



INDICE:

1. Dalle banche dati bibliografiche

pag. 2

2. Documenti

Lo-Castro A, Curatolo P.

EPILEPSY ASSOCIATED WITH AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: IS THERE A GENETIC LINK?

Brain Dev 2013 [in press]

pag. 38

Carlotta D, Borroni S, Maffei C, et al.

ON THE RELATIONSHIP BETWEEN RETROSPECTIVE CHILDHOOD ADHD SYMPTOMS AND ADULT BPD FEATURES: THE MEDIATING ROLE OF ACTION-ORIENTED PERSONALITY TRAITS.

Compr Psychiatry 2013 [in press]

pag. 47

Ronconi L, Gori S, Ruffino M, et al.

ZOOM-OUT ATTENTIONAL IMPAIRMENT IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Cortex: A Journal Devoted to the Study of the Nervous System and Behavior 2013 Apr;49:1025-33.

pag. 57

Mazza M, D'Ascenzo F, Davico C, et al.

DRUGS FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER DO NOT INCREASE THE MID-TERM RISK OF SUDDEN DEATH IN CHILDREN: A META-ANALYSIS OF OBSERVATIONAL STUDIES.

Int J Cardiol 2013 [in press]

pag. 66

3. Comunicati Stampa

"L'iperattività e il deficit di attenzione infantili (ADHD) andrebbero diagnosticati più precocemente prima che diventino una patologia da trattare anche farmacologicamente"

IRCCS Istituto di Ricerche Farmacologiche "Mario Negri

pag. 68

"L'uso degli psicofarmaci in età evolutiva necessita di ulteriori indagini accurate e protratte nel tempo"

IRCCS Istituto di Ricerche Farmacologiche "Mario Negri;
SINPIA Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza

pag. 70

4. Segnalazione

Bonati M, Poma L.

AI RAGAZZI VENGONO DATI TROPPI PSICOFARMACI?

Viveresani&belli 10 giugno 2013pag. 15

pag. 72



BIBLIOGRAFIA ADHD MAGGIO 2013

Acad Pediatr. 2013.

INCIDENCE OF ENURESIS AND ENCOPIRESIS AMONG CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN A POPULATION-BASED BIRTH COHORT.

Mellon MW, Natchev BE, Katusic SK, et al.

Objective: This study reports the incidence of enuresis and encopresis among children with attention-deficit/hyperactivity disorder (ADHD) versus those without ADHD.

Methods: Subjects included 358 children (74.5% boys) with research-identified ADHD from a 1976 to 1982 population-based birth cohort (n=5718) and 729 (75.2% boys) non-ADHD control subjects from the same birth cohort, matched by gender and age. All subjects were retrospectively followed from birth until a diagnosis of enuresis or encopresis was made or last follow-up before 18 years of age. The complete medical record for each subject was reviewed to obtain information on age of initial diagnosis of an elimination disorder, frequency and duration of symptoms, and identification of exclusionary criteria specified by DSM-IV, with confirmation of the diagnosis by expert consensus.

Results: Children with ADHD were 2.1 (95% confidence interval [CI], 1.3-3.4; $P = .002$) times more likely to meet DSM-IV criteria for enuresis than non-ADHD controls; they were 1.8 (95% CI, 1.2-2.7; $P = .006$) times more likely to do so than non-ADHD controls when less stringent criteria for a diagnosis of enuresis were employed. Though not significant, children with ADHD were 1.8 (95% CI, 0.7-4.6; $P = .23$) times more likely to meet criteria for encopresis than non-ADHD controls. The relative risk was 2.0 (95% CI, 1.0-4.1; $P = .05$) when a less stringent definition for encopresis was utilized.

Conclusions: Children with ADHD are more likely than their peers without ADHD to develop enuresis with a similar trend for encopresis.

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

Acta Paediatr Int J Paediatr. 2013;102:640-43.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER INCREASED THE RISK OF INJURY: A POPULATION-BASED FOLLOW-UP STUDY.

Kang JH, Lin HC, Chung SD.

Aim To explore the frequency and risk for injury among children with Attention-deficit/hyperactivity Disorder (ADHD) in Taiwan through a population-based study.

Methods A total of 3616 subjects aged between four and twelve years diagnosed with ADHD were selected along with a comparison cohort comprising 18 080 subjects. Each subject was individually traced for a three-year period from their index date to identify those subjects who subsequently received a diagnosis of injury. We used stratified Cox proportional hazards regressions to examine the three-year injury-free survival rates between the two cohorts.

Results Of the subjects, the incidence rate of injury during the three-year follow-up period was 7.97 (95% CI = 7.45-8.51) and 5.36 (95% CI = 5.17-5.56) for the study and comparison cohort, respectively. After adjusting for geographic region, the hazard ratio (HR) of injury for subjects with ADHD was 1.64 (95% CI=1.50-1.79) that of comparison subjects. In addition, we found children with ADHD aged between four and 6 years to demonstrate a greater HR (1.98, 95% CI=1.72-2.28) than those aged between seven and twelve (HR = 1.46, 95% CI = 1.31-1.63).

Conclusions Children with ADHD appear to be at a higher risk for injury than children that are not diagnosed with ADHD.

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Acta Pediatr Esp. 2013;71:67-76.

METHYLPHENIDATE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER: THE DIHANA STUDY.

Uson JRV.

Introduction: Attention deficit/hyperactivity disorder (ADHD) affects a significant proportion of the child and adolescent population.

Aim: This study focuses on determining the response to immediate-release methylphenidate in children and adolescents diagnosed with ADHD, as well as obtaining information on current treatment patterns and on treatment safety.

Subjects and methods: This was a multicentre, retrospective study carried out with 561 patients aged 4-16 years and with ADHD, who had started treatment with immediate-release methylphenidate. The score in terms of DSM-IV-TR parameters, subtypes of ADHD, satisfaction with treatment, use of concomitant medication, and adverse reactions were descriptively analyzed.

Results: Attention deficit was more frequent among adolescents from 6-16 years (95.45%) while hyperactivity was more frequent among children <6 years (91.18%). After 1 year of treatment with immediate-release methylphenidate a significant decrease was found both in mean CGI score (59% in <6 years and 63% between 6-16 years) and in mean DSM-IV-TR ADHD subtype values (>44% in all cases). The 73.91% of the children <6 years and the 87.84% of adolescents from 6-16 years were considered very satisfied or satisfied with treatment. There was at least one adverse reaction in 26.03% of patients, though no serious adverse reaction was found. More than 42% of patients were still on treatment with immediate release-methylphenidate, with a mean treatment time of around 3.7 years.

Conclusions: The results overall show a good response to immediate-release methylphenidate and a good safety profile for the treatment.

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ADHD Atten Deficit Hyperact Disord. 2013;5:105-09.

PARENTS' ATTITUDES TOWARD METHYLPHENIDATE USING N-OF-1 TRIAL: A PILOT STUDY.

Taragin D, Berman S, Zelnik N, et al .

To compare parents' attitudes toward methylphenidate treatment in children with attention deficit hyperactivity disorder employing two approaches: (1) a 2-week double-blind placebo-drug trial (n-of-1 trial), (2) a traditional prescription approach. The study group (N=50) and a comparison group (N=45) were recruited. The Abbreviated Acceptability Rating Profile was administered prior to and following the pediatricians' consultation, and in 2, 4, and 8 weeks after prescription. Complete data set was available for 21 children in each group. While initial attitudes were similar, a significantly more favorable attitude following the performance of an n-of-1 trial and throughout the follow-up in the study group only was noted. Adherence was significantly correlated with attitude score in the study group only. An individual n-of-1 trial with methylphenidate appears to positively affect parents' attitudes toward drug treatment and may also help adherence with this treatment.

ADHD Atten Deficit Hyperact Disord. 2013;5:93-104.

Do ADHD SYMPTOMS MODERATE THE RELATION BETWEEN POSITIVE ALCOHOL EXPECTANCIES AND ALCOHOL-RELATED OUTCOMES?

Dattilo L, Murphy KG, Van Eck K, et al.

Research indicates that attention-deficit/hyperactivity disorder (ADHD) may be a risk factor for heavy alcohol use and related problems. Research also suggests that positive alcohol expectancies (i.e., positive beliefs about the effects of alcohol) are predictive of risky alcohol use and related problems (e.g., driving while intoxicated). However, no research has examined the association between ADHD symptoms and positive expectancies or the role of ADHD symptoms in the relation between positive expectancies and alcohol use and related problems, an unexplored area addressed by the current study. Participants were 889 undergraduates (76 % female, 82.3 % Caucasian) at a Southeastern University who completed self-report measures. Parent report (59 %) of current and childhood ADHD symptoms was also collected. Findings indicated that ADHD symptoms moderated the relation between positive alcohol expectancies and alcohol-related problems, but not the relation between expectancies and alcohol use. Additional analyses revealed that ADHD symptoms moderated the specific relation between positive expectancies and social alcohol problems (e.g., engaging in unplanned sexual behavior), but not between expectancies and internal alcohol problems (e.g., feeling sad). Moderating effects were significant even after controlling for conduct disorder symptoms and stimulant medication use. Findings have implications for the identification of college students who are at particularly high risk for heavy drinking and alcohol-related problems. Results may also aid in the development of interventions aimed at reducing risky drinking among students.

Arch Dis Child. 2012;97:A71-A72.

EDUCATIONAL PROFESSIONALS' PERCEPTIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Scott DW, Worrell-Davies A.

Aims Attention deficit hyperactivity disorder (ADHD) is a condition that attracts much media attention and controversy. A critical review of the literature found a knowledge gap regarding perceptions of ADHD, particularly teachers' opinions. The aims of this study were: 1. To elicit the views of education professionals regarding ADHD. 2. To collect information that may be used to implement targeted delivery of health education to schools.

Methods Eight educational professionals were interviewed from four schools. Interviews were conducted using a semistructured format. Interview transcripts were analysed using a qualitative framework that drew on aspects of Grounded Theory and content analysis.

Results Knowledge: Education professionals had a reasonable working understanding of ADHD, but would like more training. All were able to start the referral process for an undiagnosed child with suspected ADHD. Perceptions Several themes emerged from the data: Personalisation, Conceptualisation, Stigma,

Diagnostic Value, Benefits, Overcoming Adversity, and Relationships. Educators draw upon personal experiences to gain understanding of the condition. They think of ADHD in a practical manner, focussing on triggers, symptoms, and management strategies. They are concerned about potential labelling or stigma, but are able to see the value in the diagnosis. The educators could also see the benefits of the condition itself. They encouraged young people to achieve, and overcome any difficulties they may have. They also reflected on the importance of good relationships between all involved. Satisfaction with Services The educators were satisfied with the service they receive from local ADHD teams. They would like more training. The main complaint was about a lack of communication or information not being shared.

Conclusions All healthcare professionals should be aware of the importance of communication. They should remember the important roles that school play, and provide information where possible, whilst not compromising confidentiality. Training could be provided to educational staff in order to empower them to develop their own in-house training and management strategies for children with behavioural difficulties.

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Arch Dis Child. 2012;97:A75.

ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER-TAKING A SEXUAL HISTORY.

Onugha NN, Finlay F.

Background Adolescents are having sex and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) are no exception. A number of studies have found an increase in high-risk sexual behaviour in young people with ADHD. Sexual history taking is the first step toward providing reproductive, contraceptive and sexually transmitted disease (STD) counselling.

Methods A retrospective review of the clinical notes of fifty adolescent patients aged 12-18 years with a formal diagnosis of ADHD was carried out by two researchers. Consultations with both paediatricians and ADHD nurse specialists were reviewed from the first time the young person was seen over the age of 12 years until the last consultation, with a view to establishing whether a sexual history was taken on any occasion.

Results None of the healthcare professionals took a sexual history from any of the adolescents on any occasion despite multiple clinic attendances.

Conclusion Adolescents with ADHD are more likely to engage in high-risk sexual behaviour and it is therefore the job of paediatricians and specialist nurses to educate patients regarding their increased risk, re-evaluation of lifestyle behaviours, and preventative measures. The World Health Organisation describes sexual health as a basic human right. Adolescents with ADHD should not be denied the right to holistic healthcare.

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Arch Dis Child. 2012;97:A62.

HOW DOES SOCIO-ECONOMIC DEPRIVATION AFFECT THE PREVALENCE OF ADHD IN NORTH WEST OF ENGLAND?

Ogundele MO, DeSoysa R, Omenaka IL.

Aim This study investigated the relationship between socioeconomic deprivation and the prevalence of ADHD from cross-sectional study of 3 socio-economically distinct regions in North West of England.

Method Patients diagnosed with ADHD using standard clinical procedures based on DSM-IV criteria by the community paediatric services in Liverpool, St Helens/ Knowsley and Warrington districts were studied in relation to the census derived social deprivation data (Index of Multiple Deprivation scores 2007).

Results Warrington is a relatively affluent area while the other 2 districts are among the most deprived areas of England (table 1). The prevalence of ADHD was significantly associated with the degree of deprivation in a linear fashion in both Warrington and Liverpool districts, while showing a bimodal distribution in St Helens/Knowsley with a higher peak in the most affluent Quintiles of the community (figure 1).

Conclusion Socioeconomic deprivation appears to be significantly associated with the prevalence of ADHD in children and adolescents living in the North West of England, as demonstrated by very high coefficients of correlation (up to 1.0). A bimodal distribution of prevalence was found only in the district with

the lowest rate of ADHD prevalence. This suggests that the more affluent parents are more likely to seek for medical help and diagnosis first in the presence of limited service delivery/coverage. As the rate of diagnosis and pick-up rate improves, progressively more patients from the deprived areas of the society are diagnosed, and their overall numbers eventually surpass those of children from the more affluent backgrounds. (Figure Presented).

Arch Dis Child. 2012;97:A129.

AN AUDIT OF TRANSITIONAL CARE FOR ADOLESCENTS WITH ADHD IN A NORTH WEST ENGLAND DISTRICT.

Ogundele MO, Omenaka IL.

Aim ADHD is now considered to be a chronic neuro-developmental disorder that persists from childhood into adolescence and adulthood. We aimed to analyse the transition of adolescents diagnosed with ADHD in childhood into adult specialist ADHD services in a local district.

Methods Patients were diagnosed with ADHD using the standard DSM-IV criteria. Adolescents who were eligible for transitional to adult ADHD services were identified from a community paediatric service database. Patients who reached the age of 16 years over a period of two years consecutively (June 2010 to May 2011) were studied by a retrospective analysis of the clinical records.

Results From a total of 495 patients on the specialist ADHD database, 104 adolescents were eligible for transitional to adult services over the study period. 68 adolescents (65%) were discharged from the paediatric services, often due to voluntary discontinuation of medications and self-discharge due to non-attendance at follow-up clinics (including 2 patients who moved out of the area). 19 patients (18%) were referred to CAMHS (5 of them already discharged). Only 16 patients (15%) were successfully referred to the specialist adult ADHD services (3 of them already discharged). Only one patient still remains under the community paediatric services.

