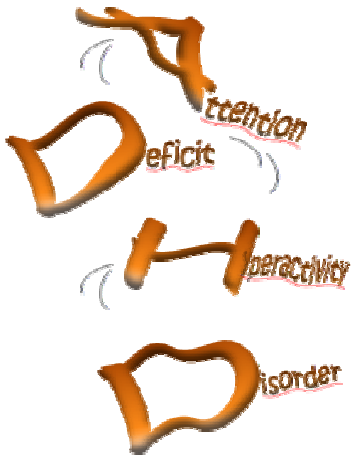
NEWSLETTER



INDICE:

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD SETTEMBRE 2014

ADHD Atten Deficit Hyperact Disord. 2014;6:221-29.

DIFFERENTIATION BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER BY THE SOCIAL COMMUNICATION QUESTIONNAIRE.

Schwenck C, Freitag CM.

The differentiation of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) poses a clinical challenge. In children, overlap of psychopathological and cognitive findings has been found for both disorders. In addition, some children suffer from both disorders. The Social Communication Questionnaire (SCQ) is a screening instrument for ASD symptoms which indicates the presence of ASD in a rapid and economic way. However, validity to differentiate ASD and ADHD as differential or comorbid diagnoses has not been studied. Here, the differential validity was compared in groups of children with ASD, ADHD, ASD + ADHD, and typically developing (TD) children and IQ > 70. ROC analyses indicated an excellent differentiation between ASD and TD with ROC-AUC = .941 and between ASD + ADHD with ROC-AUC = .993. The optimal cutoff was below the originally recommended one of 15. The differentiation between children with ASD with (ROC-AUC = .982) or without ADHD (ROC-AUC = .864) and ADHD alone also showed acceptable differential validity, and here, the optimal cutoff corresponded to the recommended. Taken together, the SCQ can be recommended as a screening instrument for a first differentiation between children with ASD and typically developing children as well as children with ADHD.

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Per la ricerca degli articoli pubblicati nella letteratura scientifica nel mese in esame sono state consultate le banche dati Medline, Embase, PsycINFO e PsycArticle utilizzando le seguenti parole chiave (o i loro sinonimi): 'Attention deficit disorder', 'Attention deficit hyperactivity disorder', 'Infant', 'Child', 'Adolescent', 'Human'. Sono qui riportate le referenze considerate rilevanti e pertinenti.

Allergy Eur J Allergy Clin Immunol 2014;69:242-43.

INCREASED VIGILANCE IN CHILDREN WITH ATOPIC DERMATITIS (AD) AND/OR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IS BASED ON DISTURBED INTRACELLULAR GRANULE BIOLOGY.

Wolfer W, Krauel K, Bonnekoh B, et al.

Background: Skin, mucosa, brain and immune system are linked by function. Up-regulated vigilance in AD-skin is known to be caused in part by disturbed intracellular granule mechanisms in several cell systems resulting in often insufficient reactions to external stimulation. We now investigated in AD-children reactions of the CNS requiring sustained granule release. Likewise, ADHD-patients unable to keep up an enduring CNS-response were tested for granule release velocity in peripheral immune cells.

Method: Fourteen confirmed ADHDinpatients 11 sex-and age-matched AD-children and 8 healthy individuals (HI) without any atopic/psychiatric background were studied in 3 modules. A Dermato-allergology: Erlanger Atopie Score (EAS), SCORAD, prick test with common aero allergens; B child psychiatry: short and long term attentiveness (S/LTA) using a computerbased test battery as well as various qestionnaires; C laboratory: total serum IgE, eosinophilic cationic protein (ECP), WBC and release velocity (i) of perforin-granules from CD8pos Tcells and (ii) of CD63pos secretory lysosomes from basophilis quantified by flow cytometry.

Results: Module A) 12/14 ADHD-children did not have any AD-symptoms nor any history of atopy, 13/14 showed a white dermographism, EAS was 9 (plus or minus) 3 (atopic skin diathesis unclear). 5/11 AD-patients had exacerbated disease (SCORAD > 10 EAS 12 (plus or minus) 3). Module B) STA: AD-and ADHD-children reacted significantly slower with more mistakes than HI. LTA: AD-children showed prolonged reaction times and slowed down even more over time as compared to HI, but did not make as many errors as ADHD-patients. Module C) ADHD-and AD-children had elevated (i) IgE levels (500 (plus or minus) 420 kU/l and 653 (plus or minus) 950 kU/l), (ii) eosinophils (8.7 (plus or minus) 9% and 7.7 (plus or minus) 6%) and (iii) ECP levels (31 (plus or minus) 30 and 39 (plus or minus) 33). AD-and ADHD-patients released cytotoxic granules, and upregulated CD63 on basophils, significantly faster and more complete as HI ($P < 0.05$).

Conclusion: AD represents an independent risk factor for ADHD. Our data suggest a cell biological basis for this phenomenon. Results in allertness tests are consistent with the hypothesis of pan-cellular granule alterations in AD/atopy as a basis of the well known increased vigilance mechanisms of skin, immune and nervous systems. Altered granule transport mechanisms in ADHD open new insights into ADHD pathophysiology. Since perforin is involved in IgE-control, the perforin-defect in these patients may contribute to their increased susceptibility for atopy.

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Allergy Eur J Allergy Clin Immunol. 2014;69:231.

ASSOCIATION BETWEEN ASTHMA AND ATTENTION-DEFICIT HYPERACTIVITY DISORDERS IN CHILDREN: POTENTIAL RISK FACTORS.

Ehlayel MSS, Bener A, Bener HZ.

Background: Childhood asthma and Attention deficit hyperactivity disorder [ADHD] share behavioral abnormalities of inattention, irritability, or hyperactivity.

Aim: To investigate the prevalence of asthma among ADHD children.

Design: Case-control study conducted June 2011 to September 2013.

Settings: Hamad General Hospital, Rumeilah Hospital, School Health and Primary Health care Clinics, Qatar.

Subjects-patients: Five hundred and twenty children with asthma and ADHD (AADHD) and 520 controls aged 5-16 years old matched controls.

Methods and subjects: Questionnaire, clinical manifestations, family history, BMI serum 25(OH) vitamin D, calcium, phosphorus and magnesium.

Results: The mean age ((plus or minus) SD, in years) for A-ADHD children vs controls was 9.92 (plus or minus) 3.3 vs 10.20 (plus or minus) 3.4. Vitamin D was lower for asthmatic-ADHD compared to controls (17.25 (plus or minus) 10.53 ng/ml vs 23.91(plus or minus) 9.82, $P < 0.0001$). Of 520 asthmatic- ADHD, 18.4% had severe vitamin D deficiency (<10 ng/ml). Obesity was commoner in A-ADHD ($P < 0.001$). Calcium & phosphorous higher in controls than AADHD ($P < 0.001$). Serum vitamin D iron, ferritin,

hemoglobin, magnesium & potassium were significantly lower for AADHD than controls (P < 0.001 for each comparison). There was significant correlation between vitamin D deficiency and with age (r =-0.224, P = 0.001); calcium (r = 0.256, P = 0.001); phosphorous (r = 0.316, P = 0.001); magnesium (r = 0.288, P = 0.001); and BMI (r = 0.452 P = 0.001) in A-ADHD. The multivariate logistic regression analysis showed that age-& gender-adjusted predictors for ADHD were the mean serum vitamin D & calcium, physical activity, nervous behavior consanguinity, BMI & child order.
Conclusion: Vitamin D deficiency was higher in ADHD children. Supplementing infants with vitamin D might be a safe and effective strategy for reducing the risk of ADHD.

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An Pediatr. 2014.
ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AND THEIR RELATIONSHIP WITH CHILD ABUSE: PREDICTOR AND CONSEQUENCE.
Cornella CJ, Juarez Lopez JR.
The current literature increasingly associates the presence of symptoms of ADHD in both physical and psychological and sexual child abuse. This implies the need for greater accuracy in the differential diagnosis, as until a few years ago, post-traumatic stress disorder was considered the reference symptoms for this type of case. Thus, it is necessary to define and conceptualize an increasingly broad and detailed world of sequels and consequences, where ADHD may be related to the psychological damage suffered by child abuse. Furthermore, the particular vulnerability of children with ADHD can, in turn, become a factor of risk that needs to be considered by the professionals who care for this type of patient.

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Arch Phys Med Rehabil. 2014 Aug;95:1556-63.
UTILIZATION OF BEHAVIORAL THERAPY SERVICES LONG-TERM AFTER TRAUMATIC BRAIN INJURY IN YOUNG CHILDREN.
Karver CL, Kurowski B, Semple EA, et al.
OBJECTIVE: To examine associations of clinical need, defined by elevated parent ratings of child behavior problems and utilization of behavioral health services in young children with traumatic brain injury (TBI) and an orthopedic injury (OI) comparison group.
DESIGN: Parents completed outcome measures 18 months after injury and at an extended follow-up conducted an average of 38 months postinjury.
SETTING: Children's hospitals and a general hospital.
PARTICIPANTS: Participants included parents of 3 groups of children injured between 3 and 7 years of age (N=139): 47 children with complicated mild to moderate TBI, 18 with severe TBI, and 74 with OI.
INTERVENTIONS: Not applicable.
MAIN OUTCOME MEASURES: Parents completed ratings of child behavior, mental health symptomology, and family functioning at both visits; at the extended follow-up, they reported utilization of behavior therapy or counseling services since the 18-month follow-up visit.
RESULTS: Children with TBI had more behavior problems than those with OI. Although clinical need at both follow-ups was associated with greater service utilization at the extended follow-up, all groups had unmet needs as defined by a clinical need in the absence of services. Lower socioeconomic status was associated with higher rates of unmet need across groups.
CONCLUSIONS: The results document unmet long-term behavioral health needs after both TBI and OI in children and underscore the importance of monitoring and treatment of postinjury behavior problems.

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Aust Fam Physician. 2014 Apr;43:169.

PAEDIATRIC PSYCHOLOGICAL PROBLEMS.

Pollack A, Harrison C, Charles J, et al.

A 2011 BEACH-based study showed that over the past 40 years there has been increasing general practitioner (GP) involvement in the management of paediatric mental health in Australia. There has also been a changing mix of psychological conditions managed, including increased management of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD).

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Behav Brain Funct. 2014;10:7.

PRELIMINARY EVIDENCE FOR ALTERED MOTION TRACKING-BASED HYPERACTIVITY IN ADHD SIBLINGS.

Reh V, Schmidt M, Rief W, et al.

BACKGROUND: It is well-established that ADHD children have deficits in executive functions such as performance variability and sustained attention. It has been suggested that these deficits are intermediate phenotypes. Hyperactivity, a core symptom of ADHD, has not yet been explored as a potential intermediate phenotype in ADHD. The computerized Quantified behavior Test (QbTest) is a combined continuous performance and activity test that assesses hyperactivity, inattention, and impulsivity separately. The aim of the present study was to (1) investigate the utility of objectively measured motor activity as a potential intermediate phenotype in ADHD, and (2) explore intermediate phenotypes for ADHD at the factor instead of single variable level.

METHOD: Forty-five ADHD children, 22 non-affected siblings, and 45 unrelated controls with no family history of ADHD performed the QbTest. Effects of familiality as well as influences of age and gender on QbTest symptom dimensions were tested.

RESULTS: ADHD children showed the greatest impairments on all three QbTest factors, followed by their non-affected siblings, with control children showing the lowest scores. Group differences between the non-affected siblings and controls were only significant for the motion tracking-based Hyperactivity factor. Results were independent of age and gender.

CONCLUSION: Hyperactivity assessed by a motion tracking system may be a useful intermediate phenotype in ADHD. Prospective research should use larger samples to further examine the QbTest factors, especially the motion tracking-based Hyperactivity factor which may be a candidate for an intermediate phenotype in ADHD.

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Best Pract Res Clin Obstet Gynaecol. 2014 Jan;28:25-35.

MATERNAL DEPRESSION, ANXIETY AND STRESS DURING PREGNANCY AND CHILD OUTCOME; WHAT NEEDS TO BE DONE.

Glover V.

Care for the emotional state of pregnant women remains a neglected aspect of obstetric medicine. Many prospective studies have shown that, if a mother is depressed, anxious, or stressed while pregnant, this increases the risk for her child having a wide range of adverse outcomes, including emotional problems, symptoms of attention deficit hyperactivity disorder, or impaired cognitive development. Although genetics and postnatal care clearly affect these outcomes, evidence for an additional prenatal causal component is substantial. Prenatal anxiety or depression may contribute 10-15% of the attributable load for emotional and behavioural outcomes. The Nurse Family Partnership remains the only intervention that starts in pregnancy and has been shown to have long-term benefits for the behaviour of the child. Several other interventions, however, are likely to be helpful. Depression, anxiety, and stress during pregnancy are frequently undetected by health professionals, and untreated. Programmes to help with this should eventually improve child outcome.

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Biol Psychol. 2014 Jan;95:86-95.

BENEFICIAL OUTCOME FROM EEG-NEUROFEEDBACK ON CREATIVE MUSIC PERFORMANCE, ATTENTION AND WELL-BEING IN SCHOOL CHILDREN.

Gruzelier JH, Foks M, Steffert T, et al.

We earlier reported benefits for creativity in rehearsed music performance from alpha/theta (A/T) neurofeedback in conservatoire studies (Egner & Gruzelier, 2003) which were not found with SMR, Beta1, mental skills, aerobics or Alexander training, or in standby controls. Here the focus was the impact on novice music performance. A/T and SMR training were compared in 11-year old school children along with non-intervention controls with outcome measures not only of rehearsed music performance but also of creative improvisation, as well as sustained attention and phenomenology. Evidence of effective learning in the school setting was obtained for A/T and SMR/beta2 ratios. Preferential benefits from A/T for rehearsed music performance were replicated in children for technique and communication ratings. Benefits extended to creativity and communication ratings for creative improvisation which were shared with SMR training, disclosing an influence of SMR on unrehearsed music performance at a novice level with its greater cognitive demands. In a first application of A/T for improving sustained attention (TOVA), it was found to be more successful than SMR training, with a notable reduction in commission errors in the children, 15/33 of whom had attention indices in the ADHD range. Phenomenological reports were in favour of neurofeedback and well-being benefits. Implementing neurofeedback in the daily school setting proved feasible and holds pedagogic promise.

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Biol Psychol. 2014 Feb;96:126-33.

INFLUENCE OF ALCOHOL ON SOCIAL ANXIETY: AN INVESTIGATION OF ATTENTIONAL, PHYSIOLOGICAL AND BEHAVIORAL EFFECTS.

Stevens S, Cludius B, Bantin T, et al.

Social anxiety disorder and alcohol use disorders are highly comorbid. It remains unclear, however, if and how alcohol influences attentional processes and physical symptoms in social anxiety. In a balanced-placebo-design, high and normally socially anxious participants gave a speech while performing a task, which simultaneously measures internal and external attention. Only high anxious participants showed a preferential processing of external probes, which was eliminated by alcohol or the mere expectation of drinking alcohol. Furthermore, alcohol reduced facial blushing as well as self-reported social anxiety during public speaking. Decreases in anxiety were significantly associated with a reduction of the external focus in the high anxious group. Understanding alcohol as a substance influencing cognitive processes as well as physiological symptoms of anxiety further contributes to our understanding of alcohol use as a safety behavior in social anxiety disorder.

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Brain. 2014;137:2423-28.

BRAIN DIFFERENCES BETWEEN PERSISTENT AND REMITTED ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Mattfeld AT, Gabrieli JDE, Biederman J, et al.

Previous resting state studies examining the brain basis of attention deficit hyperactivity disorder have not distinguished between patients who persist versus those who remit from the diagnosis as adults. To characterize the neurobiological differences and similarities of persistence and remittance, we performed resting state functional magnetic resonance imaging in individuals who had been longitudinally and uniformly characterized as having or not having attention deficit hyperactivity disorder in childhood and again in adulthood (16 years after baseline assessment). Intrinsic functional brain organization was measured in patients who had a persistent diagnosis in childhood and adulthood (n = 13), in patients who met diagnosis in childhood but not in adulthood (n = 22), and in control participants who never had attention deficit hyperactivity disorder (n = 17). A positive functional correlation between posterior cingulate and medial prefrontal cortices, major components of the default-mode network, was reduced only in patients whose diagnosis persisted into adulthood. A negative functional correlation between medial and

dorsolateral prefrontal cortices was reduced in both persistent and remitted patients. The neurobiological dissociation between the persistence and remittance of attention deficit hyperactivity disorder may provide a framework for the relation between the clinical diagnosis, which indicates the need for treatment, and additional deficits that are common, such as executive dysfunctions.

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Brain Dev. 2014 Feb;36:107-15.

DEVELOPMENT AND VERIFICATION OF CHILD OBSERVATION SHEET FOR 5-YEAR-OLD CHILDREN.

Fujimoto K, Nagai T, Okazaki S, et al.

The aim of the study was to develop a newly devised child observation sheet (COS-5) as a scoring sheet, based on the Childhood Autism Rating Scale (CARS), for use in the developmental evaluation of 5-year-old children, especially focusing on children with autistic features, and to verify its validity. Seventy-six children were studied. The children were recruited among participants of the Japan Children's Cohort Study, a research program implemented by the Research Institute of Science and Technology for Society (RISTEX) from 2004 to 2009. The developmental evaluation procedure was performed by doctors, clinical psychologists, and public health nurses. The COS-5 was also partly based on the Kyoto Scale of Psychological Development 2001 (Kyoto Scale 2001). Further, the Developmental Disorders Screening Questionnaire for 5-Years-Olds, PDD-Autism Society Japan Rating Scale (PARS), doctor interview questions and neurological examination for 5-year-old children, and the Draw-a-Man Test (DAM) were used as evaluation scales. Eighteen (25.4%) children were rated as Suspected, including Suspected PDD, Suspected ADHD and Suspected MR. The COS-5 was suggested to be valid with favorable reliability (alpha=0.89) and correlation with other evaluation scales. The COS-5 may be useful, with the following advantages: it can be performed within a shorter time frame; it facilitates the maintenance of observation quality; it facilitates sharing information with other professions; and it is reliable to identify the autistic features of 5-year-old children. In order to verify its wider applications including the screening of infants (18months to 3years old) by adjusting the items of younger age, additional study is needed.

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Cereb Cortex. 2014 Jan;24:174-85.

SHARED AND DRUG-SPECIFIC EFFECTS OF ATOMOXETINE AND METHYLPHENIDATE ON INHIBITORY BRAIN DYSFUNCTION IN MEDICATION-NAIVE ADHD BOYS.

Cubillo A, Smith AB, Barrett N, et al.

The stimulant methylphenidate (MPX) and the nonstimulant atomoxetine (ATX) are the most commonly prescribed medications for attention deficit hyperactivity disorder (ADHD). However, no functional magnetic resonance imaging (fMRI) study has as yet investigated the effects of ATX on inhibitory or any other brain function in ADHD patients or compared its effects with those of MPX. A randomized, double-blind, placebo-controlled, crossover pharmacological design was used to compare the neurofunctional effects of single doses of MPX, ATX, and placebo during a stop task, combined with fMRI within 19 medication-naive ADHD boys, and their potential normalization effects relative to 29 age-matched healthy boys. Compared with controls, ADHD boys under placebo showed bilateral ventrolateral prefrontal, middle temporal, and cerebellar underactivation. Within patients, MPX relative to ATX and placebo significantly upregulated right ventrolateral prefrontal activation, which correlated with enhanced inhibitory capacity. Relative to controls, both drugs significantly normalized the left ventrolateral prefrontal underactivation observed under placebo, while MPX had a drug-specific effect of normalizing right ventrolateral prefrontal and cerebellar underactivation observed under both placebo and ATX. The findings show shared and drug-specific effects of MPX and ATX on performance and brain activation during inhibitory control in ADHD patients with superior upregulation and normalization effects of MPX.

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Child Care Health Dev. 2014 Sep;40:698-705.

RELATIONSHIP AMONG ATTENTION-DEFICIT HYPERACTIVITY DISORDER, DIETARY BEHAVIOURS AND OBESITY.

Kim EJ, Kwon HJ, Ha M, et al.

Background Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood and can be associated with obesity. The aim of this study was to reveal the connection between ADHD symptoms, food habits and obesity.

Methods We examined 12 350 children (6010 boys, 6340 girls) from 27 elementary schools in Cheonan, the Republic of Korea. The study subjects were 5- to 13-year-old children (9.4 ± 1.7 years). Parents completed the DuPaul ADHD Rating Scale. Food habits were measured by a questionnaire adapted from the Korea Youth Risk Behavior Web-based Survey and a validated mini-dietary assessment tool. The full set of hypothesized associations was tested using covariance structural modelling.

Results The prevalence of ADHD was 7.6% and that of obesity was 4.5% in our study population. The data was well fit by the model. ADHD was associated with body mass index (BMI; standardized ß = 0.086, P < 0.001). Bulimic dietary behaviours was related to BMI (standardized ß = 0.548, P < 0.001). Socio-economic status was associated with BMI (standardized ß = -0.017, P = 0.027).

Conclusion Our analysis suggested that ADHD was a risk factor for obesity through dietary behavioural change and socio-economic status.

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Child Care Health Dev. 2014 Sep;40:706-14.

PATERNAL ADHD SYMPTOMS AND CHILD CONDUCT PROBLEMS: IS FATHER INVOLVEMENT ALWAYS BENEFICIAL?

Romirowsky AM, Chronis-Tuscano A .

Background Maternal psychopathology robustly predicts poor developmental and treatment outcomes for children with attention-deficit/hyperactivity disorder (ADHD). Despite the high heritability of ADHD, few studies have examined associations between paternal ADHD symptoms and child adjustment, and none have also considered degree of paternal involvement in childrearing. Identification of modifiable risk factors for child conduct problems is particularly important in this population given the serious adverse outcomes resulting from this comorbidity.

Methods This cross-sectional study examined the extent to which paternal involvement in childrearing moderated the association between paternal ADHD symptoms and child conduct problems among 37 children with ADHD and their biological fathers.

Results Neither paternal ADHD symptoms nor involvement was independently associated with child conduct problems. However, the interaction between paternal ADHD symptoms and involvement was significant, such that paternal ADHD symptoms were positively associated with child conduct problems only when fathers were highly involved in childrearing.

Conclusions The presence of adult ADHD symptoms may determine whether father involvement in childrearing has a positive or detrimental influence on comorbid child conduct problems.

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Clin Psychol Rev. 2014 Aug;34:496-505.

OMEGA-3 FATTY ACID AND ADHD: BLOOD LEVEL ANALYSIS AND META-ANALYTIC EXTENSION OF SUPPLEMENTATION TRIALS.

Hawkey E, Nigg JT.

Interest in the value of omega-3 (n-3) fatty acid supplementation for treatment of ADHD remains high. No prior meta-analysis has examined whether ADHD is associated with alterations in blood lipid levels and meta-analyses of supplementation have reached conflicting conclusions. Methods: We report two new meta-analyses. Study 1 examined blood levels of omega-3 fatty acids in relation to ADHD. Study 2 examined a larger sample of randomized intervention trials than previously reported. Results: Study 1 included 9 studies (n=586) and found lower overall blood levels of n-3 in individuals with ADHD versus controls (g=0.42, 95% CI=0.26–0.59; p<.001). Study 2 included 16 studies (n=1408) and found that n-3 supplementation improved ADHD composite symptoms; using the best available rating and reporter

(g=0.26, 95% CI=0.15–0.37; p<.001). Supplementation showed reliable effects on hyperactivity by parent and teacher report, but reliable effects for inattention only by parent report. Conclusions: Omega-3 levels are reduced in children with ADHD. Dietary supplementation appears to create modest improvements in symptoms. There is sufficient evidence to consider omega-3 fatty acids as a possible supplement to established therapies. However it remains unclear whether such intervention should be confined to children with below normal blood levels.

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Clin Psychopharmacol Neurosci. 2014;12:137-41.

THE AMYGDALA'S NEUROCHEMICAL RATIOS AFTER 12 WEEKS ADMINISTRATION OF 20 MG LONG-ACTING METHYLPHENIDATE IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER: A PILOT STUDY USING 1H MAGNETIC RESONANCE SPECTROSCOPY.

Wiguna T, Guerrero APS, Wibisono S, et al.

Objective: Recent pediatric studies have suggested a correlation between decreased amygdala volume and attention deficit and hyperactivity disorder (ADHD) symptoms, including the emotional dysregulation. To investigate the hypothesis that medication treatment of ADHD specifically improves amygdala function, we used 1H magnetic resonance spectroscopy (MRS) to study the effect of 12 weeks of treatment with daily 20 mg long-acting methylphenidate on the Glu/Cr, NAA/Cr, Cho/Cr, and mI/Cr ratios in the amygdala of medication- naive children with ADHD.

Methods: This was a prospective study, using a pre- and post-test design, on a single group of 21 children (average age 8.52 years, 17 males and 4 females) diagnosed with ADHD. Low Time Echo MRS scans sampled voxels of interest (1.5null1.5null2.0) from both the right and left amygdala.

Results: There was significant clinical improvement after 12 weeks of treatment with 20 mg long-acting methylphenidate. On 1H MRS, there were no statistical significant differences of NAA/Cr ratio, Cho/Cr ratio, mI/Cr ratio before and after 12 weeks administration of 20 mg long-acting methylphenidate both in the right and left amygdala. In addition, Glu/Cr ratio decreased 14.1% in the right amygdala (p=0.029) and 11.4% in the left amygdala (p=0.008). Standardized mean effect sizes ranged from 0.14-0.32.

Conclusion: The findings are consistent with the possibility that hyperglutamatergic processes in the amygdale are related to the hyperactive-impulsive symptoms of ADHD.

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Community Ment Health J. 2014 Feb;50:185-92.

COMMUNICATION ABOUT ADHD AND ITS TREATMENT DURING PEDIATRIC ASTHMA VISITS.

Sleath B, Sulzer SH, Carpenter DM, et al.

The objectives of the study were to examine provider-family communication about attention deficit disorder during pediatric asthma visits. Children with asthma, aged 8 through 16 and their parents were recruited at five pediatric practices. All medical visits were audio-taped. There were 296 asthmatic children enrolled into the study and 67 of them also had attention deficit hyperactivity disorder (ADHD). ADHD communication elements suggested by national guidelines were discussed infrequently. Providers were more likely to discuss, educate, and ask one or more questions about ADHD medications if the visit was non-asthma related. Providers included child input into the ADHD treatment regimen during 3% of visits and they included parent input during 4.5% of visits. Only one child and three parents asked questions about ADHD. Providers may neglect essential aspects of good ADHD management and communication in children who have ADHD plus another chronic condition such as asthma. Providers should set appropriate treatment expectations, establish target symptoms, and encourage children and parents to ask questions so mutual decision-making can occur.

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Curr Opin Psychiatry. 2014 Mar;27:98-104.

FOETAL ALCOHOL SPECTRUM DISORDER: IDENTIFYING THE NEUROBEHAVIOURAL PHENOTYPE AND EFFECTIVE INTERVENTIONS.

Koren G, Zelner I, Nash K, et al.

PURPOSE OF REVIEW: Since the first description of the foetal damage of alcohol in 1967, numerous studies have outlined different aspects of neurodevelopmental dysfunction, adversely affecting the lives of children worldwide. Although the cause of the syndrome is sorted out, the pathogenesis of brain damage is far from being clear. In contrast to children exhibiting the full facial dysmorphology, who are relatively easy to diagnose, in those presenting only with alcohol-related neurodevelopmental damage diagnosis is much more challenging due to poor specificity of the brain dysfunction. Hence, identifying the neurodevelopmental phenotype of foetal alcohol spectrum disorder (FASD) is a major challenge.
RECENT FINDINGS: Recently, a behavioural phenotype of FASD has been described and validated using items from the Child Behaviour Checklist. This tool has high sensitivity and specificity in separating children with FASD from those with ADHD and from healthy controls. In parallel, a number of intervention studies show promise in improving the abilities of children and adolescents with the syndrome to cope with daily tasks and improve their quality of life.
SUMMARY: The neurobehavioural screening test can facilitate screening for FASD and is an official screening tool in the FASD toolkit of the Public Health Agency of Canada. Promising new interventions may attenuate the long-term outcome of these children.

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Drug Alcohol Depend. 2014 Feb;135:88-94.

CHILDHOOD AND CURRENT ADHD SYMPTOM DIMENSIONS ARE ASSOCIATED WITH MORE SEVERE CANNABIS OUTCOMES IN COLLEGE STUDENTS.

Bidwell LC, Henry EA, Willcutt EG, et al.

BACKGROUND: Numerous studies have shown that attention deficit/hyperactivity disorder (ADHD) is associated higher risk of cannabis use disorders (CUD). However, these studies are limited in that most did not: (a) differentiate the role of hyperactivity-impulsivity (HI) and inattention (IN); (b) control for associated psychopathology; and (c) consider more fine-grained CUD-related measures. Our aim was to clarify the unique and interactive contributions of inattention and hyperactivity symptoms to age of cannabis initiation and DSM-IV cannabis dependence, craving, and severity of problems related to cannabis use while statistically controlling for symptoms of comorbid psychopathology in a non-clinical sample of young adults.
METHODS: Cannabis variables, current use of cigarettes and alcohol, current and childhood ADHD, and comorbid internalizing and externalizing psychopathology were assessed in 376 male and female undergraduates.
RESULTS: Results indicate that current and childhood IN were independently associated with more severe cannabis use, craving, and problem use-related outcomes in young adulthood (p's<.01) and that childhood HI symptoms were associated with earlier initiation of cannabis (p<.01). Further, current IN symptoms moderated the relationships between level of use and more severe outcomes (p's<.01), such that higher IN strengthened positive associations among use and problem cannabis use. Associations with ADHD symptom dimensions and current use of alcohol and cigarettes were also present.
CONCLUSIONS: Thus, current and childhood inattention symptoms as well as childhood hyperactive-impulsive symptoms emerged as significant factors in cannabis-related outcomes in young adults, even after statistically controlling for important confounding variables.

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Egypt J Neurol , Psychiatr Neurosurg. 2014;51:361-67.

