p < 0.001$ the result interpretation would not change. Caution should also be used due to the relatively small number of responders and non-responders present in this study. Further large N studies should be conducted in order to build discriminative functions that may predict treatment response to ATX.

With these assumptions in mind, the results cannot be considered definitive and further research is necessary to confirm the observed significant differences on the QEEG of ADHD children between responders and non-responders after one year of ATX treatment.

5. Conclusions

We conclude that ADHD children with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased activity in the beta band coupled with increased alpha band power, seems to be related to non-responders and stopping atomoxetine should be considered, especially if there is persistence of elevated alpha and beta and an increase of theta after 3 months of treatment. VARETA showed more widespread abnormality in non-responders than responders. R showed abnormal findings localized to frontal and temporal regions whereas in NR abnormal findings also included more posterior regions.

To our knowledge, this study represents the first tentative attempt to detect objective variables of QEEG of patients with ADHD obtained after one year treatment with ATX. These variables could be used as a predictive index of treatment response to ATX. Waiting for further research to confirm the validity of these results, the prolonged observation of the QEEG variables should be considered as reference point of a certain consistency.

Disclosure

Giuseppe Augusto Chiarenza, Robert Chabot, Robert Isenhart, Luciano Montaldi, Marco Paolo Chiarenza, Maria Grazia Lo Torto, and Leslie S. Prichep within 3 years to the time of data collection had not any institutional or commercial relationship with pharmaceutical companies that might pose a conflict of interest.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders. fifth ed. American Psychiatric Association, Arlington, VA.
Arnsten, A.F., Li, B.M., 2005. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol. Psychiatry 57, 1377–1384.
Barkley, R., 1977a. ADHD and the Nature of Self-Control. The Guilford Press, New York (410 pp).
Barkley, R., 1997b. Attention-deficit/hyperactivity disorder, self-regulation and time: toward a more comprehensive theory. Dev. Beh. Paediatrics 18, 271–279.

Barkley, R., 2006. Attention-Deficit/Hyperactivity Disorder. The Guilford Press, A handbook for diagnosis and treatment. New York (770 pp).
Barkley, R.A., Grodzinsky, G., DuPaul, G., 1992. Frontal lobe functions in attention deficit disorder with and without hyperactivity: a review and research report. J. Abnorm. Child Psychol. 20, 163–188.
Barry, R.J., Clarke, A.R., Johnstone, S.J., 2003. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin. Neurophysiol. 114, 171–183.
Barry, R.J., Clarke, A.R., Hajos, M., McCarthy, R., Selikowitz, M., Bruggemann, J.M., 2007. Acute atomoxetine effects on the EEG of children with attention-deficit/hyperactivity disorder. Neuropsychol. Rev. 17 (1), 61–72 (Mar).
Barry, R.J., Clarke, A.R., Hajos, M., McCarthy, R., Selikowitz, M., Bruggemann, J.M., 2009a. Acute atomoxetine effects on the EEG of children with attention-deficit/hyperactivity disorder. Neuropharmacology 57, 702–707.
Barry, R.J., Clarke, A.R., Johnstone, S.J., McCarthy, R., Selikowitz, M., 2009b. Electroencephalogram q/b ratio and arousal in attention-deficit/hyperactivity disorder. Biol. Psychiatry 66, 398–401.
Bolwig, T.G., Hansen, E.S., Hansen, A., Merkin, H., Prichep, L.S., 2007. Toward a better understanding of the pathophysiology of OCD SSRI responder: QEEG source localization. Acta Psychiatr. Scand. 115 (3), 237–242.
Bosch-Bayard, J., Valdes-Sosa, P., Virues-Alba, T., Aubert-Vazquez, E., John, E.R., Harmony, T., Riera-Diaz, J., Trujillo-Barreto, N., 2001. 3D statistical parametric mapping of EEG source spectra by means of variable resolution electromagnetic tomography (VARETA). Clin. Electroencephalogr. 32, 47–61.
Castellanos, F.X., Giedd, J.N., Eckburg, P., Marsh, W.L., Vaituzis, C., Kaysen, D., Hamburger, S.D., Rapoport, J.L., 1994. Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. Am. J. Psychiatry 151, 1791–1796.
Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C., J.W, Snell, Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C., Rapoport, J.L., 1996. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch. Gen. Psychiatry 53, 607–616.
Chabot, R., Serfontein, G., 1996. Quantitative electroencephalographic profiles of children with attention deficit disorder. Biol. Psychiatry 40, 951–963.
Chabot, R.J., Merkin, H., Wood, L.M., Davenport, T.L., Serfontein, G., 1996. Sensitivity and specificity of qEEg in children with attention deficit or specific developmental learning disorders. Clin. Electroencephalogr. 27, 26–34.
Chabot, R.J., Orgill, A.A., Crawford, G., Harris, M.J., Serfontein, G., 1999. Behavioral and electrophysiologic predictors of treatment response to stimulants in children with attention disorders. J. Child Neurol. 14 (6), 343–351.
Chabot, R.J., di Michele, F., Prichep, L.S., John, E.R., 2001. The clinical role of computerized EEG in the evaluation and treatment of learning and attention disorders in children and adolescents. J. Neuropsychiatr. Clin. Neurosci. 13 (2), 171–186.
Chabot, R.J., Coben, R., Hirshberg, L., Cantor, D.S., 2015. QEEG and VARETA based neurophysiological indices of brain dysfunction in attention deficit and autistic Spectrum disorder. Austin J. Autism Relat. Disabil. 1 (2), 1–8.
Chiarenza, G.A., Bosch-Bayard, J., Villa, S., Chiarenza, M.P., Galan, L., Aubert, E., Valdes Sosa, P., 2014. In: Nittono, H., Onoda, K., Ohira, H., Ozaki, H. (Eds.), Temperament, Character and qEEG in Children with ADHD-C and ADHD-C + ODD. Proceedings of the 17th World Congress of Psychophysiology (IOP2014) of the International Organization of Psychophysiology. Int. J. Psychophysiol. vol. 94,2, p. 141 (2014).
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 1998. EEG analysis in attention-deficit/hyperactivity disorder: a comparative study of two subtypes. Psychiatry Res. 81, 19–29.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2001a. EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. Psychophysiology 38, 212–221.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2001b. Age and sex effects in the EEG, differences in two subtypes of attention-deficit/hyperactivity disorder. Clin. Neurophysiol. 112, 815–826.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2001c. EEG differences in two subtypes of attention-deficit/hyperactivity disorder. Psychophysiology 38, 212–221.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2001d. Excess beta in children with attention-deficit/hyperactivity disorder: an atypical electrophysiological group. Psychiatry Res. 103, 205–2018.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2002a. Children with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: an EEG analysis. Psychiatry Res. 111, 181–190.
Clarke, A.R., Barry, R.J., Bond, D., McCarthy, R., Selikowitz, M., 2002b. Effects of stimulant medication on the EEG of children with attention-deficit/hyperactivity disorder. Psychopharmacology 164, 277–284.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., Clarke, D.C., Croft, R.J., 2003a. EEG activity in girls with attention-deficit/hyperactivity disorder. Clin. Neurophysiol. 114, 319–328.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2003b. Hyperkinetic disorder in the ICD-10: EEG evidence for a definitional widening? Eur. Child Adolesc. Psychiatry 12, 92–99.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., Magee, C., Johnstone, S.J., Croft, R., 2006a. Quantitative EEG in low-IQ children with attention-deficit/hyperactivity disorder. Clin. Neurophysiol. 117, 1708–1714.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., 2006b. EEG predictors of good response to Tofranil in children with attention deficit/hyperactivity disorder. In: Oades, R.D. (Ed.), Attention-Deficit/Hyperactivity Disorder (AD/HD) and the Hyperkinetic Syndrome (HKS): Current Ideas and Ways Forward. Nova Publishers, Inc., New York, pp. 249–267.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., Johnstone, S., 2007. Effects of stimulant medications on the EEG of girls with attention-deficit/hyperactivity disorder. Clin. Neurophysiol. 118, 2700–2708.
Clarke, A.R., Barry, R.J., McCarthy, R., Selikowitz, M., Johnstone, S.J., 2008. Effects of imipramine hydrochloride on the EEG of children with attention-deficit/hyperactivity disorder who are non-responsive to stimulants. Int. J. Psychophysiol. 68, 186–192.
Clarke, A.R., Barry, R.J., Dupuy, F.E., Heckel, L.D., McCarthy, R., Selikowitz, M., Johnstone, S.J., 2011. Behavioural differences between EEG-defined subgroups of children with attention-deficit/hyperactivity disorder. Clin. Neurophysiol. 122, 1333–1341.
Conners, C.K., 1997. Conners' Rating Scales-Revised, Technical Manual. MultiHealth Systems Inc., Toronto.
Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M.P., Castellanos, F.X., 2012. Toward systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. Am. J. Psychiatry 169, 1038–1055.
de Sonneville, L.M.J., 2014. Handbook Amsterdam Neuropsychological Tasks. Boom Test Publishers, Amsterdam.
di Michele, F., Prichep, L.S., John, E.R., Chabot, R.J., 2005. The neurophysiology of attention-deficit/hyperactivity disorder. Int. J. Psychophysiol. 58, 81–93.
Efron, D., Jarman, F., Barker, M., 1997. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. Pediatrics 100, 662–666.
Efron, D., Jarman, F.C., Barker, M.J., 2002. Medium-term outcomes are comparable with short-term outcomes in children with attention deficit hyperactivity disorder treated with stimulant medication. J. Paediatr. Child Health 36, 457–461.
Elia, J., Borcherding, B.G., Rapoport, J.L., Keysor, C.S., 1991. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? Psychiatry Res. 36, 141–155.
Evans, A.C., Collins, D.L., Neelin, P., MacDonald, D., Kamber, M., Marrett, T.S., 1994. Three-dimensional correlative imaging: applications in human brain mapping. In: Functional Neuroimaging: Technical Foundations. Edited by Thatcher R., Hallet M., Zeffiro T, John E.R., Huerta M. New York, Academic Press, pp145–161.
Gasser, T., Bacher, P., Mochs, J., 1982. Transformation towards the normal distribution of broad band spectral parameters of the EEG. EEG Clin. Neurophysiol. 53, 119–124.
Gaub, M., Carlson, C.L., 1997. Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. J. Abnorm. Child Psychol. 25, 103–111.
Goodyear, P., Hynd, G., 1992. Attention deficit disorder with (ADDH) and without (ADDWO) hyperactivity, behavioral and neuropsychological differentiation. J. Clin. Child Psychol. 21, 273–304.
Guy, W., 1976. ECDU assessment manual for psychopharmacology, revised. Bethesda (MD): US Dept. of health, education and welfare. p. 418.
Hansen, E.S., Prichep, L.S., Bolwig, T.G., John, E.R., 2003. Quantitative electroencephalography in OCD-patients treated with paroxetine. Clin. EEG Neurosci. 34, 70–74.
Hastings, J., Barkley, R.A., 1978. A review of psychophysiological research with hyperactive children. J. Abnorm. Child Psychol. 7 (413–337).
Hunt, R.D., Cohen, D.J., Anderson, G., Minderaa, R.B., 1988. Noradrengergic mechanisms in ADDH. In: Bloomingdale, L. (Ed.), Attention Deficit DisorderNew Research in Attention, Treatment, and Psychopharmacology vol. 3. Pergamon Press, New York, pp. 129–148.
Jaworska, N., Berrigan, L., Ahmed, A.G., Gray, J., Korovessis, A., Fisher, D.J., Bradford, J., Federoff, P., Knott, V.J., 2013. The resting electrophysiological profile in adults with ADHD and comorbid dysfunctional anger: a pilot study. Clin. EEG Neurosci. 44, 95–104.
John, E.R., Ahn, H., Prichep, L.S., Trepetin, M., Brown, D., Kaye, H., 1980. Developmental equations for the electroencephalogram. Science 210 (1255–1258), 1980.
John, E.R., Prichep, L.S., Ahn, H., Easton, P., Friedman, J., Kaye, H., 1983. Neurometric evaluation of cognitive dysfunctions and neurological disorders in children. Prog. Neurobiol. 21, 239–290.
John, E.R., Prichep, L.S., Friedman, J., Easton, P., 1988. Neurometrics: Computer-assisted differential diagnosis of brain dysfunctions. Science 293, 162–169.
John, E.R., Prichep, L.S., Wintere, G., Hermann, W.R., di Michele, F., Halper, J., Bolwig, T.G., Cancro, R., 2007. Electrophysiological subtypes of psychotic states. Acta Psychiatr. Scand. 1-19.
Kelsey, D.K., Summer, C.R., Casat, C.D., Coury, D., Quintana, H., Saylor, K.E., Sutton, V.K., Gonzales, J., Malcom, S.K., Schuh, K.J., Allen, A.J., 2004. Once-daily atomoxetine treatment for children with attention deficit hyperactivity disorder, including an assessment of evening and morning behaviour: a double-blind, placebo-controlled trial. Pediatrics 114, 1–8.
Klorman, R., 1992. Cognitive event-related potentials in attention deficit disorder. In: Shaywitz, S.E., Shaywitz, B.A. (Eds.), Attention Deficit Disorder Comes of Age: Toward the Twenty-First Century. Pro-Ed., Austin, TX, pp. 221–244.
Koda, K., Ago, Y., Cong, Y., Kita, Y., Takuma, K., Matsuda, T., 2010. 2010. Effects of acute and chronic administration of atomoxetine and methylphenidate on extracellular levels of noradrenaline, dopamine and serotonin in the prefrontal cortex and striatum of mice. J. Neurochem. 114 (1), 259–270. http://dx.doi.org/10.1111/j.1471-4159.2010.06750.x (Jul, Epub 2010 Apr 16).
Kondacs, A., Szabo, M., 1999. Long-term intra-individual variability of the background EEG in normals. Clin. Neurophysiol. 110, 1708–1716.
Leuchter, A.F., Cook, I.A., Gilmer, W.S., Marangbell, L.B., Burgoyne, K.S., Howland, R.H., Trivedi, M.H., Zisook, S., Jain, R., Fava, M., Iosifescu, D., Grennwald, S., 2009a. Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in major depressive disorder. Psychiatry Res. 169, 132–138 (2009a).
Leuchter, A.F., Cook, I., Marangell, L., Gilmer, W.S., Burgoyne, K.S., Howland, R.H., Trivedi, M.H., Zisook, S., Jain, R., Fava, M., Iosifescu, D., Grennwald, S., 2009b. Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in major depressive disorder: results of the BRITE-MD study. Psychiatry Res. 169, 124–131.
Leuchter, A.F., McGough, J.J., Korb, A.S., Hunter, A.M., Glaser, P.E.A., Deldar, A., Todd, M.D., Cook, I.A., 2014. Neurophysiologic predictors of response to atomoxetine in young