Conclusion There is a high rate of discontinuation of medications, loss to follow-up and a remarkably low rate of successful transition to locally commissioned adult ADHD services among adolescents diagnosed with ADHD in childhood. A total of 73% of eligible patients were either discharged or lost to follow-up. Establishing a formal transitional process early from the age of 13 years among patients with childhood ADHD may help minimise this high rate of attrition. There must be some flexibility in the referral pathway to the adult ADHD services so that the adolescents who were previously lost to follow-up can be re-referred by other primary or secondary care healthcare professionals if the need arises in the future.

Arch Dis Child. 2012;97:A514.

SLEEP PROBLEMS AND ADHD. EPIDEMIOLOGICAL STUDY IN SCHOOL CHILDREN IN ANDALUSIA, SPAIN.

Lora-Espinosa A, Diaz-Aguilar MJ, Jimenez-Ales R, et al.

ADHD and sleep-problems frequently overlap and their relationship is complex and bidirectional. The association between ADHD and sleep-problems has been little studied in our community. Objectives To find out the frequency of sleep-problems among ADHD children from 6-14 year old in Andalusia, Spain. Methods Prevalence study. Target population: school-students 6-14y=686.332 children; centres=2.493. Multistage cluster sampling centres=74. Method Questionnaires-DSM-IV-TR-ADHD and performance Vanderbilt-parents-and-teachers, sleep-questionnaire (BEARS), interview and medical examination. Results N=1963. Meet criteria-DSM-IV-R-ADHD=157, male=111, female=46; ADHD-IA=62, ADHD-HI=31, ADHD-C=64; control=197 Comorbidity ADHD-sleep-problems: Sleep-problems in the first year of life: 36%-ADHD, 25%-control. (p=0.03). Bedtime resistance:30%-ADHD, 6%-control.(p=0.000). Daytime sleepiness:10%-ADHD, 1.5%-control. (p=0.000). Night- Awakenings:14%-ADHD, 2%-control.(p=0.000). Snoring: 20%-ADHD, 5.6%-control.(p=0.000) Sleepwalking and sleep terrors:14%-ADHD, 2.5%-control.(p=0.000). Periodic limb movements in sleep: 51%-ADHD, 8%-control.(p=0.000). Enuresis:18%-ADHD, 4.6%-control.(p=0.000)Regular time for bed: only 36%-ADHD. Bedsharing:18%-ADHD.(greater-than or equal to) 3 sleep problems: 36%-ADHD. 12%- control. The association between ADHD subtypes and sleep-problems showed significant differences. Conclusions The children with ADHD had more sleep-

problems that control children. The relationship between sleep disorders and ADHD should be considered by paediatricians as part of the global approach to the management of ADHD.

Arch Dis Child. 2012;97:A478.

THE USE OF FATTY ACID SUPPLEMENTATION IN THE TREATMENT OF ADHD - IS THERE ANY EVIDENCE?

Damodaran S, Erumbala G, Abraham D, et al.

Attention deficit hyperactivity disorder (ADHD) is the most common behavioural disorder in children. The mainstay of treatment is stimulant drugs. There is significant interest in the role of omega 3 fatty acids in ameliorating ADHD symptoms. We reviewed the evidence from available randomized controlled trials. Clinical question In a child with ADHD (patient), will supplementation with LCPUFA (omega3) (intervention) improve symptoms (outcome)? Sources Pubmed, Sumsearch, Ovid and Cochrane library. 7 randomised control trials were analysed. Summary There was no uniformity in terms of the dose or duration of fatty acids. The criteria used for measuring outcome varied significantly. In the largest study, Sinn et al compared omega3 with omega3 and multivitamins and placebo. This study involved the longest treatment period. There was significant improvement in ability to switch and control attention. But, there was no improvement in any other cognitive measures. Richardson et al and Belanger et al reported statistically significant improvements in symptoms with higher doses of omega 3. However both used small sample size. The former study lacked robust inclusion criteria. Of the studies that used low dose regime, Gustafson et al demonstrated significant improvement in cognition, inattention and opposition while Voigt et al failed to show any. Interestingly, Hirayama et al showed improvement in the placebo group. The current available evidence is not sufficient to support the use of omega 3 fatty acid in the treatment of ADHD. More studies need to be conducted in the future using objective outcome criteria and good sample size.

Arch Dis Child. 2012;97:A44.

EFFECT OF IN UTERO EXPOSURE TO ISCHEMIC-HYPOXIC CONDITIONS ON CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Getahun D, Rhoads GG, Demissie K, et al.

Objective To examine the association between ischemic-hypoxic conditions (IHC) and Attention Deficit Hyperactivity Disorder (ADHD) by gestational age at delivery and race/ethnicity.

Methods A nested case-control study using the Kaiser Permanente Southern California (KPSC) medical records. Study cohort were children aged 5-11 years who were delivered and cared for in KPSC Healthcare system between 1995-2010 (n =308,634). Cases were children with a clinical diagnosis of ADHD and obtained at least 2 prescriptions specific to ADHD during the follow-up period. For each case, five controls matched to cases on child age at time of diagnosis were selected. Exposures were defined based on ICD-9 codes. A conditional logistic regression model was used to estimate adjusted odds ratios (OR).

Results Among eligible children, 13,613 (4.3%) had a diagnosis of ADHD. Compared to control children, case children were more likely to be male and of White or African-American race/ethnicity. Case children than controls were more likely to be exposed to IHC (OR=1.16, 95% confidence intervals [CI] 1.11-1.21). Analysis of cases and controls stratified by gestational age revealed that case children born at 28-33, 34-36, and 37-42 weeks of gestation, were significantly more likely to be exposed to IHC; 1.6-fold (95% CI, 1.2-2.2), 1.2-fold (95% CI, 1.0-1.4), and 1.1-fold (95% CI, 1.0-1.2), respectively, compared to control children. IHC was associated with increased odds of ADHD across all race/ethnicity groups.

Conclusion These findings suggest that IHC is independently associated with an increased risk of childhood ADHD especially in early preterm birth.

Asian J Pharm Clin Res. 2013;6:204-07.

CLINICAL AND CYTOGENETIC ANALYSIS OF ATTENTION DEFICIT/ HYPERACTIVITY DISORDER (ADHD) IN SOUTH INDIAN POPULATION.

Rajiv S, Sur S, Basak D, et al.

The study is to analyze the clinical and cytogenetic investigation on patients with Attention Deficit/ Hyperactivity Disorder (ADHD) from South Indian population. Cytogenetic analysis of 30 patients carried out by using human leukocyte culturing method and clinical analysis were carried out for all the cases with the help of physicians. A significantly higher number of chromosomal aberrations were observed in all patients when compared with the controls ($p < 0.001$). The detection of chromosomal anomalies as a probable cause of ADHD is very significant in genetic consultations genetic counseling, awareness and management of attention deficit children.

Asian J Psychiatry. 2013;6:235-42.

COMORBIDITY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND BIPOLAR DISORDER IN NORTH INDIAN CLINIC CHILDREN AND ADOLESCENTS.

Sivakumar T, Agarwal V, Sitholey P.

Objective: This study examined comorbidity between attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) in children attending child and adolescent psychiatry (CAP) services in a Medical University in North India.

Methods: Children attending CAP services, old or new, were assessed using unstructured clinical interview, kiddie-Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version (K-SADS-PL), Mental State Examination (MSE) for ADHD, Child Mania Rating Scale (CMRS) Parent Version and Children's Global Assessment Scale (C-GAS). Information was collected from both children and parents. All children were clinically evaluated, and prospectively followed up. The diagnosis was made by consensus. Subjects with DSM-IV-TR diagnosis of ADHD, BPD, and ADHD. +. BPD were compared with each other. Research criteria for broad phenotype BPD were applied in ADHD subjects without DSM-IV-TR diagnosis of BPD.

Results: 45 subjects had ADHD; 21, BPD and; 7 had lifetime DSM-IV-TR diagnosis of ADHD. +. BPD. 13.5% of ADHD subjects had comorbid BPD and 25% of BPD subjects had comorbid ADHD. ADHD-CT was the most common subtype of ADHD. Nearly two third of BPD subjects had their first mood episode before 13 years of age. ADHD. +. BPD subjects were more likely to be mentally retarded and have longer duration of mood episode compared to BPD subjects. Three subjects with DSM-IV-TR diagnosis of ADHD without BPD were additionally diagnosed with broad phenotype of BPD.

Conclusions: Variable comorbidity rates of ADHD. +. BPD in different studies are most likely due to differences in study setting, study sample, conceptualization of BPD and assessment methods.

BMC Psychiatry. 2013;13.

PREVALENCE OF OBESITY AND OVERWEIGHT AMONG CHINESE CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SURVEY IN ZHEJIANG PROVINCE, CHINA.

Yang R, Mao S, Zhang S, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is often comorbid with psychiatric and developmental disorders. This study aimed to investigate the prevalence of obesity and overweight among Chinese children with ADHD, and to explore which subtypes of the disorder may specifically be associated with obesity/overweight.

Methods: Children meeting the DSM-IV criteria for ADHD were enrolled in the study. Weight, weight z-score, height, height z-score, BMI, and BMI z-score were used to evaluate growth status. Obesity and overweight were determined using the National Growth Reference for Chinese Children and Adolescents. Relations between the prevalence of obesity/overweight and different ADHD subtypes and pubertal development were analyzed.

Results: A total of 158 children with ADHD (mean age: 9.2 years) were recruited for the study. The prevalences of obesity, overweight, and combined obesity/overweight were 12.0%, 17.1%, and 29.1%, respectively, which were significantly higher than in the general Chinese population (2.1%, 4.5%, and 6.6%, respectively). Multivariable analysis showed that the children with the combined subtype of ADHD and the onset of puberty were at a higher risk of becoming obese or overweight.

Conclusions: The prevalence of obesity in Chinese children with ADHD is higher than that of the general population. Children with the ADHD combined subtype who were at the onset of puberty were more likely to be overweight or obese.

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Brain Dev. 2013.

EPILEPSY ASSOCIATED WITH AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: IS THERE A GENETIC LINK?

Lo-Castro A, Curatolo P.

Autism Spectrum Disorders (ASDs) and Attention Deficit and Hyperactivity Disorder (ADHD) are the most common comorbid conditions associated with childhood epilepsy. The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, neurotransmission and functional connectivity. Rare clinically relevant chromosomal aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD comorbid with epilepsy. The majority of the candidate genes are involved in synaptic formation/remodeling/maintenance (NRX1, CNTN4, DCLK2, CNTNAP2, TRIM32, ASTN2, CTNTN5, SYN1), neurotransmission (SYNGAP1, GABRG1, CHRNA7), or DNA methylation/chromatin remodeling (MBD5). Two genetic disorders, such as Tuberous sclerosis and Fragile X syndrome may serve as models for understanding the common pathogenic pathways leading to ASDs and ADHD comorbidities in children with epilepsy, offering the potential for new biologically focused treatment options.

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Child & Youth Care Forum. 2013 Apr;42:87-99.

ELEMENTARY AND MIDDLE SCHOOL TEACHER PERCEPTIONS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER PREVALENCE.

Fabiano GA, Pelham J, Majumdar A, et al.

Background: Estimates of ADHD diagnosis and stimulant medication use vary across studies. Few studies ascertain the teacher perspective on these rates.

Objective: To ascertain teachers' perceptions of ADHD prevalence and medication treatment within their classrooms.

Method: The present school survey collected teacher report of identified children with ADHD as well as unidentified but suspected children with ADHD in an effort to determine the occurrence of ADHD and related behaviors in elementary and middle school classrooms. The number of children treated with stimulant medication was also collected. Results are grouped by elementary/middle school level.

Results: Results indicated 5.58 % of elementary and 3.53 % of middle school students were identified to the teacher as diagnosed with ADHD. A comparable number were suspected to have ADHD, but were not formally identified. Three-quarters of identified elementary school, and two-thirds of middle school students, received medication treatment. Few moderators of prevalence rates were identified.

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Child Psychiatry Hum Dev. 2013 Apr;44:290-304.

PERSISTENCE OF SLEEP PROBLEMS IN CHILDREN WITH ANXIETY AND ATTENTION DEFICIT HYPERACTIVITY DISORDERS.

Hansen BH, Skirbekk B, Oerbeck B, et al.

This study examines the persistence of sleep problems over 18 months in 76 referred children with anxiety disorders and/or attention deficit hyperactivity disorders (ADHD) and 31 nonreferred controls, and explores predictors of sleep problems at followup (T2) in the referred children. Diagnoses were assessed at initial assessment (T1) using the semi-structured interview Kaufman Schedule for Affective Disorders and Schizophrenia. Sleep problems were assessed using the Children's Sleep Habit Questionnaire at T1 and at T2. Persistence rate of total sleep problems in the clinical range was 72.4 % in referred children, and did not differ significantly between children with a T1 diagnosis of anxiety disorder (76.0 %), ADHD (70.6 %), anxiety disorder and ADHD (68.8 %) or nonreferred controls (50.0 %) The total sleep problems score at T1 significantly predicted the total sleep problems score at T2, whereas age, sex, parent education level and total number of life events did not.

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Child Health Care. 2013;42:116-33.

ASSESSING PARENTAL SLEEP ATTITUDES AND BELIEFS IN TYPICALLY DEVELOPING CHILDREN AND CHILDREN WITH ADHD AND ASD.

Bessey M, Coulombe JA, Smith IM, et al.

Sleep problems are commonly reported in children, yet often go untreated. Parental beliefs about sleep may be a contributing factor. This study developed a measure to assess these beliefs. The Sleep Attitudes and Beliefs Scale (SABS) was administered to parents of typically developing (TD) children (n=179) and children with attention deficit hyperactivity disorder (ADHD; n= 84) and autism spectrum disorder (ASD; n=92). Results indicated that the psychometric properties (i.e., inter-item reliability and Cohen's alpha) of the SABS are good and that, in comparison to the TD sample, parents of children with ADHD and ASD held beliefs that children's sleep problems were more intrinsic, less modifiable, and less responsive to treatment. Further work is required, but it is hoped that the SABS can be used both clinically, to determine factors that may contribute to and maintain children's sleep problems, and in research settings.

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Chin Med J. 2013;126:1144-49.

A DISTINCT PATTERN OF MEMORY AND ATTENTION DEFICIENCY IN PATIENTS WITH DEPRESSION.

Luo LL, Chen X, Chai Y, et al.

Background Depression related cognitive deficits are frequently considered as simple epiphenomena of the disorder. However, whether or not the depression might directly bring about cognitive deficits is still under investigation. This study was to investigate the distinct pattern of cognitive deficits in patients with depression by comparing the cognitive function before and after anti-depressive drug therapy.

Methods Sixty cases of patients, first-time diagnosed with depression, were assessed by 17-item Hamilton Rating Scale for Depression (HAMD17scale). The memory ability was tested by quantitatively clinical memory scale, while the attention ability by modified Ruff 2&7 Selective Attention Test. Forty-two healthy volunteers were recruited as controls. The depressive patients were treated with Venlafaxine (75-300 mg/d), Fluoxetine (20-40 mg/d), Paroxetine (20-40 mg/d), and Sertraline (50-150 mg/d). After 12 weeks treatment, patients were tested again by HAMD17scale, quantitatively clinical memory scale, and modified Ruff 2&7 selective attention test to assess the effect of anti-depressive drugs on cognitive deficits.