EFFICACY AND ATTRIBUTES OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) IN TREATMENT OF A SAMPLE OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Bayoumy IM, Khaleel SH, Nada M, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a syndrome that affects children. Repetitive transcranial magnetic stimulation (rTMS) can produce effects on dopaminergic system similar to effects of D-amphetamine

Objective: To evaluate efficacy of rTMS as a therapeutic modality in ADHD in children

Methods: This study was conducted on 41 ADHD children. All patients were subjected to clinical psychiatric and psychometric assessment using Kiddie Schedule, Wechsler Intelligence Scale and Connersnull Parent Rating Scale Revised Long-version (CPRS-R-L). Neurological assessment by diagnostic TMS, Physical and Neurological Examination for Soft Signs (PANESS) scale for neurological soft signs, and conventional EEG were done before and after rTMS given at low frequency 1Hz, 1200stimuli/day for five days

Results: EEG showed increased beta activity in 26 cases (63.4%) after rTMS. Highly significant reductions were found in all studied dimensions except perfectionism scale and psychosomatic scale. Females showed higher percent of change in psychosomatic subscale and ipsilateral silent period (ISP) latency. Boys showed significant reduction of oppositional attitude and hyperactivity. Hyperactivity and ISP duration showed significant correlation with older ages. Highly significant difference in the anxious shy was found in the inattentive subtype. Social problems showed significant change in the combined type. Psychosomatic dimension was significantly increased in the inattentive compared to combined type. ISP latency showed significant change on correlating inattentive with hyperactive impulsive type

Conclusion: Most of the used tests showed significant results but the higher difference in diagnostic TMS and PANESS scale makes them superior over psychometric tests in evaluating rTMS therapy.

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Emotional & Behavioural Difficulties. 2014 Jul;19:245.

EDITORIAL: THE PRACTICES OF DEALING WITH CHILDREN IN NEED OF SPECIAL SUPPORT: A NORDIC PERSPECTIVE.

Daniels H.

This special issue edited by Eva Hjörne and Roger Säljö to the Journal. They make a stronger case for a more nuanced understanding of the power of categories than that which is often to be found in policy documents and critiques of special education. The ‘new (ish) wave’ of categories, such as ADHD, do their own kind of work and bring with them new tensions and dilemmas for professionals working with troubled children. The collection of articles which Eva and Roger have assembled provides us with insights from Scandinavian practice. They are most welcome and provide us with perspectives that offer much to those concerned with policy and practice.

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Epilepsy Behav. 2014 Feb;31:351-55.

HOW DO WE MEASURE PSYCHIATRIC DIAGNOSES? IMPLICATIONS OF THE CHOICE OF INSTRUMENTS IN EPILEPSY.

Hesdorffer DC, Baldin E, Caplan R, et al.

We evaluated several commonly used screening instruments for the detection of mood disorders, anxiety disorders, and attention-deficit hyperactivity disorder (ADHD). These were compared to a criterion-based standardized questionnaire, the Diagnostic Interview Survey (DIS)-IV, designed to make DSM-IV-TR diagnoses in the community-based study of childhood-onset epilepsy. The DIS-IV was administered to young adult cases with epilepsy at a 15-year follow-up assessment and compared to symptom screens administered at the same visit, and at a previous 9-year assessment. Among cases, the specificity of the DIS-IV ranged from 0.77 to 0.99 and the predictive value of a negative psychiatric diagnosis was similarly high. Sensitivity was lower, ranging from 0 to 0.77, with correspondingly low predictive value of a positive diagnosis. Symptom-based instruments assess current symptom burden and are useful for determining associations with ongoing seizures or quality of life. Criterion-based standardized interviews, such as the

DIS-IV, provide psychiatric diagnoses over the lifetime, which is most useful in studies of epilepsy genetics and studies of comorbidities and prognosis of epilepsy.

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Eur Arch Otorhinolaryngol. 2014 Jan;271:199-201.

SUDDEN HEARING LOSS ASSOCIATED WITH METHYLPHENIDATE THERAPY.

Karapinar U, Saglam O, Dursun E, et al.

An 8-year-old child diagnosed with attention deficit/hyperactivity disorder presented to our Department of Otolaryngology 4 days after suffering hearing loss, loss of balance, tinnitus, and fullness sensation of the left ear. Her symptoms occured with the first dose of methylphenidate. The medical history and physical examination revealed no other diseases associated with sudden hearing loss. The audiogram revealed a total hearing loss on the left ear. Stapedial reflexes, distortion product and transient-evoked otoacoustic emissions were absent in left ear. The absence of clinical, laboratory and radiological evidence of a possible cause for complaints, an association between methylphenidate and sudden hearing loss was suggested. The patient received a standard course of oral corticosteroid and hyperbaric oxygen therapy. Weekly otological and audiological examinations were performed. Conservative and medical treatments offered no relief from hearing loss. Sudden hearing loss is a serious and irreversible adverse effect of methylphenidate. Therefore, the risk of hearing loss should be taken into consideration when initiating methylphenidate therapy.

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Eur Arch Psychiatry Clin Neurosci. 2014 Feb;264:71-81.

HUMAN CLOCK GENE-ASSOCIATED ATTENTION DEFICIT HYPERACTIVITY DISORDER-RELATED FEATURES IN HEALTHY ADULTS: QUANTITATIVE ASSOCIATION STUDY USING WENDER UTAH RATING SCALE.

Jeong SH, Yu JC, Lee CH, et al.

Circadian rhythm disturbance is highly prevalent in attention deficit hyperactivity disorder (ADHD). Recently, the association between the CLOCK gene and ADHD has been demonstrated in clinical samples, and the CLOCK gene's role was thought to be mediated by rhythm dysregulation. Meanwhile, ADHD has been suggested as the extreme end of a continuously distributed trait that can be found in the general population. Therefore, we examined two possibilities: (1) an ADHD-related continuous trait may be associated with the CLOCK gene, and (2) this association may be mediated by the degree of individuals' evening preference. To explore these possibilities, we performed a quantitative trait locus association study with a sample of 1,289 healthy adults. The Wender Utah Rating Scale (WURS) and the Composite Scale of Morningness (CSM) were utilized to measure the quantitative traits. Quantitative association analysis was performed using PLINK software. We found that rs1801260 (=T3111C) was associated with WURS scores in both allele-wise (p = 0.018) and haplotype-wise analyses (range of p values: 0.0155-0.0171) in male participants only. After controlling for the CSM total score as a covariate, the strength of the association did not change at all, suggesting that the association was not mediated by evening preference. Despite the very weak association signal, our results provide evidence that the CLOCK gene's association with ADHD in clinical samples may be generalizable to traits measured in the normal population. However, as our results failed to show a mediating role of evening preference, ongoing efforts are needed to identify the mechanisms by which the CLOCK gene determines ADHD-related traits.

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Eur J Med Genet. 2014 Jan;57:47-53.

DISTAL 10Q MONOSOMY: NEW EVIDENCE FOR A NEUROBEHAVIORAL CONDITION?

Plaisancie J, Bouneau L, Cances C, et al.

Pure distal monosomy of the long arm of chromosome 10 is a rare cytogenetic abnormality. The location and size of the deletions described in this region are variable. Nevertheless, the patients share characteristic facial appearance, variable cognitive impairment and neurobehavioral manifestations. A

Minimal Critical Region corresponding to a 600 kb Smallest Region of deletion Overlap (SRO) has been proposed. In this report, we describe four patients with a distal 10q26 deletion, who displayed attention-deficit/hyperactivity disorders (ADHD). One of them had a marked behavioral profile and relatively preserved cognitive functions. Interestingly, the SRO was not included in the deleted segment of this patient suggesting that this deletion could contain candidate genes involved in the control of neurobehavioral functions. One of these candidates was the CALY gene, known for its association with ADHD patients and whose expression level was shown to be correlated with neurobehavioral disturbances in varying animal models. This report emphasizes the importance of the behavioral problems as a cardinal feature of the 10q microdeletion syndrome. Haploinsufficiency of CALY could play a crucial role in the development of the behavioral troubles within these patients.

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European Child & Adolescent Psychiatry. 2014.

MULTILEVEL ANALYSIS OF ADHD, ANXIETY AND DEPRESSION SYMPTOMS AGGREGATION IN FAMILIES.

Segenreich D, Paez MS, Regalla MA, et al.

A strong genetic role in the etiology of attention-deficit hyperactivity disorder (ADHD) has been demonstrated by several studies using different methodologies. Shortcomings of genetic studies often include the lack of golden standard practices for diagnosis for ADHD, the use of categorical instead of a dimensional approach, and the disregard for assortative mating phenomenon in parents. The current study aimed to overcome these shortcomings and analyze data through a novel statistical approach, using multilevel analyses with Bayesian procedures and a specific mathematical model, which takes into account data with an elevated number of zero responses (expected in samples with few or no ADHD symptoms). Correlations of parental clinical variables (ADHD, anxiety and depression) to offspring psychopathology may vary according to gender and type of symptoms. We aimed to investigate how those variables interact within each other. One hundred families, comprising a proband child or adolescent with ADHD or a typically developing child or adolescent were included and all family members (both biological parents, the proband child or adolescent and their sibling) were examined through semi-structured interviews using DSM-IV criteria. Results indicated that: (a) maternal clinical variables (ADHD, anxiety and depression) were more correlated with offspring variables than paternal ones; (b) maternal inattention (but not hyperactivity) was correlated with both inattention and hyperactivity in the offspring; (c) maternal anxiety was correlated with offspring inattention; on the other hand, maternal inattention was correlated with anxiety in the offspring. Although a family study design limits the possibility of revealing causality and cannot disentangle genetic and environmental factors, our findings suggest that ADHD, anxiety and depression are variables that correlate in families and should be addressed together. Maternal variables significantly correlated with offspring variables, but the paternal variables did not.

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Eur Child Adolesc Psychiatry. 2014;23:627-36.

SUBTHRESHOLD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IS ASSOCIATED WITH FUNCTIONAL IMPAIRMENTS ACROSS DOMAINS: A COMPREHENSIVE ANALYSIS IN A LARGE-SCALE COMMUNITY STUDY.

Hong S-B, Dwyer D, Kim J-W, et al.

This study compared children who experience attention-deficit/hyperactivity disorder (ADHD) symptoms but do not meet criteria (i.e., subthreshold ADHD) with those with the full syndrome and healthy controls. Presence of ADHD symptoms was determined in a nationwide community sample of 921 children, aged 8-11 years. The main outcome measures comprised attentional symptoms, comorbidity profiles, academic performance, and neurocognitive ability (i.e., ADHD Rating Scale, Child Behavior Checklist, Learning Disability Evaluation Scale, and Stroop Color-Word Test, respectively). Subthreshold ADHD was equally prevalent in boys and girls, and more prevalent in low-income families. Throughout all the outcome measurements, subthreshold ADHD was both a significantly milder condition than full syndrome ADHD and a significantly more severe condition than non-ADHD status. The findings were consistent across the total as well as the subtest scores, and after correction for multiple comparisons ($p < 0.0017$). Children with

subthreshold ADHD were found to experience significant symptoms and functional impairments. The results of this study support the clinical relevance of subthreshold ADHD in a childhood population. Subthreshold diagnostic criteria for ADHD may be more sensitive in detecting ADHD symptoms in girls than the full syndrome criteria, and subthreshold clinical, cognitive, and behavioral symptoms of ADHD may occur in a subset of children who are possibly more sensitive to their environment. Further consideration about the diagnostic threshold for ADHD may particularly benefit girls and children in low-income families.

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Eur Child Adolesc Psychiatry. 2014;23:649-57.

IMPAIRED REFLEXIVE ORIENTING TO SOCIAL CUES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Marotta A, Casagrande M, Rosa C, et al.

The present study investigated whether another person's social attention, specifically the direction of their eye gaze, and non-social directional cues triggered reflexive orienting in individuals with Attention Deficit Hyperactivity Disorder (ADHD) and age-matched controls. A choice reaction time and a detection tasks were used in which eye gaze, arrow and peripheral cues correctly (congruent) or incorrectly (incongruent) signalled target location. Independently of the type of the task, differences between groups were specific to the cue condition. Typically developing individuals shifted attention to the location cued by both social and non-social cues, whereas ADHD group showed evidence of reflexive orienting only to locations previously cued by non-social stimuli (arrow and peripheral cues) but failed to show such orienting effect in response to social eye gaze cues. The absence of reflexive orienting effect for eye gaze cues observed in the participants with ADHD may reflect an attentional impairment in responding to socially relevant information.

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Eur Child Adolesc Psychiatry. 2014;23:623-25.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: SEEKING THE RIGHT BALANCE BETWEEN OVER- AND UNDERTREATMENT.

Hoekstra PJ, Dietrich A.

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Expert Opinion on Drug Safety. 2014;13:S69-S78.

ATOMOXETINE IN THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND SUICIDAL IDEATION.

Capuano A, Scavone C, Rafaniello C, et al.

Objective: Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric childhood disorder. The most commonly used drugs in the treatment of ADHD are methylphenidate (MPH) and atomoxetine (ATX); the former of the two is prescribed in USA more than it is in Western Europe. Some of the most important safety concerns about ADHD drug treatment are sudden cardiac death and suicidal behavior. In this study, we present a series of cases of Italian children who had presented suicidal ideation during ADHD pharmacological therapy with ATX.

Research design and methods: Data were obtained from the ADHD Italian Register. The data assessed the use of MPH and ATX, which had been prescribed to patients who were aged <18 years and diagnosed with ADHD. All patients enrolled in the ADHD Italian Register treated with ATX or MPH who experienced suicidal thoughts or thoughts of self-harming were considered and assessed.

Results: We describe the clinical cases of seven Italian children (enrolled in the ADHD Italian Register) treated with ATX and affected by suicidal ideation, self-harming or other similar symptoms. Our results highlighted that all seven patients developed suicidal ideation or intentional self-harming during pharmaceutical treatment with ATX and, particularly, after the dose increase of the drug.

Conclusion: There is a need to improve our knowledge about the efficacy and safety of ATX, MPH and other drugs used in the treatment of ADHD both in children and adults during the post-marketing experience.

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Front Human Neurosci. 2014;8.

EEG SPECTRAL ANALYSIS OF ATTENTION IN ADHD: IMPLICATIONS FOR NEUROFEEDBACK TRAINING?

Heinrich H, Busch K, Studer P, et al.

Objective: In children with attention-deficit/hyperactivity disorder (ADHD), an increased theta/beta ratio in the resting EEG typically serves as a rationale to conduct theta/beta neurofeedback (NF) training. However, this finding is increasingly challenged. As NF may rather target an active than a passive state, we studied the EEG in a condition that requires attention.

Methods: In children with ADHD of the DSM-IV combined type (ADHD-C; N = 15) and of the predominantly inattentive type (ADHD-I; N = 9) and in typically developing children (N = 19), EEG spectral analysis was conducted for segments during the attention network test (ANT) without processing of stimuli and overt behavior. Frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrodes were included in the statistical analysis. To investigate if EEG spectral parameters are related to performance measures, correlation coefficients were calculated.

Results: Particularly in the ADHD-C group, higher theta and alpha activity was found with the most prominent effect in the upper-theta/lower-alpha (5.5-10.5 Hz) range. In the ADHD-I group, a significantly higher theta/beta ratio was observed at single electrodes (F3, Fz) and a tendency for a higher theta/beta ratio when considering all electrodes (large effect size). Higher 5.5-10.5 Hz activity was associated with higher reaction time variability with the effect most prominent in the ADHD-C group. A higher theta/beta ratio was associated with higher reaction times, particularly in the ADHD-I group.

Conclusions: (1) In an attention demanding period, children with ADHD are characterized by an underactivated state in the EEG with subtype-specific differences. (2) The functional relevance of related EEG parameters is indicated by associations with performance (reaction time) measures. (3) Findings provide a rationale for applying NF protocols targeting theta (and alpha) activity and the theta/beta ratio in subgroups of children with ADHD.

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Horm Res Paediatr. 2014;82:31-37.

STIMULANT USE AND ITS IMPACT ON GROWTH IN CHILDREN RECEIVING GROWTH HORMONE THERAPY: AN ANALYSIS OF THE KIGS(REGISTERED TRADEMARK) INTERNATIONAL GROWTH DATABASE.

Miller BS, Aydin F, Lundgren F, et al.

Background: Children receiving stimulants for attention deficit hyperactivity disorder (ADHD) frequently present to pediatric endocrinology clinics for evaluation and treatment of growth disorders. The worldwide prevalence of stimulant use in children with ADHD also receiving recombinant human growth hormone (rhGH) and the impact on response to rhGH are unknown.

Methods: Data on children enrolled in the KIGS(registered trademark) (Pfizer International Growth Study) registry were evaluated for the associated diagnosis of ADHD prior to initiation of Genotropin(registered trademark) rhGH. Concomitant stimulant medications and auxological information were captured. Response to rhGH was evaluated using established growth prediction models.

Results: The prevalence of ADHD in KIGS was 2.3% (1,748/75,251), with stimulants used in 1.8% (1,326/75,251). Children with idiopathic growth hormone deficiency (IGHD) who received stimulants grew significantly less (1.1 cm) in the first year of rhGH therapy than expected for rhGH-treated non-ADHD IGHD children. After one year of rhGH, idiopathic short stature (ISS) children with ADHD were significantly shorter [0.74 cm (with stimulants) and 0.69 cm (without stimulants)] than non-ADHD ISS children.

Conclusions: We demonstrated an impaired response to rhGH in IGHD and ISS children with ADHD. Our findings suggest that the ADHD phenotype, alone or in conjunction with stimulant therapy, may impair the short-term growth response to rhGH.

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Indian J Psychiatry. 2014;56:S85.

PREVALENCE OF ADULT ADHD IN RECENTLY DIAGNOSED HIV MALES IN A TERTIARY CARE CENTER .

Shankar K, Nahar A, Aashik YS, et al.

Introduction: A majority of children with symptoms of attention deficit hyperactivity disorder (ADHD) from early childhood continue to demonstrate notable ADHD symptoms throughout life though in later life hyperactive/impulsive subtype manifests more frequently causing persistent and significant impairment among different areas of life. Impulsivity in later life has been found to predict unstable interpersonal relationships and high risk sexual behavior. There is no literature on the prevalence of adult ADHD among patients with human immunodeficiency virus (HIV) and which could pave way for further studies including planning primary prevention strategies as this is a potentially treatable condition.

Aims and Objectives: To determine the prevalence of adult ADHD in recently diagnosed young male HIV patients. 1. To determine other factors contributing to high risk sexual behavior in adult ADHD.

Materials and Methods: We recruited 100 HIV positive young adult males with less than 1 year of diagnosed HIV after informed consent. They were administered Adult ADHD Self-Report Scale (ASRS) v1.1 to screen for ADHD in adulthood. Those who scored more than cutoff were then administered the Abbreviated Conners retrospective to parent/informant and Wender-Reimherr Adult ADHD Rating Scale to confirm ADHD, The Mini-International Neuropsychiatric Interview (MINI) plus to rule out (r/o) comorbidities, mini-mental state examination (MMSE) to r/o major neurocognitive impairment, Zuckerman-Kuhlman Personality Questionnaire to screen for sensation seeking and impulsivity traits, and HIV Risk Taking Behavior Scale to assess high risk sexual behaviors.

Results: There was significantly high prevalence of adult ADHD among young males with HIV. Details will be discussed in the study.

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Indian J Psychiatry. 2014;56:S50.

COMORBID OCD AND ADHD: A CASE REPORT.

Kumar S, Gupta S, Grover S.

Background: Studies have shown thatthe neurobiology of attention deficit hyperkinetic disorder (ADHD) and obsessive compulsive disorder (OCD) may be opposite with respect to the dopamine and glutaminergic activity in the prefrontal cortex, but their co-occurrence and risk of one for another is still inconclusive.

Aim: To report a case of Obsessive Compulsive Disorder with history of ADHD.

Case description: A 15 year old boy, born of full term vaginal delivery, had developmental delay and by the age of 4 years developed features of hyperactivity, inattention, impulsive behaviour and poor scholastic performance. Additionally he developed tics at the age of 6 years. At the age of 6 years, he was diagnosed with ADHD alongwith comorbid Tic disorderandwas started on Tab. Methylphenidate with which his symptoms improved in 3-4 months. Tab. Methylphenidate was continued for the next 3 years and was then tapered off. By 15 years of age patient started to have repetitive, unwanted, intrusive, anxiety provoking thoughts of fear of harming otherswhich were recognized as own,which he would try to resist. In response to these thoughts he would indulge in controlling compulsions, which will lead to reduction in anxiety. On the basis of available information a diagnosis of OCD with past history of ADHD was considered and he was treated with Tab. Clomipramine and behaviour therapy in the form of exposure and response prevention. Patient showed significantimprovedwithin 2 months of treatment.

Conclusion: The co-occurrence of OCD and ADHD suggests that the two disorders may be related biologically and there is a need to explore the relationship between the two disorders.

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Indian J Psychiatry. 2014;56:S21-S22.

A COMPARATIVE STUDY OF THE PROFILES OF CHILDREN DIAGNOSED AS ADHD WITH NON-ADHD.

Mahajan A, Choudhary S, Sudarsanan S, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is a heritable neurobehavioral disorder associated with significant impairments in occupational, academic, neuropsychological, and social functioning. A substantial portion of bipolar disorder (BD) has a comorbid ADHD. ADHD comorbidity is frequent in juvenile BD and can influence the age of onset, phenomenology, comorbidity, and course of BD. Other disorders like depression, conduct disorder (CD), and oppositional defiant disorder should also be delineated while evaluating for ADHD and childhood BD. There is a common consensus that uncomplicated classical manic-depressive illness is rare in children. Thus, it is of immense importance that the changes and variability in the profiles of these children are studied and compared with the control group, and thus better management strategies can be formulated based on the results. Objectives: To compare the profiles of ADHD with non-ADHD children.

Materials and Methods: The study was conducted in Department of Psychiatry, Subharti Medical College and Hospital, Meerut. Studied population included 60 children (30 - ADHD and 30 - non ADHD). They were evaluated thoroughly using semistructured pro forma.

Results and Conclusions: Mean age of ADHD patients was 9.9 years, age group 10-13 years (56.6%), male:female ratio - 27:3, and 23.3% comorbidities with ADHD; and in non-ADHD mean age - 12.6 years, male:female ratio - 19:11, and age group 14-17 years (46.66%). The implications of these results along with a final conclusion would be discussed during the presentation.

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Indian J Psychiatry. 2014;56:S43.

PERCEIVED STRESS AND QUALITY OF LIFE AMONG CARE GIVERS HAVING CHILDREN WITH MENTAL RETARDATION (MR) AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) COMING FROM A RURAL POPULATION.

Dubey MJ, Mallick AK, Bhattacharyya A, et al.

Aims: Caring of someone with a mental disorder can affect dynamics of family.There are various stresses that emerge and re-emerge with time which chronically affect their life.The study is done to evaluate perceived stress and quality of life among care givers with mental retardation and ADHD, and to look for any correlation between them.

Material and Method: Care givers of children of MR and ADHD (n=20+20, 18-60yrs, bothsexes)would be taken for the study after obtaining written informed consent.They would be assessed for perceived stress using PERCEIVED STRESS SCALE and for Quality of life using QUALITY OF LIFE ENJOYMENT SATISFACTION QUESTIONAIRRE SHORT FORM. The evaluation and correlation will be done by appropriate statistical tool.

Results and Conclusions: As this is an ongoing study results will be shared at the time of presentation.

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Indian J Psychiatry. 2014;56:S19.

ROLE OF ARMODAFINIL AS AN ADJUNCT IN DRUG RESISTANT ADHD.

Singh AP, Singh PK.

Background: Attention deficit hyperactivity disorder (ADHD) affects 3-8% of children of 5-16 years of age. It is associated with co morbidities in up to two-third of the cases which poses significant diagnostic and therapeutic challenges in real world settings. We hereby report a similar therapeutic challenge and our clinical experience.

Case Report: This is case report of a 12-year-old, female patient with diagnosis of mild mental retardation, speech impairment, epilepsy, and ADHD. Her seizure disorder was well controlled on antiepileptic medication, but symptoms of ADHD in the form of hyperactivity, impulsivity, and inattention were quiet problematic. She has shown no significant response with adequate trial of atomoxetine, methylphenidate, clonidine, risperidone, aripiprazole, and tricyclic antidepressant (TCA) in monotherapy as well as in combination. She had developed breakthrough seizure with lower dosage of TCA and marked restlessness, agitation, and decrease of appetite with methylphenidate. Patient was not much cooperative for behavior therapy, due to low intelligence and speech impairment and deteriorating symptomatic status. She finally showed significant improvement with combination of methylphenidate and armodafinil.

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Indian J Psychiatry. 2014;56:S27.

ACCIDENTAL RISPERIDONE POISONING IN A 4-YEAR-OLD CHILD WITH ADHD.

Kaur D, Ajinkya S, Kalra G, et al.

Background: Risperidone is used with increasing frequency in children. There is sparse literature regarding its safety in children. Aims: To report a rare case of accidental risperidone poisoning in a child with ADHD.

Materials and Methods: Master S, a 4-year-old boy was referred for emergency psychiatric referral following ingestion of risperidone tablets accidentally. He had consumed 10 tablets of 0.5 mg of risperidone approximately 3-5 h prior to presenting in the casualty. He had vomiting, inability to talk, and move his limbs. He was recently diagnosed with attention deficit hyperactive disorder (ADHD) and was started on oral risperidone (0.5 mg/day) from a private psychiatrist.

Results: He was drowsy, slurred speech, dribbling saliva, rigidity in all four limbs, with Glasgow Coma Scale (GCS) 10/15. Blood investigations (complete blood count (CBC) and liver function test (LFT)), serial electrocardiograms (ECGs), electroencephalogram (EEG), and computed tomography (CT) imaging were normal. He was kept for observation in pediatric intensive care unit (PICU). Gastric lavage, supportive management, and intramuscular promethazine (37.5 mg over 3 days) were given. On day 3, he was shifted to pediatric ward as rigidity reduced significantly and GCS scores became normal. He was discharged on day 5 since admission.

Discussion: Children less than 12 years of age who have acutely ingested more than five times their prescribed daily dose of risperidone need intensive evaluation. Overdose management includes gastrointestinal lavage, activated charcoal, and cardiovascular monitoring. No specific antidote for risperidone poisoning is known and treatment is symptomatic and supportive.

Conclusion: World Health Organization (WHO) pharmacovigilance guidelines emphasize reporting of adverse reactions and toxicities in children particularly in ADHD.

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Indian J Psychiatry. 2014;56:S27.

ATTENTION DEFICIT HYPERACTIVITY DISORDER WITH COMORBID SEIZURE DISORDER AND MYELIN ABNORMALITIES.

Kaur D, Ajinkya S, Kalra G, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is an impairing disorder resulting from abnormal levels of inattention, hyperactivity, and impulsive behaviors.

Aims and Objectives: To present a rare case of ADHD with developmental delays and seizure disorder with myelin and white matter abnormalities on brain imaging.

Materials and Methods: A 5-year-old boy brought by parents with 1 year history of poor attention, excessive hyperactivity, and impulsive behavior seen across both settings of school and home. Third day after delivery he had two episodes of generalized tonic-clonic seizure (GTCS). His milestones were globally delayed. He was started on oral phenobarbitone 60 mg per day when he had one seizure episode of GTCS at age 3. There were no facial dysmorphisms. Systemic examination was normal. History and Mental Status Examination (MSE) fulfilled Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for ADHD. Vineland Social Maturity Scale (VSMS) functioning was 4

years. Blood investigations and electroencephalogram (EEG) were normal. Magnetic resonance imaging (MRI) brain showed abnormalities in myelin and white matter microstructure. Sodium valproate (10 mg/kg/day) was subsequently started and phenobarbitone was tapered off. ADHD symptoms reduced by 70% as per Vanderbilt assessments.
Discussion: Abnormalities in frontolimbic pathways and decreased total white matter volumes exist in ADHD. Delayed myelination, disruptions in white matter microstructure, and insufficient astrocyte functioning play a role in ADHD. Long-term exposure to antiepileptic medications especially phenobarbitone, combination of antiepileptics, early onset epilepsy, subclinical seizures, and disturbed sleep play a definite role in ADHD with seizures. Valproate reduces ADHD symptoms in such children.
Conclusion: Multiple factors need to be taken in consideration while planning comprehensive management for ADHD in children with comorbidities.

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Indian J Psychiatry. 2014;56:S54-S55.

SYMPTOM PATTERNS AND SEVERITY AMONG CHILDREN WITH ADHD: DATA FROM SOUTH INDIA.

Sivashankar P, Madhavi K, Krishna MP.

Background: Attention deficit hyper activity disorder (ADHD) is a common neuro behavioral, disorder of childhood and adolescence. These children lack inhibition and self control due to failure in brain circuitry. Children have problems of in attention, hyperactivity and impulsivity related behavior and learning. Thus, have difficulties at school and home, and in peer relationships.
AIM: The aim of the present study is to assess the symptom pattern and severity of children diagnosed as ADHD and its affect on academic performance.
Method: The study is conducted at the Department of Psychiatry, Dr. Pinnamaneni Siddhartha Institute of Medical Sciences & Research Foundation. The sample consists of 15 children between 6-12 years of age diagnosed as ADHD based on ICD 10. Child psychiatric rating scale, Conners scale, and ADHD rating scale are applied on the subjects. The data is analyzed pertaining to severity, symptom pattern and clinical manifestation.
Results: Will be discussed at the time of presentation.
Conclusion: Will be discussed at the time of presentation.

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Indian J Psychiatry. 2014;56:S43.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN TEMPORAL LOBE EPILEPSY.

Sawant N, Gulhane R, Rawat S, et al.

Aims: We report a child having temporal lobe epilepsy and attention deficit hyperactivity disorder with remarkable improvement in both following lesionectomy.
Materials And Methods: A 9 year old child had seizures since the age of one year with a frequency of oneseizure per week. He also had severe attention deficit and hyperactivity with behavioral problems of increased irritability and hitting people. His schooling was affected due to these behavioral problems. FSIQ of the child was 40. In view of refractoriness to treatment and right temporal SOL on MRI, epilepsy surgery was planned. The p re-surgical evaluation required a psychiatric fitness which was given after the patient was 50% better on Syp. Risperidone 1mg in divided doses and Tb.Atomoxetine 10mg. RESULT-Right temporal lobe lesionectomy was done and the child on 3months post- surgery follow up showed 90% improvement in hyperactivity, impulsivity and attention and with good behavioral and seizure control.
Conclusion: This child who had disruptive behavioral problem with moderate MR improved dramatically after epilepsy surgery where the removal of epileptic focus also resulted in improvement in behavior.