adults with attention deficit hyperactivity disorder: a pilot project. J. Psychiatr. Res. 54, 11–18.
Loo, S., Teale, P., Reite, M., 1999. EEG correlates of methylphenidate response among children with AD/HD: a preliminary report. Biol. Psychiatry 45, 1657–1660.
Lou, H.C., Henriksen, L., Bruhn, P., 1984. Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. Arch. Neurol. 41, 825–829.
Lou, H.C., Henriksen, L., Bruhn, P., Borner, H., Nielsen, J.B., 1989. Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch. Neurol. 46, 48–52.
Lubar, J., White, J., Swartwood, M., Swartwood, J., 1999. Methylphenidate effects on global and complex measures of EEG. Pediatr. Neurol. 21, 633–637.
Michelson, D., Allen, A.J., Busner, J., Casat, C., Dunn, D., Kratochvil, C., Newcorn, J., Salley, F.R., Sangal, R.B., Sailor, K., West, S., 2002. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. Am. J. Psychiatry 159, 1896–1901.
Monastra, V.J., 2005. Overcoming the barriers to effective treatment for attention-deficit/hyperactivity disorder: a neuro-educational approach. Int. J. Psychophysiol. 58, 71–80.
Monastra, V.J., Lubar, J., Linden, M., Van Deusen, P., Green, G., Wing, W., Phillips, A., Fenger, T., 1999. Assessing attention deficit hyperactivity disorder via electroencephalography: an initial validation study. Neuropsychology 13, 424–433.
Monastra, V.J., Lubar, J., Linden, M., 2001. The development of a quantitative electroencephalographic scanning process for attention deficit hyperactivity disorder: reliability and validity studies. Neuropsychology 15, 136–144.
Mulert, C., Pogarell, O., Juckel, G., Rujescu, D., Giegling, I., Rupp, D., Mavrogiorgou, P., Bussfeld, P., Gallinat, J., Möller, H.J., Hegerl, U., 2004. The neural basis of the P300 potential: Focus on the time-course of the underlying cortical generators. Eur. Arch. Psychiatry Clin. Neurosci. 254, 190–198.
Ogrim, G., Kropotov, J., Brunner, J.F., Candrian, G., Sandvik, L., Hestad, K.A., 2014. Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder: data from quantitative electroencephalography, event-related potentials, and a go/no-go test. Neuropsychiatr. Dis. Treat. 10, 231–242. http://dx.doi.org/10.2147/NDT.S56600. eCollection Feb 3.
Pizzagalli, D., Pascual-Marqui, R., Nitschke, J.B., Oakes, T.R., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Koger, J.V., Benca, R.M., Davidson, R.J., 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am. J. Psychiatry 158, 405–415.
Prichep, L.S., Mas, F., Hollander, E., Liebowitz, M., John, E.R., Almas, M., De Caria, C.M., Levine, R.H., 1993. Quantitative electroencephalographic subtyping of obsessive compulsive disorder. Psychiatry Res. 50, 25–32.
Prichep, L.S., John, E.R., Tom, M.L., 2001. Localization of deep white matter lymphoma using VARETA — a case study. Clin. EEG 32 (2), 62–66.
Rapaport, J.L., Zametkin, A., 1988. Drug treatment of attention deficit disorder. In: Bloomingdale, L., Sergeant, J. (Eds.), Attention Deficit Disorder: Criteria, Cognition, and Intervention. Pergamon Press, New York, pp. 161–182.
Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C.R., Simmons, A., Bullmore, E.T., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control, a study with functional MRI. Am. J. Psychiatry 156, 891–896.
Rubia, K., Taylor, E., Smith, A.B., Oksannen, H., Overmeyer, S., Newman, S., 2001. Neuropsychological analyses of impulsiveness in childhood hyperactivity. Br. J. Psychiatry 179, 138–143.
Rubia, K., Halari, R., Cubillo, A., Mohammed, A.M., Brammer, M., Taylor, E., 2011. Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-nave boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology 36, 1575–1586.
Saletu, B., Anderer, P., Saletu-Zyhlarz, G.M., Pascual-Marqui, R.D., 2002. EEG topography and tomography in diagnosis and treatment of mental disorders: evidence for a key-lock principle. Methods Find. Exp. Clin. Pharmacol. 24 (Supplement D), 97–106.
Saletu, B., Anderer, P., Saletu-Zyhlarz, G.M., Pascual-Marqui, R.D., 2005. EEG mapping and low-resolution brain electromagnetic tomography (LORETA) in diagnoses and therapy of psychiatric disorders: Evidence for a key-lock principle. Clin. EEG Neurosci. 36 (2), 108–115.
Shaywitz, S.E., Shaywitz, B.A., 1984. Diagnosis and management of attention deficit disorder: A pediatric perspective. Pediatr. Clin. N. Am. 31, 429–457.
Shaywitz, B.A., Shaywitz, S.E., Byrne, T., Cohen, D.J., Rothman, S., 1983. Attention deficit disorder: quantitative analysis of CT. Neurology 33, 1500–1503.
Suffin, S.C., Emory, W.H., 1995. Neurometric subgroups in attentional and affective disorders and their association with pharmacotherapeutic outcome. Clin. Electroencephalogr. 26 (2), 76–83.
Swanson, J., 1992. School-Based Assessment and Interventions for ADD — Irvine. KC Publishing.
Swartwood, M.O., Swartwood, J.N., Lubar, J.F., Timmermann, D.L., Zimmerman, A.W., Muenchen, R.A., 1998. Methylphenidate effects on EEG, behavior, and performance in boys with ADHD. Pediatr. Neurol. 18, 244–250.
Szatmari, P., 1992. The epidemiology of attention-deficit hyperactivity disorders. In G. Weiss (Ed)., Child and Adolescent Psychiatry Clinics of North America: Attention Deficit Disorder (pp. 361–372). Philadelphia: Saunders.
Taylor, E.A., 1986. The Overactive Child. Lippincott, Philadelphia.
Viggiano, D., Ruocco, L.A., Arcieri, S., Sadile, A.G., 2004. Involvement of norepinephrine in the control of activity and attentive processes in animal models of attention deficit hyperactivity disorder. Neural Plast. 11, 133–149.
Weiss, M., Tannock, R., Kratochvil, C., Dunn, D., Velez-Borras, J., Thomason, C., Tamura, R., Kelsey, D., Stevens, L., Allen, A.J., 2005. A randomized, placebo-controlled study of once-daily atomoxetine in the school setting in children with ADHD. J. Am. Acad. Child Adolesc. Psychiatry 44, 647–655.
Worsley, K.J., Marrett, S., Neelin, P., Evans, A.C., 1995. A unified statistical approach for determining significant signals in location and scale space images of cerebral activation. In: Myers, R., Cunningham, V.G., Bailey, D.L., Jones, T. (Eds.), Quantification of Brain Function Using PET. Academic Press, San Diego, pp. 327–333.
Zametkin, A., Rapoport, J.L., 1986. The pathophysiology of attention deficit disorder with hyperactivity, a review. In: Lahey, B., Kazdin, A. (Eds.), Advances in Clinical Child Psychology vol. 9. Plenum, New York, pp. 177–216.
Zumsteg, D., Wennberg, R.A., Treyer, V., Buck, A., Wieser, H.G., 2005. H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. Neurology 65, 1657–1660.