Results The memory quotient (MQ) was significantly lowered in depressive patients. The selection speed was also significantly decreased and the number of missing and error hits increased in the depression group as compared to control. However, there was no significant difference in clinical memory scale and Ruff 2&7 selective attention test between mild-to-moderate and severe depression group. Importantly, after anti-depressive drug therapy, the HAMD17 scale scores in depressive patients were significantly decreased, but the MQ, directional memory (DM), free recall (FR), associative learning (AL), and face

recognition were comparable with those before the treatment. Furthermore, the selection speed and the number of missing and error hits were also not significantly different after anti-depressive drugs treatment.

Conclusions Depressive patients suffer from short-term memory deficits, and attention extent, stability and rearrangement deficiency. Even though anti-depressive drugs sufficiently relieve the cardinal presentation of depression, they could not successfully alleviate the accompanying cognitive deficits. This might indicate a distinct pattern of cognitive deficits in patients with depression.

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Clin Neuropharmacol. 2013 Mar;36:37-41.

REBOXETINE TREATMENT FOR AUTISTIC SPECTRUM DISORDER OF PEDIATRIC PATIENTS WITH DEPRESSIVE AND INATTENTIVE/HYPERACTIVE SYMPTOMS: AN OPEN-LABEL TRIAL.

Golubchik P, Sever J, Weizman A.

Background: Reboxetine is a norepinephrine reuptake inhibitor that may be useful in treating pediatric depression as well as attention-deficit/hyperactivity disorder (ADHD). Both are often comorbid with autistic spectrum disorder (ASD). We evaluated the effectiveness of reboxetine treatment in pediatric patients with ASD with symptoms of depression and ADHD.

Method: Eleven adolescent patients with ASD (9 boys and 2 girls, aged 12.2 ± 3.6 years) with depressive and ADHD symptoms were treated with reboxetine (maximal dose, 4 mg/d) in an open-label trial during a 12-week period. The severity of depressive and ADHD symptoms was assessed by the Child Depression Rating Scale (CDRS) and Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS), respectively.

Results: Significant, but modest, decreases in the severity of depressive symptoms (CDRS before vs after scores: 65.5 ± 10.8 vs 58.3 ± 8.2 ; paired t test, 3.1; df, 10; $P = 0.01$) and ADHD symptoms (Attention Deficit/Hyperactivity Disorder Rating Scale before vs after: 36.4 ± 5 vs 32.8 ± 5 ; paired-t test, 2.94; df, 10; $P = 0.015$) were obtained after reboxetine treatment. The patients ($n = 5$) with high baseline scores of CDRS (T score >75) showed a trend toward larger response to reboxetine than those ($n = 6$) with low (T score <75) basal CDRS scores (12.8 ± 5.4 vs 2.3 ± 5.2 ; $P = 0.07$). A significant positive correlation was found between the changes in the total scores of the depression and the ADHD severity (Spearman correlation $r = 0.65$ [95% confidence interval, 0.09-0.9]; $n = 11$; $P = 0.029$). Most of the patients (approximately 90%) reported tolerable adverse effects.

Conclusions: Reboxetine treatment may reduce, modestly but significantly, depressive and ADHD symptoms in adolescents with ASD. High rate of adverse effects requires close monitoring.

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Clin Psychopharmacol Neurosci. 2013;11:13-17.

NO ASSOCIATION BETWEEN THE RESPONSE TO METHYLPHENIDATE AND DRD4 GENE POLYMORPHISM IN KOREAN ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CASE CONTROL STUDY.

Ji HS, Paik KC, Park WS, et al.

Recently the relationship between alleles frequency distribution, drug response and the attention deficit hyperactivity disorder (ADHD), has been actively researched. We investigated the association between the genetic type, alleles and drug response for the dopamine receptor D4 (DRD4) gene in ADHD patients in Korea.

Methods: One hundred fourteen patients diagnosed with ADHD according to the the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) diagnostic criteria were selected for the study. The clinical features of patients were confirmed by Korean version of Conners' parent rating scale, Attention deficit Diagnostic System, Korean version of Spielberger state-trait anxiety scale. Blood samples were taken from the 198 subjects. DNA was extracted from blood lymphocytes, PCR was performed for DRD4 Polymorphism. Alleles, genotype frequencies, the Clinical Global Impression (CGI) improvement score were compared using the chi-square test. Korean ADHD Rating Scale (K-ARS) and CGI severity scores were compared using the t-test.

Results: In comparing the ADHD with 4/4 repeats group and without the ADHD with 4/4 repeats group, no significant difference was seen between the DRD4 genetic type, alleles distribution, and CGI drug response.

Conclusion: As a result, it is viewed that there is no relationship between ADHD and DRD4, but final decision is indefinite. Follow up studies with larger patient or pure subgroups are expected.

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Compr Psychiatry. 2013.

ON THE RELATIONSHIP BETWEEN RETROSPECTIVE CHILDHOOD ADHD SYMPTOMS AND ADULT BPD FEATURES: THE MEDIATING ROLE OF ACTION-ORIENTED PERSONALITY TRAITS.

Carlotta D, Borroni S, Maffei C, et al.

A number of studies have reported data suggestive of a significant association between ADHD and BPD, nevertheless, the nature of this relation has not been fully understood yet. In our study, we tried to evaluate if the relationship between retrospectively assessed ADHD symptoms and adult BPD features could be mediated by selected temperament/personality traits. Four hundred forty-seven in- and outpatients consecutively admitted to the Clinical Psychology and Psychotherapy Unit of the Scientific Institute H San Raffaele of Milan, Italy, were administered the Italian versions of the following instruments: Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II), Wender Utah Rating Scale (WURS), Temperament and Character Inventory-Revised (TCI-R), Barratt Impulsiveness Scale-11 (BIS-11), and Aggression Questionnaire (AQ). Our mediation analyses showed that the combination of impulsivity, aggression, novelty seeking, and juvenile conduct problems completely mediate the relationship between retrospectively assessed ADHD symptoms and current BPD features.

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Cortex: A Journal Devoted to the Study of the Nervous System and Behavior. 2013 Apr;49:1025-33.

ZOOM-OUT ATTENTIONAL IMPAIRMENT IN CHILDREN WITH AUTISM SPECTRUM DISORDER.

Ronconi L, Gori S, Ruffino M, et al.

Autism spectrum disorder (ASD) has long been associated with an inability to experience wholes without full attention to the constituent parts. A zoom-out attentional dysfunction might be partially responsible for this perceptual integration deficit in ASD. In the present study, the efficiency of attentional focusing mechanisms was investigated in children affected by ASD. We measured response latencies to a visual target onset displayed at three eccentricities from the fixation. Attentional resources were focused (zoom-in) or distributed (zoom-out) in the visual field presenting a small (containing only the nearest target eccentricity) or large (containing also the farthest target eccentricity) cue, 100 or 800 msec, before the target onset. Typically developing children, at the short cue-target interval, showed a gradient effect (i.e., latencies are slower at the farthest eccentricity) in the small focusing cue, but not in the large focusing cue condition. These results indicate an efficient zoom-in and zoom-out attentional mechanism. In contrast, children with ASD showed a gradient effect also in the large focusing cue condition, suggesting a specific zoom-out attentional impairment. In addition, the ASD group showed an atypical gradient effect at the long cue-target interval only in the small cue condition, suggesting a prolonged zoom-in and sluggish zoom-out attentional mechanism. This abnormal attentional focusing – probably linked to a dysfunctional top-down feedback from fronto-parietal network to the early visual areas – could contribute to the atypical visual perception associated to individuals with ASD which, in turn, could have consequences in their social-communicative development.

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Curr Psychiatry Rep. 2013;15:1-8.

ENHANCING ADHD MEDICATION ADHERENCE: CHALLENGES AND OPPORTUNITIES.

Charach A, Fernandez R.

Safe and effective medication for attention deficit hyperactivity disorder (ADHD) is available and recommended as first-line treatment for the core symptoms of inattention, overactivity and impulsiveness. Despite impaired functioning during adolescence, many discontinue medication treatment. For children, healthcare decisions are usually made by the parent; older youth make their own decisions. Beliefs and attitudes may differ widely. Some families understand that ADHD is a neurobiological condition and accept that medication is indicated, for others, such treatment is unacceptable. Converging evidence describes negative perceptions of the burden associated with medication use as well as concerns about potential short and long term adverse effects. Indeed experiences of adverse effects are a frequent explanation for discontinuation among youth. Ways to improve shared decision making among practitioners, parents and youth, and to monitor effectiveness, safety and new onset of concurrent difficulties are likely to optimize outcomes.

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Dev Cognitive Neurosci. 2013 Apr;4:16-28.

PRELIMINARY DATA SUGGESTING THE EFFICACY OF ATTENTION TRAINING FOR SCHOOL-AGED CHILDREN WITH ADHD.

Tamm L, Epstein JN, Peugh JL, et al.

A pilot randomized clinical trial was conducted to examine the initial efficacy of Pay Attention!, an intervention training sustained, selective, alternating, and divided attention, in children diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD). After a diagnostic and baseline evaluation, school-aged children with ADHD were randomized to receive 16 bi-weekly sessions of Pay Attention! (n = 54) or to a waitlist control group (n = 51). Participants completed an outcome evaluation approximately 12 weeks after their baseline evaluation. Results showed significant treatment effects for parent and clinician ratings of ADHD symptoms, child self-report of ability to focus, and parent ratings of executive functioning. Child performance on neuropsychological tests showed significant treatment-related improvement on strategic planning efficiency, but no treatment effects were observed on other neuropsychological outcomes. Treatment effects were also not observed for teacher ratings of ADHD. These data add to a growing body of literature supporting effects of cognitive training on attention and behavior, however, additional research is warranted.

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Epilepsy Behav. 2013;27:443-48.

EEG IMPROVEMENTS WITH ANTIEPILEPTIC DRUG TREATMENT CAN SHOW A HIGH CORRELATION WITH BEHAVIORAL RECOVERY IN CHILDREN WITH ADHD.

Kanemura H, Sano F, Tando T, et al.

We investigated the relationship between neuropsychological disturbance, assessed using the global assessment of functioning (GAF) and the ADHD-rating scale (ADHD-RS), paroxysmal EEG abnormalities, and treatment with valproate sodium (VPA) in children with both attention deficit hyperactivity disorder (ADHD) and paroxysmal abnormality (PA). Participants with ADHD but without obvious epilepsy were recruited between April 1, 2003 and March 31, 2008. Paroxysmal abnormality was scored by measuring the spike frequency. Of 46 children, 16 showed PA; 3 of the 16 were excluded because no follow-up EEG was available. The EEG improved with VPA treatment in 5 of 8 patients with frontal PA and 3 of 5 patients with rolandic PA. While 83.3% of the patients with improvements in both assessments had frontal PA, only 16.7% had rolandic PA. The patients with frontal PA showed a significantly higher correlation between PA frequency and improvement in ADHD-RS compared with those with rolandic PA. In this study of children with ADHD, EEG improvement with antiepileptic drug treatment showed a high correlation with behavioral

improvements as shown by ADHD-RS and GAF scores. However, this was not a population-based study, and the relative importance of detecting and treating PA in ADHD has yet to be determined.

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Eur Child Adolesc Psychiatry. 2013;22:153-64.

ASSOCIATION OF ADHD SYMPTOMS AND SOCIAL COMPETENCE WITH COGNITIVE STATUS IN PRESCHOOLERS.

Ramos R, Freire C, Julvez J, et al.

We aimed to investigate the association of attention-deficit hyperactivity disorder (ADHD) symptoms and social competence outcomes with cognitive status in preschool children. The study population was drawn from three birth cohorts belonging to the Spanish INMA (Infancia y Medio Ambiente) project: Menorca (n = 289), Ribera d'Ebre (n = 60), and Granada (n = 108). Children were assessed at the age of 4 years for cognitive functions (McCarthy Scales of Children's Abilities, MSCA) by psychologists and for inattention and hyperactivity symptoms (ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, ADHD-DSM-IV) and social competence (California Preschool Social Competence Scale) by their teachers. Multiple regression analyses were conducted to examine potential associations between behavioral outcomes (ADHD symptoms and social competence) and MSCA cognitive outcomes, adjusting for confounders. The presence of general ADHD symptoms (inattention, hyperactivity, or both) and poorer social competence both showed negative associations with cognitive outcomes. When we compared children according to ADHD subtypes, those with inattention symptoms alone and those with both inattention and hyperactivity symptoms showed significantly lower cognitive function scores in comparison to children with no ADHD symptoms. Behavioral dysfunctions in preschoolers may be associated with impairment of cognitive functions.

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Eur Child Adolesc Psychiatry. 2013;22:203-16.

HOW EFFECTIVE ARE DRUG TREATMENTS FOR CHILDREN WITH ADHD AT IMPROVING ON-TASK BEHAVIOUR AND ACADEMIC ACHIEVEMENT IN THE SCHOOL CLASSROOM? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Prasad V, Brogan E, Mulvaney C, et al.

Attention-deficit hyperactivity disorder (ADHD) has a significant impact on children's classroom behaviour, daily functioning and experience of school life. However, the effects of drug treatment for ADHD on learning and academic achievement are not fully understood. This review was undertaken to describe the effects of methylphenidate, dexamfetamine, mixed amphetamine salts and atomoxetine on children's on-task behaviour and their academic performance, and to perform a meta-analysis to quantify these effects. Nine electronic databases were systematically searched for randomized controlled trials comparing drug treatment for ADHD against (i) no drug treatment, (ii) baseline (in crossover trials), or (iii) placebo; reporting outcomes encompassing measures of educational achievement within the classroom environment. Forty-three studies involving a pooled total of 2,110 participants were identified for inclusion. Drug treatment benefited children in the amount of school work that they completed, by up to 15 %, and less consistently improved children's accuracy in specific types of academic assignments, such as arithmetic. Similar improvements were seen in classroom behaviour, with up to 14 % more of children's time spent "on task". Methylphenidate, dexamfetamine and mixed amphetamine formulations all showed beneficial effects on children's on-task behaviour and academic work completion. Atomoxetine was examined in two studies, and was found to have no significant effect. These review findings suggest that medication for ADHD has the potential to improve children's learning and academic achievement.

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Eur Child Adolesc Psychiatry. 2013;1-11.

RESPONSE TIME INTRA-SUBJECT VARIABILITY: COMMONALITIES BETWEEN CHILDREN WITH AUTISM SPECTRUM DISORDERS AND CHILDREN WITH ADHD.

Adamo N, Huo L, Adelsberg S, et al.