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Indian J Psychiatry. 2014;56:S21.

A CASE REPORT OF PETROL DEPENDENCE WITH COMORBID ADHD: IS THERE A BIDIRECTIONAL RELATIONSHIP?

Gupta A, Dhawan A, Bhargava R, et al.

Aim: The present case report aims to illustrate clinical presentation and management of an adolescent boy with inhalant (petrol and liquid petroleum gas (LPG)) dependence and attention deficit hyperactive disorder (ADHD).

Methodology: A 12-year-old boy attending the outpatient clinic of National Drug Dependence Centre, All India Institute of Medical Sciences (AIIMS), New Delhi was diagnosed with inhalant dependence and ADHD according to International Classification of Diseases, tenth revision (ICD-10). A multidisciplinary team conducted detailed inpatient clinical evaluation and observation. Psychometric tests, namely, Malin's Intelligence Scale for Children and Conner's Rating Scale for Parents were administered to assess intellectual functioning and hyperactivity. Conner's Rating Scale for Parents was administered 3 weeks after admission (prior to starting atomoxetine) and 1 week after reaching optimal dose of atomoxetine.

Results: Cognitive impairment was evident. Striking features include unusual choice of substance of abuse, bidirectional relationship between psychiatric illness, and substance abuse and rapid response to treatment. An integrated management approach including pharmacotherapy and behavioral therapy led to significant improvement.

Conclusion: Petrol and LPG abuse is an unusual presentation in deaddiction settings and it can potentially lead to physical, neurocognitive, and psychiatric complications. ADHD as a comorbid psychiatric illness acted as a risk factor for and may have been exacerbated by inhalant dependence.

Implications: ADHD is frequently associated with substance abuse and its identification and management has implications for treatment of the latter. Development of diagnostic and treatment guidelines is required for effective management of such populations.

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Int J Environ Res Public Health. 2014 Jan;11:749-72.

ADAPTIVE TELE-THERAPIES BASED ON SERIOUS GAMES FOR HEALTH FOR PEOPLE WITH TIME-MANAGEMENT AND ORGANISATIONAL PROBLEMS: PRELIMINARY RESULTS.

Frutos-Pascual M, Zapirain BG, Zorrilla AM.

Attention Deficit with Hyperactivity Disorder (ADHD) is one of the most prevalent disorders within the child population today. Inattention problems can lead to greater difficulties in completing assignments, as well as problems with time management and prioritisation of tasks. This article presents an intelligent tele-therapy tool based on Serious Games for Health, aimed at the improvement of time management skills and the prioritisation of tasks. This tele-system is based on the use of decision trees within Django, a high-level Python Web framework. The technologies and techniques used were selected so as to boost user involvement and to enable the system to be easily customised. This article shows the preliminary results of the pilot-phase in an experiment performed to evaluate the use of adaptive tele-therapies within a group of typically developing children and adolescents aged between 12 and 19 years old without ADHD. To do so, we relied on the collection of parameters and the conduct of surveys for assessing time management skills, as well as measuring system usability and availability. The results of a time management survey highlighted that the users involved in the trial did not use any specific or effective time management techniques, scoring 1.98 and 2.30 out of 5 points in this area for ages under 15 and over 16 years old, respectively. The final calculations based on the usability questionnaire resulted in an average score of 78.75 out of 100. The creation of a customisable tool capable of working with different skills, in conjunction with the replication of the current study, may help to understand these users' needs, as well as boosting time management skills among teenagers with and without ADHD.

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Int J Lang Commun Disord. 2014 Jan;49:15-29.

PRAGMATIC LANGUAGE DIFFICULTIES IN CHILDREN WITH HYPERACTIVITY AND ATTENTION PROBLEMS: AN INTEGRATED REVIEW.

Green BC, Johnson KA, Bretherton L.

BACKGROUND: Diagnostic criteria for attention deficit hyperactivity disorder (ADHD) suggest a range of difficulties in the pragmatic aspects of language, including excessive talking and interrupting others. Such difficulties have been periodically reported over several decades in studies on the language abilities of children with features of ADHD, yet a comprehensive review of the literature has been lacking. AIMS: This review aims to integrate evidence from several lines of research from 1979 to the present on pragmatic language difficulties in children with ADHD or symptoms of ADHD.

METHODS & PROCEDURES: A comprehensive search of empirical literature on pragmatic language in children with ADHD or symptoms of ADHD was conducted using PsycINFO and PubMed databases and through following up relevant references cited in articles. Literature was reviewed with respect to the nature and extent of pragmatic language difficulties in ADHD.

OUTCOMES & RESULTS: Thirty studies met the review inclusion criteria, including recent questionnaire studies, observational studies of children's communication patterns, and studies of higher-level language comprehension and production. The studies indicate a consistent profile of pragmatic language impairments in children with features of ADHD, particularly in the areas of excessive talking, poor conversational turn-taking, and lack of coherence and organization in elicited speech.

CONCLUSIONS & IMPLICATIONS: Pragmatic language difficulties are common in children with features of ADHD. These difficulties are consistent with deficits in executive function that are thought to characterize ADHD, thus providing some support for the theory that executive function contributes to pragmatic language competency. As yet there is very little empirical evidence of specific relationships between particular aspects of pragmatic language and particular domains of executive function. Given the importance of pragmatic language competency for children's social and academic functioning, pragmatic language abilities should be considered during clinical assessment for ADHD and targeted for intervention.

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Int J Qual Stud Health Well -being. 2014;9:23376.

DIFFICULTIES IN EVERYDAY LIFE: YOUNG PERSONS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDERS PERSPECTIVES. A CHAT-LOG ANALYSIS.

Ahlstrom BH, Wentz E.

This study focuses on the everyday life of young persons with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). There are follow-up studies describing ADHD, and ASD in adults, and residual impairments that affect life. Few qualitative studies have been conducted on the subject of their experiences of everyday life, and even fewer are from young persons' perspectives. This study's aim was to describe how young persons with ADHD and ASD function and how they manage their everyday life based on analyses of Internet-based chat logs. Twelve young persons (7 males and 5 females aged 15-26) diagnosed with ADHD and ASD were included consecutively and offered 8 weeks of Internet-based Support and Coaching (IBSC). Data were collected from 12 chat logs (445 pages of text) produced interactively by the participants and the coaches. Qualitative content analysis was applied. The text was coded and sorted into subthemes and further interpreted into themes. The findings revealed two themes: "fighting against an everyday life lived in vulnerability" with the following subthemes: "difficult things," "stress and rest," and "when feelings and thoughts are a concern"; and the theme "struggling to find a life of one's own" with the following subthemes: "decide and carry out," "making life choices," and "taking care of oneself." Dealing with the problematic situations that everyday encompasses requires personal strength and a desire to find adequate solutions, as well as to discover a role in society. This study, into the provision of support and coaching over the Internet, led to more in-depth knowledge about these young persons' everyday lives and revealed their ability to use IBSC to express the complexity of

everyday life for young persons with ADHD and ASD. The implications of the findings are that using online coaching makes available new opportunities for healthcare professionals to acknowledge these young persons' problems.

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International Journal of Pharmacy Practice. 2014;22:12.

CAUGHT IN THE EYE OF THE STORM': EXPLAINING THE LACK OF ENGAGEMENT WITH METHYLPHENIDATE DRUG HOLIDAYS IN CHILDREN WITH ADHD.

Ibrahim K, Masters K, Donyai P.

Attention deficit hyperactivity disorder (ADHD) can be managed medically with stimulant medication such as methylphenidate. Although effective, the long-term impact of methylphenidate on children's developing brains is unknown and serious side-effects include growth retardation. UK guidelines recommend doctor-initiated 2-week breaks from stimulants after two years of prescribing to test the continuing need for medication[1]. Locally too, shared-care arrangements between consultants at Berkshire Healthcare NHS Foundation Trust (BHFT) and General Practitioners (GPs) encourage both groups to consider and discuss these drug holidays with parents of children prescribed methylphenidate. But evidence suggested little engagement with this practice. Our aim was to understand and explain why methylphenidate drug holidays rarely take place in actual practice. Semi-structured interviews were conducted with Child and Adolescent Mental Health Services (CAMHS) consultants (n = 8), GPs (n = 8), and teachers (n = 3) who deal with children with ADHD in Berkshire, UK. Both CAMHS consultants and teachers were approached via e-mail through a secondary source; GPs were approached through the post. All interviews were audio-recorded, transcribed and then analyzed using Grounded theory methodology[2]. Future parent interviews are planned as part of the ongoing validation process. This work was approved by the University of Reading Research Ethics Committee, BHFT R&D office and the Thames Valley Primary Care Research Partnership. Five main categories emerged from primary analyses during this study and these were integrated into one core category labelled 'caught in the eye of the storm' that neatly explains the low uptake of drug holidays in ADHD. Before medication, children's behaviour at home and school results in distress in both environments. When they seek medical input, doctors advise parents to start medication for the management of their child's ADHD. Stimulant medication then helps decrease the child's impulsiveness and hyperactive behaviour, improving their academic performance as a result. Everyone is therefore appreciative of the power of the medication which is perceived as a mercy that moves the child, to some extent the school, and of course the parents from a position in amidst the storm to the safety of the eye of the storm. Fear of losing this stable state of affairs by agreeing to stop medication, even for a short time accounts for the poor practice of planned drug holidays. The children in effect are caught in the eye of a storm from which it is difficult if not impossible to escape until adolescence where they themselves become the decision-makers and many stop their medication altogether at that juncture. Grounded theory has explained the lack of engagement with methylphenidate drug holidays. With parents as the main decision makers until children reach adolescence, performance at school, safety of children at school, and adults' (parents' and teachers') inability to cope with the child's behaviour become the main drivers for continuing with medication. The risk of losing this sense of security by interrupting treatment impedes efforts to introduce methylphenidate drug holidays. Help with risk assessing drug holidays might improve parents' decision making in the future.

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J Abnorm Child Psychol. 2014 Feb;42:321-32.

THE FACTOR STRUCTURE OF ANXIETY AND DEPRESSIVE DISORDERS IN A SAMPLE OF CLINIC-REFERRED ADOLESCENTS.

Gomez R, Vance A, Gomez RM.

The current study used confirmatory factor analysis (CFA) to examine the factor structure of anxiety and depressive disorders in a sample of clinic-referred adolescents, aged between 12 and 18 years, for diagnoses based on parent (N = 655; male = 441) and adolescent (N = 626; male = 417) interviews. Three

models were examined: a 1-factor model, with all anxiety and depressive disorders in a single factor; a DSM-based 2-factor model, with anxiety disorders in one factor, and depressive disorders in another factor; and an alternate 2-factor model, with fear related anxiety disorders in one factor, and other anxiety and depressive disorders in another factor. The findings indicated support for all three models. Also, ADHD and ODD/CD were associated with only the shared variances between the latent factors in the 2-factor models, and not their unique variance. The implications of the findings for taxonomy, comorbidity, and clinical practice are discussed.

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J Abnorm Child Psychol. 2014 Feb;42:291-300.

THREE DIMENSIONS OF OPPOSITIONALITY IN AUTISM SPECTRUM DISORDER.

Mandy W, Roughan L, Skuse D.

In autism spectrum disorder (ASD), symptoms of oppositional defiant disorder (ODD) are common but poorly understood. DSM-5 has adopted a tripartite model of ODD, parsing its features into 'angry and irritable symptoms' (AIS), 'argumentative and defiant behavior' (ADB) and 'vindictiveness'. This was based on findings in non-autistic populations that each of these dimensions of oppositionality has a distinct constellation of associations with internalising and externalising psychopathology. We applied the tripartite DSM-5 ODD model to ASD to test its generalisability beyond non-ASD populations; and to elucidate the nature of ODD symptoms in ASD. Participants were 216 verbally-fluent young people (mean age = 9.6 years, range 3.0 to 16.2 years, 82 % male) with ASD. Cross-sectional parent-and teacher-report data were analysed using bootstrap multiple regression to test the following predictions, derived from studies of non-ASD young people: (1) AIS will be the main predictor of internalising problems; (2) ADB will be the main predictor of ADHD symptoms; (3) all ODD traits will independently predict conduct disorder symptoms; (4) vindictiveness will be the main predictor of aggressive conduct problems. Our findings using both parent and teacher data were consistent with the non-ASD ODD literature. AIS were associated with internalising but not externalising problems; ADB and vindictiveness were associated with externalising but not internalising problems; and vindictiveness was the main predictor of aggression. The DSM-5 tripartite model of ODD appears to be generalisable to ASD: for people with an autistic disorder, AIS, ADB and vindictive dimensions of oppositionality have distinct associations with concurrent psychopathology, suggesting the need to assess them as separate constructs.

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J Appl Res Intellect Disabil. 2014 Mar;27:174-86.

MINDFULNESS-BASED STRESS REDUCTION FOR PARENTS OF YOUNG CHILDREN WITH DEVELOPMENTAL DELAYS: IMPLICATIONS FOR PARENTAL MENTAL HEALTH AND CHILD BEHAVIOR PROBLEMS.

Neece CL.

BACKGROUND: Parents of children with developmental delays (DD) typically report elevated levels of parental stress compared with parents of typically developing children. Children with DD are also at high risk for exhibiting significant behaviour problems. Parental stress has been shown to impact the development of these behaviour problems; however, it is rarely addressed in interventions aimed at reducing child behaviour problems. The current study examined the efficacy of mindfulness-based stress reduction (MBSR) for parents of children with DD by investigating whether this intervention is effective in reducing parenting stress and whether decreases in parenting stress lead to reductions in behaviour problems among children with DD.

MATERIALS AND METHODS: Forty six parents of children with DD were randomly assigned to an immediate treatment or wait list-control group. Participants completed questionnaires assessing parental stress and child behaviour problems at intake and at a second assessment, which took place after only the immediate treatment group had received the MBSR.

RESULTS: Parents who participated in MBSR reported significantly less stress and depression as well as greater life satisfaction compared with wait list-control parents. Regarding child outcomes, children whose

parents participated in MBSR were reported to have fewer behaviour problems following the intervention, specifically in the areas of attention problems and ADHD symptomatology.
DISCUSSION: Results indicated that MBSR may be an effective intervention for ameliorating parental stress and mental health problems among parents of children with DD. Additionally, these benefits may 'spill over' and improve behaviour challenges among these children.

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J Clin Child Adolesc Psychol. 2014;43:527-51.
EVIDENCE-BASED PSYCHOSOCIAL TREATMENTS FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Evans SW, Owens JS, Bunford N.
The purpose of this research was to update the Pelham and Fabiano (2008) review of evidence-based practices for children and adolescents with attention-deficit/hyperactivity disorder. We completed a systematic review of the literature published between 2007 and 2013 to establish levels of evidence for psychosocial treatments for these youth. Our review included the identification of relevant articles using criteria established by the Society of Clinical Child and Adolescent Psychology (see Southam-Gerow & Prinstein, in press) using keyword searches and a review of tables of contents. We extend the conceptualization of treatment research by differentiating training interventions from behavior management and by reviewing the growing literature on training interventions. Consistent with the results of the previous review we conclude that behavioral parent training, behavioral classroom management, and behavioral peer interventions are well-established treatments. In addition, organization training met the criteria for a well-established treatment. Combined training programs met criteria for Level 2 (Probably Efficacious), neurofeedback training met criteria for Level 3 (Possibly Efficacious), and cognitive training met criteria for Level 4 (Experimental Treatments). The distinction between behavior management and training interventions provides a method for considering meaningful differences in the methods and possible mechanisms of action for treatments for these youth. Characteristics of treatments, participants, and measures, as well as the variability in methods for classifying levels of evidence for treatments, are reviewed in relation to their potential effect on outcomes and conclusions about treatments. Implications of these findings for future science and practice are discussed.

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J Psychiatr Res. 2014 Mar;50:106-12.
A META-ANALYSIS OF BEHAVIOR THERAPY FOR TOURETTE SYNDROME.
McGuire JF, Piacentini J, Brennan EA, et al.
Individual randomized controlled trials (RCTs) of habit reversal training and a Comprehensive Behavioral Intervention for Tics (collectively referred to as behavior therapy, BT) have demonstrated efficacy in reducing tic severity for individuals with Tourette Syndrome and Chronic Tic Disorders (collectively referred to as TS), with no examination of treatment moderators. The present meta-analysis synthesized the treatment effect sizes (ES) of BT relative to comparison conditions, and examined moderators of treatment. A comprehensive literature search identified eight RCTs that met inclusion criteria, and produced a total sample of 438 participants. A random effects meta-analysis found a medium to large ES for BT relative to comparison conditions. Participant mean age, average number of therapy sessions, and the percentage of participants with co-occurring attention deficit hyperactivity disorder (ADHD) were found to moderate treatment effects. Participants receiving BT were more likely to exhibit a treatment response compared to control interventions, and identified a number needed to treat (NNT) of three. Sensitivity analyses failed to identify publication bias. Overall, BT trials yield medium to large effects for TS that are comparable to treatment effects identified by meta-analyses of antipsychotic medication RCTs. Larger treatment effects may be observed among BT trials with older participants, more therapeutic contact, and less co-occurring ADHD.

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J Sleep Res. 2014 Jun;23:318-25.

THE IMPACT OF DAYTIME SLEEPINESS ON THE SCHOOL PERFORMANCE OF COLLEGE STUDENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A PROSPECTIVE LONGITUDINAL STUDY.

Langberg JM, Dvorsky MR, Becker SP, et al.

This prospective longitudinal study evaluated the impact of daytime sleepiness on the school performance of 62 college students diagnosed comprehensively with attention deficit hyperactivity disorder. The primary goal of the study was to determine if self-reported daytime sleepiness rated at the beginning of the academic year could predict academic and overall functioning at the end of the academic year while also considering potentially important covariates, including symptoms of inattention, hyperactivity and impulsivity, medication status and whether or not students lived at home or on-campus. Self-reported daytime sleepiness predicted longitudinally school maladjustment, overall functional impairment and the number of D and F grades (i.e. poor and failing) students received in courses above and beyond both self- and parent-report of symptoms, but did not predict overall grade point average. Living at home served as a protective factor and was associated with less school maladjustment and overall impairment. Gender was the only significant predictor in the overall grade point average model, with female gender associated with higher overall grades. The implications of these findings for monitoring and treatment of sleep disturbances in college students with attention deficit hyperactivity disorder are discussed.

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J Tradit Chin Med. 2014 Aug;34:450-54.

DOES ACUPUNCTURE HAVE A POSITIVE EFFECT ON SCHOOL SUCCESS IN CHILDREN?

Tas D, Acar HV.

OBJECTIVE: To evaluate school success in pediatric patients undergoing acupuncture treatment for various indications.

METHODS: The grades achieved during both school terms by children undergoing acupuncture treatment for various indications at the pediatric outpatient clinic of Ulus State Hospital were analyzed. Exam grades in mathematics, social studies, and Turkish was compared between the first and the second terms. Forty children were included in the study, with 22 male and 18 female, and their average age was 11.1 years. These patients were undergoing acupuncture treatment for attention deficit-hyperactivity disorder (ADHD), enuresis nocturna, migraine, obesity, atopic dermatitis, alopecia areata, and Tourette's syndrome. Treatments were done at the beginning of the second term. Four of the 25 patients with ADHD had borderline intelligence quotients. The report cards of all 40 patients were examined, and their grades in the first and the second school term were compared.

RESULTS: There was a statistically significant increase in the grades obtained in mathematics, social studies, and Turkish ($P < 0.005$) by the students from the first to the second school term. When 4 ADHD patients with borderline deficiency in intelligence were excluded, and the grades among the 21 patients with ADHD were compared for both terms, there was also a statistically significant increase in mathematics, social studies, and Turkish grades ($P < 0.05$).

CONCLUSION: Acupuncture contributed to the academic success of the children who underwent acupuncture treatment for their primary symptoms.

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J Youth Adolesc. 2014 Jan;43:127-36.

VIDEO GAME VIOLENCE USE AMONG "VULNERABLE" POPULATIONS: THE IMPACT OF VIOLENT GAMES ON DELINQUENCY AND BULLYING AMONG CHILDREN WITH CLINICALLY ELEVATED DEPRESSION OR ATTENTION DEFICIT SYMPTOMS.

Ferguson CJ, Olson CK.

The issue of children's exposure to violent video games has been a source of considerable debate for several decades. Questions persist whether children with pre-existing mental health problems may be influenced adversely by exposure to violent games, even if other children are not. We explored this issue with 377 children (62 % female, mixed ethnicity, mean age = 12.93) displaying clinically elevated attention

deficit or depressive symptoms on the Pediatric Symptom Checklist. Results from our study found no evidence for increased bullying or delinquent behaviors among youth with clinically elevated mental health symptoms who also played violent video games. Our results did not support the hypothesis that children with elevated mental health symptoms constitute a "vulnerable" population for video game violence effects. Implications and suggestions for further research are provided.

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JAMA Psychiatry. 2014;71:1015-24.

SUBTYPING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER USING TEMPERAMENT DIMENSIONS: TOWARD BIOLOGICALLY BASED NOSOLOGIC CRITERIA.

Karalunas SL, Fair D, Musser ED, et al.

Importance Psychiatric nosology is limited by behavioral and biological heterogeneity within existing disorder categories. The imprecise nature of current nosologic distinctions limits both mechanistic understanding and clinical prediction.We demonstrate an approach consistent with the National Institute of Mental Health Research Domain Criteria initiative to identify superior, neurobiologically valid subgroups with better predictive capacity than existing psychiatric categories for childhood attention-deficit/hyperactivity disorder (ADHD). Objective To refine subtyping of childhood ADHD by using biologically based behavioral dimensions (ie, temperament), novel classification algorithms, and multiple external validators. Design, Setting, and Participants A total of 437 clinicallywell-characterized, community-recruited children, with and without ADHD, participated in an ongoing longitudinal study. Baseline data were used to classify children into subgroups based on temperament dimensions and examine external validators including physiological and magnetic resonance imaging measures. One-year longitudinal follow-up data are reported for a subgroup of the ADHD sample to address stability and clinical prediction. Main Outcomes and Measures Parent/guardian ratings of children on a measure of temperament were used as input features in novel community detection analyses to identify subgroups within the sample. Groups were validated using 3 widely accepted external validators: peripheral physiological characteristics (cardiac measures of respiratory sinus arrhythmia and pre-ejection period), central nervous system functioning (via resting-state functional connectivitymagnetic resonance imaging), and clinical outcomes (at 1-year longitudinal follow-up). Results The community detection algorithm suggested 3 novel types of ADHD, labeled as mild (normative emotion regulation), surgent (extreme levels of positive approachmotivation), and irritable (extreme levels of negative emotionality, anger, and poor soothability). Types were independent of existing clinical demarcations including DSM-5 presentations or symptom severity. These types showed stability over time and were distinguished by unique patterns of cardiac physiological response, resting-state functional brain connectivity, and clinical outcomes 1 year later. Conclusions and Relevance Results suggest that a biologically informed temperament-based typology, developed with a discovery-based community detection algorithm, provides a superior description of heterogeneity in the ADHD population than does any current clinical nosologic criteria. This demonstration sets the stage for more aggressive attempts at a tractable, biologically based nosology.

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J Adolesc. 2014;37:1171-79.

DOES DIAGNOSIS AFFECT THE PREDICTIVE ACCURACY OF RISK ASSESSMENT TOOLS FOR JUVENILE OFFENDERS: CONDUCT DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Khanna D, Shaw J, Dolan M, et al.

Studies have suggested an increased risk of criminality in juveniles if they suffer from co-morbid Attention Deficit Hyperactivity Disorder (ADHD) along with Conduct Disorder. The Structured Assessment of Violence Risk in Youth (SAVRY), the Psychopathy Checklist Youth Version (PCL:YV), and Youth Level of Service/Case Management Inventory (YLS/CMI) have been shown to be good predictors of violent and non-violent re-offending. The aim was to compare the accuracy of these tools to predict violent and non-violent re-offending in young people with co-morbid ADHD and Conduct Disorder and Conduct Disorder only. The sample included 109 White-British adolescent males in secure settings. Results revealed no

significant differences between the groups for re-offending. SAVRY factors had better predictive values than PCL:YV or YLS/CMI. Tools generally had better predictive values for the Conduct Disorder only group than the co-morbid group. Possible reasons for these findings have been discussed along with limitations of the study. (copyright) 2014 The Foundation for Professionals in Services for Adolescents.

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Journal of Applied School Psychology. 2014 Jul;30:209-22.

CLASSROOM BEHAVIOR OF PARTICIPANTS WITH ADHD COMPARED WITH PEERS: INFLUENCE OF TEACHING FORMAT AND GRADE LEVEL.

Steiner NJ, Sheldrick RC, Frenette EC, et al.

Few studies examine the classroom behavior of children with attention deficit hyperactivity disorder (ADHD) in comparison with classroom peers and which teaching formats best support classroom engagement. Observations (N = 312) of second- and fourth-grade students with ADHD and their randomly selected classroom peers were conducted using a systematic classroom observation method. Linear regressions analyzed classroom behavior compared with peers and effects of teaching format, grade, and treatment status on classroom behavior. Children with ADHD displayed lower engagement (p <.001) and higher inattention (p <.001) during teacher-led instruction compared with other teaching formats, and lower engagement in fourth grade than in second grade (p <.05). Despite treatment plans, children with ADHD present with increased classroom behavior challenges. Adapting teaching formats to benefit children with ADHD should be considered.

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J Child Adolesc Psychopharmacol. 2014;24:336-40.

SALIVARY NEUROSTEROID LEVELS AND BEHAVIOURAL PROFILES OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER DURING SIX MONTHS OF METHYLPHENIDATE TREATMENT.

Wang L-J, Wu C-C, Lee S-Y, et al.

Objective: This prospective study aimed to investigate the relationships between salivary levels of neurosteroids, including dehydroepiandrosterone (DHEA), cortisol, and DHEA/cortisol ratios, and behavioral symptoms in patients with attention-deficit/hyperactivity disorder (ADHD) during treatment with methylphenidate (MPH).

Methods: Fifty-eight ADHD patients (48 boys and 10 girls) were included in the study initially. Forty patients (mean age: 7.77(plus or minus)1.64 years; 32 boys and 8 girls) who completed the study received treatment with oral MPH with a dose range of 5-15 mg/day (mean dose: 12.47(plus or minus)7.74 mg/day.) for 6 months at the discretion of the psychiatrist. DHEA and cortisol levels were determined from saliva samples collected at 0800 h at baseline and 6 months from baseline. ADHD symptoms were evaluated with the Child Behavior Checklist (CBCL).

Results: Salivary DHEA levels (mean difference=9.05 pg/mL, p=0.027) and DHEA/cortisol ratios (mean difference=32.42, p=0.007) in ADHD patients were significantly increased, but the cortisol levels did not change significantly. During a 6 month follow-up, all behavioral problems assessed using the CBCL improved significantly. Changes in salivary DHEA levels were positively correlated with changes in salivary cortisol levels (r=0.44, p=0.004); however, changes in salivary levels of DHEA, cortisol, and the DHEA/cortisol ratio were not significantly correlated with change in any subscales of the CBCL. Mean doses of MPH were not significantly correlated with changes in neurosteroid levels and behavioral symptoms.

Conclusions: These findings provide evidence that MPH administration might affect DHEA levels and DHEA/cortisol ratios. Whether levels of neurosteroids are directly associated with brain function or behavioral problems in ADHD patients warrants further investigation.

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J Child Adolesc Psychopharmacol. 2014;24:302-10.

CARDIOVASCULAR SAFETY OF STIMULANTS IN CHILDREN WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: A NATIONWIDE PROSPECTIVE COHORT STUDY.

Dalsgaard S, Kvist AP, Leckman JF, et al.

Objective: The purpose of this study was to determine whether stimulant users are at higher risk of a later cardiovascular event than are non-users, examining this association in both a national cohort and a population-based sample of children and adolescents diagnosed with attention-deficit/ hyperactivity disorder (ADHD). We also aim to examine a possible dose-response relationship in such an association.

Methods: We conducted a longitudinal, prospective cohort study of all children born in Denmark between 1990 and 1999. Within this cohort, children with ADHD were identified. Data from national health registers on psychiatric and somatic diagnoses, stimulant prescriptions, cardiovascular risk factors, pre- and perinatal and sociodemographic covariates in all children and their parents were merged, using the unique personal identification number. Hazard ratios (HR) for cardiovascular events were estimated using Cox regression, adjusted for other known risk factors.

Results: In the total population (n=714,258 contributing a total of 6,767,982 person-years) use of stimulants increased the risk of a cardiovascular event; adjusted HR=1.83 (1.10-3.04). In children with ADHD (n=8300) stimulant treatment also increased the risk of a cardiovascular event (adjusted HR=2.20 [2.15-2.24]), with a complex time-dependent dose-response relationship.

Conclusions: This is the first nationwide cohort study of the cardiovascular safety of stimulants in children and adolescents, and it represents, to our knowledge, the longest prospective follow-up study. Cardiovascular events were rare but twice as likely in stimulant users as in non-users, both in the total national population and in children with ADHD. We found a complex, time- and dose-dependent interrelationship between cardiovascular adverse events and stimulant treatment in children and adolescents. Our results suggest a safety signal with an increased risk of cardiovascular disease associated with stimulant treatment in children and adolescents, even after adjusting for a number of potential confounders.

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J Child Adolesc Psychopharmacol. 2014;24:341-46.

A 36 MONTH NATURALISTIC RETROSPECTIVE STUDY OF CLINIC-TREATED YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Hong M, Lee WH, Moon DS, et al.

Objective: The purpose of this study was to investigate factors for pharmacotherapy adherence in patients with attention-deficit/hyperactivity disorder (ADHD), with an emphasis on medication possession ratio (MPR).

Methods: The medical records of 300 clinic-treated youth diagnosed with ADHD were retrospectively reviewed. Patients from March 2005 through January 2009 were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) and psychological tests. Patients were classified based on the time period from the initial visit to the last visit. We selectively compared the early dropout group within 6 months and the long-term medication group over 36 months (LMed) to identify long-term follow-up characteristics. The short-term follow-up group was divided into an early dropout group without pharmacotherapy commencement (EDO) and a short-term medication group (SMed). Sociodemographic data, psychological test scores, and average MPR of the EDO, SMed, and LMed groups were compared.