Journal of Child Neurology
2014, Vol. 29(10) 1383-1389

DOI: 10.1177/0883073814534317
jcn.sagepub.com
SAGE

Tourette Syndrome and Comorbid Conditions: A Spectrum of Different Severities and Complexities

Renata Rizzo, MD, PhD[1], Mariangela Gulisano, MD, PhD[1], Alessandra Pellico, MD[1], Paola Valeria Calì, MD[1], and Paolo Curatolo, MD[2]

Abstract

To investigate clinical correlates of Tourette syndrome and to identify the impact of comorbidities, we retrospectively recruited 92 young people affected by Tourette syndrome compared with 102 healthy controls. Neuropsychological assessment included: Youth Quality of Life–Research, Multidimensional Anxiety Scale for Children, Children's Depression Inventory, and Conner's and Child Behavior Checklist; moreover, Tourette syndrome patients completed the Yale Global Tic Severity Rating Scale and the Yale-Brown Obsessive Compulsive Scale. Four clinical subgroups were identified: pure Tourette syndrome (49.8%), Tourette syndrome plus attention-deficit hyperactivity disorder (ADHD) (22.2%), Tourette syndrome plus obsessive-compulsive disorder (21.5%), and Tourette syndrome plus ADHD plus obsessive-compulsive disorder (6.5%). Our findings suggested that emotional lability appeared in all Tourette syndrome subgroups, independently from comorbidities, representing a clinical feature of Tourette syndrome itself. Moreover, our data suggested that all 4 clinical subgroups had higher statistically significant behavioral problems compared with the healthy controls ($P = .000$), whereas affective and anxiety symptoms were overrepresented in Tourette syndrome plus comorbidities subgroups. Finally, Tourette syndrome patients had a lower quality of life compared with the healthy controls. These differences were statistically significant between the pure Tourette syndrome subgroups and Tourette syndrome plus comorbidities subgroups, as well as Tourette syndrome plus comorbidities subgroups and healthy controls.

Keywords

emotional lability, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, tic, Tourette syndrome

Received July 22, 2013. Received revised April 03, 2014. Accepted for publication April 08, 2014.

Gilles de la Tourette syndrome is an early childhood-onset neurodevelopmental disorder that is marked by the appearance of multiple involuntary movements and vocalizations (tics).[1] The prevalence of Tourette syndrome has been reported as 0.4% to 1%[2]; recent studies have suggested that the prevalence of tics was 1.3% according to maternal reports and 4.4% according to adolescent reports.[3] Pure Tourette syndrome is characterized by the presence of motor and vocal tics without any other comorbid conditions; different rates (10%-53%) have been reported for this condition.[4,5] Tourette syndrome is commonly associated with comorbid conditions such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, and behavioral problems.[6]

According to reports, 80% to 90% of patients with Tourette syndrome have both tics and psychiatric manifestations.[7] In addition, the overall quality of life of patients with Tourette syndrome is impaired by the accompanying psychiatric disorders, primarily obsessive-compulsive disorder and ADHD.[8,9] Our previous studies showed that the most disabling comorbid disorder in patients with Tourette syndrome was obsessive-compulsive disorder, which causes significant impairment, poor self-esteem, and a low quality of life.[10,11] Several genes, including *SLITRK1*, LIM homeobox (*LHX6*, *LHX8*), and *HDC* have been suggested to be responsible for the different clinical phenotypes.[12,13] Furthermore, different symptom dimensions in Tourette syndrome have been associated with dysfunction in distinct cortical areas and have presented clear implications for the current neuroanatomic model of this syndrome.[14]

[1] Section of Child Neuropsychiatry, Dipartimento di Scienze Mediche e Pediatriche, Catania University, Via Santa Sofia, Catania, Italy
[2] Section of Child Neuropsychiatry, Department of Neurosciences, University Tor Vergata, Via Montpellier, Rome, Italy

Corresponding Author:
Renata Rizzo, MD, PhD, Dipartimento di Scienze Mediche e Pediatriche, Catania University, Via Santa Sofia 78, 95123, Catania, Italy.
Email: rerizzo@unict.it

However, little is known about the neuropsychological differences between Tourette syndrome clinical subgroups and healthy controls. The present study aimed to clarify these differences, to study the impact of these comorbidities on Tourette syndrome, and to evaluate anxiety, depression, and the quality of life in patients with Tourette syndrome compared to healthy controls.