Despite the common co-occurrence of symptoms of attention deficit hyperactivity disorder (ADHD) in individuals with autism spectrum disorders (ASD), the underlying mechanisms are under-explored. A potential candidate for investigation is response time intra-subject variability (RT-ISV), a hypothesized marker of attentional lapses. Direct comparisons of RT-ISV in ASD versus ADHD are limited and contradictory. We aimed to examine whether distinct fluctuations in RT-ISV characterize children with ASD and with ADHD relative to typically developing children (TDC). We applied both a priori-based and data-driven strategies to RT performance of 46 children with ASD, 46 with ADHD, and 36 TDC (aged 7-11.9 years). Specifically, we contrasted groups relative to the amplitude of four preselected frequency bands as well as to 400 frequency bins from 0.006 to 0.345 Hz. In secondary analyses, we divided the ASD group into children with and without substantial ADHD symptoms (ASD+ and ASD-, respectively). Regardless of the strategy employed, RT-ISV fluctuations at frequencies between 0.20 and 0.345 Hz distinguished children with ADHD, but not children with ASD, from TDC. Children with ASD+ and those with ADHD shared elevated amplitudes of RT-ISV fluctuations in frequencies between 0.18 and 0.345 Hz relative to TDC. In contrast, the ASD- subgroup did not differ from TDC in RT-ISV frequency fluctuations. RT-ISV fluctuations in frequencies 0.18-0.345 Hz (i.e., periods between 3 and 5 s) are associated with ADHD symptoms regardless of categorical diagnosis and may represent a biomarker. These results suggest that children with ADHD and those with ASD+ share common underlying pathophysiological mechanisms of RT-ISV.

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Eur Child Adolesc Psychiatry. 2013;1-8.

EFFICACY OF LISDEXAMFETAMINE DIMESYLATE THROUGHOUT THE DAY IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: RESULTS FROM A RANDOMIZED, CONTROLLED TRIAL.

Coghill DR, Banaschewski T, Lecendreux M, et al.

Lisdexamfetamine dimesylate (LDX) is a long-acting, prodrug stimulant therapy for patients with attention-deficit/hyperactivity disorder (ADHD). This randomized placebo-controlled trial of an optimized daily dose of LDX (30, 50 or 70 mg) was conducted in children and adolescents (aged 6-17 years) with ADHD. To evaluate the efficacy of LDX throughout the day, symptoms and behaviors of ADHD were evaluated using an abbreviated version of the Conners' Parent Rating Scale-Revised (CPRS-R) at 1000, 1400 and 1800 hours following early morning dosing (0700 hours). Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference treatment, but the study was not designed to support a statistical comparison between LDX and OROS-MPH. The full analysis set comprised 317 patients (LDX, n = 104; placebo, n = 106; OROS-MPH, n = 107). At baseline, CPRS-R total scores were similar across treatment groups. At endpoint, differences (active treatment - placebo) in least squares (LS) mean change from baseline CPRS-R total scores were statistically significant ($P < 0.001$) throughout the day for LDX (effect sizes: 1000 hours, 1.42; 1400 hours, 1.41; 1800 hours, 1.30) and OROS-MPH (effect sizes: 1000 hours, 1.04; 1400 hours, 0.98; 1800 hours, 0.92). Differences in LS mean change from baseline to endpoint were statistically significant ($P < 0.001$) for both active treatments in all four subscales of the CPRS-R (ADHD index, oppositional, hyperactivity and cognitive). In conclusion, improvements relative to placebo in ADHD-related symptoms and behaviors in children and adolescents receiving a single morning dose of LDX or OROS-MPH were maintained throughout the day and were ongoing at the last measurement in the evening (1800 hours).

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Eur Child Adolesc Psychiatry. 2013;22:199-202.

IS THERE A FUTURE FOR RESTRICTED ELIMINATION DIETS IN ADHD CLINICAL PRACTICE?

Rommelse N, Buitelaar J.

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Eur Neuropsychopharmacol. 2013;23:542-54.

LONG-TERM RELATIONSHIP BETWEEN METHYLPHENIDATE AND TOBACCO CONSUMPTION AND NICOTINE CRAVING IN ADULTS WITH ADHD IN A PROSPECTIVE COHORT STUDY.

Bron TI, Bijlenga D, Kasander MV, et al.

Patients with Attention-Deficit/Hyperactivity disorder (ADHD) have higher smoking rates, a younger age of smoking onset, and increased difficulty to stop smoking as compared to controls. Methylphenidate induced acute effects of increased smoking in laboratory studies, but long-term effects are unknown. We studied the acute and long-term relationship between methylphenidate use and tobacco consumption and nicotine craving among ADHD patients naive for methylphenidate (. N=325). Patients filled out the Smoking Questionnaire (SQ) at baseline, and after two-weeks and three-months of methylphenidate use. The SQ involved questions on demographics, tobacco consumption, nicotine craving, life events, psychiatric diagnoses and use of medication. At baseline, smoking prevalence of ADHD patients was twice as high (50.2%) as the national norm (25.6%; $p < .001$). Tobacco consumption increased with 1.3 cigarettes per day after three-months of methylphenidate use. When translated into pack years, tobacco consumption increased by about 23 packs per year. Reports of increased nicotine craving after methylphenidate, increased with 20.3% after two weeks and 29.2% after three months. Light smokers (1-12 cigarettes/day) were especially at risk for increased tobacco consumption (. $p < .05$). Thus although methylphenidate is the drug of choice in medical treatment for ADHD, tobacco consumption and nicotine craving increased acutely and stabilized at increased levels after three-months of methylphenidate use. Although the net effect of methylphenidate on smoking behavior and craving should be further investigated within a randomized, placebo-controlled design, the results suggest that active prevention of increased smoking is needed in patients prescribed methylphenidate.

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Indian J Pediatr. 2013;80:207-10.

PREVALENCE OF PARENT-RATED ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ASSOCIATED PARENT-RELATED FACTORS IN PRIMARY SCHOOL CHILDREN OF NAVI MUMBAI - A SCHOOL BASED STUDY.

Ajinkya S, Kaur D, Gursale A, et al.

Objectives: To study the prevalence of parent-rated attention deficit hyperactivity disorder and associated parent-related factors in primary school children of Navi Mumbai.

Methods: One hundred twenty two children including both boys and girls aged between 6 y and 11 y were selected from a school at Navi Mumbai and their parents were given the National Innovative for Children's Healthcare Quality (NICHQ) Vanderbilt Assessment Scale to be filled and returned, which was subsequently analyzed using SPSS (version 16).

Results: The prevalence of attention deficit hyperactivity disorder was 12.3 % with boy to girl ratio of 3:2. It was more prevalent in nuclear type of family and in families where a single parent was working especially where the father was the sole breadwinner and doing semi-skilled or unskilled type of work. No significant relation was found between the numbers of work-related hours when parents were away from children and attention deficit hyperactivity disorder.

Conclusions: Attention deficit hyperactivity disorder is prevalent in the primary school-going population of Navi Mumbai, especially in boys. The increased prevalence in nuclear families and families with single working parent should further be explored. Further studies with larger sample size and longer period of follow up may be recommended. The study also recommends screening of school children for symptoms of attention deficit hyperactivity disorder (ADHD) for early diagnosis and treatment.

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Int J Cardiol. 2013.

DRUGS FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER DO NOT INCREASE THE MID-TERM RISK OF SUDDEN DEATH IN CHILDREN: A META-ANALYSIS OF OBSERVATIONAL STUDIES.

Mazza M, D'Ascenzo F, Davico C, et al.

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Int J Pediatr Endocrinol. 2012;2012.

WEIGHT LOSS ON STIMULANT MEDICATION: HOW DOES IT AFFECT BODY COMPOSITION AND BONE METABOLISM? - A PROSPECTIVE LONGITUDINAL STUDY.

Poulton A, Briody J, McCorquodale T, et al.

Objective: Children treated with stimulant medication for attention deficit hyperactivity disorder (ADHD) often lose weight. It is important to understand the implications of this during growth. This prospective study was designed to quantify the changes in body composition and markers of bone metabolism on starting treatment.

Methods: 34 children (29 boys) aged 4.7 to 9.1 years newly diagnosed with ADHD were treated with dexamphetamine or methylphenidate, titrating the dose to optimise the therapeutic response. Medication was continued for as long as clinically indicated. Body composition and bone density (dual-energy X-ray absorptiometry) were measured at baseline, 6 months and 3 years; changes were analysed in Z-scores based on data from 241 healthy, local children. Markers of bone turnover were measured at baseline, 3 months and 3 years.

Results: Fat loss of 1.4(plus or minus) 0.96kg (total fat 5.7(plus or minus) 3.6 to 4.3 (plus or minus) 3.1kg, $p<0.001$) occurred in the first 6 months. There were significant reductions over 3 years in the sex and height corrected Z-scores for lean tissue, bone mineral content, bone mineral density and ratio of central to total fat (-0.84(plus or minus) 0.86, $p=0.003$; -0.55 (plus or minus) 0.31, $p<0.0001$; -0.41(plus or minus) 0.28, $p<0.0001$ and -0.55(plus or minus) 0.62, $p=0.006$ respectively). Propeptide of type I collagen indicated a significant reduction in bone turnover after 3 months (564(plus or minus) 202 to 458(plus or minus) 96ng/ml, $p=0.019$), which was fully recovered after 3 years (619(plus or minus) 276ng/ml).

Conclusions: Stimulant medication was associated with early fat loss and reduced bone turnover. Lean tissue including bone increased more slowly over 3 years of continuous treatment than would be expected for growth in height. There was long-term improvement in the proportion of central fat for height. This study shows that relatively minor reductions in weight on stimulant medication can be associated with long-term changes in body composition. Further study is required to determine the effects of these changes on adult health.

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Int J Pediatr Otorhinolaryngol. 2013.

THE PREVALENCE OF PSYCHIATRIC SYMPTOMS IN PRESCHOOL CHILDREN WITH ADENOTONSILLAR HYPERTROPHY.

Soylu E, Soyly N, Yildirim YS, et al.

Objectives: The aim of this study was to determine the prevalence of psychiatric disorders and symptoms in preschool-age children who are indicated for operation due to adenotonsillar hypertrophy.

Materials and methods: Forty-eight patients between the ages of three and five years with indication for adenotonsillectomy were included in the study, as well as 40 control patients. Cases underwent routine ear nose throat (ENT) examination, flexible nasopharyngoscopy and tympanometry. The Early Childhood Inventory-4 (ECI-4) parent form and Strengths and Difficulties Questionnaire (SDQ) parent form were completed by the parent caring for the child. The SPSS for Windows 16.0 program was used for statistical analysis.

Results: Groups were compared according to they received at least one psychiatric diagnosis measured by ECI-4, the group of adenotonsillar hypertrophy was diagnosed more than the control group. Attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and sleep disorders were detected at a higher rate in patients with adenotonsillar hypertrophy. It also was established that in the

comparison of the severity of psychiatric symptoms determined by ECI-4, symptom severity of ADHD, ODD, anxiety disorders, and sleep disorders was higher in the adenotonsillar hypertrophy group than in the control group. In the evaluation of the SDQ parent form, it was determined that attention deficit, hyperactivity, behavioral, and peer relations problems occurred more frequently in the adenotonsillar hypertrophy group.

Conclusions: In addition to oral respiration, snoring, and disordered breathing during sleep, adenotonsillar hypertrophy may also be associated with psychiatric disorders and symptoms.

Int J Psychophysiol. 2013;87:340-48.

EVENT-RATE EFFECTS IN THE FLANKER TASK: ERPs AND TASK PERFORMANCE IN CHILDREN WITH AND WITHOUT AD/HD.

Johnstone SJ, Galletta D.

Demanding tasks require a greater amount of effort, in which case individuals are required to alter their energetic-state to a level appropriate to perform the task. According to the Cognitive-Energetic Model (CEM), children with AD/HD are unable to effectively modulate their energetic state, leading to task underperformance. Using an Eriksen flanker task with varying event-rates, the current study compared the ability of typically-developing children and children with AD/HD to modulate their energetic state. In line with the CEM, it was predicted that children with AD/HD would underperform in the fast and slow event-rates. Results indicated that the groups did not differ in commission errors (i.e., incorrect responses). However, children with AD/HD made more omission errors to incongruent stimuli at the fast and slow event-rates, compared to controls. N2 amplitude was significantly larger for the AD/HD than control group in the slow event-rate. It is concluded that the energetic state modulation dysfunction in children with AD/HD results in an inability to attend to the task, as opposed to an inability to perform the task itself. Furthermore, these task performance differences did not manifest in either the N2 or P3 ERP components. Therefore, inattention in children with AD/HD may have its locus in response preparation, as opposed to stimulus processing, but more research is required to validate these conjectures.

Ir J Med Sci. 2013 Jun;182:237-43.

PRIMARY CARE SUPPORT FOR YOUTH MENTAL HEALTH: A PRELIMINARY EVIDENCE BASE FOR IRELAND'S MID-WEST.

Healy D, Naqvi S, Meagher D, et al .

BACKGROUND: Mental and substance use disorders are leading causes of morbidity. Prevention/treatment amongst young people are global health priorities. International data have highlighted primary care and general practice as important in addressing these.

AIMS: Survey of 128 physicians (GPs) in Ireland's Mid-West (Counties Limerick, Clare, North Tipperary) to document the spectrum of youth mental health problems, describe strategies adopted by GPs in dealing with these, identify barriers (perceived by GPs) to effective care of young mental health patients and collate GP proposals for improved care of this cohort.

METHODS: Self-administered questionnaire on physician and practice demographics, case management and barriers to care in youth mental health.

RESULTS: Thirty-nine GPs (31 %) responded. Mental health and family conflict represented the most frequent reasons why young people attended GPs. Depression, anxiety, family conflict, suicidal thoughts/behaviour, and attention deficit hyperactivity disorder (ADHD) were the most common issues followed by substance abuse and antisocial behaviours. GP referral practices for young people with mental/substance use disorders varied, with distinctions between actual and preferred management due to insufficient access to dedicated youth services and training. GPs stated need for improved access to existing services (i.e., Psychiatry, counseling/psychology, social/educational interventions). A number of GPs surveyed were located, or provided care, in Limerick's 'Regeneration Areas'. Young people in these areas predominantly attended GPs due to mental/substance use issues and antenatal care, rather than acute or general medical problems.

CONCLUSIONS: GPs play an important role in meeting youth mental health needs in this region and, in particular, in economically deprived urban areas

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JAMA. 2013 May;309:1843.

JAMA PATIENT PAGE. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Goodman DM, Livingston EH.

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J Abnorm Child Psychol. 2013 Apr;41:485-95.

INCREASED INTRASUBJECT VARIABILITY IN BOYS WITH ADHD ACROSS TESTS OF MOTOR AND COGNITIVE CONTROL.

Shiels Rosch K, Dirlikov B, Mostofsky SH.