Results: The number of EDO patients was 69 (23.0%) out of the 300 total patients who were studied, and there were 59 SMed patients (19.3%), and 60 LMed patients (20.0%). Compared with other groups, the EDO group included significantly more younger patients, younger parents, higher maternal education level, lower Short Form Korean-Conners' Parent Rating Scale (K-CPRS) score, and higher full scale and performance intelligence quotient (IQ). There was no significant correlation between the average MPR and the treatment duration.

Conclusions: Within the first 6 months of visiting the hospital, >40% of the patients dropped out of treatment regardless of methylphenidate (MPH) use. Twenty percent of the subjects showed adherence to MPH medication after 36 months.

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J Clin Psychiatry. 2014;75:779.

DOUBTING THE EFFICACY/EFFECTIVENESS OF ELECTROENCEPHALOGRAPHIC NEUROFEEDBACK IN TREATING CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IS AS YET UNJUSTIFIED: DR VAN DONGEN-BOOMSMA REPLIES.

Van Dongen-Boomsma M.

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J Clin Psychiatry. 2014;75:778-79.

DOUBTING THE EFFICACY/EFFECTIVENESS OF ELECTROENCEPHALOGRAPHIC NEUROFEEDBACK IN TREATING CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IS AS YET UNJUSTIFIED.

Dagenais E, Leroux-Boudreault A, El-Baalbaki G, et al.

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J Intellect Disabil Res. 2014.

DEVELOPMENTAL CHANGES IN COGNITIVE AND BEHAVIOURAL FUNCTIONING OF ADOLESCENTS WITH FRAGILE-X SYNDROME.

Frolli A, Piscopo S, Conson M.

Background: Individuals with fragile-X syndrome exhibit developmental delay, hyperexcitation and social anxiety; they also show lack of attention and hyperactivity. Few studies have investigated whether levels of functioning change with increasing age. Here, we explored developmental changes across adolescence in the cognitive and behavioural profile of individuals with fragile-X syndrome. To this scope, we assessed intellectual functioning, adaptive behaviour, autistic symptomatology, behavioural problems (e.g. hyperactivity/lack of attention) and strengths (prosocial behaviours).

Method: Thirty-six participants underwent standardised outcome measures (i.e. the Wechsler Intelligence Scales-Revised, the Childhood Autism Rating Scale, the Vineland Adaptive Behavior Scales, and the Strengths and Difficulty Questionnaire) in three time points (Time 1: 9-11; Time 2: 11-13, and Time 3: 13-15 years).

Results: Verbal IQ improved across time, whereas Nonverbal IQ declined and Full Scale IQ was quite unchanged. Autism ratings decreased; communication and social aspects of adaptive behaviour also enhanced. Finally, elevated levels of hyperactivity/lack of attention at Time 1 significantly improved across the three time points, whereas emotional symptoms, behavioural difficulties, problems with peers and prosocial behaviours remained stable over time.

Conclusion: These findings revealed specific developmental changes in cognitive and behavioural functioning of individuals with fragile-X syndrome, likely related to a progressive maturation of brain systems devoted to attentional control.

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J Am Acad Child Adolesc Psychiatry. 2014;53:1010-19.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) AND MOTOR TIMING IN ADOLESCENTS AND THEIR PARENTS: FAMILIAL CHARACTERISTICS OF REACTION TIME VARIABILITY VARY WITH AGE.

Thissen AJAM, Luman M, Hartman C, et al.

Objective There is consistent evidence that attention-deficit/hyperactivity disorder (ADHD) is strongly related to impaired motor timing as reflected in decreased accuracy and increased reaction time variability

(RTV). It is not known whether motor timing impairments are present in adolescents and adults with ADHD and their unaffected relatives to the same extent as has been reported in children, and whether ADHD and motor timing share familial underpinnings, as reflected in parent-offspring co-segregation and sibling cross-correlations.
Method A total of 589 parents and 808 children/adolescents from families with ADHD and control families (parent/offspring average age: 48.6/17.3 years) were included. All participants were thoroughly assessed for ADHD and performed a 40-trial motor timing task (1-second interval production). Dependent neurocognitive measures included RT median (RTM: representing accuracy), RTV and ex-Gaussian component (tau) ((tau): representing infrequent long response times). Generalized estimating equations were used for analyses.
Results Unaffected children from families with ADHD had RTV (but not RTM or (tau)) scores in between those of affected and control children. However, during middle-to-late adolescence, unaffected offspring were not impaired compared to control offspring and differed from ADHD probands, whereas during late adolescence/early adulthood, all offspring groups performed equally. Affected and unaffected parents of families with ADHD showed increased RTV compared to controls, regardless of age (not significant after adjusting for IQ). There were indications for shared familiality between RTV and ADHD as reflected by sibling cross-correlations and between RTM and ADHD as reflected by sibling cross-correlations and a maternal parent-offspring relation (parent-of-origin effect).
Conclusions RTV and its familial characteristics are influenced by development during adolescence. Increased RTV in children with ADHD appears to reflect immaturities in their neurocognitive functioning. Maternal ADHD effects might be involved in transmission of RTM (not RTV), but overall RTM showed less compelling (familial) relationships with ADHD than RTV.

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Journal of the Bahrain Medical Society. 2014;25:98-100.
NON-COMPLIANCE OF CHILDREN WITH ADHD TO OUTPATIENT CLINIC APPOINTMENTS AT THE PSYCHIATRIC HOSPITAL, KINGDOM OF BAHRAIN.
Al-Ansari AMS, Al-Khunaizi M.
Introduction and Objectives: Non-adherence to clinic appointments by children with ADHD is considered a major obstacle to treatment. The aims of the study were to determine the rate of non-compliance to treatment and to identify the reasons for non attendance, as well as the characteristics of children who did not comply with clinic appointments.
Method: A retrospective cross-sectional survey was undertaken of all children aged 18 years and under who attended the Child Psychiatric Unit, Psychiatric Hospital, Bahrain, from June 2010 until September 2011 and who were subsequently diagnosed with ADHD according to DSM-IV and Conners' Parent and Teacher checklist (n=53).
Results: More than 60% of the cases did not keep their clinic appointments. Their families were characterized by a higher level of education and social status compared to other parents attending the same clinic. Non-compliant children were characterized by the presence of comorbidity (53%), and were in the older age group.
Discussion and Conclusion: The degree of compliance to outpatient clinic appointments of children with ADHD should be monitored regularly in team meetings. Problems should be analyzed and solved quickly to ensure better compliance. Education of parents and children should be an integral part of the management plan and presented to families as soon as diagnosis is reached.

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MMW-Fortschritte der Medizin. 2014;156:40.
ADHD, BULLYING AND SUICIDALITY IN CHILDREN AND ADOLESCENTS.
Fuessl HS.

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Neurosci Lett. 2014;580:158-62.

EVALUATION OF SEVERAL MICRO RNA (MIRNA) LEVELS IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kandemir H, Erdal ME, Selek S, et al.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent childhood disorders, although disorders etiology and pathogenesis remains unknown, several theories about ADHD development have been proposed and many researchers believe that it is caused by both genetic and environmental factors. In this study we evaluated miR18a-5p, miR22-3p, miR24-3p, miR106b-5p, miR107, miR125b-5p and miR155a-5p levels in child and adolescent ADHD patients. The research sample consisted a group of 52 ADHD patients, and 52 healthy volunteer controls. There was no significant difference in age and sex between the two groups ($p > 0.05$). miRNA 18a-5p, 22-3p, 24-3p, 106b-5p and 107 levels were statistically significantly decreased in ADHD patients($p < 0.05$). miRNA 155a-5p levels were increased in patients group ($p < 0.05$). The positive predictive value (PPV) and negative predictive value of miR107 was estimated for the cutoff point of 0.4480. PPV was 70% and NPV was 86.5% for the taken cut off point. There could be a close relationship between levels of circulating miRNAs and ADHD. If we could understand how the signaling pathways arranged by miRNAs, impact on CNS development, function and pathology this can improve our knowledge about ADHD etiology and treatment.

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NeuroToxicology. 2014 Jan;40:16-22.

EXPOSURE TO METALS DURING PREGNANCY AND NEUROPSYCHOLOGICAL DEVELOPMENT AT THE AGE OF 4 YEARS.

Forns J, Fort M, Casas M, et al.

BACKGROUND: There is insufficient epidemiological evidence for deciding whether prenatal exposure to the current low-levels of metals in developed countries may affect neuropsychological function in early childhood.

OBJECTIVES: Our goal was to evaluate potential neurotoxic effects of prenatal exposure to seven metals (cobalt, copper, arsenic, cadmium, antimony, thallium and lead), during the 1st and 3rd trimester of pregnancy, on child neuropsychological development at 4 years of age.

MATERIALS AND METHODS: This study was based on a population-based birth cohort established in Sabadell (Catalonia, Spain) as part of the INMA [Environment and Childhood] Project. Metals were measured in 485 urine samples collected from mothers during the 1st and 3rd trimester of pregnancy. We assessed the neuropsychological development of 553 4-year-olds with the McCarthy Scales of Childrens' Abilitites (MSCA), together with their ADHD symptomatology, using the ADHD-DSM-IV criteria. A total of 385 children were included in the present study.

RESULTS: We found no statistically significant associations between metals and general cognitive scale or executive function of the MSCA. We found negative coefficients for the exposure to cadmium 1st trimester, cadmium 3rd trimester and lead 3rd trimester on the general cognitive score of MSCA, although these results were not significant. We did not find any association between prenatal exposure to metals and ADHD symptomatology at the age of 4 years.

CONCLUSIONS: Our results do not suggest that prenatal exposure to current low-levels of metals impairs children's cognitive development during preschool years.

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Nord J Psychiatry. 2014 May;68:236-42.

USES AND MISUSES OF TREATMENTS FOR ADHD. THE SECOND BIRGIT OLSSON LECTURE.

Taylor E.

BACKGROUND: Medication in attention deficit/hyperactivity disorder (ADHD) is so controversial that in some countries many children go untreated, while in others the prevalence of medication has become very high, and possibly even higher than the rate of ADHD.

AIMS: This lecture addresses the reasons for overuse and the obstacles to adequate use.

METHODS: Clinical and scientific literature is reviewed, with emphasis on published meta-analyses and national guidelines.
RESULTS AND CONCLUSIONS: The lecture suggests that overuse is associated with economic forces affecting prescribers, while underuse may come about in some European countries because we have overestimated the hazards of drugs, overestimated the value of non-pharmaceutical interventions or underestimated the severity of disorder.

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Paediatrics and Child Health (Canada). 2014;19:e54-e55.

EFFECTS OF DOSAGE ON SLEEP DURATION DURING STIMULANT TREATMENT OF ADHD IN YOUTH.

Santisteban JA, Stein MA, Gruber R.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by impulsivity, hyperactivity, and inattention, which affects 5% to 10% of school-age children. The first-line treatments for ADHD are stimulant medications, such as methylphenidate and amphetamine. These medications are highly effective, but not always tolerated. Sleep side effects, such as insomnia, can lead to treatment discontinuation. They are reported for both methylphenidate and amphetamine stimulants and are usually, but not always, mild and transitory. Poor tolerability may limit efficacy by compromising the ability to prescribe optimal doses. Few studies have directly compared dose response effects of long-acting methylphenidate and amphetamine formulations in youth with ADHD, and it is unclear if there are differential effects of drug and/or dose on sleep. MAS increase norepinephrine (NE) and dopamine (DA) levels release as well as reuptake, in contrast to d-MPH, and hence could affect sleep differently.
Objectives: We sought to determine if there are significant differences in the dose-response effects of ER D-MPH and ER MAS on objective measures of sleep.
Design/Methods: Children, aged 10 to 17 (n=37), participated in a double-blind crossover study comparing two stimulants (extended release D-MPH, MAS) at three doses (10 mg, 20 mg, 30 mg) and placebo. Each treatment session lasted one week, for a total protocol duration of eight weeks. Sleep was assessed in all conditions using actigraphy and sleep questionnaires.
Results: Sleep duration revealed a significant dose effect on actual sleep duration ($F[1, 36]=8.112$, $P<0.05$), with significantly shorter actual sleep duration for subjects receiving 30mg compared to those on placebo ($P<0.05$). Sleep schedule measures showed a significant effect for dosage on sleep start time ($F[1, 36]=6.284$; $P<0.05$), with a significantly later sleep start time when children were on 20mg or 30mg dosages, compared to placebo ($P<0.05$). No significant differences were found between medications.
Conclusions: Increased dosages of stimulants lead to shorter sleep duration and later sleep start times for both ER-MAS and ER D-MPH.

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Pediatric Diabetes. 2014;15:45-46.

SULFONYLUREA THERAPY CORRECTS HYPOTONIA, ATTENTION DEFICITS, IMPROVES COMPLEX NEUROPSYCHOLOGICAL FUNCTIONS AND MOTRICITY IN PATIENTS WITH NEONATAL DIABETES SECONDARY TO MUTATION IN POTASSIUM CHANNEL SUBUNITS, THROUGH A CENTRAL NERVOUS SYSTEM EFFECT.

Beltrand J, Vaivre-Douvret L, Busiah K, et al.

Introduction: Sulfonylurea therapy (SU) allows a better metabolic control than insulin in patients with neonatal diabetes secondary to mutation in potassium channel subunits (ND-K). Most of these patients have neurological and neuromotor developmental impairments whose changes under SU has not been studied in a systematic and prospective way in a large cohort.
Objective: To demonstrate the beneficial effect of SU on neuropsychological functioning in ND-K patients.
Patients and methods: 18 patients (15 boys - 0.1 to 18.5 years). Neurological (MRI, electroencephalogram, electromyography (EMG) and quantitative neuropsychological and neuropsychomotor evaluations were performed before and 12 months after the switch from insulin to SU.
Results: SU improved HbA1C (Mean: (plus or minus)1.55%, range -3.8 to 0.1% $p < 0.01$). 17 patients presented neuro-motor developmental delay or defect (hypotonia, developmental coordination or attention

disorders). One showed pyramidal signs and epilepsy. MRI was abnormal in 12 patients (periventricular white matter abnormalities, multiple punctate white matter or brainstem hyper intensities). At M12, Hypotonia was corrected in 12 out 15 affected patients and visual attention deficits in 10 out 13. In all patients younger than 4 years (n = 8), global motricity impairments were corrected and fine motricity in 3. In older patients (n = 10), gesture conception and realization were also improved (two hands praxia improved in 4 out 8 affected patients, imitation of gesture and body spatial integration in 6). Motor and sensitive nerve conduction and membrane excitability studies with EMG were normal at baseline and at M12. SU didnt significantly improved intelligence scores.
Conclusion: SU therapy in ND-K allows a measurable improvement of neuropsychomotor impairments greater in younger patients. EMG shows that it is not a peripheral but rather a central effect. All efforts should be made for an early genetic diagnosis allowing a rapid switch to SU in ND-K.

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Pediatric Diabetes. 2014;15:44.

MENTAL DISORDER AND TYPE 1 DIABETES: INITIATION AND DISCONTINUATION OF CSII IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH ADHD, DEPRESSION, EATING DISORDER, NEEDLE PHOBIA, ANXIETY OR OBSESSIVE COMPULSIVE DISORDER OR PSYCHOSIS. A GERMAN/AUSTRIAN DPV ANALYSIS.

Scheuing N, Bachle C, Becker M, et al.

Objectives: The risk of suicide or manipulation, but also coping with complex electronic devices, may deter treatment teams from using insulin pumps (CSII) in patients with mental disorder (MD). Therefore, we analyzed the use and discontinuation of CSII in type 1 diabetes (T1D) patients with and without clinically recognizedMD.
Methods: The multicenter, prospective German/Austrian diabetes patient registry (www.d-p-v.eu) was searched for the diagnosis and/or specific treatment of MD in T1D. Between 2005-2013, 48,716 T1D patients aged 5 to <30 years (median [Q1; Q3]: 15.6 [12.0; 17.7]) with documented insulin dose were registered. A diagnosis of attention deficit hyperactivity disorder (ADHD) was documented in 1,405 patients (2.9%, males only: 4.6%). Further comorbid MDs included depression (n = 447, 0.9%), eating disorders (ED; n = 397, 0.8%, females only: 1.4%), needle phobia (n = 326, 0.7%), anxiety/obsessive compulsive disorders (OCD; n = 260, 0.5%) and psychosis/ neuroleptic medication (n = 206, 0.4%). Multivariable regression models adjusted for age, sex, diabetes duration and migration background were created; adjusted estimates were calculated. Statistical package: SAS 9.4.
Results: AnMDwas recognized in 6.2% of T1D patients. Compared to non-MD patients (34.6%), the use of CSII was more common in patients with depression (42.8%), anxiety/OCD (41.9%), or needle phobia (76.5%) and less common in patients with psychosis (26.7%) (each $p < 0.05$). Patients with ADHD (35.9%) or ED (33.8%) revealed a similar use. Except for psychosis (3.6%, $p > 0.05$), the discontinuation rate of CSII was higher in MD patients (no MD vs. ADHD, depression, ED, anxiety/OCD, and needle phobia: 5.1 vs. 10.0, 8.8, 10.0, 5.8, and 5.8%). For ADHD, depression and ED the differences were significant ($p < 0.05$).
Conclusions: Low rates of MDs probably point to difficulties in recognizing MDs in T1D. However, early recognition is important as most comorbid MDs seem to contribute to discontinuation of CSII.

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Pediatrics. 2014 Jul;134:e293-e301.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SUBSTANCE ABUSE.

Harstad E, Levy S.

Attention-deficit/hyperactivity disorder (ADHD) and substance use disorders are inextricably intertwined. Children with ADHD are more likely than peers to develop substance use disorders. Treatment with stimulants may reduce the risk of substance use disorders, but stimulants are a class of medication with significant abuse and diversion potential. The objectives of this clinical report were to present practical strategies for reducing the risk of substance use disorders in patients with ADHD and suggestions for safe stimulant prescribing.

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PLoS ONE. 2014;9.

LINGUISTIC ANALYSIS OF THE PRESCHOOL FIVE MINUTE SPEECH SAMPLE: WHAT THE PARENTS OF PRESCHOOL CHILDREN WITH EARLY SIGNS OF ADHD SAY AND HOW THEY SAY IT?

Perez E, Turner M, Fisher A, et al.

A linguistic analysis was performed on the Preschool Five Minute Speech Sample (PFMSS) of 42 parents. PFMSS is a validated measure for Expressed Emotion (EE) to assess parent-child relationship. Half of these parents (n = 21, clinical group) had preschool children with early symptoms of attention deficit hyperactivity disorder (ADHD), the rest had typically developing children. Early symptoms of ADHD were identified with the Werry-Weiss Peters Rating Scale. The linguistic component of the PFMSS was analysed with keyword and linguistic pattern identification. The results of these two complementary analyses (i.e., EE and linguistic analysis) provided relevant recommendations that may improve the efficacy of psychological treatment for ADHD such as parenting interventions. We discuss the practical implications of these findings.

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Psychiatr Clin North Am. 2014 Mar;37:125-40.

NEUROPSYCHIATRY OF PEDIATRIC TRAUMATIC BRAIN INJURY.

Max JE.

Pediatric traumatic brain injury (TBI) is a major public health problem. Psychiatric disorders with onset before the injury are more common than population base rates. Novel (postinjury onset) psychiatric disorders (NPD) are also common and complicate child function after injury. Novel disorders include personality change due to TBI, secondary attention-deficit/hyperactivity disorder, other disruptive behavior disorders, and internalizing disorders. This article reviews preinjury psychiatric disorders as well as biopsychosocial risk factors and treatments for NPD.

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Psychiatriki. 2011 Oct;22:314-19.

PSYCHOTROPIC MEDICATION USE IN CHILDREN AND ADOLESCENTS IN AN INPATIENT SETTING.

Pejovic-Milovancevic M, Miletic V, Popovic-Deusic S, et al.

Medication can be an effective part of treatment for several psychiatric disorders of childhood and adolescence but its use should be based on a comprehensive psychiatric evaluation and treatment plan. The aim of this study was to evaluate psychotropic medication use for children and adolescents treated as inpatients and to compare it with principles of rational pharmacotherapy, thus identifying possible downsides of current practices and pointing a way towards safer and more efficient practices. This is a descriptive study of prescribing trends at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade, during the period from September 2009 to September 2010. Analyzed demographic data (age, gender) and the number of hospitalizations were obtained from medical histories, while diagnoses were obtained from discharge notes. Prescribed therapy was copied from medication charts. Drug dosages were analyzed as average daily doses prescribed during the hospitalization. Psychiatric diagnoses were classified according to The International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). During the examined time period, 264 patients were hospitalized (61.4% males), with an average age of 11.4+/-5.1 years. We have found that 66.3% of admitted patients were treated with pharmacotherapy in addition to other treatment modalities. There was a highly significant correlation between the age of patients and the prescribed dosage (Spearman's rho=0.360, p<0.001) as well as the number of prescribed drugs (Spearman's rho=0.405, p<0.001). The most commonly diagnosed psychiatric disorders were: autism spectrum disorders (20.8%), conduct disorders(19.7%), mixed developmental disorder (14.8%), adjustment disorder (7.2%), mental retardation (7.2%),acute psychosis (4.5%), and ADHD (2.3%). The most commonly prescribed medications were antipsychotics(45.9%), followed by antidepressants (17.2%), mood stabilizers (16.1%), benzodiazepines (14.4%), and other psychotropic drugs (6.4%). The most commonly prescribed antipsychotic was risperidone, used for more than 50% of the patients treated with antipsychotics. Taken

together risperidone and chlorpromazine were more than 75% of all prescribed antipsychotics. 98.4% of prescribed antidepressants belonged to the SSRIs,with sertraline and fluoxetine accounting for almost 90% of them. All prescribed dosages were in accordance with the official guidelines. This is the first survey in Serbia to document the practice of prescribing psychotropic medication in the field of child and adolescent psychiatry. Current drug-prescribing practices at the Clinical Department for Children and Adolescents of the Institute of Mental Health in Belgrade are in accordance with current practices in the United States and Europe. Not every child with symptoms of mental health problems needs pharmacological treatment; when they do, the general rule of thumb should be "start low, go slow, and taper slowly". Follow-up studies are necessary to assess the change of trends, as well as studies in different patient populations and health centers, in order to globally evaluate psychotropic medication use in children and adolescents in Serbia.

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Psychiatriki. 2012 Jun;23 Suppl 1:49-59.

THE COURSE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) OVER THE LIFE SPAN.

Koumoula A.

Attention Deficit Hyperactivity Disorder is a neurodevelopmental disorder, associated with the maturation of the nervous system and appearing on a standard proceeding with special cognitive impairments. For many years ADHD was concerned as a typical childhood disorder. Long-term studies though, showed that an important percentage of children with ADHD grew as adults with ADHD. The clinical picture varies with the developmental stage. In pre-school years (3-5 years) the clinical picture is characterized by excessive physical activity, difficulty in cooperation with peers and non-compliance to the recommendations of adults. In school age (6-12 years), apart from the nuclear symptoms of the disorder, as described in the classification systems, i.e. inattention, hyperactivity and impulsivity, oppositional behavior often occurs, conflicts with peers and academic problems. In adolescence hyperactivity lessens, conflicts with parents continue and high risk behaviors often appear. In adults physical activity usually decreases significantly, while inattention and impulsivity still remain. With the passing of time the number of symptoms are usually reduced, however the impact and impairment caused by the disorder remain. The diagnosis of ADHD in adults requires a retrospective diagnosis of ADHD in childhood. Since childhood, comorbid disorders are common, most times continuing until adult life. The Oppositional Defiant Disorder during childhood is related to the presenting of Antisocial Personality Disorder in adults. On the other hand, emotional disorders, which are also rather common in children, adolescents and adults with ADHD, can be due to either common biological mechanisms or the long-standing effect of psychosocial and environmental factors which follow people with ADHD. The relationship between ADHD and substance abuse has been a subject of research, with the view of the existence of Conduct Disorder being necessary for a person to present a Substance Use Disorder, currently prevailing. Smoking and alcohol drinking do not seem to require this mediation and ADHD can be itself a predictor for smoking and alcoholism. Stimulant treatment in childhood offers some protective effect against drug abuse and alcoholism in adolescence. The diagnosis of Borderline Personality Disorder is common in adults with ADHD and the most common reason is the overlap of symptoms between the two disorders. The question is whether the diagnosis of Borderline Personality Disorder in adults is appropriate and useful in the presence of ADHD, because when ADHD proceeds the symptoms and the impairment in functioning are due to this disorder. In general, when another diagnosis or several symptoms as a part of another disorder are also present, treatment of the primary disorder, i.e. ADHD, is beneficial and effective for all the presenting problems.

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Psychiatriki. 2012 Jun;23 Suppl 1:15-26.

CONTINUITIES AND DISCONTINUITIES OF PSYCHOPATHOLOGY FROM CHILDHOOD TO ADULTHOOD.

Karantanos G.

Important data about possible continuities and discontinuities of psychopathology from childhood to adulthood have been provided by findings from well scheduled prospective longitudinal studies of community-based samples. Findings from clinical populations have contributed as well. This presentation

relies on data from selected studies of reference. An effort is made to combine results demonstrating the extent of continuity at a more general level with those indicating continuities or discontinuities concerning disorders commonly presented in clinical practice. These disorders are those included in the internalizing (anxiety and mood disorders) and externalizing (ADHD, oppositional, conduct disorder-antisocial personality disorder) domains of psychopathology. Discontinuities do exist, however findings also suggest considerable longitudinal links between childhood-adolescence and adulthood. Reports from the Dunedin longitudinal study showed that half of those with psychiatric diagnoses at the age of 26 had met criteria for psychiatric disorder by the age of 15, and that figure approached 75% by the age of 18. Homotypic continuity is the most prominent. There are also heterotypic continuities, while homotypic and heterotypic continuities may co-occur. Among common disorders, findings suggest continuity tendencies even for anxiety disorders and for subclinical cases with obsessive and compulsive symptoms as well. Comorbidity between different anxiety disorders (strict homotypic continuity) as well as between them and depression (broad homotypic continuity) is very common. In the externalizing domain, longitudinal links between conduct disorder and antisocial personality disorder, including adverse consequences in psychosocial functioning, have been repeatedly found. Childhood onset subtype of conduct disorder is more prone to this adverse outcome, however all cases with conduct disorder need early recognition and intervention. During the course of conduct disorder, substance use is now recognized as a kind of homotypic continuity. About half of attention deficit-hyperactivity disorder (ADHD) cases continue into adulthood. These individuals usually face problems in several aspects of their adult life, such as interpersonal relationships, educational and occupational functioning. In ADHD cases, the emergence of conduct disorder worsens the adverse outcome; therefore prevention of this complication is of significant importance for intervention. There are indications that oppositional disorder cases may be heterogeneous and that this may explain the heterotypic continuities that have been found so far. Many aspects are open to further study, particularly those concerning the possible mechanisms involved in continuities or discontinuities in various disorders. Data suggesting the extent of continuities are important for both child psychiatry and psychiatry. Attention should be focused on early intervention, services provision and cooperation. The latter is of vital importance during the transition from child to adult services.

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Psychiatriki. 2012 Jun;23 Suppl 1:101-06.

OBSESSIVE-COMPULSIVE DISORDER IN CHILDREN AND ADOLESCENTS AND ITS CONTINUATION THROUGHOUT LIFE.

Liakopoulou M.

Obsessive-compulsive disorder (OCD) appears in children at the ages of 7-12 years and it usually stays undiagnosed. Its prevalence is approximately 0.6-1% and it is comorbid especially with Tourette's syndrome, chronic tics and Attention Deficit and Hyperactivity Disorder (ADHD), as well as with other disorders. Comorbidity runs up to the 75% of children and adults alike. In children it is most often represented by the above mentioned disorders. Prevalence of OCD is similar to children as in adults. One third of adults or 50% of them are affected from the illness during childhood. As in adult OCD, the main etiological disturbance seems to be located at the basal ganglia and the cortex. One of the main current pathophysiological hypotheses is that OCD is a disorder of the neuronal circuit involving the cortex-thalamus-striatum-cortex. The disease has a familial character as shown in studies where 1st degree relatives of children with OCD have increased prevalence of OCD and OC symptoms compared to controls. Cognitive behavioral therapy is indicated for children and adolescents as it is for adults with OCD. It is successful as monotherapy for the 50% of children and adolescents. Monotherapy with cognitive behavioral therapy is not indicated for patients with a family history of OCD and it should be augmented with the addition of Selective Serotonin Reuptake Inhibitors (SSRIs). The therapeutic result is similar for children and adults (70-80%). Also, the therapeutic effectiveness of SSRIs in OCD for children and adolescents supports the hypothesis that the control serotonergic routes are related to the pathophysiology of the illness. Follow-up studies of childhood OCD show the chronicity of the illness. In these studies, 50% of the children still suffered from OCD at follow-up whereas only 11% were symptom free. Prognosis is worse if the duration of the illness is long, if there is comorbidity, inpatient hospitalization and reduced initial therapeutic response. Early detection and treatment of the child and its family are related to better prognosis. Childhood OCD seems to belong to a subgroup of the illness with specific clinical and familial

pattern. Nevertheless more long-term follow-up studies are needed in order to differentiate subgroups of OCD. More studies on the pathophysiology of the illness are needed in order to have better treatments for OCD in children and adults.

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Psychiatriki. 2012 Oct;23:304-13.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER OR BIPOLAR DISORDER IN CHILDHOOD?

Lazaratou H.

Attention-deficit hyperactivity disorder (ADHD) is considered one of the most common neurodevelopmental disorders of childhood, characterized by inattention and/or hyperactivity-impulsivity. Even though a strict definition of this entity is constantly sought, ADHD is an often redefined and reconceptualized syndrome. Epidemiological studies show large differences in the incidence, pointing out that the effort of actual taxonomic systems to offer objective diagnostic criteria have not yielded substantial results. Bipolar Disorder (BD) with onset in childhood is distinguished from the adult form by the scarcity of affective symptoms. Very often, neither depressive mood, nor hypomanic euphoria are in the front line being covered by irritability with crises of violence. Children or adolescents have consecutive cycles, which include brief episodes of depressive, hypomanic, manic or mixed periods without free intervals. There was a delay in the recognition of this clinical picture. Tauhe diagnostic criteria in the actual taxonomic systems are not separated from those of adults and according to some studies the disorder is under diagnosed mainly in European countries. The contemporary literature deals largely with the relationship A.

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Psychiatriki. 2012 Jun;23 Suppl 1:74-81.