Methods

Study Population

A total of 92 young patients with Tourette syndrome were recruited at the Tourette syndrome Clinic of the Neuropsychiatric Unit, Catania University, and compared with 102 neurologically intact healthy controls recruited from local schools.

Procedures

This study received approval from a local ethics committee, and all participants provided written informed consent.

A paediatric neurologist with extensive experience made the diagnoses of Tourette syndrome and other clinical conditions in accordance with the *Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision* criteria. All patients with Tourette syndrome were initially assessed during semistructured interviews according to the National Hospital Interview Schedule for Gilles de la Tourette syndrome.[15] Patients with Tourette syndrome and healthy controls completed the Wechsler Intelligence Scale for Children–III,[16] the Youth Quality of Life Instrument–Research Version,[17] the Multidimensional Anxiety Scale for Children,[18] the Children's Depression Inventory,[19] the Conner's ADHD/DSMV-IV Scale,[20] and the Child Behavior Checklist.[21] The Multidimensional Anxiety Scale for Children is a validated and widely used tool for assessing anxiety disorders in children and adolescents. It contains 3 subscales (physical, harm, and social) that are combined to generate a total score.[18] The Children's Depression Inventory is a self-rated instrument that enables the diagnosis of major depressive or dysthymic disorders in children and adolescents aged 7 to 17 years.[19] The Conner's ADHD/DSMV-IV Scale provided an indication of the ADHD-related symptoms, and the Child Behavior Checklist was used to assess a range of emotional and behavioral difficulties. We calculated the Child Behavior Checklist anxiety/depression, aggression, and attention scale scores to evaluate mood dysregulation among patients with Tourette syndrome.[22] Specifically, the Child Behavior Checklist anxiety/depression, aggression, and attention score is the sum of the anxiety/depression, aggression, and attention scales and is useful when determining deficient emotional self-regulation in children. Biederman et al[22] defined deficient emotional self-regulation (emotional lability) as an aggregate cut-off score of 180 to 210, and severe dysregulation with the risk of bipolar disorder development as an aggregate cut-off score $\geq$210.

Moreover, patients with Tourette syndrome completed 2 additional scales, the Yale Global Tic Severity Rating Scale[23] to measure the tic severity and the Children's Yale-Brown Obsessive Compulsive Scale[24] to assess obsessive-compulsive disorder–related symptoms.

Entry Criteria

This was a retrospective study. From a database of 500 patients with Tourette syndrome, we included those who presented with normal IQ scores and who had been evaluated at least twice (at onset and after 1 year) in order to confirm the correct diagnosis. Patients who were unable to complete the evaluations at onset and at the follow-up visit were excluded. Moreover, we excluded all patients who were too young to complete the Multidimensional Anxiety Scale for Children and Children's Depression Inventory scales and who showed evidence of severe neurologic or physical impairment. Healthy controls were defined as individuals with neither chronic diseases nor psychiatric disorders who received scores of <10 on the abbreviated Conners scales and normal results on the Child Behavior Checklist.

Statistical Analysis

An analysis of variance was performed to compare the behavioral and cognitive characteristics among the different groups. Student *t* test was used to compare the differences between each clinical group and the control group; a *P* value $\leq$.01 was considered statistically significant. As the distributions of the gender differed between the cases and controls, the analysis was repeated after excluding female patients.

Results

Demographic and Clinical Data

A total of 92 patients with Tourette syndrome (76 male patients; age range, 7 to 17 years, mean age $\pm$ standard deviation, 12.5 $\pm$ 2.9 years) and 102 healthy controls (68 male patients; mean age $\pm$ standard deviation, 13.11 $\pm$ 1.71 years) were recruited into the study.

The patients with Tourette syndrome were classified according to their clinical phenotypes into 4 clinical subgroups as follows: pure Tourette syndrome, 49.8%; Tourette syndrome plus ADHD, 22.2%; Tourette syndrome plus obsessive-compulsive disorder, 21.5%; and Tourette syndrome plus ADHD plus obsessive-compulsive disorder, 6.5%.

The age distribution did not differ significantly among the Tourette syndrome subgroups relative to the healthy controls. However, there were statistically different age distributions among the Tourette syndrome subgroups; the pure Tourette syndrome, Tourette syndrome plus ADHD, Tourette syndrome plus obsessive-compulsive disorder, and Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroups had mean ages ($\pm$ standard deviation) of 12.8 $\pm$ 2.1 years, 9.7 $\pm$ 3.3 years, 14.2 $\pm$ 3.8 years, and 13.9 $\pm$ 1.1 years, respectively.

Regarding gender, 82.6% of the patients with Tourette syndrome and 66.6% of the healthy controls were male.

The symptom severities, which were calculated from the Yale Global Tic Severity Rating Scale scores, did not differ significantly between the Tourette syndrome subgroups (Table 1).

Behavioral Problems

T scores. The patients with Tourette syndrome in all 4 subgroups had higher T scores than did the healthy controls, and these differences were statistically significant ($P < .01$). The T scores of the Tourette syndrome plus ADHD, Tourette syndrome plus obsessive-compulsive disorder, and Tourette

Table 1. Clinical Feature of the Sample.[a]

Healthy controls (n = 102)	
Sex M:F	68:34
Mean age	13.11 (1.71)
Tourette syndrome (n = 92)	
Sex M:F	76:16
Mean age	
TS	12.8 (2.1)
TS+ADHD	9.7 (3.5)
TS+OCD	14.2 (3.8)
TS+ADHD+OCD	13.9 (1.1)
Clinical diagnosis (%)	
TS	49.8
TS+ADHD	22.2
TS+OCD	21.5
TS+ADHD+OCD	6.5
YGTSS	
TS	28.3
TS+ADHD	29.1
TS+OCD	28.7
TS+ADHD+OCD	29.4
Age at onset (y)	5.6 (1.9)
Mean age (y)	12.5 (2.9)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; F, female; M, male; OCD, obsessive-compulsive disorder; TS, Tourette syndrome; YGTSS, Yale Global Tic Severity Rating Scale.
[a]Standard deviation is shown within parentheses.

syndrome plus ADHD plus obsessive-compulsive disorder subgroups were higher than that of the pure Tourette syndrome subgroup, and these differences were also statistically significant ($P < .01$). However, the differences in T scores between the Tourette syndrome subgroups with comorbidities were not statistically significant (Table 2).

Anxiety/depression, aggression, and attention scores. Patients with Tourette syndrome in all 4 groups had higher scores than did the healthy controls, and these differences were statistically significant. In our sample, 55 patients with Tourette syndrome (approximately 60% of the sample) had Child Behavior Checklist anxiety/depression, aggression, and attention scores >180. Specifically, 41 of 55 patients (75%) had scores of 180 to 210 (patients with emotional lability) and 14 of 55 (15%) had scores of >210 (patients at risk of developing bipolar disorder). Regarding the differences between the clinical phenotype subgroups, the difference between the pure Tourette syndrome and Tourette syndrome plus ADHD subgroups was not statistically significant. Similarly, the difference between the Tourette syndrome plus obsessive-compulsive disorder and Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroups was also not statistically significant (Table 2).

Affective and Anxiety Symptoms

Multidimensional Anxiety Scale for Children. The pure Tourette syndrome subgroup scores did not differ statistically from the healthy control scores. However, the Tourette syndrome subgroups with comorbidities always had significantly higher scores than did the pure Tourette syndrome subgroup. Moreover, the Tourette syndrome subgroups with comorbidities had higher scores than did the pure Tourette syndrome subgroup and these differences were always statistically significant. Finally, the presence of obsessive-compulsive disorder led to an increase in the scores.