Increased intrasubject variability (ISV), or short-term, within-person fluctuations in behavioral performance is consistently found in Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is also associated with impairments in motor control, particularly in boys. The results of the few studies that have examined variability in self-generated motor output in children with ADHD have been inconsistent. The current study examined variability in motor control during a finger sequencing task among boys with and without ADHD as well as the relationship between intrasubject variability during motor and cognitive control tasks. Changes in performance over the course of the task and associations with ADHD symptom domains were also examined to elucidate the nature of impaired motor control in children with ADHD. Fifty-one boys (ages 8 to 12 years) participated in the study, including 28 boys with ADHD and 23 typically developing (TD) boys. Participants completed a finger sequencing task and a Go/No-Go task providing multiple measures of response speed and variability. Boys with ADHD were slower and more variable in both intertap interval on the finger sequencing task and reaction time on the Go/No-Go task, with measures of speed and variability correlated across the two tasks. For the entire cohort, the only unique predictor of parent ratings of hyperactive-impulsive symptoms was variability in intertap interval during finger sequencing, whereas inattentive symptoms were only predicted by reaction time variability on the Go/No-Go task. These findings suggest that inefficient motor control is implicated in the pathophysiology of ADHD, particularly in regards to developmentally inappropriate levels of hyperactivity and impulsivity.

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J Abnorm Child Psychol. 2013 Apr;41:473-83.

READING COMPREHENSION IN CHILDREN WITH ADHD: COGNITIVE UNDERPINNINGS OF THE CENTRALITY DEFICIT.

Miller AC, Keenan JM, Betjemann RS, et al.

We examined reading comprehension in children with ADHD by assessing their ability to build a coherent mental representation that allows them to recall central and peripheral information. We compared children with ADHD (mean age 9.78) to word reading-matched controls (mean age 9.89) on their ability to retell a passage. We found that even though children with ADHD recalled more central than peripheral information, they showed their greatest deficit, relative to controls, on central information—a centrality deficit (Miller and Keenan, *Annals of Dyslexia* 59:99–113, 2009). We explored the cognitive underpinnings of this deficit using regressions to compare how well cognitive factors (working memory, inhibition, processing speed, and IQ) predicted the ability to recall central information, after controlling for word reading ability, and whether these cognitive factors interacted with ADHD symptoms. Working memory accounted for the most unique variance. Although previous evidence for reading comprehension difficulties in children with ADHD have been mixed, this study suggests that even when word reading ability is controlled, children with ADHD have difficulty building a coherent mental representation, and this difficulty is likely related to deficits in working memory.

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J Abnorm Child Psychol. 2013 Apr;41:497-507.

RESPONSE INHIBITION AND ADHD TRAITS: CORRELATES AND HERITABILITY IN A COMMUNITY SAMPLE.

Crosbie J, Arnold P, Paterson A, et al.

Endophenotypes or intermediate phenotypes are of great interest in neuropsychiatric genetics because of their potential for facilitating gene discovery. We evaluated response inhibition, latency and variability measures derived from the stop task as endophenotypes of ADHD by testing whether they were related to ADHD traits in the general population, heritable and shared genetic risk with ADHD traits. Participants were 16,099 children and adolescents, ages 6 to 18 years who visited a local science center. We measured ADHD traits using the Strengths and Weaknesses of ADHD-symptoms and Normal-Behavior (SWAN) rating scale and performance on the stop signal task (SST)—response inhibition (SSRT), response latency (GoRT), and response variability (GoRTSD). Regression analysis was used to assess the relationship of cognitive measures and ADHD traits while controlling for family, age, sex, ethnicity, socioeconomic status and treatment status. Heritability of ADHD and cognitive traits was estimated using SOLAR in 7,483 siblings from 3,507 families that included multiple siblings. Bivariate relationships between pairs of variables were examined. Individuals with greater ADHD trait scores had worse response inhibition, slower response latency, and greater variability. Younger participants and girls had inferior performance although the gender effects were minimal and evident in youngest participants. Inhibition, latency, variability, total ADHD traits, inattention and hyperactivity-impulsivity scores were significantly heritable. ADHD traits and inhibition, but not latency or variability were coheritable. In the largest study in the general population, we found support for the validity of response inhibition as an endophenotype of ADHD.

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J Abnorm Psychol. 2013 May;122:558-65.

ANTERIOR CINGULATE CORTEX AND SYMPTOM SEVERITY IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bledsoe JC, Semrud-Clikeman M, Pliszka SR.

The cause of attention-deficit/hyperactivity disorder (ADHD) has been linked to abnormalities in prefrontal-striatal-cerebellar networks, but the brain-behavioral correlates are relatively equivocal. Children with ADHD and healthy controls underwent MRI and neuropsychological testing. Brain cortical thickness was analyzed for the bilateral rostral and caudal anterior cingulate cortex (ACC). Inhibitory control was assessed with the Stroop Inhibition test, and ADHD symptom severity was assessed with parent and teacher behavioral questionnaires. Brain-behavior relationships were calculated between cortical thickness and behavioral measures with regression models. Children with ADHD had significant cortical thinning in the right rostral ACC but nonsignificant thinning in right caudal, left caudal, or left rostral ACC compared with healthy control children after statistical correction for multiple comparisons. Further, right rostral ACC thickness predicted a significant amount of the variance in parent- and teacher-reported symptoms of ADHD. Exploratory analysis showed that cortical thickness was not related to psychostimulant medication history. Symptoms of ADHD may be related to reductions in cortical thickness in the right anterior attention network, a region implicated in behavioral error detection, impulsivity, and inhibitory control.

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J Adolesc Health. 2013;52:606-12.

CHILDHOOD BEHAVIOR PROBLEMS AND ADOLESCENT SEXUAL RISK BEHAVIOR: FAMILIAL CONFOUNDING IN THE CHILD AND ADOLESCENT TWIN STUDY IN SWEDEN (CATSS).

Donahue KL, Lichtenstein P, Lundstrom S, et al.

Objective: Previous studies have found associations between childhood behavior problems and adolescent sexual risk behavior. Using a quasi-experimental approach, we examined the extent to which this association may be due to between-family differences (i.e., unmeasured familial confounds) not adequately explored in prior research.

Methods: We used data from a longitudinal, population-based cohort of young twins in Sweden (first assessment: age 9 or 12 years; second assessment: age 15; n = 2,388). We explored the nature of the association between symptom scores for attention deficit hyperactivity disorder (ADHD), oppositional

defiant disorder (ODD), and conduct disorder (CD) at age 9 or 12 and the likelihood of having had sexual intercourse and number of sexual partners by age 15. Two-level mixed-effects models were used to estimate the effect of symptom score on each outcome after controlling for potential unmeasured familial confounds.

Results: Higher ADHD, ODD, and CD scores were associated with significantly increased likelihood of sexual intercourse by age 15. Higher ADHD and ODD scores were also associated with increased number of sexual partners. After controlling for unmeasured familial confounds, however, behavior problems were no longer significantly associated with either outcome.

Conclusion: The association between childhood behavior problems and sexual risk behaviors may be due to characteristics shared within families. Hence, prevention strategies aimed at reducing these behaviors might need to address broader risk factors that contribute to both behavior problems and a greater likelihood of sexual risk behavior.

J Affective Disord. 2013.

FAMILY FUNCTIONING DEFICITS IN BIPOLAR DISORDER AND ADHD IN YOUTH.

Young ME, Galvan T, Reidy BL, et al.

Background: Rates of diagnosis and treatment for bipolar disorder (BD) in youth continue to rise. Researchers and clinicians experience difficulty differentiating between BD in youth and other conditions that are commonly comorbid or share similar clinical features with BD, especially attention-deficit/hyperactivity disorder (ADHD). Comparative studies of the phenomenology and psychosocial correlates of these conditions help to address this. Family functioning is an important topic for both BD and ADHD since both are associated with numerous family-related deficits. One previous study suggested that manic/hypomanic youths' family functioning differed from ADHD and typically developing control (TDC) groups. However, many family functioning studies with BD and ADHD youth have methodological limitations or fail to use comprehensive, validated measures.

Methods: This investigation used an adolescent report on the Family Assessment Device (FAD), based on the McMaster Model of family functioning. Youth were recruited in BD (n=30), ADHD (n=36), and TDC (n=41) groups.

Results: Groups were similar on most demographic variables, but the TDC group scored somewhat higher than the others on IQ and socioeconomic status. FAD results indicated that BD and ADHD groups scored worse than TDC on the General Functioning and Roles scales of the FAD. In addition, the BD group showed impairment on the Problem Solving scale relative to TDC.

Limitations: sample size, lack of parent report, ADHD comorbidity in BD group.

Conclusions: Family functioning deficits distinguish both clinical groups from TDC, and problem-solving dysfunction may be specific to BD. These findings may apply to treatment models for both conditions.

J Autism Dev Disord. 2013;43:1065-79.

THE SPECIFICITY OF INHIBITORY IMPAIRMENTS IN AUTISM AND THEIR RELATION TO ADHD-TYPE SYMPTOMS.

Sanderson C, Allen ML.

Findings on inhibitory control in autism have been inconsistent. This is perhaps a reflection of the different tasks that have been used. Children with autism (CWA) and typically developing controls, matched for verbal and non-verbal mental age, completed three tasks of inhibition, each representing different inhibitory subcomponents: Go/No-Go (delay inhibition), Dog-Pig Stroop (conflict inhibition), and a Flanker task (resistance to distractor inhibition). Behavioural ratings of inattention and hyperactivity/impulsivity were also obtained, as a possible source of heterogeneity in inhibitory ability. CWA were only impaired on the conflict inhibition task, suggesting that inhibitory difficulty is not a core executive deficit in autism. Symptoms of inattention were related to conflict task performance, and thus may be an important predictor of inhibitory heterogeneity.

J Autism Dev Disord. 2013;43:1157-70.

A COMPARISON OF SOCIAL COGNITIVE PROFILES IN CHILDREN WITH AUTISM SPECTRUM DISORDERS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A MATTER OF QUANTITATIVE BUT NOT QUALITATIVE DIFFERENCE?

Demopoulos C, Hopkins J, Davis A.

The aim of this study was to compare social cognitive profiles of children and adolescents with Autism Spectrum Disorders (ASD) and ADHD. Participants diagnosed with an ASD (n=137) were compared to participants with ADHD (n=436) on tests of facial and vocal affect recognition, social judgment and problem-solving, and parent- and teacher-report of social functioning. Both groups performed significantly worse than the normative sample on all measures. Although the ASD group had more severe deficits, the pattern of deficits was surprisingly similar between groups, suggesting that social cognitive deficit patterns may be more similar in ASD and ADHD than previously thought. Thus, like those with ASDs, individuals with ADHD may also need to be routinely considered for treatments targeting social skills.

J Child Adolesc Psychopharmacol. 2013;23:252-61.

FAST VS. SLOW SWITCHING FROM STIMULANTS TO ATOMOXETINE IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Cardo E, Porsdal V, Quail D, et al.

Objective: To compare fast versus slow switching from stimulants to atomoxetine (ATX) in children and adolescents with attention-deficit/ hyperactivity disorder (ADHD).

Methods: This was a randomized, controlled, open-label study in 6-16-year-old ADHD patients, previously treated with stimulants and cross-titrated (fast switch, over 2 weeks, or slow switch, over 10 weeks) to ATX because of unsatisfactory response and/or adverse events. Study duration was 14 weeks with an ATX standard target dose of 1.2 mg/kg/day. Primary measure was the change from baseline in the investigator-rated ADHD-Rating Scale (ADHD-RS) at weeks 2 and 10. Secondary measures included Global Impression of Perceived Difficulties (GIPD) and Child Health and Illness Profile-Child Edition (CHIP-CE).

Results: The majority of the 111 patients were male (83.8%, n=93) and mean (SD) age was 11.5 (2.38) years. Mean baseline ADHD-RS total score was 36.0 in the fast and 38.0 in the slow group. Adjusted mean change after 2 weeks was -8.1 (-10.1;-6.1) in the fast and -8.0 (-9.9;-6.0) in the slow group (p=0.927), and after 10 weeks -15.0 (-17.4;-12.6) and -14.3 (-16.7;-12.0), respectively, (p=0.692). GIPD scores did not show differences between groups. Significant differences at week 10 were found in the CHIP-CE achievement domain favoring slow (p=0.036) and the comfort domain favoring fast cross-titration (p=0.030). No significant differences were found for adverse events, and differences for systolic blood pressure (BP) and weight were not considered clinically relevant.

Conclusions: ADHD-RS and GIPD scores improved in both switching groups. No clinically relevant differences between fast and slow switching from stimulants to ATX were found.

J Child Adolesc Psychopharmacol. 2013;23:200-07.

CLINICAL OUTCOMES FROM AN OPEN-LABEL STUDY OF EDIVOXETINE USE IN PEDIATRIC PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Jin L, Xu W, Krefetz D, et al.

Objective: The purpose of this study was to assess the clinical outcomes from an open label study of edivoxetine, a selective norepinephrine reuptake inhibitor, in pediatric patients with attention-deficit/hyperactivity disorder (ADHD).

Methods: This was a multi-cohort open-label study of edivoxetine consisting of a single-dose administration period (Part 1) and an open-label once daily (QD) dose long-term period (Part 2). Adolescents ages 12-17 years and children ages 6-11 years were enrolled in Part 1 and continued to Part 2 where they received 0.05 to 0.3 mg/kg edivoxetine QD for (less-than or equal to) 12 months. Safety was assessed by adverse events, vital signs, weight, electrocardiograms, and laboratory tests. In Part 2,

Attention-Deficit/Hyperactivity Disorder Rating Scale-Version IV-Parent Reported: Investigator Scored (ADHDRS-IV) and Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) scores were determined.

Results: Fifty-three patients enrolled in Part 1, and 49 continued to Part 2 with a mean exposure duration of 22 weeks. The 31 patients completing Part 2 then entered another long-term open-label study. One serious adverse event of mania was reported; all other treatment-emergent adverse events were mild or moderate in severity. Nausea, decreased appetite, somnolence, increased blood pressure, and upper respiratory tract infection were most frequently reported (three events each). No clinically relevant changes were noted in the laboratory parameters. ADHDRS-IV total score, inattention and hyperactivity/impulsivity subscores, and CGI-ADHD-S scores were statistically significantly improved at endpoint compared with baseline.

Conclusions: This study provides preliminary evidence to suggest that edivoxetine at doses (less-than or equal to) 0.3 mg/kg/day is safe and may improve ADHD symptoms in pediatric patients. These results require confirmation in larger, double-blind, placebo-controlled trials.

J Child Adolesc Psychopharmacol. 2013 Mar;23:91-100.

THE IRON STATUS OF CHILDREN AND YOUTH IN A COMMUNITY MENTAL HEALTH CLINIC IS LOWER THAN THAT OF A NATIONAL SAMPLE.

Gottfried RJ, Gerring JP, Machell K, et al.

Objective: Iron plays a key role in brain function, and a deficiency of iron has been implicated in various cognitive, motor, and psychiatric disorders. Because of recent evidence that iron deficiency may be related to attention-deficit/hyperactivity disorder (ADHD) and other psychiatric disorders, the goal of this study was to compare the iron status of children and youth seen in a community mental health clinic with a national sample of same-aged subjects.