SPECIFIC DEVELOPMENTAL DISORDER OF SPEECH AND LANGUAGE IN ADULTHOOD.

Vlassopoulos M, Anagnostopoulos DC.

Specific developmental disorder of speech and language is part of a more general category of neurodevelopmental disorders, which is encountered in 7-10% of the childhood population. These children exhibit a significant impairment in speech and language development, which cannot be justified by hearing impairment, cognitive impairment, neuromuscular or orofacial disorders, as well as by emotional or environmental factors. Specific developmental disorders of speech and language are often comorbid with other neurodevelopmental disorders, such as motor coordination disorder and ADHD. These disorders are usually detected in early childhood and commonly treated during the preschool and school years. Despite this fact clinical and empirical evidence suggest that often these disorders persist beyond the school years, even though the symptomatology may be differentiated. In this literature review, we address the question of whether specific developmental language disorders are encountered only during childhood, and, if they persist, how they are manifested in adulthood. Finally, possible factors which may lead to these manifestations are analyzed. A considerable body of research has shown that even though the symptoms of children with specific developmental language disorders are resolved before the end of childhood, a significant part of this population continues to have persisting difficulties through adolescence and into adulthood. The continuity of this disorder may sometimes be directly linked to language disorder, as in the case of learning impairments or, on the other hand, symptoms may be related with those of conduct disorders, social adjustment disorder, emotional and psychiatric disorders in adolescence and adulthood. It therefore appears that specific developmental language disorder is often an early symptom of other disorders in the future. Even though the precise mechanisms which are responsible for these disorders are not yet known, it is possible that a fragile neurobiological substratum in these disorders may explain why early symptoms are usually manifested as language disorders and later develop into other disorders over time. However, these symptom changes may be linked to other parameters, such as the increasing social and emotional demands made on these individuals with increasing age, which may be a contributing environmental parameter to an already vulnerable system. Despite all of the limitations in the longterm study of these children, it is suggested that in some way, and not in all cases, pathology may continue into adulthood, although with a different symptomatology, which is linked to behavioural and social adjustment,

as well as with more pervasive psychiatric disorders. In conclusion, it is suggested that a continuum of services may be necessary for these cases into adulthood.

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Psychol Med. 2014 Feb;44:617-31.

SPECIFICITY OF BASIC INFORMATION PROCESSING AND INHIBITORY CONTROL IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Salum GA, Sergeant J, Sonuga-Barke E, et al.

BACKGROUND: Both inhibitory-based executive functioning (IB-EF) and basic information processing (BIP) deficits are found in clinic-referred attention deficit hyperactivity disorder (ADHD) samples. However, it remains to be determined whether: (1) such deficits occur in non-referred samples of ADHD; (2) they are specific to ADHD; (3) the co-morbidity between ADHD and oppositional defiant disorder/conduct disorder (ODD/CD) has additive or interactive effects; and (4) IB-EF deficits are primary in ADHD or are due to BIP deficits.

METHOD: We assessed 704 subjects (age 6-12 years) from a non-referred sample using the Development and Well-Being Assessment (DAWBA) and classified them into five groups: typical developing controls (TDC; n = 378), Fear disorders (n = 90), Distress disorders (n = 57), ADHD (n = 100), ODD/CD (n = 40) and ADHD+ODD/CD (n = 39). We evaluated neurocognitive performance with a Two-Choice Reaction Time Task (2C-RT), a Conflict Control Task (CCT) and a Go/No-Go (GNG) task. We used a diffusion model (DM) to decompose BIP into processing efficiency, speed-accuracy trade-off and encoding/motor function along with variability parameters.

RESULTS: Poorer processing efficiency was found to be specific to ADHD. Faster encoding/motor function differentiated ADHD from TDC and from fear/distress whereas a more cautious (not impulsive) response style differentiated ADHD from both TDC and ODD/CD. The co-morbidity between ADHD and ODD/CD reflected only additive effects. All ADHD-related IB-EF classical effects were fully moderated by deficits in BIP.

CONCLUSIONS: Our findings challenge the IB-EF hypothesis for ADHD and underscore the importance of processing efficiency as the key specific mechanism for ADHD pathophysiology.

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Psychol Med. 2014 Jan;44:435-46.

RAPID VISUAL INFORMATION PROCESSING AS A COGNITIVE ENDOPHENOTYPE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Gau SS, Huang WL.

BACKGROUND: Deficits in sustained attention and reaction time are core features of attention deficit hyperactivity disorder (ADHD). However, little is known about attention performance in unaffected siblings. Hence, we examined sustained attention and reaction time in youths with ADHD, unaffected siblings and controls to test whether impaired performance in attention tasks can be a potential endophenotype of ADHD.

METHOD: We recruited 438 probands with clinical diagnosis of ADHD according to DSM-IV criteria, 180 unaffected siblings, and 173 healthy controls without lifetime ADHD. They were assessed using psychiatric interviews, Conners' Continuous Performance Test, and the tasks involving attention performance of the Cambridge Neuropsychological Test Automated Battery (CANTAB): Rapid Visual Information Processing (RVP), Reaction Time (RTI) and Match to Sample Visual Search (MTS). Multi-level models were used for data analysis.

RESULTS: Compared with the controls, probands with ADHD and unaffected siblings had significantly higher total misses, lower probability of hits in the RVP task and probands with ADHD performed worse in the RTI and MTS tasks after controlling for sex, age, co-morbidity, parental educational levels and IQ. The duration of methylphenidate use and IQ but not psychiatric co-morbidity or current use of methylphenidate were associated with deficits in sustained attention in probands with ADHD.

CONCLUSIONS: Our findings suggest that attention performance assessed by the RVP task, but not the RTI or MTS tasks, of the CANTAB may be a useful cognitive endophenotype for ADHD genetic studies.

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Psychol Med. 2014 Feb;44:633-46.

DRUG-SPECIFIC LATERALITY EFFECTS ON FRONTAL LOBE ACTIVATION OF ATOMOXETINE AND METHYLPHENIDATE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER BOYS DURING WORKING MEMORY.

Cubillo A, Smith AB, Barrett N, et al.

BACKGROUND: The catecholamine reuptake inhibitors methylphenidate (MPH) and atomoxetine (ATX) are the most common treatments for attention deficit hyperactivity disorder (ADHD). This study compares the neurofunctional modulation and normalization effects of acute doses of MPH and ATX within medication-naive ADHD boys during working memory (WM).

METHOD: A total of 20 medication-naive ADHD boys underwent functional magnetic resonance imaging during a parametric WM n-back task three times, under a single clinical dose of either MPH, ATX or placebo in a randomized, double-blind, placebo-controlled, cross-over design. To test for normalization effects, brain activations in ADHD under each drug condition were compared with that of 20 age-matched healthy control boys.

RESULTS: Relative to healthy boys, ADHD boys under placebo showed impaired performance only under high WM load together with significant underactivation in the bilateral dorsolateral prefrontal cortex (DLPFC). Both drugs normalized the performance deficits relative to controls. ATX significantly enhanced right DLPFC activation relative to MPH within patients, and significantly normalized its underactivation relative to controls. MPH, by contrast, both relative to placebo and ATX, as well as relative to controls, upregulated the left inferior frontal cortex (IFC), but only during 2-back. Both drugs enhanced fronto-temporo-striatal activation in ADHD relative to control boys and deactivated the default-mode network, which were negatively associated with the reduced DLPFC activation and performance deficits, suggesting compensation effects.

CONCLUSIONS: The study shows both shared and drug-specific effects. ATX upregulated and normalized right DLPFC underactivation, while MPH upregulated left IFC activation, suggesting drug-specific laterality effects on prefrontal regions mediating WM.

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Psychol Addict Behav. 2014 Sep;28:816-27.

EVALUATION OF UNDERLYING MECHANISMS IN THE LINK BETWEEN CHILDHOOD ADHD SYMPTOMS AND RISK FOR EARLY INITIATION OF SUBSTANCE USE.

Vitulano ML, Fite PJ, Hopko DR, et al.

Although there has been support for attention-deficit/hyperactivity disorder (ADHD) as a risk for early substance use, this link is not fully established or understood. Furthermore, the potential mechanisms explaining these associations are unclear. The current study examined peer rejection, school bonding, and internalizing problems as potential mediators of the association between childhood ADHD symptoms and risk for early initiation of substance use. The sample included a control group of 126 students with problematic aggression (79% African American, 66% male) from an intervention study following children from fourth to ninth grade. Results suggested that ADHD symptoms follow a path to early initiation of tobacco use through the combined effects of peer rejection and internalizing problems as well as through internalizing problems alone. ADHD symptoms were also associated with the cubic slope of marijuana use initiation, such that increased ADHD symptoms were associated with a strong cubic trend (e.g., a more rapid acceleration of risk for initiation). ADHD symptoms were not associated with risk for early initiation of alcohol use. Identification of important vulnerability factors in children with ADHD symptoms highlight the need for primary prevention and psychological interventions that target these factors and decrease the likelihood of early tobacco and marijuana use initiation.

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Psychology Research and Behavior Management. 2014 Sep;7.

PHARMACOLOGICAL INTERVENTIONS FOR ADOLESCENTS AND ADULTS WITH ADHD: STIMULANT AND NONSTIMULANT MEDICATIONS AND MISUSE OF PRESCRIPTION STIMULANTS.

Weyandt LL, Oster DR, Marraccini ME, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity that cause functional impairment. Recent research indicates that symptoms persist into adulthood in the majority of cases, with prevalence estimates of approximately 5% in the school age population and 2.5%–4% in the adult population. Although students with ADHD are at greater risk for academic underachievement and psychosocial problems, increasing numbers of students with ADHD are graduating from high school and pursuing higher education. Stimulant medications are considered the first line of pharmacotherapy for individuals with ADHD, including college students. Although preliminary evidence indicates that prescription stimulants are safe and effective for college students with ADHD when used as prescribed, very few controlled studies have been conducted concerning the efficacy of prescription stimulants with college students. In addition, misuse of prescription stimulants has become a serious problem on college campuses across the US and has been recently documented in other countries as well. The purpose of the present systematic review was to investigate the efficacy of prescription stimulants for adolescents and young adults with ADHD and the nonmedical use and misuse of prescription stimulants. Results revealed that both prostimulant and stimulant medications, including lisdexamfetamine dimesylate, methylphenidate, amphetamines, and mixed-amphetamine salts, are effective at reducing ADHD symptoms in adolescents and adults with ADHD. Findings also suggest that individuals with ADHD may have higher rates of stimulant misuse than individuals without the disorder, and characteristics such as sex, race, use of illicit drugs, and academic performance are associated with misuse of stimulant medications. Results also indicate that individuals both with and without ADHD are more likely to misuse short-acting agents than long-acting agents. These findings have implications for intervention, prevention, and future research.

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Res Dev Disabil. 2014;35:3217-25.

STATE-RELATED ELECTROENCEPHALOGRAPHIC DEVIANCES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Buyck I, Wiersema JR.

This study investigated the stability and state-related characteristics of electroencephalographic (EEG) deviances in attention-deficit/hyperactivity disorder (ADHD). Three minutes resting EEG with eyes closed and eyes open were compared between 21 children with ADHD and 29 typically developing children. Across resting conditions, children with ADHD exhibited divergent topographic distribution for theta, alpha and beta power compared to typically developing children. In addition, less alpha and theta suppression to eye opening was found in children with ADHD, but only in those without comorbid ODD/CD. Findings of the present study refer to a consistent divergence in topographic distribution in ADHD across resting state conditions, yet demonstrate that state-related factors and comorbidity may also contribute to resting EEG deviances in ADHD. The state-related findings are in accord with several theoretical accounts emphasizing the role of contextual and state factors defining deficits in ADHD.

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Res Dev Disabil. 2014;35:3191-98.

SOCIAL COGNITION IN ADHD: IRONY UNDERSTANDING AND RECURSIVE THEORY OF MIND.

Caillies S, Bertot V, Motte J, et al.

The main goal of the present study was to characterise the social cognition abilities of French children with ADHD, in terms of their understanding of people's recursive mental states and their irony comprehension. We hypothesised that these children have difficulty understanding second-order false beliefs and ironic remarks, owing to the executive dysfunction that is characteristic of ADHD. We therefore conducted an experiment in which children with ADHD and typically developing matched controls performed second-order false-belief and executive function tasks. They then listened to ironic stories and answered questions

about the ironic comments and about the speakers' beliefs and attitudes. The groups differed significantly on second-order theory of mind, irony comprehension and executive functions, confirming that children with ADHD have impaired social cognition.

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Revista Mexicana de Pediatria. 2014;81:89-92.

RISK FACTORS ASSOCIATED WITH ATTENTION DEFICIT IN CHILDREN WITH OR WITHOUT HYPERACTIVITY.

Munoz-Perez MJ, Perez-Garcia JC, Arroyo C, et al.

Objective: to compare perinatal risk factors in children with ADD/H (attention deficit disorder with or without hyperactivity) and healthy children.

Material and methods: It was performed a retrospective case-control study in children with AD/HD. From the clinical history we obtained data of factors that might be associated with the occurrence of AD/HD.

Results: Statistically significant differences were found between the group of children with AD/HD and control group in factors such as weeks of gestation ($p = 0.0117$), perinatal hypoxia ($p = 0.007$). The case of post-term birth was a protective factor ($p = 0.028$). Language disorders were associated with subsequent development of AD/HD ($p < 0.0001$).

Conclusions: In this article were found associated with the TDA factors such as the late development of the language and as a protective factor is the delivery post-term.

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ScientificWorldJournal. 2014;2014:710570.

EARLY SYMPTOMATIC SYNDROMES ELICITING NEURODEVELOPMENTAL CLINICAL EXAMINATIONS.

Gillberg C, Fernell E, Minnis H.

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Sleep Medicine 2014 [Articles in Press]

A PROSPECTIVE STUDY OF SLEEP PROBLEMS IN CHILDREN WITH ADHD.

Lycett K, Mensah FK, Hiscock H, et al.

Background: Behavioral sleep problems are common in children with attention-deficit/hyperactivity disorder (ADHD), yet their persistence or otherwise is unknown. We examined behavioral sleep problem trajectories, types of sleep problems experienced, and associated risk/protective factors.

Methods:**Design**: Prospective cohort study. Setting: Twenty-one pediatric practices across Victoria, Australia.

Participants: A total of 195 children with ADHD (5-13 years).

Outcomes: Sleep problem trajectories classified as never, transient, or persistent on the basis of sleep problem severity measured at baseline, 6, and 12 months.

Explanatory variables: Types of sleep problems, internalizing and externalizing comorbidities, ADHD symptom severity and medication use, autism spectrum disorder, caregiver mental health, and sociodemographic factors.

Analyses: Multinomial logistic regression models.

Results: Sleep problems fluctuated over 12 months, but for 10% of children they persisted. In adjusted analyses, co-occurring internalizing and externalizing comorbidities were a risk factor for persistent (odds ratio (OR) 9.2, 95% confidence interval (CI) 1.6, 53.9, $p = 0.01$) and transient (OR 3.7, 95% CI 1.5, 8.8, $p = 0.003$) sleep problems, while greater ADHD symptom severity and poorer caregiver mental health were risk factors for persistent and transient sleep problems, respectively.

Conclusions: Sleep problems in children with ADHD are commonly transient, but in a subgroup they are characterized as persistent. Early preventive/intervention strategies should target children at risk of persistent sleep problems.

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Swed Dent J. 2014;38:93-100.

PARENTAL ATTITUDES AND EXPERIENCES OF DENTAL CARE IN CHILDREN AND ADOLESCENTS WITH ADHD--A QUESTIONNAIRE STUDY.

Staberg M, Noren JG, Johnson M, et al.

Attention deficit hyperactivity disorder (ADHD) is a common psychiatric condition characterized by age-inappropriate levels of inattention, hyperactivity-impulsiveness or a combination of these. The aim of this study was to analyze parental attitudes to and experience of dental care, oral hygiene and dietary habits in children/adolescents with ADHD. Twenty- six parents of 31 subjects, 20 boys and 11 girls, aged 5-19 years with ADHD registered at the Gothenburg Child Neuropsychiatric Clinic, were invited. The parents answered a questionnaire regarding different oral problems when visiting the Clinic of Pediatric Dentistry, Gothenburg, for an oral examination of their child. The parents felt the dental care at the Public Dental Service was good, but noted a lack of knowledge regarding child neuropsychiatry among the dental staff which may influence the dental treatment. Fifteen parents reported their children had experienced mouth pain and 15 reported their child had suffered from both discomfort and pain from local anesthesia. Thirteen of the children had a dental trauma and 12 parents reported pain in connection to the dental treatment. Pain related to filling therapy was stated by 11 parents. According to the parents, five children suffered from dental fear but 15 reported the child had a general fear. Pursuant to the parents, the beverage for dinner was mainly milk or water, while sweet drinks were more frequent when thirsty. Seventeen parents reported their children had poor oral hygiene or could not manage to brush their teeth and 14 of the 31 children only brushed once a day or less. The results show that the parents experience a lack of child neuropsychiatric knowledge, care and patience from the dental staff, which may influence the treatment. Oral hygiene/tooth brushing is neglected and the frequent consumption of sugar is difficult for the parents to handle.

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The Indian Journal of Pediatrics. 2014.

ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Kulkarni M.

Attention Deficit Hyperactivity Disorder (ADHD) is a common behavioral disorder in children. It is characterized by motor hyperactivity, impulsivity and inattention inappropriate for the age. Approximately 5-10 % of school age children are diagnosed to have ADHD. The affected children show significant impairment in social behavior and academic performance. The DSM-5 criteria are useful in diagnosing three subtypes of ADHD based on presence of symptoms described in 3 domains viz., inattention, hyperactivity and impulsivity. Co-morbidities like specific learning disability, anxiety disorder, oppositional defiant disorder are commonly associated with ADHD.Education of parents and teachers, behavioral therapy and medication are main components of management. Methylphenidate and Atomoxetine are effective in controlling symptoms of ADHD in most children. Research studies estimated that 30-60 % of children continue to show symptoms of ADHD in adulthood. The general practitioner can play an important role in early diagnosis, appropriate assessment and guiding parents for management of children with ADHD.

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Tijdschr Geneeskd. 2014;70:1065-69.

ADHD IN ADULTS WITH SUD: A GUIDELINE FOR THE DIAGNOSIS AND TREATMENT.

Matthys F, Joostens P, van den Brink W, et al.

Various guidelines are available for attention deficit hyperactivity disorder (ADHD) in children and adults, but not for patients with ADHD and a comorbid substance use disorder (SUD). The Addiction Medicine Working Party, a division of the Association for Alcohol and other Drug Problems, developed a practice guideline for the diagnosis and treatment of ADHD in patients with an addiction. Given the high prevalence of ADHD in treatment- seeking patients with SUD and the availability of valid screening instruments, all patients with SUD should be screened for the presence of ADHD as soon as their drug use has stabilized. Acquiring information from external sources as well as clinical observation and semi-structured interviews

are important tools for the diagnosis of ADHD. An integrated treatment primarily includes psycho-education, coaching and cognitive behavioural therapy in addition to pharmacotherapy. Evidence-based treatments for addiction may also be effective in patients with concomitant ADHD, provided the methods are adapted to the limitations associated with this condition.

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Trials. 2014;15:54.

AGGREGATED N-OF-1 TRIALS OF CENTRAL NERVOUS SYSTEM STIMULANTS VERSUS PLACEBO FOR PAEDIATRIC TRAUMATIC BRAIN INJURY--A PILOT STUDY.

Nikles CJ, McKinlay L, Mitchell GK, et al.

BACKGROUND: In 2006 there were 432,700 people in Australia who had acquired brain injury (ABI) with some limitation of activities; 90% of these were traumatic brain injuries (TBIs) and nearly a third sustained injury below age 15 years. One to four years post injury, 20% to 46% of children with traumatic brain injury (TBI) have clinically significant disorders of attention. There is controversy as to whether central nervous system (CNS) stimulants can be an effective method of treating these.Objectives were to determine the efficacy of CNS stimulants for children with TBI, and to calculate the sample size for a larger trial using the Conners' 3 Parent Rating Scales Score as the primary endpoint.

METHODS: Pilot series of aggregated prospective randomised, double-blind, n-of-1 trials of stimulant versus placebo within individual patients.

SETTING: tertiary children's public hospital. PARTICIPANTS: ten children aged 6 to 16 years more than 12 months post TBI with attention, concentration and behavioral difficulties on stimulants.

INTERVENTIONS: Three cycles of methylphenidate or dexamphetamine orally at doses titrated by physician compared to placebo.

MAIN OUTCOME MEASURES: Conners 3 Parent (Conners 3-P) and Teacher (Conners 3-T) Rating Scales (Global Index), Behaviour Rating Inventory of Executive Function (BRIEF) and Eyberg Child Behaviour Inventory (ECBI).

RESULTS: Five of ten patients completed the study. Data from 18 completed cycles from seven patients were analysed. The posterior mean difference between stimulant and placebo scores for the Conners 3-PS (Global Index) was 2.3 (SD 6.2; 95% credible region -1.0 to 6.1; posterior probability that this mean difference was greater than zero was 0.92), and for the Conners 3-T (Global Index) the posterior mean difference was 5.9 (SD 4.5; 95% credible region -3.1 to 14.9; posterior probability 0.93). Posterior mean differences suggest improvement in behaviour and executive function and a decrease in number and intensity of child behaviour problems when taking stimulants compared to placebo. Taken together these data are suggestive of a small benefit at group level.

CONCLUSIONS: In this pilot study, there was sufficient evidence that stimulants may be useful in management of behavioral and cognitive sequelae following TBI, to warrant a larger trial.

TRIAL REGISTRATION: he trial was registered with the Australian and New Zealand Clinical Trials Registry: registration number ACTRN12609000873224

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Z Kinder Jugendpsychiatr Psychother. 2014 Jul;42:271-75.

DMS-5 - ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Banaschewski T, Dopfner M.

Modifications to the DSM-5 criteria for the diagnosis of attention-deficit/hyperactivity disorders are described and discussed. The main modifications concern the onset of the disorder, the reduction on the number of criteria fulfilled for a diagnosis in patients aged 17 years or older, and the elimination of autism spectrum disorders as an exclusion criterion for this diagnosis. These changes are mainly welcomed. However, the demanded increase in the age for the latest onset of the disorder may prove to be problematic.

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Z Kinder- Jugendpsychiatr Psychother. 2014;42:337-47.

GINKGO BILOBA EXTRACT EGB 761(REGISTERED TRADEMARK) IN CHILDREN WITH ADHD: PRELIMINARY FINDINGS OF AN OPEN MULTILEVEL DOSE-FINDING STUDY.

Uebel-Von SH, Rothenberger A, Albrecht B, et al.

Objectives: The side effects, nonresponse, and prejudices against conventional pharmacological treatments call for complementary or alternative medical treatments (CAM) for ADHD. One possible treatment, at least for cognitive problems, might be the administration of Ginkgo biloba, though evidence is currently rare. This study tests the clinical efficacy of a Ginkgo biloba special extract (EGb 761(registered trademark)) and its correlation with brain electrical activity in children with ADHD combined type according to DSM-IV.

Method: In this open clinical pilot study, EGb 761(registered trademark) was administered to 20 children with ADHD over 3 to 5 weeks. Dosage was increased to a maximum of 240mg daily if attention problems persisted. Possible drug side effects were assessed using the Side Effect Rating Scale. Efficacy was assessed in a multilevel approach including clinical assessment, quality of life (QoL), as well as performance and preparatory brain-electrical activity evoked during a Continuous Performance Test (Cue-CNV in the CPT).

Results: A very low rate of mild adverse effects occurred during the observation period. Following EGb 761(registered trademark) administration, possible improvements in QoL, ADHD core symptoms as well as CPT performance were detected. Improved core symptoms were positively related to elevated CNV amplitude.

Conclusion: This preliminary evidence suggests that EGb 761(registered trademark) at a maximal dosage of 240mg daily might be a clinically useful alternative treatment for children with ADHD, but further evidence is required before firm conclusions can be made.

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ORIGINAL CONTRIBUTION

Impaired reflexive orienting to social cues in attention deficit hyperactivity disorder

Andrea Marotta · Maria Casagrande · Caterina Rosa · Lisa Maccari · Bianca Berloco · Augusto Pasini

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Abstract The present study investigated whether another person's social attention, specifically the direction of their eye gaze, and non-social directional cues triggered reflexive orienting in individuals with Attention Deficit Hyperactivity Disorder (ADHD) and age-matched controls. A choice reaction time and a detection tasks were used in which eye gaze, arrow and peripheral cues correctly (congruent) or incorrectly (incongruent) signalled target location. Independently of the type of the task, differences between groups were specific to the cue condition. Typically developing individuals shifted attention to the location cued by both social and non-social cues, whereas ADHD group showed evidence of reflexive orienting only to locations previously cued by non-social stimuli (arrow and peripheral cues) but failed to show such orienting effect in response to social eye gaze cues. The absence of reflexive orienting effect for eye gaze cues observed in the participants with ADHD may reflect an attentional impairment in responding to socially relevant information.

Keywords Attention deficit hyperactivity disorder · Eye gaze · Joint attention · Reflexive orienting

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral syndrome characterized by inattention, impulsivity and hyperactivity and has recently been estimated to affect 3.5 % of school-aged children worldwide [69], being one of the most commonly diagnosed condition in children and adolescents today [4]. Although ADHD symptoms tend to decline with age, at least 50 % of children with ADHD continue to manifest symptoms as adults [8]; in other words, it is a chronic and sometimes life-long disorder. ADHD is associated with impairments in cognitive, academic, familial and occupational functioning [7]. Moreover, social consequences are often some of the most debilitating negative sequelae of this disorder [47], as children with ADHD are less accepted by their peers and are perceived as less socially competent than comparison groups [18, 33]. These problems are known to be a strong predictor of serious negative outcomes in later adolescence and adulthood [27, 63]. A factor that might contribute to these deficits is the failure to perceive, attend and respond adequately to social cues of communication partners, which could limit the ability to accurately read and respond appropriately to social situations. Consistent with this view, several studies reported in ADHD various deficits in domains of social cognition such as facial affect recognition [16, 67, 79], theory of mind [80] and empathy [11, 19]. Moreover, alterations in the perception of social cues such as emotional faces have been seen in neurobiological studies. Abnormal N170 amplitude has been reported in ADHD during face and facial affect processing [36, 88] as well as abnormal activity of frontal and posterior cingulated cortex activated by emotional expressions, indexed by fMRI [58]. In the present study, we have further investigated this factor by evaluating for the first time joint visual attention ability in children and adolescents with ADHD.

Joint visual attention—operationalized here as the ability to accurately encode other people's direction of attention (i.e. attentional orienting in response to eye gaze

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direction)—is critical for efficient social interactions, given that social cues, such as another individual's eye gaze, provide important information regarding an individual's interests and mental states [9, 20, 62]. Indeed, this behaviour is known to be a significant predictor of adult social competence, for example it can support language acquisition, cultural learning and theory-of-mind development in infants [9, 12, 84]. For the above-mentioned reasons, several recent studies have investigated mechanisms underlying this phenomenon by means of computerized laboratory experiments, suggesting that seeing another's gaze automatically orients one's attention to the object and direction signalled by the gaze [17, 45, 54].

It is important to distinguish between automatic and controlled spatial orienting of attention. Salient properties of external stimuli can attract attention automatically, causing one to reflexively orient towards it in space in a bottom-up fashion, or it can be deemed significant by internally developed expectancies or goals, causing one to move attention in a controlled, voluntary manner. In a spatial cueing paradigm, symbolic and centrally presented cues (e.g. an arrow presented at the centre of the screen that indicates the likely target location) have been used to investigate endogenous orienting, whereas peripheral cues (e.g. the abrupt onset of an object in the periphery not providing any information regarding the location of the upcoming target) have been employed to study exogenous orienting [39, 70]. Interestingly, centrally presented eye gaze cues exhibit some of the reflexive characteristics of peripheral (automatic) cues. Specifically, gaze cues result in a speeding up of reaction time to targets appearing in the looked-at location compared to other locations (the so-called facilitation effect) even when the gaze direction is not predictive of the subsequent target location [21, 25]. Furthermore, this effect occurs even when the time interval between the presentation of the cue and the target is very short (around 100 ms; [22, 45, 73]) and even when participants are told to expect targets at the opposite location [17, 23]. It should be noted that similar reflexive shifts of attention have been observed when uninformative arrows were used as central cues [24, 32, 44, 73, 82, 83]. However, arrow cues appear to be more susceptible to top-down control [74] and trigger a different type of attentional selection as compared to gaze cues [56]. Moreover, attentional effects in response to both eye gaze and arrow cues appear to be independent by peripheral cueing [59]. Thus, in typically developed population, gaze cues demonstrate effects different by those observed by means of both peripheral cues and symbolic central cues, suggesting that they rely on separate neural systems [28, 55, 73].

Most spatial cueing studies reported intact orienting effects in ADHD (for a review see [34]) and no differences in those effects between children with ADHD and typically developing controls using peripheral cues [13, 35, 64] and symbolic central cues [61, 81, 85]. However, to our knowledge, no previous experiment has used a central gaze cue to examine reflexive orienting in children with ADHD.

The main purpose of the present study is to examine reflexive attentional orienting as a function of eye gaze within individuals with ADHD and typically developing people. A gaze cueing procedure, in which the reflexive orienting effect to the cued location is thought to reflect the operation of a specialized social processing, is compared to both peripheral and central arrow cue procedures in which orienting effects are observed in response to stimuli with no socio-biological significance.

Moreover, in the present study, we administer both target detection and discrimination versions of the spatial cueing paradigm to determine the impact of this factor upon study outcome. Compared to simple target detection, target discrimination demands additional and more complex processing and response strategies. It has been suggested that if such complex processing is impaired in ADHD, the use of a discrimination task should elicit a disproportionate decrement of visual attention-related performance in relation to typically developing people, compared to that revealed by a simple detection task [65]. On the basis of such hypothesis, discrimination tasks should be more sensible to catch a differentiation between participants with ADHD and controls, thus increasing their potential clinical utility.

The predictions were straightforward: since people with ADHD show impairments in social cognitive functions, they should show impairments in reflexive attentional orienting in response to eye gaze, which rely on social cognition. Intact gaze cueing effects should be observed only within typically developing participants. In contrast, no difference between ADHD group and matched comparison group should be observed for both peripheral and arrow cues, since normal levels of attentional orienting have been generally reported with no-social cues in individuals with ADHD [34]. Finally, if an attentional impairment in responding to eye gaze cues will be actually observed in ADHD, the more difficult task (i.e. the discrimination task) should probably show the larger effect of this impairment.