Children's Depression Inventory. The pure Tourette syndrome subgroup scores did not differ statistically from the healthy control scores, whereas the Tourette syndrome subgroups with comorbidities always exhibited significantly higher scores than did the healthy controls. Moreover, the Tourette syndrome subgroups with comorbidities had higher scores than did the pure Tourette syndrome subgroup, and these differences were always statistically significant. Comparisons between the Tourette syndrome plus ADHD and Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroups and between the Tourette syndrome plus obsessive-compulsive disorder and Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroups did not reveal statistically significant differences (Table 3).

Quality of Life

The patients with Tourette syndrome in all 4 subgroups had lower quality of life scores in comparison with the healthy controls.

Specifically, the differences between the pure Tourette syndrome subgroup and the healthy controls were statistically significant only in the relationship domain. In all other domains, there were no significant differences between the patients with pure Tourette syndrome and the healthy controls.

The Tourette syndrome plus ADHD and Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroups had similar scores in all domains but statistically significantly lower scores than the healthy controls and the pure Tourette syndrome subgroup across all domains.

The Tourette syndrome plus obsessive-compulsive disorder subgroup had statistically significantly lower scores than did the healthy controls and patients with pure Tourette syndrome in the total, relationship, and general domains, whereas no significant differences were observed in the self and environment domains in comparison to the patients with pure Tourette syndrome and healthy controls (Table 4).

Discussion

Our findings suggest that emotional lability, which were measured according to the Child Behavior Checklist anxiety/depression, aggression, and attention scores, was observed in all Tourette syndrome subgroups and that these values were significantly different from the values obtained in the healthy controls. In our opinion, emotional lability represents an intrinsic core feature of Tourette syndrome that is unrelated to comorbidity.

Table 2. Comparison Between Child Behavior Checklist Scores.[a]

	Pure TS	TS+ADHD	TS+OCD	TS+ADHD+OCD	HC	*P* value
AAA	188.1 (10.28)	187.4 (27.6)	218.8 (22.3)	221.1 (13.7)	102.4 (20.1)	<.01*
T score	90.9 (1.3)	95.2 (2.3)	94.6 (3.4)	96.0 (2.1)	85.2 (3.2)	<.01*
			AAA (*P* value)		*T* score (*P* value)	
Pure TS vs TS+ADHD			0.89		<.01*	
Pure TS vs TS+OCD			<.01*		<.01*	
Pure TS vs TS+OCD+ADHD			<.01*		<.01*	
Pure TS vs HC			<.01*		<.01*	
TS+ADHD vs TS+OCD			<.01*		.51	
TS+ADHD vs TS+OCD+ADHD			<.01*		.45	
TS+ADHD vs HC			<.01*		<.01*	
TS+OCD vs TS+OCD+ADHD			.80		.35	
TS+OCD vs HC			<.01*		<.01*	
TS+OCD+ADHS vs HC			<.01*		<.01*	

Abbreviations: AAA, anxiety/depression, aggression, and attention; ADHD, attention-deficit hyperactivity disorder; HC, healthy control; OCD, obsessive-compulsive disorder; TS, Tourette syndrome.
[a]Standard deviation is shown within parentheses.
*$P \leq .01$.

Table 3. Comparison Between Multidimensional Anxiety Scale for Children and Children's Depression Inventory Scores.[a]

	Pure TS	TS+ADHD	TS+OCD	TS+ADHD+OCD	HC	*P* value
CDI	6.8 (5.1)	10.5 (9.5)	12.6 (7.7)	14.0 (6.3)	8.7 (8.7)	.024
MASC	30.6 (20.9)	38.6 (12.7)	41.6 (5.1)	52.3 (6.1)	33.26 (17.4)	.005
			CDI (*P* value)		MASC (*P* value)	
Pure TS vs TS+ADHD			.09		.07	
Pure TS vs TS+OCD			<.01*		<.01*	
Pure TS vs TS+OCD+ADHD			<.01*		.01*	
Pure TS vs HC			.12		.41	
TS+ADHD vs TS+OCD			.50		.01*	
TS+ADHD vs TS+OCD+ADHD			.44		.03	
TS+ADHD vs HC			.01*		.07	
TS+OCD vs TS+OCD+ADHD			.68		<.01*	
TS+OCD vs HC			.01*		.01*	
TS+OCD+ADHS vs HC			<.01*		<.01*	

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CDI, Children's Depression Inventory; HC, healthy control; MASC, Multidimensional Anxiety Scale for Children; OCD, obsessive-compulsive disorder; TS, Tourette syndrome.
[a]Standard deviation is shown within parentheses.
*$P \leq .01$.

Emotional lability could be defined as a deficit in self-regulation along with difficulties in the inhibition of inappropriate behaviors in response to either positive or negative emotions, problems with refocusing attention from strong emotions, and disorganized coordinated behaviors in response to emotional activation. Traits associated with emotional lability include a low tolerance of frustration, impatience, easy excitability in response to emotional reactions, and irritability along with volatile and changeable emotions.[25] Recently, patients with Tourette syndrome were reported to exhibit emotional dysregulation that often impaired their quality of life to an extent greater than that associated with tics.[9] In adult patients with Tourette syndrome, emotional lability was previously reported and measured by using the Ten-Item Personality Index.[26]

The pathogenesis of emotional lability might be explained by analyzing the emotional regulation circuits. These comprise the ventral striatum, subgenual and orbitofrontal cortices, amygdala, and hippocampus.[27,28] Rivero et al[29] reported that compared with healthy controls, children with ADHD and emotional lability exhibited reduced connectivity between the ventral striatum and orbitofrontal cortex. Moreover, these authors identified an inverse correlation between emotional regulation circuit connectivity and emotional lability such that emotional lability increased as the connectivity between the ventral striatum and left orbitofrontal cortex decreased.[29]

In addition, our data revealed the possibility of defining a gradient related to the presence and severity of comorbid conditions that might worsen the long-term prognosis of the disorder.

In our series, the pure Tourette syndrome subgroup did not exhibit any significant differences when compared with the healthy controls with the exception of the relationship quality

Table 4. Comparison Between QoL Scores.[a]

	Pure TS	TS+ADHD	TS+OCD	TS+ADHD+OCD	HC	*P* value
QoL Total	317.1 (53.6)	287.8 (67.5)	284.3 (48.4)	278.82 (58.03)	320.0 (47.7)	.003
QoL Self	100.1 (16.6)	83.2 (28)	98.1 (27.4)	83.6 (23.1)	101.2 (20.0)	.051
QoL Relationship	98.4 (21.3)	86.5 (35.6)	84.7 (14.1)	83.5 (33.3)	114.7 (22.0)	.000
QoL Environment	82.6 (18.0)	76.5 (16.8)	81.5 (10.1)	74.2 (14.7)	83.2 (11.4)	.203
QoL General	26.4 (4.6)	21.7 (10.08)	23.6 (4.6)	20.7 (5.5)	25.7 (5.8)	.009
	QoL Total	QoL Self	QoL Relationship	QoL Environment	QoL General	
Pure TS vs TS+ADHD	<.01*	<.01*	<.01*	<.01*	<.01*	
Pure TS vs TS+OCD	<.01*	.63	<.01*	.59	<.01*	
Pure TS vs TS+OCD+ADHD	<.01*	<.01*	<.01*	<.01*	<.01*	
Pure TS vs HC	.67	.66	<.01*	.77	.34	
TS+ADHD vs TS+OCD	.42	<.01*	.63	.01*	<.01*	
TS+ADHD vs TS+OCD+ADHD	.30	.91	0.53	.29	.37	
TS+ADHD vs HC	<.01*	<.01*	<.01*	<.01*	<.01*	
TS+OCD vs TS+OCD+ADHD	.81	.20	.91	.20	.20	
TS+OCD vs HC	<.01*	.35	<.01*	.26	<.01*	
TS+OCD+ADHD vs HC	<.01*	<.01*	<.01*	<.01*	<.01*	

Abbreviations: ADHD, attention-deficit hyperactivity disorder; HC, healthy control; OCD, obsessive-compulsive disorder; QoL, quality of life; TS, Tourette syndrome.
[a]Standard deviation is shown within parentheses.
*$P \leq .01$.

of life domain, likely because the presence of tics regularly interfered with peer relationships.