Methods: In this study, a consecutive series of 108 patients (79 males) referred to a community mental health clinic was compared with a National Health and Nutrition Examination Survey (NHANES) sample on measures of iron status. Wilcoxon sign rank and median tests were used to compare distributions of ferritin. Quantile regression was performed to compare the ferritin level in the two samples while adjusting for demographic differences. Chi squared (χ^2) was used to compare rates of low hemoglobin in the two samples.

Results: The iron status of the clinic sample, as measured by ferritin levels (median = 23 $\mu\text{g/L}$), was significantly lower than that of the national sample (median = 43 $\mu\text{g/L}$). After adjustment for age, gender, and race, the clinic sample was found to have 19.2 $\mu\text{g/L}$ lower ferritin than the national sample (95%CI from 7.6 to 30.9, p value = 0.001). There were also significantly more subjects in the clinic sample with low hemoglobin than in the national sample. There were no differences in ferritin levels between those patients in the clinic sample with and without an ADHD or other specific psychiatric diagnosis.

Conclusions: The ferritin levels of children and youth in a mental health clinic sample were significantly lower than those of the same-aged subjects in a national sample. Therefore, compromised iron status may be an additional biological risk factor for cognitive, behavioral, and psychiatric problems in pediatric populations served by the community mental health clinic.

Journal of Clinical Nursing. 2013 Apr;22:1133-39.

RELATIONSHIP BETWEEN ATTENTION DEFICIT HYPERACTIVE DISORDER SYMPTOMS AND PERCEIVED PARENTING PRACTICES OF SCHOOL-AGE CHILDREN.

Kim DH, Yoo IY.

Aims and objectives: To examine the relationship between the perception on parenting practices and attention deficit hyperactivity disorder (ADHD) symptoms in school-age children.

Background: Psychosocial attention deficit hyperactivity disorder intervention approaches emphasise environmental risk factors at the individual, family and community level. Parenting variables are strongly related to attention deficit hyperactivity disorder symptom severity.

Design: A cross-sectional questionnaire survey.

Methods: The participants were 747 children and their parents in two elementary schools. The instruments used were Korean Conners Abbreviated Parent Questionnaire and Korean version Maternal Behavior Research Instrument (measuring four dimensions of parenting practices: affection, autonomy, rejection, control). Descriptive and logistic regression analyses were performed.

Results: The rejective parenting practice was statistically significant in logistic regression controlling gender and age of children, family structure, maternal education level and socio-economic status. The rejection parenting is associated with attention deficit hyperactivity disorder symptoms in children (OR=1.356).

Conclusions: These results suggest the importance of specific parenting educational programmes for parents to prevent and decrease attention deficit hyperactivity disorder symptoms. It would be more effective rather than focusing only on the child's attention deficit hyperactivity disorder symptoms, developing educational programmes for parents to prevent rejection parenting practice and improve parenting skills in the family system.

Relevance to clinical practice: When developing a treatment programme for children with attention deficit hyperactivity disorder, healthcare providers should consider not only the child's attention deficit hyperactivity disorder symptoms, but also the parenting practices. Comprehensive interventions designed to prevent rejection and improve parenting skills may be helpful in mitigating attention deficit hyperactivity disorder symptoms.

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Journal of Cognitive and Behavioral Psychotherapies. 2013 Mar;13:75-87.

THE DISCRIMINATIVE POWER OF THE CBCL 1.5-5 BETWEEN AUTISM SPECTRUM DISORDERS AND OTHER PSYCHIATRIC DISORDERS.

Predescu E, ipos R, Dobrean A, et al.

We assessed the capacity of the Child Behavior Checklist (CBCL) 1.5-5 DSM-oriented scales to discriminate children with autism spectrum disorder (ASD) from children with other clinical disorders: attention deficit and/or hyperkinesia disorder (ADHD), developmental delay. Data were collected from 233 children aged 1.5-5 years divided into 4 groups (ASD, ADHD, developmental delay, healthy control subjects). The CBCL 1.5-5 was completed by the caregivers. We used analysis of variance (ANOVA), Scheffe posthoc, and multiple logistic regression to test performance differences in the five scales between the four groups of subjects included in the study. Scores on the pervasive developmental problems scale differentiate the ASD group from the ADHD group, and the control group, but there are no significant performance differences for this scale between the ASD group and the developmental delay group. The pervasive developmental problems scale demonstrated a significantly better discriminative performance than a random test, with a sensitivity range between 67.96 and 96.12 and specificity range between 67.65 and 88.57. Consistent with previous research, the results confirm the scale effectiveness as a screening tool for the various emotional and behavioral problems associated with ASD, ADHD or developmental delay diagnosis.

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J Comp Eff Res. 2013;2:261-71.

MANAGEMENT OPTIONS FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A REGIONAL PERSPECTIVE ON VALUE.

Ollendorf DA, Migliaccio-Walle K, Colby JA, et al.

Use of comparative effectiveness information in local healthcare decisions can be confounded by variations in practice, barriers to access and population demographics. The New England Comparative Effectiveness Public Advisory Council was convened as a public deliberative panel that considers evidence on the comparative clinical effectiveness and comparative value of a variety of therapeutic interventions. The council is tasked with making summary judgments on the evidence and recommendations for applying the evidence in medical and drug coverage policy, as well as initiating educational efforts for patients and

clinicians. The New England Comparative Effectiveness Public Advisory Council met in June 2012 to discuss management options for attention-deficit/ hyperactivity disorder, guided by a recent comparative effectiveness review from the Agency for Healthcare Research and Quality and supplementary economic analyses conducted by the Institute for Clinical and Economic Review. This article summarizes the deliberations and reflects on lessons learned regarding use of region-specific economic analyses to guide decision-making.

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J Med Syst. 2012;36:2675-88.

DECISION SUPPORT ALGORITHM FOR DIAGNOSIS OF ADHD USING ELECTROENCEPHALOGRAMS.

Abibullaev B, An J.

Attention deficit hyperactivity disorder is a complex brain disorder which is usually difficult to diagnose. As a result many literature reports about the increasing rate of misdiagnosis of ADHD disorder with other types of brain disorder. There is also a risk of normal children to be associated with ADHD if practical diagnostic criteria are not supported. To this end we propose a decision support system in diagnosing of ADHD disorder through brain electroencephalographic signals. Subjects of 10 children participated in this study, 7 of them were diagnosed with ADHD disorder and remaining 3 children are normal group. Our main goal of this study is to present a supporting diagnostic tool that uses signal processing for feature selection and machine learning algorithms for diagnosis. Particularly, for a feature selection we propose information theoretic which is based on entropy and mutual information measure. We propose a maximal discrepancy criterion for selecting distinct (most distinguishing) features of two groups as well as a semi-supervised formulation for efficiently updating the training set. Further, support vector machine classifier trained and tested for identification of robust marker of EEG patterns for accurate diagnosis of ADHD group. We demonstrate that the applicability of the proposed approach provides higher accuracy in diagnostic process of ADHD disorder than the few currently available methods.

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J Neural Transm. 2013;1-7.

BIPOLAR DISORDER RISK ALLELES IN CHILDREN WITH ADHD.

Schimmelmann BG, Hinney A, Scherag A, et al.

Bipolar disorder (BD) and attention deficit/hyperactivity disorder (ADHD) may share common genetic risk factors as indicated by the high co-morbidity of BD and ADHD, their phenotypic overlap especially in pediatric populations, the high heritability of both disorders, and the co-occurrence in families. We therefore examined whether known polygenic BD risk alleles are associated with ADHD. We chose the eight best SNPs of the recent genome-wide association study (GWAS) of BD patients of German ancestry and the nine SNPs from international GWAS meeting a 'genome-wide significance' level of $(\alpha) = 5 \times 10^{-8}$. A GWAS was performed in 495 ADHD children and 1,300 population-based controls using HumanHap550v3 and Human660 W-QuadV1 BeadArrays. We found no significant association of childhood ADHD with single BD risk alleles surviving adjustment for multiple testing. Yet, risk alleles for BD and ADHD were directionally consistent at eight of nine loci with the strongest support for three SNPs in or near NCAN, BRE, and LMAN2L. The polygene analysis for the BP risk alleles at all 14 loci indicated a higher probability of being a BD risk allele carrier in the ADHD cases as compared to the controls. At a moderate power to detect association with ADHD, if true effects were close to estimates from GWAS for BD, our results suggest that the possible contribution of BD risk variants to childhood ADHD risk is considerably lower than for BD. Yet, our findings should encourage researchers to search for common genetic risk factors in BD and childhood ADHD in future studies.

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J Neuroimmunol. 2013 May;258:67-70.

ANTI-PURKINJE CELL ANTIBODY AS A BIOLOGICAL MARKER IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A PILOT STUDY.

Passarelli F, Donfrancesco R, Nativio P, et al.

An autoimmune hypothesis has been suggested for several disorders in childhood. The aim of the study was to clarify the role of the cerebellum in ADHD and to evaluate the possible association between anti-Yo antibodies and ADHD. The presence/absence of antibodies was tested by indirect immunofluorescence assay on 30 combined subtype ADHD children, on 19 children with other psychiatric disorders (Oppositional-defiant and Conduct Disorders, Dyslexia) and 27 healthy controls. Results showed a significant positive response to the anti-Yo antibody immunoreactivity in the Purkinje cells of the cerebellum of ADHD children, compared with the control group and the psychiatric non-ADHD children. This association points to an immune dysregulation and the involvement of the cerebellum in ADHD.

J Psychiatr Res. 2013.

HIGHER RISK OF DEVELOPING MOOD DISORDERS AMONG ADOLESCENTS WITH COMORBIDITY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND DISRUPTIVE BEHAVIOR DISORDER: A NATIONWIDE PROSPECTIVE STUDY.

Chen MH, Su TP, Chen YS, et al.

Attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) are frequently comorbid. Previous studies suggested that the comorbidity of CD and ODD in ADHD may increase the risk of a further development of mood disorder, but most studies had a small sample size. Using a population-based prospective study design, a large sample composed of 1277 adolescents with ADHD-alone, 46 with ADHD + ODD, 87 with ADHD + CD, and 5640 age/gender-matched controls were enrolled in 2003. These cases were followed to 2010 to identify the cases developing unipolar depressive disorder and bipolar disorder. ADHD + CD groups exhibited a higher prevalence of unipolar depressive disorder (23.0% vs. 13.0% vs. 8.7% vs. 0.7%, $p < 0.001$) and bipolar disorder (3.4% vs. 2.2% vs. 1.3% vs. 0.2%, $p < 0.001$) than ADHD + ODD group, ADHD-alone group, and control group. Adolescents with ADHD + CD, those with ADHD + ODD, and those with ADHD-alone had a higher likelihood of developing unipolar depressive disorder (hazard ratio [HR]: 44.34, 95% confidence interval [CI]: 23.95-71.36; HR: 18.76, 95%CI: 7.87-44.71; HR: 13.01, 95%CI: 8.99-18.82) and bipolar disorder (HR: 14.39, 95%CI: 4.00-51.80; HR: 8.32, 95%CI: 1.06-65.32; HR: 5.24, 95%CI: 2.44-11.24) than the controls. Adolescents with ADHD had elevated risks of unipolar depression and bipolar disorder in their later life, and especially, those with ADHD and comorbidity of CD or ODD exhibited the highest risk. Further study would be required to evaluate whether prompt intervention for ADHD and disruptive behavior problems would decrease the risk of developing mood disorder.

J Am Acad Child Adolesc Psychiatry. 2013;52:537-46.

EMOTIONAL FACE IDENTIFICATION IN YOUTHS WITH PRIMARY BIPOLAR DISORDER OR PRIMARY ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Seymour KE, Pescosolido MF, Reidy BL, et al.

Objective: Bipolar disorder (BD) and attention-deficit/hyperactivity disorder (ADHD) are often comorbid or confounded; therefore, we evaluated emotional face identification to better understand brain/behavior interactions in children and adolescents with either primary BD, primary ADHD, or typically developing controls (TDC).

Method: Participants included individuals 7 to 17 years of age (overall sample mean age 12.40 (plus or minus) 3.01 years), with "narrow-phenotype" pediatric BD (n=30) or ADHD (n=38), or typically developing controls (TDC) with no psychiatric disorders themselves or in their first-degree relatives (n=41). In the BD group, comorbid diagnoses were allowed; however, youth in the ADHD group were excluded for comorbid mood or anxiety disorders. Patient groups were not excluded for psychotropic medication use. Emotional

face identification was assessed using the computerized Diagnostic Analysis of Non-Verbal Accuracy (DANVA).

Results: Participants with BD made significantly more identification errors on child happy faces than either TDCs ($p=.03$) or participants with ADHD ($p=.01$). Furthermore, youth with BD (0.33 (plus or minus) 0.55) were more likely than youth with ADHD (0.11 (plus or minus) 0.31) to make errors on low-intensity child happy faces ($p=.05$) but not high-intensity happy faces ($p = NS$). Participants with BD and ADHD made significantly more total errors in child face labeling than did TDCs, although participants with BD and ADHD did not differ from one another.

Conclusion: Our data suggest that youths with BD have specific alterations in emotional face identification of happy faces, an important finding that supports theories that response to positively valenced emotional stimuli may be especially salient in BD.

Clinical trial registration information - Brain Imaging and Computer Games in Children With Either Bipolar Disorder, ADHD, Anxiety or Healthy Controls (BBPP); <http://clinicaltrials.gov/>; NCT01570426.

J Am Acad Child Adolesc Psychiatry. 2013;52:482-92.

IMPACT OF TREATMENTS FOR DEPRESSION ON COMORBID ANXIETY, ATTENTIONAL, AND BEHAVIORAL SYMPTOMS IN ADOLESCENTS WITH SELECTIVE SEROTONIN REUPTAKE INHIBITOR-RESISTANT DEPRESSION.

Hilton RC, Rengasamy M, Mansoor B, et al.

Objective: To assess the relative efficacy of antidepressant medication, alone and in combination with cognitive behavioral therapy (CBT), on comorbid symptoms of anxiety, attention, and disruptive behavior disorders in participants in the Treatment of Resistant Depression in Adolescents (TORDIA) trial.

Method: Adolescents with selective serotonin reuptake inhibitor (SSRI)-resistant depression ($N=334$) were randomly assigned to a medication switch alone (to another SSRI or to venlafaxine) or to a medication switch plus CBT. Anxiety, attention-deficit/hyperactivity disorder (ADHD), and disruptive behavior disorder (DBD) symptoms were assessed by psychiatric interview and self-report at regular intervals between baseline and 24 weeks. The differential effects of medication and of CBT, and the impact of remission on the course of comorbid symptoms and diagnoses, were assessed using generalized linear mixed models.

Results: Remission was associated with a greater reduction in scalar measures of anxiety, ADHD, and DBDs, and a greater decrease in the rate of diagnosed anxiety disorders. The correlations between the changes in symptoms of depression on the CDRS-R and anxiety, ADHD, and oppositional symptoms were modest, ranging from $r=0.12$ to $r=0.28$. There were no significant differential treatment effects on diagnoses, or corresponding symptoms.