Method

Participants

A total of 44 children and adolescents (aged 7–16 years) participated in the study: 22 were diagnosed with ADHD (mean age 11.2 ± 2.5 years; 19 males/3 female) and 22 were typically developing individuals (mean age

11.4 ± 2.5 years; 19 males/3 female). The ADHD group included 18 participants who met the criteria for the ADHD/C subtype (exhibit both inattentiveness and hyperactivity/impulsiveness symptoms) and 4 who met the criteria for ADHD/I (show prevalently inattentive symptoms; Diagnostic and Statistical Manual of Mental Disorders [4th ed., text rev.; DSM-IV-TR; APA, [4]). All participants with ADHD were drug-naïve patients first admitted to the Day Hospital of the Child Psychiatry Unit of the University of Rome "Tor Vergata." All participants included in this study did not have a prior history of pharmacological psycho stimulant treatment. A psychopathological evaluation was performed by a team of child psychiatrists by means of the Kiddie Schedule of Affective Disorders (K-SADS; [40]), the Conners' Parent Rating Scale (CPRS), the Conners' Teacher Rating Scale (CTRS; [14]), the Children Depression Inventory [43], and the Multidimensional Anxiety Scale for Children [53]. The inclusion criteria to participate in the study were the diagnosis of ADHD (based on the DSM-IV TR criteria and confirmed by K-SADS), no history of mental retardation, brain trauma, neurological diseases or physical impairment, a lack of comorbid mental disorders with the exception of oppositional defiant disorder (ODD), and learning disabilities. The participants for the control group were matched in gender and age with the ADHD group and were selected from a wider group of 86 children and adolescents recruited from two public schools in Rome. The control group participants had no history of cerebral injury or other neurological or psychiatric disorders. All participants aged 11 years and older had a full-scale IQ that fell above the 75th percentile on the Progressive Standard Matrices (PSM; [71, 72]), and all children aged 10.5 years or younger had an IQ greater than 80 on the Progressive Coloured Matrices (PCM; [71, 72]). The presence of ADHD in participants from the control group was assessed via an independent evaluation carried out by both a teacher and one parent who completed a DSM-IV-TR report card [4]. Any participant with a possible indication of ADHD was not considered. The mean age and IQ scores of participants from the two groups did not differ significantly ($F_{1,42} = 0.07$; $p < 0.79$ and $F_{1,42} = 0.01$; $p < 0.92$, respectively). The Ethical Committee of Child Psychiatry and Neurology Institute approved the study. All parents or legal guardians of children gave written informed consent before testing.

Stimuli and apparatus

In the eye gaze paradigm, the fixation was a central schematic face (3° × 2.5° degree of visual angle) with the pupils straight; the spatial cue was the same central schematic face with the pupils directed either to the left or to the right.[1] In the arrow cueing paradigm, a horizontal line (0.5° × 2°) was used as fixation. An arrow-head directed either to the left or to the right was used as arrow cue. In the peripheral cueing paradigm, a central fixation cross was flanked by two peripheral boxes (2.5° × 2.5°). The brightening of one of the boxes (either at the left or at the right) was used to produce peripheral cues. The target was either the letter "O" or the letter "X," (0.9° × 0.9°). The two target letters appeared with a probability of 50 %. Stimuli were presented on a 21-in. colour VGA monitor. An IBM-compatible PC running E-Prime software controlled the presentation of the stimuli, timing operations and data collection. Responses were gathered with a standard keyboard. In the detection task, the participants pressed the space bar key when either an "O" or an "X" appeared. In the discrimination task, the participants pressed the "C" key for one target and the "M" key for the other target. The assignment of targets to response keys was counterbalanced across participants within each group.

Procedure

Participants were seated 60 cm directly in front of a computer monitor, in a dimly lit, sound-attenuated room and their heads were held steady with a chin/head rest. A trial sequence of the procedure is shown in Fig. 1. In this study, we chose to use schematic faces to ensure that we could match arrow, eye gaze and peripheral cues in relation to some of their lower level features.

Each trial began with a display consisting of a central fixation stimulus. For gaze cue, the fixation stimulus was a schematic face with the pupils centred vertically in the eyes. For arrow cue, the fixation stimulus was a horizontal line centred on the screen. For peripheral cue, the fixation stimulus was a central cross flanked by two peripheral boxes. After 700 ms, a cue was presented. The cue appearance was achieved by the movement of the eyes, the appearance of arrowheads on one of the sides of the horizontal line or the brightening of one of the peripheral boxes. These cues were not predictive of target location. Finally, the target appeared to either the left or right of the screen. Cue and target remained on the screen until a response was given or until 1,500 ms had elapsed. Cue-target SOA, measured from the appearance of the cue to the appearance of the target, was fixed at 300 ms. The participants were encouraged to respond as quickly and

[1] There are evidences to suggest that the differences in the effects of peripheral and central cues (e.g. arrow and eye-gaze) are largely independent of the stimulus parameters such as stimulus size and contrast [30] in healthy participants. However, the impact of the different stimulus parameters have never directly compared in ADHD. Further research will be necessary to shed light upon this issue.

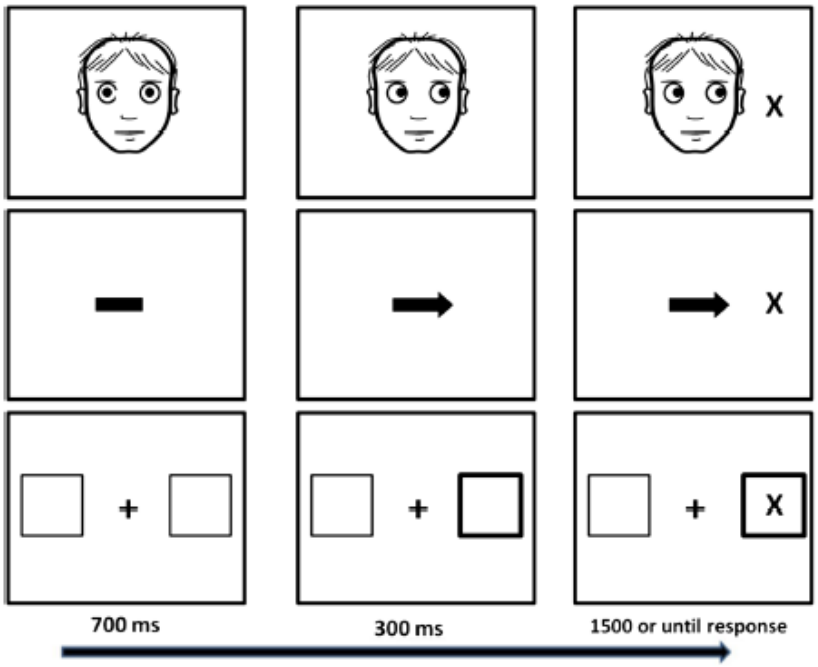

Fig. 1 Illustration of the trial sequence. The *panel* above depicts the displays observed in the gaze cue condition, the central panel depicts those in the arrow cue condition, and the *panel* below depicts those in the peripheral onset cue condition. A valid trial is represented in all the *panels*

accurately as possible. They were also informed that the location signalled by peripheral or central cues did not predict target location, and that they should ignore it, while maintaining central fixation throughout each trial. Each of the two experimental sessions (one for each task type) was composed of 15 practice trials followed by 204 experimental trials (68 for each cue type). Four catch trials, in which no target was presented, occurred randomly in each block. Cued location and target location were randomly selected within each block of trials. The cue types (gaze, arrow and peripheral) were separated into different blocks and the order of blocks was randomized across participants.

Design

The experiment consisted of a 2 (Group: people with ADHD vs. typically developing people) × 2 (Task: detection vs. discrimination) × 3 (Cue Type: eye gaze, arrow, and peripheral onset) × 2 (Validity: valid trials vs. invalid trials) mixed factor design. Task, Validity and Cue Type were manipulated within participants and the Group was manipulated between participants. Trials with reaction times (RTs) faster than 100 ms (5.2 % of the trials) or slower than 1,000 ms (6.5 % of the trials) as well as incorrect responses (misses and mistakes) were excluded from the RTs analysis. Misses referred to target trials in which no response was made. Mistakes referred to incorrect responses in the discrimination task. Mean RTs were computed for each experimental condition using the remaining observations. Mean RTs and error percentages are displayed in Table 1. Only misses are shown for the detection task, since mistakes could not occur in this task. Mistakes, misses and false alarm rate (i.e. the proportion of responses in catch trials) were examined separately for the ADHD group and control group.

When appropriate, the Geisser–Greenhouse (G–G) procedure was applied to correct degrees of freedom [26]. The G–G correction was used whenever a significant violation of the sphericity assumption was detected in repeated measures ANOVA (with more than two degrees of freedom) (see [87]). The degrees of freedom indicated in the text are always those before the Greenhouse–Geisser correction. A level of $p < 0.05$ after correction was accepted as statistically significant.

Results

Reaction times

ANOVA revealed a significant main effect of Task, namely a greater overall RTs in response to the discrimination compared to the detection task ($F_{1,42} = 201.74$; $p < 0.001$; $\eta_p^2 = 0.82$), a significant main effect for Cue Type with longest RTs for the peripheral cue condition ($F_{2,84} = 8.27$; $p < 0.002$, $\varepsilon = 0.837$; $\eta_p^2 = 0.16$), and a significant main

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Table 1 Mean correct response times (RT, in ms), Percentages of errors (%IR, percentage of incorrect responses; %M, percentage of misses) and standard deviations (SD, in ms) for each experimental condition in the detection task and the discrimination task

Task	Validity	ADHD group								Control group							
		Gaze				Arrow				Gaze				Arrow			
		RT	IR (%)	M (%)	SD	RT	IR (%)	M (%)	SD	RT	IR (%)	M (%)	SD	RT	IR (%)	M (%)	SD
Detection	Valid	393.25		4.12	87.81	387.58		3.41	72.51	402.64		1.42	104.11	406.54		1.56	97.6
	Invalid	388.71		3.98	86.12	413.45		3.41	80.17	429.16		0.85	114.86	418.21		1.42	108.83
Discrimination	Valid	596.06	18.7	5.68	112.95	589.67	19.4	5.25	87.07	593.57	9.1	1.85	103.4	584.65	12	2.13	99.26
	Invalid	599.99	20.3	5.68	118.01	605.41	18.7	7.81	102.19	613.87	9	1.70	113.49	603.71	10.8	2.41	109.43

Task	Validity	Peripheral onset				Peripheral onset			
		RT	IR (%)	M (%)	SD	RT	IR (%)	M (%)	SD
Detection	Valid	408.51		4.69	69.55	452.32		1.42	106.34
	Invalid	428.15		6.25	71.35	483.32		1.42	130.74
Discrimination	Valid	558.63	16.1	7.39	116.67	598.21	7.8	1.28	98.46
	Invalid	609.78	20.2	6.53	130.54	652.11	10.3	3.41	108.71

effect of Validity ($F_{1,42} = 46.39$; $p < 0.001$; $\eta_p^2 = 0.52$), with faster responses for valid trials. The main effect of Group was not significant ($F_{1,42} < 1$). The following interactions were significant: Cue Type by Group ($F_{2,84} = 5.63$; $p < 0.009$, $\varepsilon = 0.837$; $\eta_p^2 = 0.12$), Cue Type by Task ($F_{2,84} = 8.30$; $p < 0.001$, $\varepsilon = 0.947$; $\eta_p^2 = 0.16$), Cue Type by Validity ($F_{2,84} = 16.39$; $p < 0.001$, $\varepsilon = 0.926$; $\eta_p^2 = 0.28$), Cue Type by Task by Validity ($F_{2,84} = 3.67$; $p < 0.03$, $\varepsilon = 0.995$; $\eta_p^2 = 0.08$), and Cue Type by Group by Validity ($F_{2,84} = 4.28$; $p < 0.02$, $\varepsilon = 0.926$; $\eta_p^2 = 0.09$, see Fig. 2). To further examine these complex patterns, analyses were conducted for each Cue Type separately.

The ANOVA for the *gaze cue* condition revealed significant effects of Task ($F_{1,42} = 176.31$; $p < 0.001$; $\eta_p^2 = 0.81$) and Validity ($F_{1,42} = 8.16$; $p < 0.007$; $\eta_p^2 = 0.16$) but no significant main effect of Group ($F < 1$). Importantly, the critical Validity by Group interaction was significant ($F_{1,42} = 8.59$; $p < 0.006$; $\eta_p^2 = 0.17$). Planned comparisons showed that RTs were significantly faster on valid trials than on invalid trials only in the control group ($F_{1,42} = 16.74$; $p < 0.001$). In contrast, no differences were found between valid and invalid trials in the ADHD group ($F < 1$). No other effects or interactions approached significance ($F < 1$).

The analysis for the *arrow cue* condition showed the main effects of both Validity ($F_{1,42} = 28.72$; $p < 0.001$; $\eta_p^2 = 0.41$) and Task ($F_{1,42} = 207.33$; $p < 0.001$; $\eta_p^2 = 0.83$), but no significant main effect of Group ($F < 1$). Of interest, the interaction Validity by Group was not significant ($F < 1$): planned comparisons revealed that the effect of Validity was significant both in ADHD ($F_{1,42} = 19.01$; $p < 0.001$) and in control group ($F_{1,42} = 10.36$; $p < 0.003$). No other effects or interactions approached significance ($F < 2$).

The analysis for the *peripheral cue* condition showed the main effects of both Validity ($F_{1,42} = 48.91$; $p < 0.001$; $\eta_p^2 = 0.54$) and Task ($F_{1,42} = 138.96$; $p < 0.001$; $\eta_p^2 = 0.77$), but no significant main effect of Group ($F_{1,42} = 2.57$; $p = 0.12$). Significant interaction existed between Validity and Task ($F_{1,42} = 12.31$; $p = 0.001$; $\eta_p^2 = 0.23$), confirming the bigger facilitation effect generally observed in a discrimination task (i.e. X vs. O) rather than a simple detection task with peripheral onset cues [50–52]. Of relevance, the interaction Validity by Group was not significant ($F < 1$): planned comparisons revealed that the effect of Validity was significant both in ADHD ($F_{1,42} = 20.22$; $p < 0.001$) and in control group ($F_{1,42} = 29.08$; $p < 0.001$). No other effects or interactions approached significance ($F < 2$).

Errors

Mistake percentages of the discrimination task were submitted to a three-way ANOVA (Group × Type of Cue × Validity).

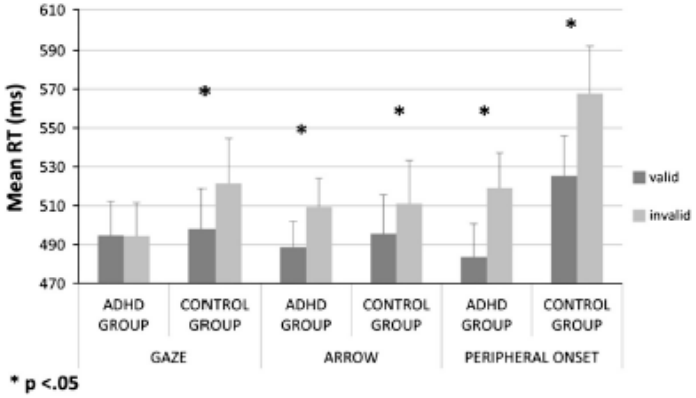

Fig. 2 Mean reaction time as a function of validity (valid or invalid) for each combination of cueing procedure (gaze, peripheral onset, and arrow) and group (ADHD group or control group)

The main effect of Group ($F_{1,42} = 7.11$; $p < 0.01$) was significant, indicating that the ADHD group committed significantly more mistakes compared to the control group. No other main effect or interactions were found ($F < 2$). Moreover, a one-way ANOVA with Group as between-subject factor revealed that the ADHD group committed significantly more false alarms compared to the control group ($F_{1,42} = 16.45$; $p < 0.001$; percentages of false alarms = 50 vs. 20). Analyses of misses showed no significant effects.

Discussion

The present study examined reflexive attentional orienting effects following eye gaze, arrow and peripheral onset cues, either congruent or incongruent with target presentation, in people with and without ADHD. When no social stimuli (arrow and peripheral onset) were used, all participants were quicker in detecting and discriminating the target presented in the cued location, which replicated previous findings (for a review see [34]). In contrast, when eye gaze was used, important differences were observed between participants with ADHD and the control group: a significant attentional orienting effect (RTs advantage for validly cued than for invalidly cued trials) was only observed in typically developing individuals, while participants with ADHD failed to show such gaze cueing orienting effect. These results suggest an attentional impairment in responding to socially relevant information in ADHD,[2] consistent with the impairment in social cognition generally observed in individuals with ADHD [86]. These findings support the claim that eye gaze represents a special attention stimulus to study social attention [17, 21, 45, 57]. Moreover, we observed that this impairment in social attentional orienting occurred in both detection and discrimination tasks. When the same groups of individuals are used for all conditions (in order to exclude potential participant-related confounds) different task responses can influence the outcome of the study and thus our understanding of the disorder. For example, the use of the target detection task alone would have led us to describe gaze cueing attentional effect in ADHD as abnormal only in relation to this specific task. However, testing such function by means of a more demanding task (e.g. discrimination task) reveals that effectively this effect is more general and independent of response-related demands. Importantly, this study demonstrates that participants with ADHD do not utilize eye gaze direction to orienting attention, regardless of the perceptual or motor demands of the task. We interpret these findings to reflect a deficit in responding to socially relevant information.

The gaze-specific attentional impairment that we have demonstrated in this study might be reflective of the right hemisphere dysfunction in attention deficit hyperactivity disorder. Neuropsychological [76], magnetic resonance imaging [66], blood perfusion [48], and transcranial magnetic stimulation studies [1] have generally shown in ADHD a dysfunctional activity in right hemisphere, the brain area mainly involved in orienting to gaze cues [28, 41, 55, 73]. Moreover, various other brain regions have been implicated in ADHD, including the temporal and parietal cortex and basal ganglia [78], and these regions have also been linked to processing of eye gaze cues guiding social attention [46].

The finding that ADHD results in a deficit in orienting attention toward gaze direction might have profound implications. Such a deficit would leave individuals with

[2] The lack of eye-gaze cueing effect found in ADHD participants could alternatively be attributed to a greater ability to control the extent that gaze information influences the performance. While further research is necessary to shed light upon this issue, the fact that several studies have reported impairments in executive control in individuals with ADHD [29, 38, 42, 64] makes unlikely that they are engaged in more effective controlled processing when eye-gaze is used as a distracting stimulus.

ADHD clue less as to what others are attending to, and their consequential intention or desire.

This impairment could thus be linked to the development of the higher levels of interpersonal problems generally observed in ADHD as compared to controls [18, 33]. Since social problems are known to strongly predict negative outcomes in later adolescence and adulthood [27, 63], the study of the possible underlying deficient processes such as social attention visual ability will be clearly of importance to further research in this area.

Furthermore, our results are similar to those reported by recent studies with patients with schizophrenia [3, 15], who are generally referred to as impaired in social attention behaviour [77]. In particular, Dalmaso and colleagues [15] found that patients failed to show evidence of a cueing effect for eye gaze cues, whereas showed normal levels of cueing effects for arrow and pointing finger cues. Taken together, these findings suggest that cueing effect to eye gaze direction may represent a key instrument to study social attention in populations with typical and atypical social development. Future studies will be important in clarifying and strengthening this conclusion.

Limitations

Our results suggest an attentional impairment in responding to socially relevant information in ADHD, consistent with a broad body of research about social cognition impairment (for a review see [86]). Future studies examining social attentional orienting in ADHD will benefit from addressing limitations present in this study. First, a larger sample including groups of different ADHD subtypes is required. The majority of our participants were diagnosed with ADHD/C subtype. This has to be kept in mind because results can be generalized only with regard to this proportion that is not representative of the disorder as a whole. There is reason to believe that different subtypes of ADHD, or subjects with different ADHD typology (accordingly with DSM-5, [5]) may differ in social attention because they have been found to differ along important classification dimensions (e.g. demographics, family history, symptom presentation), suggesting that children with ADHD/I may have a distinct disorder and not a subtype of ADHD [2, 6, 60]. Moreover, it would be relevant to compare the present results with those eventually obtained with other disorders that occur comorbidly with ADHD, such as bipolar disorder and schizophrenia [10, 37, 49].

Conclusions

For the first time, an eye gaze cueing paradigm has been used to assess attentional orienting effects in ADHD. It is important to note that our patients were drug-naïve, whereas most of the previous studies have considered participants with ADHD that were medication free either on the day of testing or just 24–72 h prior to testing. It has allowed us to investigate attentional performances in ADHD without the influence of medication. Of particular relevance is the different attentional behaviour shown by participants with ADHD when social (eye gaze) or no-social (arrow or peripheral onset) cues were used. This dissociation highlights that people with ADHD demonstrate to have preserved attentional orienting processes, but they present a specific impairment in social attention. Social cognitive deficits such as social attentional impairments could account at least partially for the higher levels of interpersonal problems generally observed in ADHD [18, 33]. Implementing interventions to improve social skills and joint attention could be, therefore, quite important for children with ADHD. Unfortunately, current psychosocial intervention (i.e. social skills training) programs for ADHD [31, 68, 75] do not include joint attention abilities (e.g. following and/or attending to eye gaze direction). Thus, the study of basic social attention deficits should represent both an important research area in ADHD and a key topic for therapy in the future.

Conflict of interest None.

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Case Series

EXPERT OPINION

Atomoxetine in the treatment of attention deficit hyperactivity disorder and suicidal ideation

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Objective: Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric childhood disorder. The most commonly used drugs in the treatment of ADHD are methylphenidate (MPH) and atomoxetine (ATX); the former of the two is prescribed in USA more than it is in Western Europe. Some of the most important safety concerns about ADHD drug treatment are sudden cardiac death and suicidal behavior. In this study, we present a series of cases of Italian children who had presented suicidal ideation during ADHD pharmacological therapy with ATX.

Research design and methods: Data were obtained from the ADHD Italian Register. The data assessed the use of MPH and ATX, which had been prescribed to patients who were aged < 18 years and diagnosed with ADHD. All patients enrolled in the ADHD Italian Register treated with ATX or MPH who experienced suicidal thoughts or thoughts of self-harming were considered and assessed.

Results: We describe the clinical cases of seven Italian children (enrolled in the ADHD Italian Register) treated with ATX and affected by suicidal ideation, self-harming or other similar symptoms. Our results highlighted that all seven patients developed suicidal ideation or intentional self-harming during pharmaceutical treatment with ATX and, particularly, after the dose increase of the drug.

Conclusion: There is a need to improve our knowledge about the efficacy and safety of ATX, MPH and other drugs used in the treatment of ADHD both in children and adults during the post-marketing experience.

Keywords: attention deficit hyperactivity disorder, adverse drug reaction, atomoxetine, suicidal ideation

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric childhood disorder [1]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, ADHD is a condition with symptoms that include excessive restlessness, poor attention and impulsive behavior. After examining the symptoms, three kinds of ADHD can be defined: predominantly inattentive type (ADHD-I); predominantly hyperactive-impulsive type (ADHD-H) and combined type (ADHD-C) [2]. Moreover, people (adults and children) affected by ADHD are statistically more likely to have an anxiety disorder, depression, bipolar disorder or other comorbid psychiatric diseases [3]. According to Dell'Agnello *et al.*, almost

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85% of patients with ADHD have at least one psychiatric comorbidity, and approximately 60% have at least two [4]; in particular, almost 40% of patients with ADHD have an oppositional defiant disorder (ODD) as comorbidity [5].

The most appropriate interventions for preschool and school-age children with ADHD are group parent training programs and classroom behavioral intervention, which represent the first-line of treatment. When classical symptoms of ADHD become severe, interventions are more effective when combined with pharmacological therapies, which includes the administration of stimulants (methylphenidate [MPH] and amphetamine) and non-stimulants (atomoxetine [ATX]), tricyclic antidepressants and α agonists [6,7].

However, the most commonly used drugs in the treatment of ADHD are ATX and MPH. Data from a study which have described the trend use of antidepressant, stimulant (including MPH) and antipsychotic medication in pediatric patients revealed that the prevalence of use of these drugs was 1.5 – 3 times greater in the USA than in Western European countries [8]. ATX is a selective noradrenaline reuptake inhibitor that is not classified as a stimulant [9]; it is generally well tolerated in children and adolescents with ADHD [10]. Data from review and *post hoc* analyses, including safety data from 25 ATX trials (1998 – 2009) in patients (adults and children) with ADHD, showed that the most commonly reported adverse drug reactions (ADRs) were headache, abdominal pain, decreased appetite, vomiting, somnolence, nausea, insomnia and urinary hesitancy/urinary retention. ATX is generally associated with increases in both heart rate and blood pressure [10]. MPH is a mild stimulant, which acts to increase the levels of dopamine in the central nervous system. MPH has similar pharmacological properties to amphetamines and predominantly effects on the central nervous system while displaying minimal effects on the cardiovascular system [11]. Although its pharmacodynamic properties are not known, MPH is thought to activate the brainstem arousal system, cortex and subcortical structures to produce its stimulant effect through enhancing the dopaminergic firing [12]. The most common ADRs associated with MPH are headache, dizziness, anxiety, anorexia and nausea [13].

Other two extremely serious side effects rarely associated with ADHD drug treatment are sudden cardiac death and suicidal behavior [14]. In particular, relatively to suicidal behavior, specific evidences for stimulants are not publically available; nevertheless, the Summaries of Product Characteristics (SPC) of MPH contain caution about suicidality as a possible adverse event (AE). The same correlation between ATX and suicidal ideation was already revealed in September 2005 by the US FDA. Specifically, the FDA ordered Eli Lilly and Co., the manufacturer of Strattera® (ATX), to revise the Patient Information Leaflet (PIL) and the SPC for this product including a box warning and additional warning statements that alert healthcare providers to an increased risk of suicidal thinking in children and adolescents being treated with this drug [14].

From 2005 to date, there are little clinical evidence regarding the relationship between ATX and MPH and the onset of suicidal related events; moreover, the most of clinical available data came out from clinical trials. Based on this consideration, the aim of our study was to describe cases of suicidal behavior in children diagnosed with ADHD and pharmacologically treated in the real-life setting. In particular, we present a series of seven cases of Italian children who had presented suicidal ideation during ADHD pharmacological therapy with ATX.

2. Methods

2.1 Study design

Data were obtained from the ADHD Italian Register, instituted in 2007, which covers all Italian children, aged < 18 years, enrolled by reference prescription centers (located throughout Italy), diagnosed with ADHD and treated with MPH or ATX; thus, it allows to capture all cases of ADHD in Italy. The ADHD Italian Register, coordinated by Italian National Institute of Health (Istituto Superiore di Sanità [ISS]) and Italian Medicines Agency (Agenzia Italiana del Farmaco [AIFA]), aimed to assess the benefit–risk profile of the treatment of ADHD with ATX and MPH. In order to achieve diagnostic accuracy and avoid the improper use of medicines, the ADHD Italian Register allows the prescription of ATX and MPH only within biannual therapeutic plan which must be approved by the clinical center of reference. All patients treated with ATX and MPH are recorded in an anonymous database located at ISS. The treatment of personal data is subject to receiving the parents' written informed consent. From 2007 to June 2012, the ADHD Italian Register enrolled 2239 patients of which 1268 were treated with MPH (56.7%) and 971 patients were with ATX (43.3%).

Starting from clinical and demographic data available from ADHD Italian Register (gender, age, ADHD subtype, comorbidity, pharmacological treatment), we selected all the Italian children enrolled in the register and treated with ATX or MPH who presented suicidal ideation, self-harming behavior or other similar symptoms. Then we recorded seven cases of children which fit all the above criteria; specifically, all the selected patients were treated with ATX; no patient diagnosed with ADHD and treated with MPH showed the study event. Data of demographics, clinical types of ADHD, comorbidities, pharmacological therapies and AE, regarding the previously mentioned patients, are shown in **Table 1**. In order to verify the relationship between the study event and ATX and, in that way, evaluate the causality assessment, we used the Naranjo algorithm [15], which consists of 10 questions that are answered as either 'Yes', 'No' or 'Do Not Know'. Different point values (-1, 0, +1, and +2) are assigned to each answer; then, the total score obtained categorize the causal relation into *definite*, *probable*, *possible* and *doubtful*. Until the relation event/drug is not confirmed, it is common to refer to the event as an 'AE' or a 'suspected ADR'; conversely, once the relation is confirmed, the event is considered as an ADR.

Table 1. Patient demographics, clinical types of ADHD, pharmacological therapies and adverse events.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gender	F	M	F	M	M	M	M
Year of birth/age when ADHD was diagnosed	1999/9 years	1998/10 years	1998/9 years	1997/10 years	1996/13 years	1998/10 years	1995/10 years
ADHD subtype	ADHD-C	ADHD-C	ADHD-C	ADHD-C	ADHD-C	ADHD	ADHD
Comorbidity	ODD	ODD, idiopathic epilepsy, learning disability	Depression and tic disorders	ODD, anxiety	Learning disability, mental retardation	ODD	ODD, mood disorder
ADHD pharmacological therapy	ATX	ATX	ATX	ATX	ATX	ATX	ATX
Concomitant drugs	10 – 28 mg/day -	25 – 40 mg/day Sodium valproate niaprazine	25 – 40 mg/day Haloperidol	60 – 78 mg/day -	25 – 50 mg/day -	10 – 40 mg/day -	18 – 50 mg/day Niaprazine
Adverse drug reaction	Negative thoughts	Dysphoria, irritability, self-destructive behavior	Suicidal ideation/ suicidal threat	Suicidal ideation	Intentional self-destructive behavior	Suicidal ideation, worsening of ODD	Suicidal ideation, intentional self-harming behavior
Time to event	6 months	5 months	4 months	9 months	23 months	19 months	2 months
Time to event after the increase in dosage	5 months	2 months	2 months	3 months	1 month	5 months	1 month
Treatment provided	ATX withdrawal	Dosage reduction for ATX to 25 mg/day Sodium valproate withdrawal	ATX withdrawal	ATX withdrawal	ATX withdrawal	Dosage reduction from 40 to 25 mg/day	ATX withdrawal
Outcome	Not available	Not available	Not available	Resolved	Resolved	Resolved	Resolved
Causality assessment	Possible	Possible	Possible	Probable	Probable	Probable	Possible

ADHD: Attention deficit hyperactivity disorder; ATX: Atomoxetine; F: Female; M: Male; ODD: Oppositional defiant disorder.