The Tourette syndrome plus ADHD subgroup exhibited an increased incidence of behavioral problems and a poorer quality of life in all subscales relative to the pure Tourette syndrome subgroup and healthy controls; however, no differences were reported between this subgroup and the Tourette syndrome plus obsessive-compulsive disorder subgroup, and the latter did not differ from patients with pure Tourette syndrome and healthy controls with respect to anxiety and depression. The presence of obsessive-compulsive disorder increased the severity of behavioral problems and the risk of developing bipolar disorder. Moreover, a higher frequency of mood disorders was observed in these patients compared with the pure Tourette syndrome subgroup and healthy controls. In terms of the quality of life, the patients with Tourette syndrome plus obsessive-compulsive disorder presented significantly lower scores than the healthy controls and patients with pure Tourette syndrome in the total, relationship, and general domains, whereas the self and environment domain scores were similar to those of the patients with pure Tourette syndrome and healthy controls. The Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroup exhibited the most disabling behavioral problems along with the highest risk of developing bipolar disorder, the most severe mood disorders, and the poorest quality of life.

The long-term clinical course of Tourette syndrome is not well known; our previous study suggested that the long-term clinical phenotype of Tourette syndrome is unstable and that different clinical phenotypes suggest different prognoses and treatment methods; children who presented with pure Tourette syndrome at onset had very positive long-term clinical courses.[10]

The presence of ADHD has been extensively reported to cause the worsening of symptoms and the risk of developing disruptive and aggressive behaviors that are more disabling than Tourette syndrome itself.[7] Furthermore, young patients with Tourette syndrome without ADHD are less prone to angry outbursts, disruptive behaviors, and social maladaptation than are those with both conditions.[30] A study of the combined condition course over a 4-year period revealed that the tic symptoms were considerably more likely to remit than were the symptoms of ADHD.[31] Tic severity was generally found to be similar in patients with pure Tourette syndrome and those with Tourette syndrome plus ADHD; high ADHD symptom scores were also related to a poorer quality of life within the self and relationship domains.[32] Our previous work showed that symptoms of inattentiveness caused less distress to the patients than did symptoms of hyperactivity and that appropriate ADHD treatment in young patients with Tourette syndrome might prevent many behavioral problems in adulthood.[10]

Previous studies of patients with Tourette syndrome plus obsessive-compulsive disorder have been somewhat inconclusive. A recent study of more than 5000 children with Tourette syndrome also found that the presence of comorbid obsessive-compulsive disorder was associated with higher rates of additional comorbid diagnoses.[33] In contrast, researchers of a study on 306 children found that patients with Tourette syndrome plus obsessive-compulsive disorder did not exhibit an elevated rate of comorbid diagnoses when compared with patients with pure Tourette syndrome or those with pure obsessive-compulsive disorder.[34] Some authors have observed greater tic severity in patients with Tourette syndrome plus obsessive-compulsive disorder, thus supporting the hypothesis that the comorbidity represents a more severe subtype of Tourette syndrome,[35] and that the presence of obsessive-compulsive disorder symptoms was associated with more widespread difficulties in the self, relationship, environment, and general quality

of life domains.[11] Our previous study reported that in comparison with ADHD, obsessive-compulsive disorder was the more disabling comorbid condition, especially with regard to the long-term prognosis and treatment difficulties.[5]

To our knowledge, little has been reported about the Tourette syndrome plus ADHD plus obsessive-compulsive disorder subgroup and its pathophysiology. The presence of untreated comorbid psychopathologies such as ADHD and obsessive-compulsive disorder has been shown to adversely affect the long-term outcomes of patients with Tourette syndrome and to cause significant impairments in daily life.[11]

Previous studies have reported that the presence of comorbidities might be considered an important factor responsible for poor function in patients with Tourette syndrome,[10] and that these might determine a more severe prognosis[5] and poorer quality of life.[11,36] It is essential to consider the presence of comorbidities in patients with Tourette syndrome; often, such comorbidities can impair functioning to an extent greater than the presence of a single set of symptoms.[29] The needs of patients with Tourette syndrome and comorbidities are very different from the needs of patients with pure Tourette syndrome, and early interventions are required to avoid negative consequences such as stigmatization or discrimination and the labeling of certain cultural lifestyles.

These different clinical correlates between Tourette syndrome subgroups could be explained according to the different neuroanatomic features of Tourette syndrome. Patients with pure Tourette syndrome exhibited enlarged thalamic nuclei along with disturbances in the sensorimotor cortex, striatum, and globus pallidus, whereas patients with Tourette syndrome plus ADHD exhibited deficient cortical inhibition and cortical thinning in motor brain areas,[37] which induced a state of hyperarousal. Patients with Tourette syndrome plus obsessive-compulsive disorder exhibited reduced hippocampal volume and altered hippocampal morphology similar to the volumetric and voxel-based morphometries observed in patients with obsessive-compulsive disorder without tics.[38] In addition, patients with Tourette syndrome plus obsessive-compulsive disorder exhibited reduced thickness in the anterior cingulate cortex. The anterior cingulate cortex and hippocampus are functionally heterogeneous limbic system components that have been implicated in the assessment and regulation of emotional information and anxiety.[39] The hippocampus is involved in the regulation of aversive emotional states (fear and anxiety) as well as emotionally driven memorization and conditioning.[40] Consequently, both structures might mediate the expression of anxiety observed in obsessive-compulsive disorder and the risk of developing bipolar disorder.

The management of patients with Tourette syndrome and comorbidities might present challenges to clinicians.[41] An early and comprehensive treatment program, including medications and other measures such as cognitive-behavioral, psychoeducational, and psychosocial interventions, is typically recommended, and it might prevent increase in the symptom severity.

Our study had some limitations. First, the patients were recruited from a tertiary neuropsychiatric university clinic, and therefore our results might not be generalizable to all affected individuals. Second, the clinical subgroup samples were relatively small; studies with larger groups are needed to confirm or refute our results. Despite these limitations, our data suggest that emotional lability is an intrinsic core feature of Tourette syndrome that is unrelated to comorbidity.

Author Contributions

RR and PC contributed equally to this work. These authors revised the manuscript and overviewed the article preparation, patient evaluation, and statistical analysis. MG wrote the first draft of the manuscript and analyzed the data. PVC and AP conducted the neuropsychological patient evaluations.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

The study was approved by the local Ethical Committee on September 5, 2012 (protocol number 168/2012).