Conclusion: The achievement of remission had a beneficial effect on anxiety, ADHD, and DBD symptoms, regardless of the type of treatment received. There were no differential effects of medication or CBT on outcome, except for a nonsignificant trend that those adolescents treated with SSRIs showed a greater decrease in rates of comorbid DBDs relative to those treated with venlafaxine.

Clinical trial registration information - Treatment of SSRI-Resistant Depression In Adolescents (TORDIA); <http://clinicaltrials.gov/>; NCT00018902.

J Can Acad Child Adolesc Psychiatry. 2013;22:153-58.

SENSITIVITY OF SCALES TO EVALUATE CHANGE IN SYMPTOMATOLOGY WITH PSYCHOSTIMULANTS IN DIFFERENT ADHD SUBTYPES.

Grizenko N, Rodrigues Pereira RM, Joober R.

Objective: To assess the sensitivity of scales (Conners' Global Index Parent and Teacher form [CGI-P, CGI-T], Clinical Global Impression Scale [CGI], Continuous Performance Test [CPT], and Restricted Academic Situation Scale [RASS]) in evaluating improvement in symptomatology with methylphenidate in different Attention Deficit Hyperactivity Disorder (ADHD) subtypes.

Method: Four hundred and ninety children (309 with ADHD Combined/Hyperactive [ADHD-CH] and 181 with ADHD Inattentive subtype [ADHD-I]) participated in a two week double-blind placebo-controlled crossover methylphenidate trial.

Results: CGI-P showed small effect size for ADHD-I and medium effect size for the ADHD-CH subtype. CGI-T showed medium effect size for ADHD-I and large effect size for ADHD-CH subtype. CGI and RASS showed large effect size while CPT showed medium effect size for both subtypes.

Conclusion: Acute behavioural assessments by clinicians (CGI, RASS) are better at detecting improvement with medication in all subtypes than parent or teacher reports (CGI-P, CGI-T). CGI-T is better than CGI-P for ADHD-I in detecting change in symptomatology as there is a greater demand for attention at school.

J Can Acad Child Adolesc Psychiatry. 2013;22:139-46.

CHILDREN WITH AUTISM AND ATTENTION DIFFICULTIES: A PILOT STUDY OF THE ASSOCIATION BETWEEN SENSORY, MOTOR, AND ADAPTIVE BEHAVIORS.

Mattard-Labrecque C, Ben Amor L, Couture MM.

Objectives: This pilot study aimed to compare sensory processing, motor skills and adaptive behaviors in children with a double diagnosis of Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) (ASD+ADHD) with children with ADHD alone and to examine the association of sensory processing and motor skills with adaptive behaviors (self-care).

Method: Thirty children aged 5-14 years diagnosed with ASD+ADHD (n=13) or ADHD (n=17) were evaluated on their sensory processing and motor skills and adaptive behaviors. Analysis of covariance compared the groups on these dimensions. Correlation analyses examined the association between sensory processing and motor skills and adaptive behaviors.

Results: Compared to children with ADHD alone, children with ASD+ADHD had poorer skills in sensory processing ($p<0.001$), motor ($p=0.001$) and adaptive behaviors ($p<0.001$). For all children, increased autonomy in self-care was correlated with better sensory processing ($p<0.001$) and motor skills ($p=0.002$).

Conclusion: Children with ASD+ADHD have poorer sensory processing, motor and adaptive skills than those with ADHD alone. Sensory processing and motor deficits were negatively associated with autonomy in self-care. Interventions aiming to improve sensory processing and motor skills and autonomy in self-care should become important targets for these children.

NeuroImage. 2013;77:44-51.

MEASURING NETWORK'S ENTROPY IN ADHD: A NEW APPROACH TO INVESTIGATE NEUROPSYCHIATRIC DISORDERS.

Sato JR, Takahashi DY, Hoexter MQ, et al.

The application of graph analysis methods to the topological organization of brain connectivity has been a useful tool in the characterization of brain related disorders. However, the availability of tools, which enable researchers to investigate functional brain networks, is still a major challenge. Most of the studies evaluating brain images are based on centrality and segregation measurements of complex networks. In this study, we applied the concept of graph spectral entropy (GSE) to quantify the complexity in the organization of brain networks. In addition, to enhance interpretability, we also combined graph spectral clustering to investigate the topological organization of sub-network's modules. We illustrate the usefulness of the proposed approach by comparing brain networks between attention deficit hyperactivity disorder (ADHD) patients and the brain networks of typical developing (TD) controls. The main findings highlighted that GSE involving sub-networks comprising the areas mostly bilateral pre and post central cortex, superior temporal gyrus, and inferior frontal gyri were statistically different ($p\text{-value} = 0.002$) between ADHD patients and TD controls. In the same conditions, the other conventional graph descriptors (betweenness centrality, clustering coefficient, and shortest path length) commonly used to identify connectivity abnormalities did not show statistical significant difference. We conclude that analysis of topological

organization of brain sub-networks based on GSE can identify networks between brain regions previously unobserved to be in association with ADHD.

Neurosci Biobehav Rev. 2013.

ENVIRONMENTAL TOBACCO SMOKE EXPOSURE AND BRAIN DEVELOPMENT: THE CASE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Pagani LS.

Environmental tobacco smoke, inhaled by active firsthand smokers and their entourage, is associated with morbidity and mortality. Many children are passively exposed to secondhand smoke worldwide. Infants and young children account for the largest global disease burden associated with prenatal and postnatal secondhand smoke, probably due to underdeveloped neurological, immune, and respiro-circulatory systems. There is an increasingly robust association between tobacco smoke exposure, before and after birth, and executive function problems in children, adding to current and future disease burden estimates in public health. This review summarizes research advancements which address the link between environmental tobacco smoke and the development of attention deficits and hyperactive behavior, both as symptoms and as part of a mental health disorder in childhood. The multiple effects of tobacco smoke inhalation are best understood in terms of disruptions in normative processes involving cellular communication, structural development, and epigenetic influences which have the potential to become intergenerational. It is concluded that public health efforts be directed toward increasing parental awareness and compliance with existing guidelines that recommend no safe level of exposure.

Nutr Rev. 2013 May;71:268-81.

MECHANISMS OF BEHAVIORAL, ATOPIC, AND OTHER REACTIONS TO ARTIFICIAL FOOD COLORS IN CHILDREN.

Stevens LJ, Kuczek T, Burgess JR, et al.

review examines the research on mechanisms by which artificial food colors (AFCs) and common foods may cause behavioral changes in children with and without attention-deficit/hyperactivity disorder (ADHD). Children with ADHD show excess inattention, impulsivity, and hyperactivity. Studies have shown that a subgroup of children (with or without ADHD) react adversely to challenges with AFCs. Many early studies found few children who reacted to challenges with 20-40 mg of AFCs. However, studies using at least 50 mg of AFCs showed a greater percentage of children who reacted to the challenge. Three types of potential mechanisms are explored: toxicological, antinutritional, and hypersensitivity. Suggestions for future studies in animals and/or children include dose studies as well as studies to determine the effects of AFCs on the immune system, the intestinal mucosa, and nutrient absorption. Given the potential negative behavioral effects of AFCs, it is important to determine why some children may be more sensitive to AFCs than others and to identify the tolerable upper limits of exposure for children in general and for children at high risk.

Patient Educ Couns. 2013.

SHARED DECISION-MAKING TO IMPROVE ATTENTION-DEFICIT HYPERACTIVITY DISORDER CARE.

Brinkman WB, Hartl Majcher J, Poling LM, et al.

Objective: To examine the effect of a shared decision-making intervention with parents of children newly diagnosed with attention-deficit/hyperactivity disorder.

Methods: Seven pediatricians participated in a pre/post open trial of decision aids for use before and during the office visit to discuss diagnosis and develop a treatment plan. Encounters pre- (n=21, control group) and post-intervention implementation (n=33, intervention group) were compared. We video-recorded encounters and surveyed parents.

Results: Compared to controls, intervention group parents were more involved in shared decision-making (31.2 vs. 43.8 on OPTION score, $p < 0.01$), more knowledgeable (6.4 vs. 8.1 questions correct, $p < 0.01$), and less conflicted about treatment options (16.2 vs. 10.7 on decisional conflict total score, $p=0.06$). Visit duration was unchanged (41.0 vs. 41.6 min, $p=0.75$). There were no significant differences in the median number of follow-up visits (0 vs. 1 visits, $p=0.08$), or the proportion of children with medication titration (62% vs. 76%, $p=0.28$), or parent-completed behavior rating scale to assess treatment response (24% vs. 39%, $p=0.36$).

Conclusions: Our intervention increased shared decision-making with parents. Parents were better informed about treatment options without increasing visit duration.

Practice implications: Interventions are available to prepare parents for visits and enable physicians to elicit parent preferences and involvement in decision-making.

PLoS ONE. 2013;8.

TWIN AND SIBLING STUDIES USING HEALTH INSURANCE DATA: THE EXAMPLE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Langner I, Garbe E, Banaschewski T, et al.

Background and Aims: Twin studies are used to assess the contribution of genetic factors to the aetiology of diseases. To show the feasibility of such research on the basis of health insurance data, we analysed twin and sibling data on the attention deficit/hyperactivity disorder (ADHD) in the German Pharmacoepidemiological Research Database (GePaRD).

Methods: The GePaRD consists of data from four statutory health insurances, including around 17% of the total population of Germany. Among those insured in 2005, we identified 286,653 non-twin sibling pairs and 12,486 twin pairs. Each pair consisted of an index child (6 to 12 years old) and a co-sibling of equal age or up to five years older. ADHD cases were identified by hospital or ambulatory ICD-10 diagnoses (F90.0 or F90.1) and prescriptions. We estimated tetrachoric correlations, percentage of concordant pairs, concordance rates, and heritability. Weighted estimates for the indirect assessment of mono- and dizygotic pairs were derived.

Results: Tetrachoric correlations were highest for twin pairs of the same sex (males: 0.85, 95% CI 0.81-0.89; females: 0.81, 95% CI 0.73-0.88) and lowest for opposite-sex non-twin sibling pairs (0.43, 95% CI 0.41-0.45). Heritability estimates were 0.88 (95% CI: 0.79-0.97) for males and 0.77 (95% CI: 0.60-0.95) for females.

Conclusions: The study clearly reproduced the well-known strong genetic component in the aetiology of ADHD. This approach could be used for further assessments of genetic components in other diseases.

PLoS ONE. 2013;8.

MALE-BIASED AUTOSOMAL EFFECT OF 16P13.11 COPY NUMBER VARIATION IN NEURODEVELOPMENTAL DISORDERS.

Tropeano M, Ahn JW, Dobson RJB, et al.

Copy number variants (CNVs) at chromosome 16p13.11 have been associated with a range of neurodevelopmental disorders including autism, ADHD, intellectual disability and schizophrenia. Significant sex differences in prevalence, course and severity have been described for a number of these conditions but the biological and environmental factors underlying such sex-specific features remain unclear. We tested the burden and the possible sex-biased effect of CNVs at 16p13.11 in a sample of 10,397 individuals with a range of neurodevelopmental conditions, clinically referred for array comparative genomic hybridisation (aCGH); cases were compared with 11,277 controls. In order to identify candidate phenotype-associated genes, we performed an interval-based analysis and investigated the presence of ohnologs at 16p13.11; finally, we searched the DECIPHER database for previously identified 16p13.11 copy number variants. In the clinical referral series, we identified 46 cases with CNVs of variable size at 16p13.11, including 28 duplications and 18 deletions. Patients were referred for various phenotypes, including

developmental delay, autism, speech delay, learning difficulties, behavioural problems, epilepsy, microcephaly and physical dysmorphisms. CNVs at 16p13.11 were also present in 17 controls. Association analysis revealed an excess of CNVs in cases compared with controls (OR=2.59; $p=0.0005$), and a sex-biased effect, with a significant enrichment of CNVs only in the male subgroup of cases (OR=5.62; $p=0.0002$), but not in females (OR=1.19, $p=0.673$). The same pattern of results was also observed in the DECIPHER sample. Interval-based analysis showed a significant enrichment of case CNVs containing interval II (OR=2.59; $p=0.0005$), located in the 0.83 Mb genomic region between 15.49-16.32 Mb, and encompassing the four ohnologs NDE1, MYH11, ABCC1 and ABCC6. Our data confirm that duplications and deletions at 16p13.11 represent incompletely penetrant pathogenic mutations that predispose to a range of neurodevelopmental disorders, and suggest a sex-limited effect on the penetrance of the pathological phenotypes at the 16p13.11 locus.

PLoS ONE. 2013;8.

DNA VARIATION IN THE SNAP25 GENE CONFERS RISK TO ADHD AND IS ASSOCIATED WITH REDUCED EXPRESSION IN PREFRONTAL CORTEX.

Hawi Z, Matthews N, Wagner J, et al.

Background: The Coloboma mouse carries a ~2 cM deletion encompassing the SNAP25 gene and has a hyperactive phenotype similar to that of ADHD. Such mice are 3 fold more active compared to their control littermates. Genetic association studies support a role for allelic variants of the human SNAP25 gene in predisposing to ADHD.

Methods/Principal Findings: We performed association analysis across the SNAP25 gene in 1,107 individuals (339 ADHD trios). To assess the functional relevance of the SNAP25-ADHD associated allele, we performed quantitative PCR on post-mortem tissue derived from the inferior frontal gyrus of 89 unaffected adults. Significant associations with the A allele of SNP rs362990 ($(\chi^2=10$, p -corrected=0.019, OR=1.5) and three marker haplotypes (rs6108461, rs362990 and rs362998) were observed. Furthermore, a significant additive decrease in the expression of the SNAP25 transcript as a function of the risk allele was also observed. This effect was detected at the haplotype level, where increasing copies of the ADHD-associated haplotype reduced the expression of the transcript.

Conclusions: Our data show that DNA variation at SNAP25 confers risk to ADHD and reduces the expression of the transcript in a region of the brain that is critical for the regulation of attention and inhibition.

PLoS ONE. 2013;8.

NO BEHAVIORAL OR ERP EVIDENCE FOR A DEVELOPMENTAL LAG IN VISUAL WORKING MEMORY CAPACITY OR FILTERING IN ADOLESCENTS AND ADULTS WITH ADHD.

Spronk M, Vogel EK, Jonkman LM.

Attention-deficit/hyperactivity disorder (ADHD) patients have both working memory (WM) and attention problems. Good attention skills are important for WM performance; individuals have higher WM capacity when being able to prevent storage of irrelevant information through efficient filtering. Since it is unknown how filtering ability is associated with WM performance in ADHD, this was investigated in the present study. A visuospatial working memory (VSWM) change detection task with distracting stimuli was administered to adolescents (12-16 years old) and adults (20-46 years old) with and without ADHD matched on education/IQ. Besides performance, contralateral delay activity (CDA) was measured; a neural correlate of the number of targets and distracters encoded and maintained in WM during the retention interval. Performance data showed similar WM-load, WM-distracter interference and developmental effects in ADHD and control groups. Adolescents' performance on the WM task deteriorated more than that of adults in the presence of distracters and with higher WM-load, irrespective of Diagnosis. The CDA data suggested that initially all groups encoded/maintained distracting information, but only adults were able to bounce this information from memory later in the retention interval, leading to better WM performance. The only effect

of Diagnosis was a smaller CDA in adolescents and adults with ADHD than in age/IQ-matched controls when maintaining a low 1-item load, which was possibly related to an inability to keep attention focused at cued stimuli with low task demands. Overall, the development of filtering efficiency and VSWM storage capacity in adolescents with ADHD was not different from that in typically developing peers.