In fact, according to the Good Pharmacovigilance Practices of European Medicines Agency [16], an 'AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment', whereas an 'ADR is a response to a medicinal product which is noxious and unintended' [16]. Each suspected ADR was reported to the AIFA and recorded in the Italian spontaneous reporting database (Rete Nazionale di Farmacovigilanza [RNF]).

3. Case presentation

3.1 Case one

A 9-year-old girl, diagnosed with ADHD-C and ODD in June 2006, began therapy with ATX in October 2007. The patient was prescribed a dosage of 10 mg/day. One week later the dosage was increased to 25 mg/day. In April 2008, during the 6 months follow up, the patient was diagnosed with symptoms of depression at the Paediatric Neuropsychiatric Unit at "Azienda Sanitaria Nazionale SS Antonio e Biagio e Cesare Arrigo" sited in Piemonte. During the psychiatric evaluation, the patient showed the classical symptoms of mood swings, common in clinically depressed patients (continuous low mood or sadness, feeling helpless, having low self-esteem, feeling guilt-ridden, feeling anxious or worried, having suicidal thoughts or thoughts of self-harming). The clinical interview and the Children's Depressive Inventory confirmed the presence of 'suicidal ideation'. The AE was classified as 'negative thoughts'. Due to these findings and according to patient's psychiatrist, ATX dosage was reduced first to 18 mg/day and then to 10 mg/day. Despite the dosage reduction, the patient still felt depressed and the pharmacological treatment was suspended. On 12 May 2008, 'negative thoughts' was reported as non-serious event into the RNF.

The appearance of the study event was observed 6 months after the drug administration and, specifically, after 5 months of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *possible* (**Table 1**).

3.2 Case two

A 10-year-old boy, with a family history of anxiety disorder and motor hyperactivity, was diagnosed with ADHD-C, ODD and learning disability in 2007. Since early childhood the patient had shown motor hyperactivity, attention deficit, no respect for rules and altered sleep/wake patterns. When he was 18 months, he presented his first episode of febrile convulsion. In the period between 2005 and 2006 he had another four episodes. The electroencephalograms (EEGs) were normal. He was not prescribed any pharmacological therapy. The patient arrived to the Paediatric Neuropsychiatric Unit 'Azienda Ospedaliera Policlinico – Bari' in November 2006. In June 2007, he was hospitalized and the following diagnosis was made: 'generalized epilepsy, ADHD-C, ODD, learning disability, sleep disorder'. The patient began therapy with sodium valproate (Depakin®) 600 mg/day and niaprazine (Nopron®) 7 ml/day. In September 2007, the NMR was normal. In October 2008, clinicians noted a worsening of behavior; therefore, they prescribed ATX 18 mg/day, reduced sodium valproate from 600 to 400 mg/day and suspended the therapy with niaprazine. One month later (November 2008) and again in January 2009, ATX dosage was increased to 25 and 40 mg/day, respectively, with evident clinical improvement. In March 2009, ATX dosage was decreased to 25 mg/day due to the presentation of the following symptoms: dysphoria, irritability, self-destructive behavior (an attempt of self-strangulation with a scarf, a further attempt of choking with a knife). Despite the dosage reduction, symptoms have not disappeared; for this reason, clinicians decided to suspend ATX therapy with evident clinical improvement (self-destructive behavior was no longer reported). During the consecutive clinical visit, the patient presented a worsening of irritability and oppositional symptoms. In August 2009, the therapy with sodium valproate was gradually suspended. December 2009 was the last recorded day of hospital visit. Unofficial data report that the patient is presently not undergoing pharmacological therapy and is being followed by his local neuropsychiatric unit.

The appearance of the study event was observed 5 months after the drug administration and, specifically, after 2 months of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *possible* (**Table 1**).

3.3 Case three

A 9-year-old girl was visited in February 2007 at the Paediatric Neuropsychiatric Unit 'Centro IRCCS Burlo' located in Trieste for a vocal tic associated with complex motor tic and she was diagnosed with Tourette's syndrome. The patient had socialization and behavioral problems. She underwent a psychological visit and, after 4 months, began therapy with haloperidol 1.2 mg/day, with partial clinical improvement of tics. In the same year (2007), tics decreased but there were new oppositional and attention problems. Despite therapy with haloperidol, the patient still presented tics and new cases of coprolalia. While the aspects of phobias and obsession were under control, the patient had gained weight and a worsening of learning activities. The patient was diagnosed with ADHD in October 2010. Clinicians decided to begin pharmacological therapy with ATX and psychological therapy. The parents opted to postpone the psychological treatment. Clinical data confirmed attention and cognitive deficit and huge self-esteem problems. In January 2011, the girl, in therapy with haloperidol 1.20 mg/day, was also prescribed ATX at dosage of 25 mg/day. One month later the patient had lost 3 kg and reported somnolence and weakness, but her mood was described as good. Haloperidol dosage was decreased to 0.90 mg/day. Three weeks later, scholastic production improved but patient still had tics. Throughout clinical visit, her mood was defined as indifferent and, for that reason,

ATX dosage was increased to 40 mg/day. After 3 weeks the patient arrived at the emergency department during an anxiety attack. Clinicians decided to suspend ATX for 2 days and then return to the dosage of 25 mg/day. One month later, her parents autonomously suspended the drug due to a suicidal threat attempt by the girl (she had climbed onto the roof and locked her parents out and threatened to commit suicide). The day before the clinical visit, the patient had done the same thing at school. On the contrary to what happened in the past, the patient admitted to having suicidal ideation, obsessive thoughts and a sense of guilt. For these reasons, clinicians confirmed the suspension of ATX. One month later, the patient had a rapid weight gain. She still had symptoms of Tourette's and scholastic difficulties. In February 2013, the patient was treated with haloperidol and aripiprazole.

The appearance of the study event was observed 4 months after the drug administration and, specifically, after 2 months of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *possible* (**Table 1**).

3.4 Case four

A 10-year-old boy, affected by ODD and anxiety with a family history of ADHD, was diagnosed with ADHD-C in June 2007 at the Paediatric Neuropsychiatric Unit 'Azienda Ospedaliero-Universitaria – Cagliari'. He began pharmacological therapy with ATX (60 mg/day) in July 2007. From July to December 2007, the patient underwent periodical clinical visits. In that period, his clinical conditions were good, including cardiac parameters. He also showed a marked improvement in ODD symptoms and anxiety. In January 2008, dosage was increased to 78 mg/day (1.4 mg/kg/day). In April 2008, ATX treatment was suspended due to the presentation of serious AE 'suicidal ideation'. Following discontinuation of the drug, the patient showed an evident clinical improvement. One month later (May 2008), the patient was prescribed MPH.

The appearance of the study event was observed 9 months after the first administration of ATX and, specifically, after 3 months of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *probable* (**Table 1**).

3.5 Case five

A 13-year-old boy was diagnosed with ADHD in November 2009 at the Paediatric Neuropsychiatric Unit 'Azienda Ospedaliero-Universitaria – Cagliari'. In the same month he began pharmacological therapy ATX at the initial dosage of 25 mg/day. Since the beginning of the pharmacological therapy, the patients underwent periodical clinical visits and day-hospital visits. In that period, his mood was described as good and there were no abnormalities in electrocardiogram (ECG) and EEG. In September 2011, clinicians decided to adjust the dosage which was increased to 50 mg/day. One month later (October 2011), the patient presented symptoms attributable to intentional self-harming. Due to the presentation of this event, the pharmacological treatment was suspended with clinical global improvement of symptoms. In the same year, the study event was reported as 'intentional self-harm' in RNF.

The appearance of the study event was observed 23 months after the first administration of ATX and, specifically, after 1 month of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *probable* (**Table 1**).

3.6 Case six

A 10-year-old boy with learning disability was diagnosed with ADHD and ODD in July 2007 at the Paediatric Neuropsychiatric Unit 'Azienda Ospedaliera Santobono-Pausilipon' sited in Napoli. The patient was adopted when he was 6 years old. He had always been exposed to a violent family, taking an aggressive attitude against his little brother. In those years, the patient had undergone speech therapy, psychomotor therapy and psychotherapy. In July 2007, he was prescribed ATX 10 mg/day. In December 2007 and in April 2008, ATX dosage was increased, respectively, to 28 and 38 mg/day. In that period, the patient underwent periodical clinical visit; blood pressure and ECG were normal. In September 2008, ATX dosage was increased again to 40 mg/day. In February 2009, the patient presented signs of suicidal ideation and his ODD symptoms had got worse. For these reasons, the dosage of ATX was reduced to 25 mg/day with clinical improvement and disappearance of the symptom. The patient was treated with ATX until October 2009.

The appearance of the study event was observed 19 months after the first administration of ATX and, specifically, after 5 months of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *probable* (**Table 1**).

3.7 Case seven

A 10-year-old boy, with a family history of ADHD, ODD and depression, was visited in 2005 at the Paediatric Neuropsychiatric Unit sited in Livorno and was diagnosed with ADHD, ODD and mood swings, often irritable or sad with a sense of inadequacy and low self-esteem. The patient had previously been prescribed niaprazine (Nopron) for sleep disorder. From September 2005 to February 2007, during a clinical study, the patient was treated with ATX at the dosage of 18 mg/day. The parents decided to interrupt pharmaceutical treatment. Following this decision, the patient got worse clinically and had more problems with social skills and school. For this reason, in September 2007, the patient was re-administered ATX at 18 mg/day and then on 25 September the dosage was increased to 40 mg/day. The only side effects registered were light stomachache and drowsiness. Blood pressure and ECG were normal. In October 2007, during a checkup, the patient showed signs of slight improvement

and the dosage of ATX was increased to 50 mg/day. During the following clinical visit, in November 2007, there was an initial improvement in the symptoms of ADHD but it was referred that the patient had been self-harming (during a cruise he had repeatedly verbalized suicidal ideation by throwing himself in the sea). The clinicians decided to suspend the administration of ATX. In the same month, during an outpatient visit, the patient still showed signs of suicidal ideation. However, in December 2007, self-harming was no longer reported but there were still signs of ODD. Despite the patient underwent individual psychotherapy, in 2010 he presented a worsening of symptoms of ODD with irritability, hypomanic symptoms, sexual disinhibition, compulsive masturbation and fetishism. In that period, the patient had run away from home on one occasion. The parents reported verbalization of intent of self-harm. For such reasons, the patient has been exposed to therapy with sodium valproate 900 mg/day from 2010 to 2013, resulting in overall clinical improvement and disappearance of fetishism symptoms.

The appearance of the study event was observed 2 months after the first administration of ATX and, specifically, after 1 month of increase in dosage. The evaluation of causality assessment between ATX and the study event resulted in *possible* (**Table 1**).

4. Discussion

Our results demonstrate that all seven patients developed suicidal ideation or intentional self-harming during pharmaceutical treatment with ATX and, particularly, after the increase in the dosage of the drug. The occurrence of suicidal ideation during the treatment with ATX is already cited in the SPC and PIL of the drug; moreover, the link between pharmacological therapies of ADHD and the risk of suicide or suicidal ideation has been discussed in several studies [14,17-21]. Data from a meta-analysis of five double-blind, placebo-controlled comparative studies of ATX and MPH showed an association between these drugs and suicide-related events. Among 1024 patients enrolled in these trials, including 559 receiving ATX and 465 receiving MPH, there were 5 cases of suicide-related events (3 with ATX and 2 with MPH) (0.49%). Specifically, according to the FDA classification of AEs related to suicidality, two cases were reported as 'suicidal ideation' (one associated to ATX and one to MPH), one case as 'self-injurious behavior' induced by ATX, and two cases of nonfatal suicide-related events (one associated to ATX and one to MPH). There were no suicide attempts or completed suicides [17]. Moreover, data from a meta-analysis of 12 double-blind, placebo-controlled studies in pediatric patient, which included 1357 patients treated with ATX and 851 treated with placebo, revealed an higher risk of suicidal ideation and suicidal behavior in the ATX treatment group compared with placebo group. Specifically, six patients (0.44%) presented suicidal ideation and suicidal behavior. None of the patients treated with placebo presented any suicidal-related events. As for the previous meta-analysis, also in this one no patient committed suicide [18].

The prevalence of suicide-related events in children enrolled in clinical trials and treated with ATX and MPH is almost 0.44% [14]. This low incidence in suicide-related events may be due to the following reasons: the exclusion of suicidal subjects from trials, a short time base and the lack of systematic assessment. However, epidemiological data to date do not allow to suggest that the observed low incidence of suicidal behavior in children treated with ATX and MPH is greater than the expected rate in the general population [14].

Similarly, post-marketing authorization studies, which have evaluated the benefit–risk profile of ATX and MPH in the treatment of ADHD, showed a low incidence of suicidal behavior [19,20]. One of these studies, conducted using data from the ADHD Italian Register, assessed medical prescriptions to children and adolescents (aged 6 – 18) with ADHD in the centers of reference for ADHD accredited by the Italian regions. During the study period, 2007 – 2011, 1098 children and adolescents were treated with MPH and 951 patients were treated with ATX. Results revealed that patients treated with ATX were more likely to experience an AE compared to those treated with MPH (Relative Risk [RR] = 2.8; 95% CI: 1.9 – 4.2), as well as the possibility of a serious AE among those treated with ATX compared to those with MPH (RR = 2.8; 95% CI: 1.8 – 4.2). A total number of 110 serious AEs were observed in 75% of patients treated with ATX and in 25% of patients treated with MPH. These serious AEs led to the interruption of treatment with 98 exiting from the registry. In particular, the incidence of suicidal ideation was 4.5/1000 (0.45%) patients treated with ATX; no patient treated with MPH had presented suicide-related events [19]. Moreover, data obtained from a case report published on *Journal of Paediatrics and Child Health* in 2008 revealed another case of suicidal ideation and acute agitation occurred in an 11-year-old boy who was in treatment with ATX (60 mg/day) [21]. Post-marketing surveillance activities, such as the intensive monitoring of drug studies [22,23], are important to allow the early detection of unexpected and/or serious adverse reactions, which have a considerable negative impact on both health and healthcare costs [24]. Therefore, as ADHD is a chronic disorder that requires pharmacological treatment for many years, and as suicidal-related events are rare, further long-term safety studies are needed.

In our study, we observed seven cases of suicide-related events occurred in children diagnosed with ADHD and treated with ATX (0.72%); even if no analytical but only descriptive, our findings seem to be consistent with the ones mentioned above.

However, in spite of these results, findings from a secondary analysis of data from two multicenter, single-arm, open-label studies, which evaluated changes in items on the Pediatric Adverse Event Rating Scale related to emotional well-being (depressed mood, self-harm, irritability/agitation, drowsiness and euphoria) of children and adolescents with ADHD treated

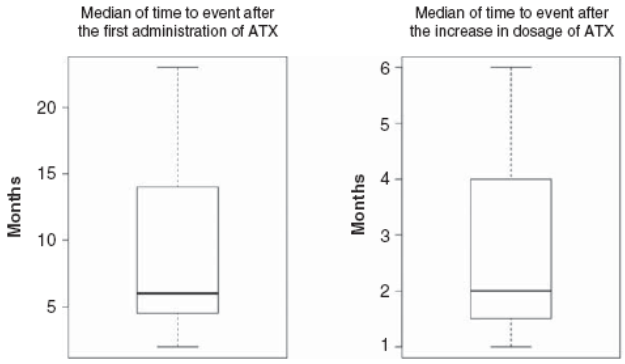

Figure 1. Month stem-and-leaf plot of median of time to event after the first administration of ATX and after the increase in dosage.
ATX: Atomoxetine.

with ATX, suggested that attempts to self-harm or thoughts of self-harm are not aggravated by treatment with ATX [25]. Moreover, other studies debate the direct correlation between ADHD and suicide or suicidal ideation as a consequence of comorbid conditions associated with ADHD, such as anxiety disorder, ODD, depression, bipolar disorder and other comorbid psychiatric disorders, and other studies consider that there is also a strong correlation between ADHD and suicidal attempts [26-29].

In particular, earlier findings suggest that depressed mood, generalized anxiety disorder and ODD as comorbid conditions of ADHD may represent risk factors for suicide events. This information was obtained from a sample of 1056 students diagnosed with ADHD-I and ADHD-H who have provided personal data relating to mood, suicidal behavior and ADHD symptoms [26]. Moreover, data came from James *et al*. study revealed that children with ADHD and ODD and/or conduct disorder (CD) have a more severe clinical features, hyperactivity, impulsive behavior and worse outcome than children affected by ADHD alone. In particular, hyperactivity, one of the main symptoms of ADHD, could potentially predispose to a later psychiatric diagnosis, violence and antisocial behavior. In fact, data obtained from the same study showed that there is a higher incidence of suicide attempt among hyperactive patient with persistent antisocial behavior than hyperactive patients without antisocial behavior [27]. Further, Impey and Heun reported that the main cause of the occurrence of suicide-related events lies in the typical symptoms of ADHD, which include impulsivity and lack of risk awareness. Effectively, patients with high impulsivity could potentially commit much self-injurious actions [28].

Finally, the correlation between ADHD/comorbidity and suicide-related events, discussed in the studies presented above, is also confirmed by the results of a pilot study which have evaluated the rate of ADHD in 23 adolescents attempting suicide. Among those, 65% (n = 15) were diagnosed with ADHD; specifically, three patients had pure ADHD, while the remaining twelve were affected by the combination ADHD/major depression, personality disorder, posttraumatic stress disorder or CD [29].

In regard to our seven patients, according to the Naranjo algorithm, the causality assessment resulted *possible* for four cases (patients 1, 2, 3 and 7) and *probable* for three cases (patients 4, 5 and 6). As we explained in each case, the appearance of the study event took place after a period of time ranging from 2 to 23 months since the first administration of ATX. In particular, we observed a median *time to event* of 6 months (**Figure 1**; **Table 2**). Analysis of our data has also shown that the *time to event* drastically reduced after the increasing in the dosage of ATX for all patients, except for patient 1, with a median *time to event* of 2 months (**Figure 1**; **Table 2**). In fact, before the increase in dosage, all patients, treated for a long period of time (different for each patient), did not show the study event, but after the increase in dosage to a cut-off dose of 40 mg/day, patients presented suicide-related events with a similar time to event. Consistent with our data, in the study of Paxton and Cranswick, the time elapsed until the onset of suicidal ideation was 17 days after the first administration of ATX and, specifically, 3 days after the increase in the dosage (ATX dosage was increased from 25 to 60 mg/day); in fact, as in our patients, the onset of the study event occurred after increasing the dosage for this patient too [21]. Contrary to our results, the *time to event* related to the six patients in the Bangs *et al*. meta-analysis ranged from 9 to 32 days [18].

Regarding the outcome of suicide-related events, although our patient 6 showed an improvement of clinical symptoms after the reduction of the dosage (from 40 to 25 mg/day), patients 4, 5 and 7 had a total resolution of symptoms after the discontinuation of ATX; for cases 1, 2 and 3, the outcome information are not available.

Table 2. Time-to-event analysis of the seven cases after the first administration of ATX and the increase in dosage of ATX.

	Time to event after the first administration of ATX	Time to event after the increase in dosage of ATX
Median (months)	6.00	2.00
Variance	65.238	3.810
STD	8.077	1.952
Range (months)	2 – 23	1 – 6
Kurtosis	-0.588 (1.587)	-0.785 (1.587)

ATX: Atomoxetine; STD: Standard deviation.

To date, the mechanisms by which the suicidal ideation or attempts occur are unclear. However, one of the possible explanations of the occurrence of the study event could be the moderate effect that ATX has on serotonin reuptake; specifically, agitation and suicidal ideation are events known in children treated with selective serotonin reuptake inhibitors [21].

5. Study limitations

Our study has several limitations. First, this is an observational analysis based on ADHD Italian Register; for this reason and for privacy policy, it was not possible to obtain baseline and previous clinical and psychiatric information related to the seven cases. Therefore, the limited number of patients (included in the study) and also the lack of information (related to those patients) does not allow us to draw firm conclusions. Further, because of the observational nature of the study, we cannot rule out the presence of other possible confounding variables that might have affected our results. In fact, we know that other important variables, like personality factors and social support, which may be also associated with suicide-related events, were not included in our study. In respect to these variables, the heterogeneity found in the patients' features, such as different ADHD subtype (although the predominant subtype was the ADHD-C) and especially different comorbidity, could probably influence the onset of the study event. For such reasons, our results are not generalizable to the entire population of children affected by ADHD.

Finally, other important factors which could trigger the development of the study event are concomitant medications. In fact, three out of seven cases were treated with ATX in association with haloperidol, sodium valproate and niaprazine. Therefore, we cannot rule out the influence of the administration of concomitant drugs on the development of clinical symptoms.

Despite this limitation, our study considered a number of relevant variables, such as dose of medications, time of treatment and current psychiatric comorbidities; moreover, it is important to consider that our data came out from a disease national register, which represents a very useful component of post-marketing pharmacovigilance systems. In fact, although often limited by lack of important patients' data, ADHD Italian Register improves the monitoring of safety profiles of ATX and MPH and allows proactive detection of potential safety issues [30].

6. Conclusion

In an attempt to describe the suicide-related events associated with ADHD pharmacological treatment in a real-life setting, we analyzed seven cases of suicidal ideation/intentional self-harming that occurred in children enrolled in the ADHD Italian Register. However, data obtained from the mentioned cases and from literature review and studies did not result in adequate results to clarify the correlation between ADHD pharmacological treatment and the appearance of suicidal ideation and the other suicide-related events. Finally, in order to better define the relation between suicidal-related events and ADHD pharmacological treatment/comorbidity/ADHD itself, there is a need to conduct further *ad hoc* observational etiological studies.

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Declaration of interest

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Developmental changes in cognitive and behavioural functioning of adolescents with fragile-X syndrome

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Abstract

Background Individuals with fragile-X syndrome exhibit developmental delay, hyperexcitation and social anxiety; they also show lack of attention and hyperactivity. Few studies have investigated whether levels of functioning change with increasing age. Here, we explored developmental changes across adolescence in the cognitive and behavioural profile of individuals with fragile-X syndrome. To this scope, we assessed intellectual functioning, adaptive behaviour, autistic symptomatology, behavioural problems (e.g. hyperactivity/lack of attention) and strengths (prosocial behaviours).

Method Thirty-six participants underwent standardised outcome measures (i.e. the Wechsler Intelligence Scales-Revised, the Childhood Autism Rating Scale, the Vineland Adaptive Behavior Scales, and the Strengths and Difficulty Questionnaire) in three time points (Time 1: 9–11; Time 2: 11–13, and Time 3: 13–15 years).

Results Verbal IQ improved across time, whereas Nonverbal IQ declined and Full Scale IQ was quite unchanged. Autism ratings decreased; communication and social aspects of adaptive behaviour also enhanced. Finally, elevated levels of hyperactivity/lack of attention at Time 1 significantly improved across the three time points, whereas emotional symptoms, behavioural difficulties, problems with peers and prosocial behaviours remained stable over time.

Conclusion These findings revealed specific developmental changes in cognitive and behavioural functioning of individuals with fragile-X syndrome, likely related to a progressive maturation of brain systems devoted to attentional control.

Keywords ADHD, adolescence, autism, development, fragile-X syndrome, Strengths and Difficulty Questionnaire

Introduction

Fragile-X syndrome is the most common inherited form of developmental delay in males, and to a lesser extent in females, caused by the expansion of a triplet CGG repeat of the FMR1 gene ('Fragile-X Mental Retardation 1') on the X chromosome. In subjects with a full mutation, a maximum expansion of the triplet repeats (larger than 200) interferes with the physiology of the FMR1 gene that loses the capacity to produce the FMRP protein. The FMRP protein plays a central role in the physiology and development of neurons, and the lack of its expression is considered to be the main cause of the

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cognitive and behavioural deficits typical of fragile-X syndrome (Visootsak *et al.* 2005; Cornish *et al.* 2007a).

Several data demonstrated that the central cognitive deficit of fragile-X syndrome is an inefficient attentional control (Cornish *et al.* 2012, 2013) leading to problems in language processing, problem solving and working memory; from a behavioural point of view, there is marked hyperactivity, impulsivity and, more generally, a lack of inhibitory control over automatic responses (Cornish *et al.* 2004a,b). These attentional deficits seem to increase the behavioural expression of other typical aspects of the fragile-X syndrome, such as hyperexcitation and social anxiety that further compromise cognitive efficiency through maladapted feedback processes (Cornish *et al.* 2004a, 2007a). This clinical picture strongly overlaps with the symptomatology of attention-deficit/hyperactivity disorder (ADHD). In fact, approximately 70–80% of boys with fragile-X syndrome have a diagnosis of ADHD and most have hyperactivity combined with attentional difficulties (Hagerman 1996). It is worth noting here that psychostimulant medications usually employed for treatment of attentional deficits and impulsiveness in ADHD (methylphenidate, Ritalin) are effective for improving attention and social skills in children with fragile-X syndrome as well (e.g. Hagerman *et al.* 1988).

Longitudinal studies in children and adolescents with ADHD showed that attentional symptoms tend to persist from childhood into adolescence to a greater extent than hyperactivity-impulsivity, suggesting that inattention and hyperactivity might have different developmental trajectories (e.g. Larsson *et al.* 2006). However, dissociations between inattention and hyperactivity can only be observed in some individuals, while in other cases the two deficits show the same age-related changes (Larsson *et al.* 2011). Recently, in a 3-year prospective longitudinal study Cornish *et al.* (2012) assessed basic attentional processes and their impact on developmental trajectories in children (8 years at entry into the study) with fragile-X syndrome. Results confirmed the presence of attentional impairments and also showed that these defects improved over time, while non-verbal intelligence declined; behavioural difficulties (i.e. autistic symptomatology and hyperactivity) remained stable over the 3-year time frame. In a subsequent study, Cornish *et al.* (2013) demonstrated that improvement in attentional defects of children with fragile-X syndrome paralleled developmental changes of typical boys.

Evidence reviewed above on developmental changes in individuals with fragile-X syndrome mainly concerned childhood. Instead only a few studies investigated whether levels of functioning changed across adolescence and results were inconsistent (Cornish *et al.* 2007b). Fisch *et al.* (1999, 2002, 2007) observed decreases in scores on measures assessing intelligence and adaptive behaviour from childhood to middle/late adolescence. On the contrary, other authors found that cognitive performance of boys with fragile-X syndrome continued to increase at the same rate as developmental aged matched typical individuals (Hatton *et al.* 2003; Skinner *et al.* 2005; Cornish & Wilding 2006). Thus, developmental pathways from late childhood onwards need to be further defined to clarify age-related cognitive and behavioural changes in fragile-X syndrome (Cornish *et al.* 2007b).

The aim of the present study was to track longitudinal changes across adolescence, i.e., from 9 to 15 years, in cognitive and behavioural profile of individuals with fragile-X syndrome. Intellectual abilities (verbal, non-verbal and general), adaptive functioning and behavioural symptoms (e.g. inattention/hyperactivity) were systematically measured three times at approximately two-year intervals. Moreover, following data showing that commonalities exist between fragile-X syndrome and autism in different cognitive domains, and that these phenotypic analogies may vary depending on age (for a review see Cornish *et al.* 2007b), here we also assessed autistic symptomatology. Finally, fragile-X syndrome is a disorder affecting more males than females, and there are a significant number of females with the full mutation who do not have an intellectual disability (ID); by contrast, ID is a hallmark feature of fragile-X syndrome in males (for a review see Kraan *et al.*, 2013). Therefore, since studying females can create a complicated picture we decided to recruit for the study male participants only.

Starting from evidence reviewed above, we hypothesised that specific changes could be found in cognitive and behavioural functioning of

adolescents with fragile-X syndrome mostly involving domains of hyperactivity/inattention (Larsson *et al.* 2011; Cornish *et al.* 2012), non-verbal intelligence (Fisch *et al.* 2002; Skinner *et al.* 2005) and adaptive behaviour (Hatton *et al.* 2003).

Methods

Participants

Forty-seven white Caucasian boys with a confirmed diagnosis of fragile-X syndrome were recruited through developmental evaluation centres and support groups for children and families with fragile-X syndrome in southern Italy. All participants were screened as part of a larger study on cognitive functioning and adaptive behaviour in individuals with developmental delay. Boys were included if they were aged between 9 and 11 years and had an intellectual quotient (Full Scale IQ) ≥ 55 points on the Wechsler Intelligence Scales for Children-Revised (Orsini 1993). Boys were excluded from the study if they showed severe ID or debilitating neurological disorders (i.e. drug-resistant epilepsy, complex motor disturbances), if they were using medication for the treatment of inattention and hyperactivity symptoms, or if they were taking anti-psychotic and mood stabilising drugs during the study. Thirty-eight individuals met the inclusion criteria, but two boys dropped out because they moved with their families to another city. Thus, the final sample included 36 boys (mean age at the entry into the study, Time 1: 10 years, 3 months, SD = 0.7; range 9–11 years). All participants were followed and assessed again 24 months (Time 2: age range 11–13 years) and 24 months later (Time 3: age range 13–15 years). Written informed consent was obtained from the parents of each participant involved in the study; the local institutional review board approved the study protocol.

Measures

The measures were administered at the Neuropsychology Laboratory, Department of Psychology, Second University of Naples (Italy) by a clinical psychologist and a child psychiatrist trained in psychological assessment of individuals with neurobehavioural disorders. The following measures were included.

The Wechsler Intelligence Scales for Children-Revised (WISC-R; Orsini 1993) to measure the IQ; in particular, the WISC-R evaluates Verbal IQ, Nonverbal (Performance) IQ and Full Scale IQ (general intellectual functioning). Standardised values follow the usual psychometric convention of mean = 100 and SD = 15; thus scores below 2 SD from the mean (<70) imply the presence of ID.

The Childhood Autism Rating Scale (CARS; Schopler *et al.* 1993) evaluates the autistic symptomology: the CARS assesses a range of behavioural responses such as relationship to people, imitation, adaptation to change, fear or nervousness, verbal and non-verbal communication, activity level and intellectual response. Each item is rated on a scale from 1 (within normal limits for age) to 4 (severely abnormal for age). Total scores below 30 suggest that the individual is not autistic, total scores from 30 to 36.5 indicate mild to moderate autism, and scores of 37 or higher indicate severe autism.