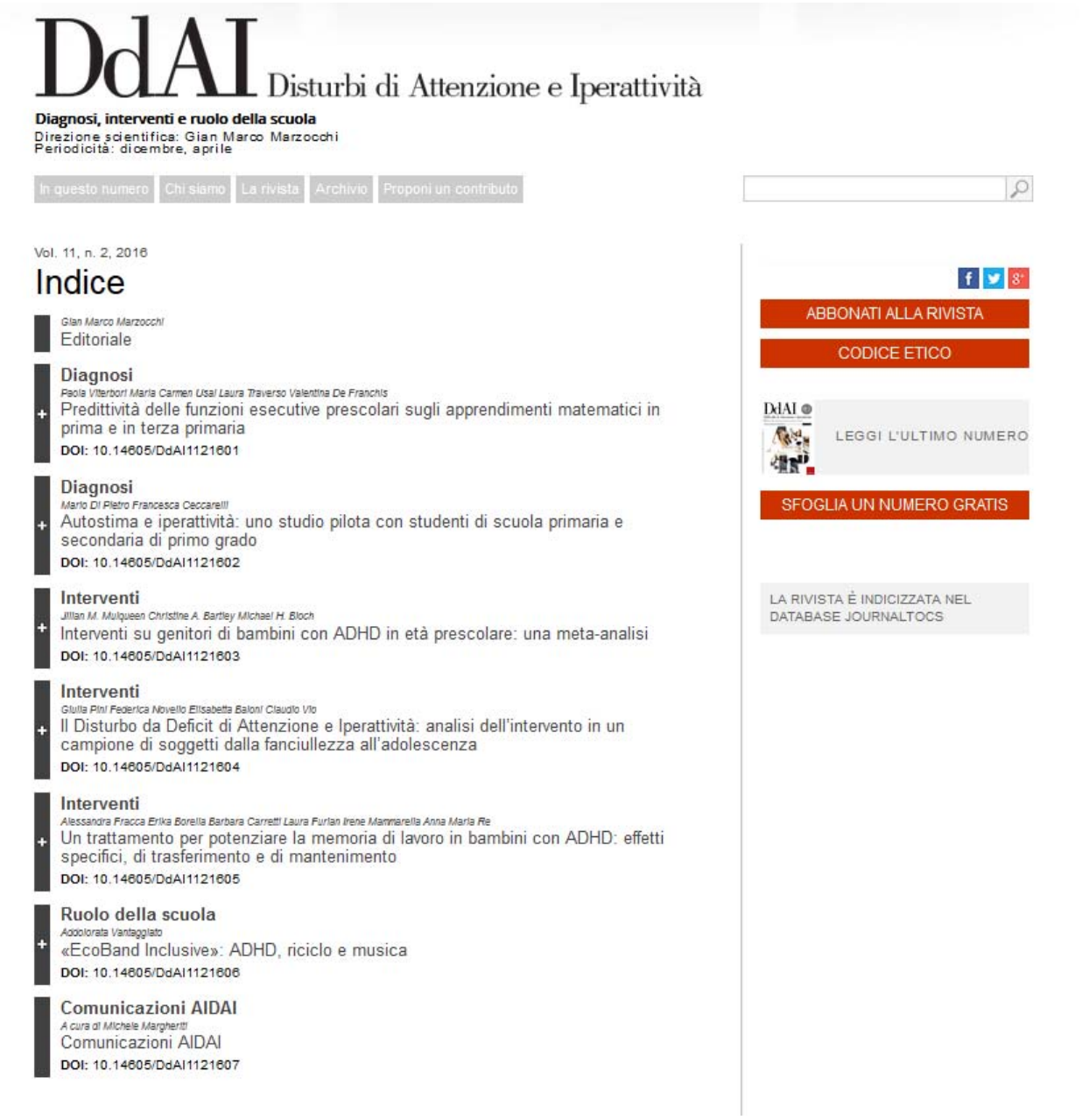
References

1. Paschou P. The genetic basis of Gilles de la Tourette syndrome. *Neurosci Biobehav Rev*. 2013;37:1026-1039.
2. Robertson MM.The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. *J Psychosom Res*. 2008;65:461-472.
3. Steinberg T, Tamir I, Zimmerman-Brenner S, et al. Prevalence and comorbidity of tic disorder in Israeli adolescents: results from a national mental health survey. *Isr Med Assoc J*. 2013;15:94-98.
4. Bloch MH, Leckman JF. Clinical course of Tourette syndrome. *J Psychosom Res*. 2009;67:497-501.
5. Rizzo R, Gulisano M, Calì PV, Curatolo P. Long term clinical course of Tourette syndrome. *Brain Dev*. 2012;34:667-673.
6. Ghanizadeh A, Mosallaei S. Psychiatric disorders and behavioral problems in children and adolescents with Tourette syndrome. *Brain Dev*. 2009;31:15-19.
7. Robertson MM. The Gilles de la Tourette syndrome: the current status. *Arch Dis Child Educ Pract Ed*. 2012;97:166-175.
8. Müller-Vahl K, Dodel I, Müller N, et al. Health-related quality of life in patients with Gilles de la Tourette's syndrome. *Mov Disord*. 2010;25:309-314.
9. Ludolph AG, Roessner V, Münchau A, Müller-Vahl K. Tourette syndrome and other tic disorders in childhood, adolescence and adulthood. *Dtsch Arztebl Int*. 2012;109:821-288.
10. Rizzo R, Curatolo P, Gulisano M, et al. Disentangling the effects of Tourette syndrome and attention deficit hyperactivity disorder on cognitive and behavioral phenotypes. *Brain Dev*. 2007;29:413-420.

11. Eddy CM, Rizzo R, Gulisano M, et al. Quality of life in young people with Tourette syndrome: a controlled study. *J Neurol*. 2011;258:291-301.
12. Karagiannidis I, Rizzo R, Tarnok Z, et al. Replication of association between a SLITRK1 haplotype and Tourette syndrome in a large sample of families. *Mol Psychiatry*. 2012;17:665-668.
13. Paschou P, Stylianopoulou E, Karagiannidis I, et al. Evaluation of the LIM homeobox genes LHX6 and LHX8 as candidates for Tourette syndrome. *Genes Brain Behav*. 2012;11:444-451.
14. Worbe Y, Gerardin E, Hartmann A, et al. Distinct structural changes underpin clinical phenotypes in patients with Gilles de la Tourette syndrome. *Brain*. 2010;133:3649-3660.
15. Robertson MM, Eapen V. The National Hospital Interview Schedule for the assessment of Gilles de la Tourette. *Int J Methods Psychiatr Res*. 1996;6:203-226.
16. Wechsler D. *Wechsler Intelligence Scale for Children—Third Edition*. San Antonio, TX: The Psychological Corporation; 1991.
17. Topolski TD, Edwards TC, Patrick DL. Youth Quality of Life Instruments. US version. User's manual and Interpretation Guide. First version. Seattle Quality of Life Group. University of Washington. Department of Health Services. 2003.
18. March JS, Parker JD, Sullivan K, et al. The Multidimensional Anxiety Scales for Children (MASC): factor structure, reliability and validity. *J Am Acad Child Adolesc Psychiatry*. 1997;36:544-552.
19. Kovacs M. *Children's Depression Inventory (CDI)*. Italian ed. Florence, Italy: Organizzazioni Speciali; 1988.
20. Conners CK. Rating scales for use in drug studies with children. *Psychopharmacol Bull*. 1973;9:24-29.
21. Achenbach T. *Manual for the Child Behavior Checklist 4–18*. Burlington, VT: University Associate on Psychiatry; 1991.
22. Biederman J, Petty CR, Monuteaux MC, et al. The Child Behavior Checklist–Pediatric Bipolar Disorder profile predicts a subsequent diagnosis of bipolar disorder and associated impairments in ADHD youth growing up: a longitudinal analysis. *J Clin Psychiatry*. 2009;70:732-740.
23. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry*. 1989;28:566-577.
24. Scahill L, Riddle MA, McSwiggin-Harden M, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry*. 1997;36:844-852.
25. Skirrow C, Asherson P. Emotional lability, comorbidity and impairment in adults with attention-deficit hyperactivity disorder. *J Affect Disord*. 2012;147:80-86.
26. Eddy CM, Rickards HE, Critchley HD, Cavanna AE. A controlled study of personality and affect in Tourette syndrome. *Compr Psychiatry*. 2013;52:105-110.
27. Posner J, Nagel BJ, Maia TV, et al. Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2011;50:828-837.
28. Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;61:720-724.
29. Rivero O, Sich S, Popp S, et al. Impact of the ADHD-susceptibility gene CDH13 on development and function of brain networks. *Eur Neuropsychopharmacol*. 2013;23:492-507.
30. Murphy T, Muter V. Risk factors for comorbidity in ADHD and GTS: looking beyond a single-deficit model. *Appl Neuropsychol Child*. 2012;1:129-136.
31. Roessner V, Becker A, Banaschewski T, et al. Developmental psychopathology of children and adolescents with Tourette syndrome-impact of ADHD. *Eur Child Adolesc Psychiatry*. 2007;16:24-35.
32. Eddy CM, Cavanna AE, Gulisano M, et al. The effects of comorbid obsessive-compulsive disorder and attention deficit hyperactivity disorder on quality of life in Tourette syndrome. *J Neuropsychiatry Clin Neurosci*. 2012;24:458-462.
33. Wanderer S, Roessner V, Freeman R, et al. Relationship of obsessive-compulsive disorder to age-related comorbidity in children and adolescents with Tourette syndrome. *J Dev Behav Pediatr*. 2012;33:124-133.
34. Lewin AB, Chang S, McCracken J, et al. Comparison of clinical features among youth with tic disorders, obsessive-compulsive disorder (OCD), and both conditions. *Psychiatry Res*. 2010;178:317-322.
35. Tukel R, Polat A, Ozdemir O, et al. Comorbid conditions in obsessive-compulsive disorder. *Compr Psychiatry*. 2002;43:204-209.
36. Cavanna AE, Luoni C, Selvini C, et al. Parent and self-report health-related quality of life Measures in young patients with Tourette syndrome. *J Child Neurol*. 2013;28:1305-1308.
37. Narr KL, Woods RP, Lin J, et al. Widespread cortical thinning is a robust anatomical marker for attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48:1014-1022.
38. Ludolph AG, Juengling FD, Libal G, et al. Grey-matter abnormalities in boys with Tourette syndrome: magnetic resonance imaging study using optimised voxel-based morphometry. *Br J Psychiatry*. 2006;188:484-485.
39. Paus T, Castro-Alamancos MA, Petrides M. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *Eur J Neurosci*. 2001;14:1405-1411.
40. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*. 2010;65:7-19.
41. Rizzo R, Gulisano M, Calì PV, Curatolo P. Tourette syndrome and comorbid ADHD: current pharmacological treatment options. *Eur J Paediatr Neurol*. 2013;112:415-444.