The Vineland Adaptive Behavior Scales (VABS; Sparrow *et al.* 1984) investigate adaptive behaviour: in particular, the VABS are used to gather parent report on the domains of communication, daily living skills, and socialisation skills from birth to adulthood, and motor skills for preschool children only. Standard scores on the VABS domains follow the psychometric convention of mean = 100 and SD = 15, with the cut-off point set at 70.

The Strengths and Difficulty Questionnaire (SDQ; Goodman 1997) is composed of 25 items that ask about behavioural attributes of the child and are combined to form five sub-scales (composed of 5 items each). The SDQ specifically assesses the following domains: (i) emotional symptoms, (ii) behavioural problems at school, (iii) hyperactivity/lack of attention, (iv) problems with similar age subjects, and (v) prosocial behaviour. In all cases, answer options for each item are: 'not true' 'somewhat true' or 'certainly true', and these are scored 0, 1 or 2, giving a total score out of a possible 10 for each sub-scale. High score on the prosocial behaviour sub-scale reflects strength, while high scores on the other four SDQ sub-scales reflect

difficulties. In the present study we adopted the parent version of the SDQ.

Statistical analysis

We aimed at testing whether participants' performance on the above cognitive and behavioural measures changed over time depending on both the assessed ability and the time point. We investigated intellectual functioning by computing a two-way repeated-measure analysis of variance (ANOVA) on IQ standard scores, with IQ Scale (Verbal, Nonverbal and Full Scale) and time point (Time 1, Time 2 or Time 3) as within-subject factors. We also examined autistic symptomatology: first, we conducted a one-way ANOVA on CARS total score, with time point as a within-subject factor; then, we performed a two-way repeated measures ANOVA on CARS raw scores, with CARS item (i.e. relationship to people, verbal communication and activity level) and time point as within-subject factors. Moreover, a two-way repeated measures ANOVA was performed on VABS standard scores, with VABS sub-scale (communication, daily living and social abilities) and time point as within-subject factors. Finally, we conducted a two-way repeated measures ANOVA on SDQ raw scores, with SDQ sub-scale (emotional symptoms, behavioural problems, hyperactivity/lack of attention, problems with peers or prosocial behaviour) and time point as within-subject factors.

When a significant interaction was found post-hoc analyses (*t*-tests with Bonferroni's correction for multiple comparisons) were performed.

Results

Intellectual functioning

The two-way repeated-measure ANOVA showed significant main effects of IQ Scale ($F_{2,70} = 49.092$, $P = 0.0001$, $\eta^2_p = 0.584$) and of time point ($F_{2,70} = 4.750$, $P = 0.012$, $\eta^2_p = 0.120$). There was a significant interaction between IQ Scale and time point ($F_{4,140} = 246.520$, $P = 0.0001$, $\eta^2_p = 0.876$). Post-hoc comparisons (paired *t*-tests with $P < 0.005$ after Bonferroni's correction) on the interaction showed a different developmental trend of the three IQ Scales (Fig. 1). Verbal IQ significantly improved across the three time points (all $P < 0.0001$),

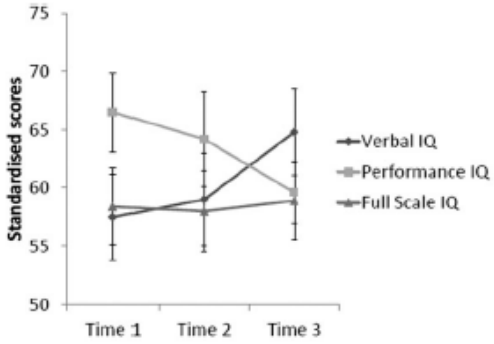

Figure 1 Mean (bars are SD) Verbal IQ, Nonverbal (Performance) IQ and Full Scale IQ of adolescents with fragile-X syndrome plotted against the three time points.

whereas Nonverbal IQ significantly declined across the three time points (all $P < 0.0001$). Full Scale IQ significantly changed only when comparing Time 2 and Time 3 ($P < 0.001$), but not when considering the other time point comparisons (all $P > 0.05$).

Autistic symptomatology

Autistic symptomatology changed across the three time points, as shown by results of the one-way ANOVA on CARS total score ($F_{2,70} = 355.958$, $P = 0.0001$, $\eta^2_p = 0.910$), with a progressive drop of the total score from Time 1 (mean = 39.7, SD = 1.3), to Time 2 (mean = 36.3, SD = 2.1) and Time 3 (mean = 30.9, SD = 2.6). The two-way repeated measures ANOVA computed taking into account CARS raw scores on specific items (relationship to people, verbal communication and activity level) did not show significant main effects of item ($F_{2,70} = 0.039$, $P = 0.962$, $\eta^2_p = 0.001$), and of time point ($F_{2,70} = 3.122$, $P = 0.059$, $\eta^2_p = 0.082$). Instead, the interaction between CARS item and time point was significant ($F_{4,140} = 7.455$, $P = 0.0001$, $\eta^2_p = 0.176$). Post-hoc comparisons (paired *t*-tests with $P < 0.005$ after Bonferroni's correction) on the interaction showed that scores on the three items had a different trend (Fig. 2). Indeed, relationship to people and verbal communication did not change across the three time points (all $P > 0.05$), whereas activity level significantly dropped at Time 3 with respect to both Time 1 and Time 2 (all $P < 0.002$).

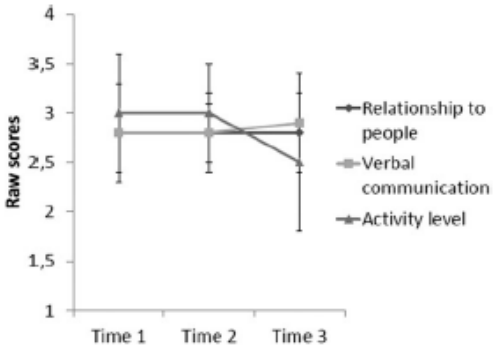

Figure 2 Mean scores (bars are SD) of adolescents with fragile-X syndrome on CARS items assessing relationship to people, verbal communication and activity level plotted against the three time points.

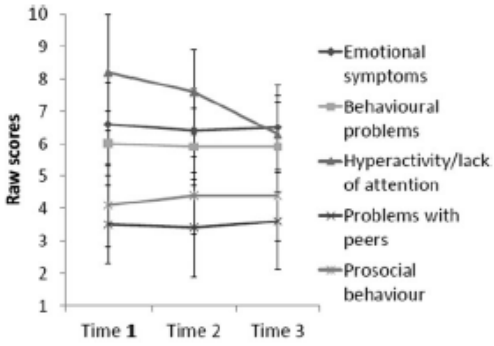

Figure 4 Mean raw scores (and SD) of adolescents with fragile-X syndrome on the five SDQ scales plotted against the three time points.

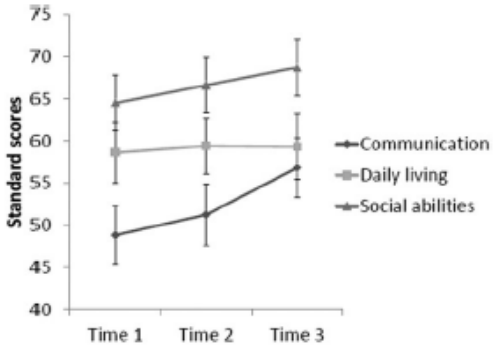

Figure 3 Mean standard scores (bars are SD) of adolescents with fragile-X syndrome on the three VABS sub-scales separately for Time 1, 2 and 3.

Adaptive behaviour

The two-way repeated measures ANOVA showed significant main effects of sub-scale ($F_{2,70} = 256.568$, $P = 0.0001$, $\eta^2_p = 0.880$), and of time point ($F_{2,70} = 305.555$, $P = 0.0001$, $\eta^2_p = 0.897$). Moreover, we found a significant interaction between VABS sub-scale and time point ($F_{4,140} = 89.331$, $P = 0.0001$, $\eta^2_p = 0.718$). Post-hoc comparisons (paired *t*-tests with $P < 0.005$ after Bonferroni's correction) on the interaction showed that scores on the three sub-scales had a different trend (Fig. 3); in fact, communication and social abilities significantly improved across the three time points (all $P < 0.0001$), whereas daily living skills did not change across time (all $P > 0.05$).

Behavioural problems and strengths

The two-way repeated measures ANOVA showed a significant main effect of sub-scale ($F_{4,140} = 92.232$, $P = 0.0001$, $\eta^2_p = 0.725$), but not of time ($F_{2,70} = 3.563$, $P = 0.054$, $\eta^2_p = 0.081$). Moreover, we found a significant interaction between SDQ sub-scale and time point ($F_{8,280} = 7.285$, $P = 0.0001$, $\eta^2_p = 0.172$). Post-hoc comparisons (paired *t*-tests with $P < 0.005$ after Bonferroni's correction) on the interaction showed that hyperactivity/lack of attention score had a different trend with respect to the scores on the other four scales (Fig. 4); indeed, hyperactivity/lack of attention score significantly improved across the three time points (all $P < 0.0001$), whereas scores on the other scales remained flat across time (all $P > 0.05$).

Discussion

In the present study, we assessed longitudinal changes across adolescence (from 9 to 15 years at approximately two-year intervals) in cognitive and behavioural profile of individuals with fragile-X syndrome. To this scope, we measured intellectual functioning, autistic symptomatology, adaptive behaviour and several behavioural symptoms.

Results showed that Verbal IQ improved across the three time points, whereas Nonverbal IQ declined and Full Scale IQ remained quite stable over time. Autistic symptomatology progressively decreased across the three time points, with a specific improvement on CARS item assessing the activity level. VABS domains of communication and social abilities improved across time, while daily living skills did not. Relevant here, analysis on SDQ showed that elevated levels of hyperactivity/lack of attention at Time 1 significantly improved across the three time points, whereas scores on the other scales (emotional symptoms, behavioural problems, prosocial behaviours and problems with peers) remained flat.

Recently, Cornish *et al.* (2013) investigated whether cognitive performance of young boys (4–10 years at the entry into the study) with fragile-X syndrome showed a delayed onset and a developmental delay (but similar to patterns of improvement of typical boys) or, on the contrary, reached an age-specific plateau of peak development and then diverged from typical trajectories over time. Results demonstrated significant weaknesses of attention in boys with fragile-X syndrome, with no significant improvement over chronological age. More relevant, when comparing performance against typical boys matched for mental age, boys with fragile-X syndrome showed a delay, but also a profile and longitudinal improvements similar to typical individuals. Thus, Cornish *et al.* (2013) inferred that attention, although delayed in fragile-X syndrome, undergoes a developmental change rather than an 'arrest' across childhood.

In a series of studies, Fisch *et al.* (1999, 2002, 2007) found decreases in scores on measures assessing intelligence and adaptive behaviour from childhood to middle/late adolescence. In particular, Fisch *et al.* (2002) compared and followed-up (from 6–8 to 8–10 years) boys with fragile-X or autism to determine whether developmental changes in cognitive ability and adaptive behaviour were similar in the two groups. Results showed decreases in IQ scores in young children from both clinical populations, but declines in IQ scores were steeper among children with fragile-X. Moreover, children with fragile-X syndrome showed declines in all domains of adaptive behaviour (communication, daily living skills, and socialisation). This cognitive and behavioural decline continued in older children and early adolescents with fragile-X syndrome.

In the present study, we found that adolescents with fragile-X showed a significant decline in Nonverbal IQ, whereas Verbal IQ improved and Full Scale IQ remained unchanged over time. Furthermore, we found that VABS domains of communication and social abilities enhanced across the three time points, whereas daily living skills did not. These differences between Fisch *et al.*'s (2002) and the present study could lie in that Fisch *et al.* assessed and followed-up participants from late childhood to early adolescence (from 6–8 to 8–10 years), whereas we followed-up participants from early adolescence to middle adolescence (from about 10 to 14–15 years). Therefore, the two studies focused on different adolescent age-ranges, thus likely giving rise to non-overlapping results. Instead, the present findings are more consistent with data showing that cognitive and behavioural skills of adolescents with fragile-X syndrome tend improve at the same rate as developmental aged matched typical individuals (Hatton *et al.* 2003; Skinner *et al.* 2005; Cornish & Wilding 2006). Cornish *et al.* (2013) posited that changes in cognitive functioning (mainly attentional processes) of individuals with fragile-X syndrome do not reflect 'developmental freeze', but rather a delay in typical pattern of cognitive development. The present findings support the view of a delay rather than a 'freeze' in cognitive and behavioural development of boys with fragile-X syndrome and suggest that substantial changes in the domain of attention and hyperactivity can exert a more widespread influence on intellectual functioning and adaptive behaviour. This interpretation could also account for the decrease of autistic symptoms across time. In fact, although our results showed a reduction of CARS total score (but see Hatton *et al.* 2006), the in-depth analysis on specific CARS items (i.e. relationship to people, verbal communication and activity level) revealed that relationship to people and verbal communication did not change, whereas activity level significantly dropped across time. Thus, reduction of autistic symptoms (CARS total scores) might mainly reflect improvements of the activity level, likely due to the amelioration of inattention/hyperactivity. Testing relationships between inattention/hyperactivity and autistic symptoms in fragile-X syndrome was

outside of the main purposes of the present study, but future investigations should focus on this issue.

Recent neuroimaging data on brain maturation showed that relevant structural and functional brain changes occur during the transition from childhood to adolescence and across adolescent development; these changes involve a number of areas important for attentional control (Dennis & Thompson 2013) and intelligence (Ramsden *et al.* 2011). We could speculate that a 'maturational lag' characterises the cognitive development of individuals with fragile-X syndrome. The construct of 'maturational lag' was originally developed for interpreting developmental changes in individuals with ADHD (Shaw *et al.* 2007). This model is supported by evidence showing that brain maturation seems to progress in a similar manner regionally in both children with and without ADHD (with primary sensory areas attaining peak cortical thickness before high-order association areas), but with a marked delay in ADHD in attaining peak thickness throughout most of the cerebral cortex. This delay is most prominent in prefrontal regions that are important for high-order cognitive processes, such as attention and inhibitory control (Shaw *et al.* 2007). Recently, Hall *et al.* (2013) investigated brain networks underlying cognitive and behavioural symptoms in persons with fragile-X syndrome aged 10 to 23 years. Results showed a specific neural profile in individuals with the syndrome compared with age- and IQ-matched controls. Although persons with fragile-X syndrome generally showed a diffuse reduction of neural connectivity, functional and structural data revealed alterations in the left insular cortex, a region that seems to be involved in cognitive and behavioural symptoms of autism (Hall *et al.* 2013). In another relevant study, Hoeft *et al.* (2011) found that compared with individuals with developmental delay but not autism, males with fragile-X syndrome showed decreased gray matter density in the frontal and temporal regions (including the insula), whereas males with autism had increased gray matter density in these regions. Moreover, the neuroanatomic profile of individuals with autism was more similar to that of individuals with developmental delay but without autism than to those with fragile-X syndrome. In the same vein, in a structural longitudinal imaging study on preschoolers with fragile-X syndrome Hazlett *et al.* (2012) also observed different patterns of brain growth that distinguished boys with fragile-X syndrome from children with autism.

Following these neuroimaging findings, the present results and evidence reviewed above on similarities between fragile-X syndrome and ADHD would suggest that future imaging studies should directly investigate shared and different brain maturation patterns in these two neurodevelopmental syndromes in order to reveal disease-specific imaging biomarkers.

Limitations

In the present study, we did not collect data on experimentally controlled behavioural tasks assessing attention, for instance as in the case of studies by Cornish and colleagues (Cornish *et al.* 2012, 2013; Scerif *et al.* 2012). We, instead, mainly focused on parent-report and observational measures, thus implying that parents were likely to be well aware of symptoms related to fragile-X syndrome (for instance see Russell *et al.* 2013). However, when relying on informant report measures assessed across time one should consider that the informants might have remembered their responses from one time point to the next, or that parents had expectations about how their sons' skills would change with age.

Other limitations of the present study relate to the single group design we adopted here. If we had included a comparison group, our results would have been able to provide a stronger test for the idea of a delay in cognitive development of adolescents with fragile-X syndrome. For instance, by combining within a single research design cross-sectional and longitudinal assessments of children with fragile-X syndrome and typical children matched on mental age, Cornish *et al.* (2013) could clearly demonstrate that the fragile-X syndrome is related to a delay in typical pattern of cognitive development.

Despite these limitations our results showed that cognitive and behavioural signatures of a developmental delay in fragile-X syndrome could be detected across adolescence, thus providing a further contribution to the issue of whether developmental trajectories of fragile-X syndrome are delayed or arrested.

Conclusions

In the present study we explored developmental changes across adolescence (three time points; Time 1: 9–11; Time 2: 11–13, and Time 3: 13–15 years) in cognitive and behavioural profile of individuals with fragile-X syndrome. We measured intellectual functioning, autistic symptomatology, adaptive behaviour and several behavioural symptoms. Verbal intelligence improved across the three time points, while non-verbal intelligence declined and general intelligence was almost unchanged. Autism ratings decreased (in particular activity level), whereas adaptive behaviour generally improved across time. Finally, inattention/ hyperactivity significantly improved across time, whereas emotional symptoms, behavioural problems at school, problems with similar-age subjects and prosocial behaviour remained flat. These results demonstrated specific developmental changes in cognitive and behavioural functioning of individuals with fragile-X syndrome, likely related to a progressive maturation of neural systems involved in attentional control (Cornish *et al.* 2013; Dennis & Thompson 2013).

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9°RASSEGNA
SUL CINEMA PER L'INFANZIA
E PER L'ADOLESCENZA
È un'iniziativa di
Nepios ONLUS
Associazione a tutela dell'infanzia
L'AMORE CONDIVISO
Storie di fratelli e sorelle: un difficile EQUILIBRIO AFFETTIVO
A cura di Stefano Conte Neuropsichiatra Infantile U.S.C. di Neuropsichiatria Infantile – A.O. Papa Giovanni XXIII
Giovedì 9 ottobre 2014 ore 20.30
1
Non pensarci
di Gianni Zanasi
Interverrà Claudio Rozzoni, Responsabile del Centro per il Bambino e la Famiglia ASL, Bergamo
2
Giovedì 16 ottobre 2014 ore 20.30
Rachel sta per sposarsi
di Jonathan Demme
Interverranno
Susanna Ambrosino, Psicologa USC di Neuropsichiatria Infantile A.O. Papa Giovanni XXIII, Bergamo
Stefano Asperti, Dipartimento L.L.S.S. e Comunicazione dell'Università degli Studi, Bergamo
Giovedì 23 ottobre 2014 ore 20.30
3
Pulce non c'é
di Giuseppe Bonito
Interverranno
Emma Avezzù, Procuratore Capo Minorenni, Brescia
Mara Azzi, Direttore Generale ASL, Bergamo
4
Giovedì 30 ottobre 2014 ore 20.30
Elle s'appelle Sabine
di Sandrine Bonnaire
Interverrà Emi Bondi, Direttore Psichiatria 1, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo
PER LE TRAME DEI FILM www.nepios.org
La rassegna propone, attraverso la visione e la successiva discussione di quattro film, una riflessione sul tema del rapporto tra fratelli e sorelle sottolineando in particolare l'importanza di questi legami nello sviluppo della crescita e della personalità.
CINEMA CAPITOL
BERGAMO, VIA T. TASSO 41
LA PARTECIPAZIONE ALLE SERATE È RICONOSCIUTA DAL CENTRO SERVIZI E DALL'ASL DI BERGAMO COME MONTE ORE DESTINATO ALL'AGGIORNAMENTO DEGLI INSEGNANTI E DEGLI OPERATORI

L'AMORE CONDIVISO

Storie di fratelli e sorelle: un difficile EQUILIBRIO AFFETTIVO

I TEMI PRINCIPALI DEI FILM VERRANNO COMMENTATI E DISCUSSI INSIEME AD ESPERTI CHE CONOSCONO - ANCHE ATTRAVERSO LA LORO ESPERIENZA QUOTIDIANA - LA REALTÀ DELLE PROBLEMATICHE PROPOSTE.

CINEMA CAPITOL
BERGAMO, VIA T. TASSO 41

Nepios ONLUS

All'origine di ogni associazione c'è innanzitutto un io, una persona spinta ad offrire il proprio impegno. Quando nasce la volontà di servire l'altro, inizia la ricerca dell'appoggio di un gruppo, per operare insieme e diventare una presenza sociale concreta. Così nel 2001 è nata a Bergamo *Nepios*, associazione senza scopo di lucro a tutela dell'infanzia e della famiglia. *Nepios* opera grazie a un fondo incrementato dai contributi diretti degli associati e di terzi pubblici o privati. Incoraggia e gestisce iniziative di carattere culturale, ricreativo e di sensibilizzazione sociale, atte a reperire ulteriori fondi da destinare a progetti in linea con gli scopi statutari. Opera in stretta collaborazione con le Istituzioni cittadine ed è sovvenzionata dalla generosità delle imprese del territorio bergamasco, che sempre si dimostrano sensibili alle iniziative del territorio.

9 ottobre 2014, ore 20.30

1

Non pensarci

di Gianni Zanasi con Valerio Mastandrea, Giuseppe Battiston, Anita Caprioli, Gisella Burinato,Teco Celio, Caterina Murino - Sceneggiatura di Gianni Zanasi e Michele Pellegrini - Italia 2007 - 112 minuti - 01 Distribuzione.

Stefano Nardini un musicista punk rock di 35 anni ritorna a casa dalla sua famiglia dopo un lungo soggiorno a Roma. Amareggiato dall'esito di una carriera che era iniziata con i migliori auspici e deluso da una relazione sentimentale conclusa inaspettatamente, Stefano spera di poter finalmente trovare riparo e conforto nel calore delle mure domestiche e nella quiete della provincia romagnola, suo luogo di origine. Con sorpresa, scopre una realtà familiare ben diversa perché: il fratello Alberto che ha ereditato la gestione dell'azienda alimentare familiare, annaspa tra debiti e personali sconforti; la sorella Michela, dopo aver interrotto gli studi universitari, sembra voler occupare tutte le sue energie e capacità rinchiudendosi nello spazio di una piscina ammaestrando delfini; il padre in pensione, dopo un infarto, impiega tutto il suo tempo a giocare a golf e la madre infine si affida a tecniche sciamaniche per cercare di contenere tutte le ansie, i rimorsi e le preoccupazioni per una famiglia che vede frantumarsi in problematiche sempre più complesse e distanti dalle sue aspettative. Sarà proprio l'intervento di Stefano con la sua prorompente vitalità a smuovere il torpore della vita provinciale dei fratelli attivandosi coraggiosamente e generosamente verso di loro.
Sorretto da una sceneggiatura in grado di saper trovare sempre i risvolti più ironici e paradossali di ogni sviluppo drammatico della vicenda, il film conserva nel tempo una insolita freschezza mantenendo sempre una misura garbata e nello stesso tempo pungente nello sviluppo narrativo. Gran parte della riuscita del film è sicuramente dovuta alla straordinaria aderenza ai personaggi di tutti gli attori, tutti davvero in stato di grazia. Nella bravura generale spicca l'abilità di Valerio Mastandrea che è in grado di conferire al personaggio di Stefano quell'impronta di romanità apparentemente cinica e distaccata ma in realtà sempre affettuosamente partecipe alle vicende della commedia umana.
"Non pensarci" ha meritatamente vinto il Premio Pasinetti come miglior film alla Mostra del Cinema di Venezia - Giornata degli Autori del 2007.

2

16 ottobre 2014, ore 20.30

Rachel sta per sposarsi

di Jonathan Demme con Anne Hathaway, Rosemarie De Witt, Bill Irwin, Debra Winger, Tunde Adebimpe - Sceneggiatura di Jenny Lumet - Stati Uniti 2008 - 108 minuti - Sony Pictures.

Kym lascia la clinica di riabilitazione per tossicodipendenza per poter partecipare al matrimonio della sua sorella maggiore Rachel. La cerimonia diventa occasione per una riunione familiare di una benestante famiglia del Connecticut di oggi. La riunione familiare tuttavia appare problematica fin dall'inizio sia per l'esasperato narcisismo di Kym, sia per il costante stato di apprensione della sposa. Emergono inoltre in misura evidente le preoccupazioni, in particolar modo paterne, circa lo stato di salute di Kym, la cui instabilità emotiva suscita il riemergere di conflitti e di angosce solo assopite dal tempo. Da una parte infatti Kym rivendica un ruolo ed uno spazio affettivo all'interno della sua famiglia nonostante la malattia ed un evento drammatico di cui è stata protagonista. Dall'altra parte Rachel, studentessa di psicologia che, nello sforzo di capire ed accettare la sorella minore, si scopre lei stessa fragile e bisognosa di quell'attenzione familiare che le è sempre mancata e che richiede soprattutto adesso che sta per diventare moglie e futura madre. Tra le due sorelle vediamo i genitori che dopo il fallimento della loro relazione coniugale, hanno cercato di avere nuove possibilità affettive ma che tuttavia appaiono, con diversa sensibilità, costretti a fare inevitabilmente i conti con un passato che li soffoca per il carico di rimpianti e di dolore. Girato con assoluta maestria da un regista in grado costantemente di rinnovarsi (qui c'è un uso straordinario della camera a mano), il film modella ritratti familiari che attingono da un lato alla grande stagione della letteratura americana del Novecento (da O'Neil a Steinbeck da Capote a Williams) dall'altra sembra far riferimento al cinema di Ingmar Bergman ed alla recente cinematografia danese (da Lars Von Trier a Susanne Blier) pur mantenendo tradizioni ed ambienti tipicamente statunitensi. Oltre che per la qualità e quantità di riferimenti culturali, il film si apprezza per la straordinaria interpretazione di tutti gli attori ed in particolare di Anne Hathaway che riesce a dare al personaggio di Kym l'espressione autentica di un dolore vivo. Il film è stato scritto da Jenny Lumet figlia del grande regista Sidney Lumet.

23 ottobre 2014, ore 20.30

3

Pulce non c'é

di Giuseppe Bonito con Pippo Delbono, Marina Massironi, Francesca Di Benedetto, Ludovica Falda, Piera Degli Esposti, Giorgio Colangeli. Sceneggiatura di Monica Zapelli e Gaia Rayneri, Italia 2012 - Durata 97 minuti - Academy 2 - Distribuzione.

Esordio alla regia di un lungometraggio di un promettente regista italiano, "Pulce non c'è" è un film coraggioso ed onesto che affronta problematiche importanti con una sensibilità che raramente si incontra nel cinema italiano di oggi. Tratto dall'omonimo romanzo di Gaia Rayneri (Einaudi Editore), il film è la cronaca autobiografica dei giorni dell'allontanamento e dell'inserimento, in una struttura protetta, di Margherita (chiamata dai familiari "Pulce") bambina affetta da autismo, a seguito di un sospetto abuso compiuto su di lei dal padre. Per cercare di attenuare l'isolamento di Pulce, i genitori si sono affidati ad una metodologia di approccio comunicativo che tuttavia si è rilevata inaffidabile in quanto ha fatto sorgere appunto il sospetto di una violenza, denunciato inizialmente degli insegnanti, che si è rilevato poi del tutto infondato. "Pulce non c'è" descrive, attraverso il racconto di Giovanna, sorella maggiore di Margherita, lo stupore ed il disorientamento di un nucleo familiare di fronte all'ostinato accanimento degli organi sanitari e giudiziari che interpretano con assoluta superficialità ed incompetenza prove prive di fondamento. Il film riesce a conservare la spontaneità e l'ironia con la quale Giovanna annota nel romanzo tutte le vicissitudini familiari rimarcando soprattutto sia l'estrema solitudine di famiglie che devono gestire condizioni di disabilità e sia la fragilità delle istituzioni che dovrebbero tutelare la salute dei minori e delle loro famiglie. Impreziosito dal contributo interpretativo di grandi attori italiani di scuola teatrale, il film si impone, tra gli altri indiscussi meriti, come acuta testimonianza di una adolescente il cui percorso di crescita è comunque condizionato dalla presenza di una sorella disabile.

4

30 ottobre 2014, ore 20.30

Elle s'appelle Sabine

di Sandrine Bonnaire con Sabine Bonnaire, Sandrine Bonnaire - 2007 - Francia 2007 - Durata 85 minuti - Distribuzione Italiana Vivo Film.

Esordio alla regia di una delle più importanti ed affermate attrici francese degli ultimi venti anni, Sandrine Bonnaire ha scelto di dirigere un documentario coraggioso e di grande intensità emotiva dedicato a Sabine sua sorella minore. Sabine fin da bambina aveva evidenziato gravi problematiche di inserimento sociale aggravate da scoppi di aggressività spesso difficilmente controllabili. Nonostante indubbie capacità cognitive, arricchite peraltro da una particolare predisposizione per la musica, la crescita di Sabine è stata determinata da un progressivo isolamento sociale e da un sofferto allontanamento dal nucleo familiare per la difficoltà sempre più evidente di gestione del comportamento di Sabine, incontrollabile ed esplosivo. Per il peggioramento del suo stato mentale, con diagnosi approssimative che inquadravano i disturbi psichici di Sabine all'interno di uno spettro autistico, i familiari hanno deciso di ricoverare la ragazza in una istituzione per malattie mentali. Grazie alla determinazione di Sandrine divenuta attrice famosa, dopo una degenza durata ben cinque anni, caratterizzata da pesanti contenimenti di tipo farmacologico cha hanno determinato un grave deterioramento delle competenze cognitive, Sabine è finalmente approdata in una comunità in grado di accogliere le sue esigenze e restituirle una possibilità di vita più dignitosa.
Noi incontriamo Sabine proprio in questa nuova struttura ed il film ne descrive la sua vita quotidiana con il suo tentativo di aderire alle proposte di interazione sociale effettuate dagli educatori e di accettazione di cure (anche farmacologiche) più umane ed adeguate. Il documentario è costruito sull'alternanza tra le scene di questa vita comunitaria attuale con i filmati familiari di quando Sabine appariva bellissima adolescente non completamente devastata e svuotata dalla malattia mentale. Il film è una riflessione struggente sulla malattia mentale e nello stesso tempo è una dei più emozionanti ed intense dichiarazioni di affetto che una sorella possa fare verso una sorella malata.

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

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