Dal 2016 “Disturbi di Attenzione e Iperattività” ha referee nazionali ed è indicizzata nel JournalTOCS (http://rivistedigitali.erickson.it/disturbi-di-attenzione-iperattivita/) aumenta quindi l’interesse e l’opportunità di pubblicare lavori scientifici su questa rivista.

Gian Marco Marzocchi
Direttore scientifico



DdAI Disturbi di Attenzione e Iperattività

Diagnosi, interventi e ruolo della scuola
Direzione scientifica: Gian Marco Marzocchi
Periodicità: dicembre, aprile

In questo numero | Chi siamo | La rivista | Archivio | Proponi un contributo

Vol. 11, n. 2, 2016

Indice

Gian Marco Marzocchi
Editoriale

Diagnosi
Paola Viterbori Maria Carmen Usai Laura Traverso Valentina De Franchis
Predittività delle funzioni esecutive prescolari sugli apprendimenti matematici in prima e in terza primaria
DOI: 10.14605/DdAI1121601

Diagnosi
Mario Di Pietro Francesca Ceccarelli
Autostima e iperattività: uno studio pilota con studenti di scuola primaria e secondaria di primo grado
DOI: 10.14605/DdAI1121602

Interventi
Jillian M. Mulqueen Christine A. Bartley Michael H. Bloch
Interventi su genitori di bambini con ADHD in età prescolare: una meta-analisi
DOI: 10.14605/DdAI1121603

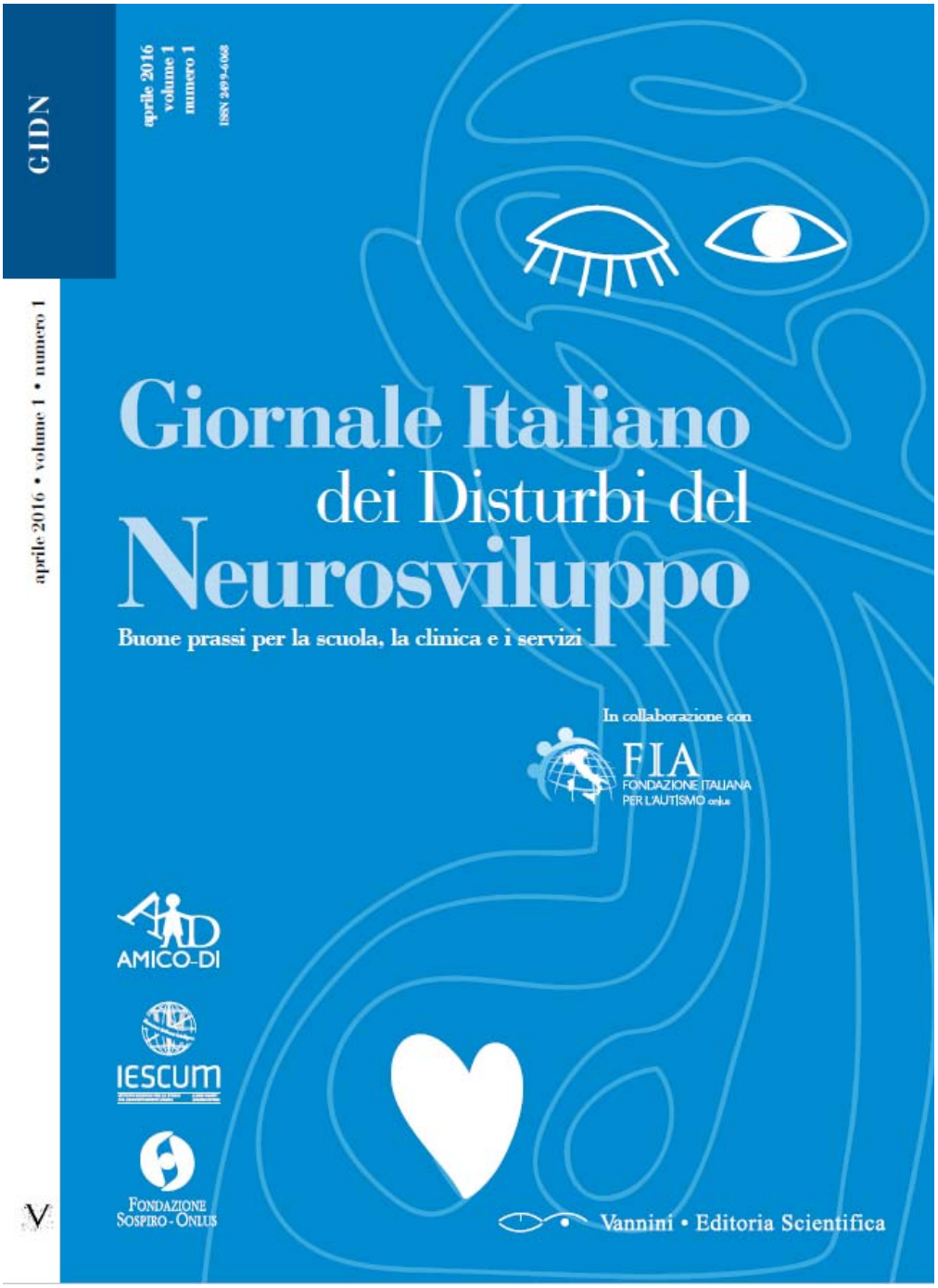
Interventi
Giulia Pini Federica Novello Elisabetta Baloni Claudio Vio
Il Disturbo da Deficit di Attenzione e Iperattività: analisi dell'intervento in un campione di soggetti dalla fanciullezza all'adolescenza
DOI: 10.14605/DdAI1121604

Interventi
Alessandra Fracca Erika Borella Barbara Carretti Laura Furlan Irene Mammarella Anna Maria Re
Un trattamento per potenziare la memoria di lavoro in bambini con ADHD: effetti specifici, di trasferimento e di mantenimento
DOI: 10.14605/DdAI1121605

Ruolo della scuola
Addolorata Vantaggiato
«EcoBand Inclusive»: ADHD, riciclo e musica
DOI: 10.14605/DdAI1121606

Comunicazioni AIDAI
A cura di Michele Margheriti
Comunicazioni AIDAI
DOI: 10.14605/DdAI1121607

ABBONATI ALLA RIVISTA
CODICE ETICO
LEGGI L'ULTIMO NUMERO
SFOGLIA UN NUMERO GRATIS
LA RIVISTA È INDICIZZATA NEL DATABASE JOURNALTOCS


GIDN
aprile 2016
volume 1
numero 1
ISSN 2499-6068
aprile 2016 • volume 1 • numero 1
Giornale Italiano
dei Disturbi del
Neurosviluppo
Buone prassi per la scuola, la clinica e i servizi
In collaborazione con
FIA
FONDAZIONE ITALIANA PER L'AUTISMO onlus
AMICO-DI
IESCUM
FONDAZIONE SOSPIRO - ONLUS
Vannini • Editoria Scientifica

Giornale Italiano dei Disturbi del Neurosviluppo

Buone prassi per la scuola, la clinica e i servizi

ISSN 2499-6068

Sede legale: Via Mandolossa, 117/A - Uffici: Via Padana Superiore, 90 - 25045 Castegnato (BS) - Tel. 030 313374 - Fax 030 314078
e-mail: scientifica@vanninieditrice.it - web: www.vanninieditrice.com

Abbonamenti 2016
Annuale cartaceo € 35,00 - Singolo numero € 15,00 - I prezzi indicati sono comprensivi di Iva.

Autorizzazione del Tribunale di Brescia n° 15/2016 del 20/04/2016

Finito di stampare nel mese di Aprile 2016 presso Tipografia Sagittario Franchi Paolo s.n.c. di Franchi Giuseppe & C. - Bibione (VE)

Giornale Italiano dei Disturbi del Neurosviluppo

Buone prassi per la scuola, la clinica e i servizi

Volume 1, Numero 1
Aprile 2016

INDICE

WebCenter

Questionario per la valutazione della Newsletter ADHD

Gent.mi lettori,

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

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

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

Si confida nella Vs preziosa collaborazione.

Per ricevere la newsletter iscriversi al seguente indirizzo:
http://www.adhd.marionegri.it/index.php/newsletter/iscrizione-newsletter

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
(Delibera n. 406 - 2014 del 04/06/2014 Progetti NPI)
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3798 del 08/05/2014 e n. 778 del 05/02/2015)
Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia" "*Percorsi diagnostico-terapeutici per l'ADHD*".

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