Res Dev Disabil. 2013;34:2127-32.

Outpatient rehabilitation utilization and medical expenses in children aged 0-7years with ADHD: Analyses of population-based national health insurance data.

Lin JD, Chen YH, Lin LP.

Medical costs of attention-deficit/hyperactivity disorder (ADHD) are substantial and have a large impact on the public health system. The present study presents information regarding outpatient rehabilitation care usage and medical expenditure for children with ADHD. A cross-sectional study was conducted by analyzing data from the Taiwan National Health Insurance claims database for the year 2009. A total of 6643 children aged 0-7. years with ADHD (ICD-9-CM codes 314.0. x: attention deficit disorder, 314.00: attention deficit disorder without hyperactivity, or 314.01: attention-deficit disorder with hyperactivity) who had used outpatient rehabilitation care were included in the analyses. Results showed that the mean annual rehabilitation care was 22.24 visits. Among the care users, 76% of patients were male, and 24% were female. More than half of the children with ADHD had comorbid mental illnesses as well. A logistic regression analysis of outpatient rehabilitation expenditure (low vs. high) showed that of those children with ADHD, those aged 0-2. years tended to incur more medical costs than those aged 6-7. years. Other factors such as frequency of rehabilitation visits, hospital medical setting and ownership, location of medical care setting, and types of rehabilitation were also significantly correlated with medical expenditure. The results from this study suggest that health care systems should ensure accurate diagnosis and measurement of impairment to maintain appropriate and successful management of rehabilitation needs for children with ADHD.

Res Dev Disabil. 2013;34:1870-80.

DOMAIN-GENERAL AND DOMAIN-SPECIFIC ASPECTS OF TEMPORAL DISCOUNTING IN CHILDREN WITH ADHD AND AUTISM SPECTRUM DISORDERS (ASD): A PROOF OF CONCEPT STUDY.

Demurie E, Roeyers H, Baeyens D, et al.

It has been shown that delayed consumable rewards are discounted to a higher degree than money, which has been referred to as the "domain effect". Until now the effects of reward type on temporal discounting (TD) have mainly been studied in adults. Although there is evidence that children with attention-deficit/hyperactivity disorder (ADHD) tend to show steeper TD of money than typically developing peers or children with autism spectrum disorders (ASD), it remains untested whether the domain effect is also seen in children with ADHD and ASD. To explore this we compared TD of children (8-16 year) with ADHD, ASD and typically developing controls with five different reward types. Seventy-two participants with ADHD, 69 with ASD and 130 controls performed two hypothetical TD-tasks: a monetary TD-task and a TD-task with one of four alternative rewards (material rewards, rewarding activities, food, social rewards). TD was seen for all reward types, but the rate of discounting was steeper for food, praise and rewarding activities compared to money, and for food and praise compared to material rewards. For the ADHD and control groups, but not the ASD group, money and material rewards were equally highly discounted. High correlations between TD of money and of activities, food and material rewards were found. In conclusion, a domain effect was observed in typically developing children, as well as in children with ADHD or ASD, although the pattern was somewhat different for ASD children. Despite this domain effect, there is also evidence for a domain-general aspect in TD.

Soc Sci Med. 2013;88:30-38.

THE IMPORTANCE OF CHILDREN'S ADHD FOR PARENTS' RELATIONSHIP STABILITY AND LABOR SUPPLY.

Kvist AP, Nielsen HS, Simonsen M.

Children with attention-deficit/hyperactivity disorder (ADHD) have much worse long-term outcomes than other children. This paper uses Danish register-based data on children born from 1990 to 1997 to investigate the significance of children's ADHD for parents' outcomes. We observe 172,299 pairs of parents from 1990 to 2007 of which 2457 have a firstborn child diagnosed with ADHD and 169,842 have a firstborn child without ADHD. Ten years after the birth of the child, parents of children diagnosed with ADHD have a 75% higher probability of having dissolved their relationship and a 7-13% lower labor supply. Parents of children with ADHD are, however, particularly disadvantaged in terms of socioeconomic background and mental health. We explain about half of the gaps in partnership stability and labor supply when these factors are taken into consideration, but a statistically and economically significant gap remains to be explained. Additionally, we find that the receipt of a diagnosis to some extent moderates the influence of underlying ADHD on partnership stability. Still, our study concludes that poor child health in terms of ADHD reduces parental socioeconomic status (SES) by lowering their labor supply (and earnings) and reducing relationship stability.

Sci World J. 2013;2013.

APPLYING AN ESSENCE FRAMEWORK TO UNDERSTANDING ADULT AUTISM SPECTRUM DISORDER AND ADHD: RETROSPECTIVE PARENT REPORTS OF CHILDHOOD PROBLEMS.

Plenty S, Heurlin D, Arlinde C, et al.

Diagnoses of autism spectrum disorder (ASD) and attention-deficit/ hyperactivity disorder (ADHD) are increasingly being made in adulthood. However, assessments can fail to address the diverse range of problems that patients have experienced. The current study applied an early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE) framework to explore retrospectively reported childhood developmental and behavioral problems. It examined if adult ASD and ADHD patients would show problems outside those reflected in the respective diagnostic criteria, and also if these patient groups would show more extensive childhood problems than other psychiatric patients. Parents of adults with ADHD (n=130), ASD (n=57), coexisting ADHD and ASD (n=38), and other psychiatric disorders (n=56) reported on a range of childhood problems. Descriptions of the ADHD, ASD, and ADHD+ASD groups reflected greater impairment than descriptions for patients with other psychiatric disorders in most problem areas. Although differences were observed between ADHD and ASD patients in the core diagnostic areas, these syndromes also shared a number of childhood difficulties. The ESSENCE approach can assist in understanding the symptom history of adult ADHD and ASD patients and can be helpful to distinguish their childhood experiences from other psychiatric patients' experiences.

Sci World J. 2013;2013.

EATING PROBLEMS AND OVERLAP WITH ADHD AND AUTISM SPECTRUM DISORDERS IN A NATIONWIDE TWIN STUDY OF 9- AND 12-YEAR-OLD CHILDREN.

Rastam M, Taljemmark J, Tajnia A, et al.

Aim. To establish the prevalence of restrictive eating problems, the overlap and association with attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorders (ASD) and to estimate the heritability of eating problems in a general population sample of twins aged 9 and 12.

Methods. Parents of all Swedish 9- and 12-year-old twin pairs born between 1993 and 1998 (n=12,366) were interviewed regarding symptoms of ADHD, ASD, and eating problems (EAT-P). Intraclass correlations and structural equation modelling were used for evaluating the influence of genetic and environmental factors. Cross-twin, cross-trait correlations were used to indicate a possible overlap between conditions.

Results. The prevalence of eating problems was 0.6% in the study population and was significantly higher in children with ADHD and/or ASD. Among children with eating problems, 40% were screened positive for

ADHD and/or ASD. Social interaction problems were strongly associated with EAT-P in girls, and impulsivity and activity problems with EAT-P in boys. The cross-twin, cross-trait correlations suggested low correlations between EAT-P and ADHD or EAT-P and ASD. Genetic effects accounted for 44% of the variation in liability for eating problems.

Conclusions. In the group with eating problems, there was a clear overrepresentation of individuals with ADHD and/or ASD symptoms.

Value Health. 2013;16:A57.

PREDICTORS OF USE OF ATYPICAL ANTIPSYCHOTICS AND LONG ACTING STIMULANTS POLYPHARMACY AMONG CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Bali V, Kamble P, Aparasu RR.

OBJECTIVES: Psychotropic polypharmacy is common in pediatric Attention Deficit/Hyperactivity Disorder (ADHD). This study examined determinants of the long acting stimulant (LAS) and atypical antipsychotic (AAP) polypharmacy in children and adolescents with ADHD.

METHODS: This study used 4 years (January 2004 to December 2007) of IMS LifeLink(trademark) claims data involving 6-16 years old children with ADHD and at least one LAS prescription between July 2004 to December 2006 and continuous eligibility 6 months before and 1 years after the index LAS prescription. Polypharmacy was defined as the concurrent prescription for LASs and AAPs for at least 14 days within the 365 days after the index LAS claim. Multiple logistic regression analysis was performed to examine predictors of LASs and AAPs polypharmacy in pediatric ADHD.

RESULTS: The study cohort consisted of 39,981 children and adolescents. Of these, 1,560 (3.90%) received LAS and AAP polypharmacy and the rest 38,421 (96.10%) received LAS monotherapy. Multivariate logistic regression analysis revealed that factors positively associated with psychotropic polypharmacy were: male, year of cohort entry (2005 and 2006), initiation of LAS in summer, psychiatrist visit, depression, conduct disorder, enuresis, tics, bipolar disorder, oppositional disruptive disorder, psychosis and pervasive developmental disorders, use of psychotropic medications from other drug class such as (alpha)2-agonists, antidepressants, mood stabilizers and other miscellaneous medications, and mental health-related hospital visit in the past 6 months. Children with public health insurance, those residing in Midwest and West regions, those who initiated use of index LAS in spring, those seen by pediatrician, and those with comorbidity of substance abuse and dependence were less likely to receive LAS and AAP polypharmacy.

CONCLUSIONS: Various patient, clinical and treatment factors were associated with the receipt of polypharmacy among ADHD youths. Understanding of these factors can help to manage psychotropic polypharmacy and improve quality of care in pediatric ADHD.

Value Health. 2013;16:A56-A57.

NATIONAL TRENDS IN PSYCHOTROPIC MEDICATIONS USE AMONG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN THE UNITED STATES.

Potukuchi PK, Li C.

OBJECTIVES: Stimulants are recommended first-line treatments for attention deficit hyperactivity disorder (ADHD), but increased use of other psychotropic medications such as antipsychotics and antidepressants has been reported. However, recent nationally representative estimates are lacking. This study examined the recent trends in use of psychotropic medications among children with ADHD in the US.

METHODS: This retrospective study utilized the data from Medical Expenditure Panel Survey for the years 2002-2010. Trends in use of psychotropic medications (stimulants, antipsychotics, antidepressants, anxiolytics/sedatives/hypnotics, mood stabilizers and clonidine) were examined. Unadjusted logistic regressions were conducted to assess the significance of trends in medication use over time. Logistic regressions were conducted to identify the socio demographic characteristics and comorbid psychotic

disorders (schizophrenia, bipolar disorder, depression/anxiety, autistic disorders) associated with the use of each psychotropic medication class.

RESULTS: Use of stimulants was most common during the study period, which increased sharply from 43.0% in 2002 to 80.8% in 2006 but decrease afterwards to 62.2% in 2010. Use of antidepressants accounted for 10.4% and with no statistical significant trend over time annually. Antipsychotics was used for 9.3% of ADHD children annually but increased in recent years from 7.2% in 2002-2004 to 11.3% in 2008-2010 (OR: 1.6, 95% CI: 1.1-2.6). Having schizophrenia (OR 26.6: CI 2.95-239.6) or bipolar disorder (OR 20.1: CI 12.3-33.1) significantly increased the use of antipsychotic medication in children with ADHD.

CONCLUSIONS: Stimulants remained the mainstay of treatment for ADHD in children, although its use decreased after 2006 which is consistent with other studies. Antipsychotic use was less common but increased significantly in recent years.

Value Health. 2013;16:A64-A65.

DEVELOPMENT OF A CONCEPTUAL DISEASE MODEL TO INFORM STRATEGY TO EVALUATE TREATMENT IMPACT IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Pokrzywinski R, Setyawan J, Khan S, et al.

OBJECTIVES: To build a conceptual model describing disease experience in adolescent ADHD (aged 13-17) and impact of treatment, in order to inform the development of a measurement strategy to evaluate interventions. Conceptual models that summarize key concepts in describing disease experience are useful for developing strategies to measure meaningful treatment outcomes. Adolescents are increasingly participating in making decisions about their health care. Hence, it is important to evaluate outcomes that are meaningful to them.

METHODS: In preparation for patient interviews, focused searches of databases, clinical and regulatory guidelines, ADHD specific tools and conference abstracts were conducted as part of the literature review to identify concepts to understand the experiences of adolescents with ADHD from various perspectives. In addition, concept elicitation interviews with 10 clinicians, 3 teachers, 10 peers and 10 siblings of adolescents with ADHD were conducted using semi-structured guides. Results from this preliminary stage were analyzed systematically; transcripts from the peer and sibling interviews were analyzed using a pre-defined coding dictionary, to identify concepts for the model.

RESULTS: Disease-defining concepts in ADHD included core ADHD symptoms, problems with cognitive functions and problems with emotional dysregulation. ADHD was seen to impact everyday activities, social interactions and emotional functioning. These impacts had implications for the achievements at school; self-esteem and indulgence in risky behavior. Variables that moderate these impacts were also identified. The interrelationships among variables will be presented. The model was used to inform a strategy to evaluate outcomes of pharmacological treatments in adolescents with ADHD. The plausibility of the model was confirmed based on discussions with clinicians and drug development experts.

CONCLUSIONS: An ADHD disease conceptual model was developed based on information from literature and stakeholders interviews, to describe ADHD in adolescents. It will be used to develop a strategy for PRO development in adolescent ADHD and identify new outcomes.

Value Health. 2013;16:A60-A61.

TRENDS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER MEDICATION USE AND EXPENDITURES IN THE UNITED STATES: AN ANALYSIS OF 2000-2010 MEDICAL EXPENDITURE PANEL DATA.

Oladapo AO, Desai P, Adeyemi A, et al.

OBJECTIVES: To determine trends in Attention Deficit Hyperactivity Disorder (ADHD) medication use and expenditures in the US from 2000 to 2010.

METHODS: This was a retrospective cross-sectional analysis of the household component of the Medical Expenditure Panel Survey (MEPS) data from 2000 to 2010 (using the full-year consolidated data files and prescribed medicines files) involving all ADHD patients (International Classification of Disease 9th revision

[ICD-9] code 314) on any FDA approved ADHD medication. Outcome measures were ADHD medication utilization and cost (adjusted to 2010 dollars). Since MEPS employs a complex, probabilistic survey design, standard error estimates were computed using the 'SURVEY' procedures of SAS.

RESULTS: The percentage of the total US population on ADHD medications grew from 0.7% in 2000 to 1.4% in 2010 with an estimated average annual utilization growth rate of 13.1%. Aggregate spending on all ADHD medications increased from \$684.9 million in 2000 to \$3.6 billion in 2010 with an estimated average annual spending growth rate of 42.7%. Average spending on ADHD medication per user increased from \$356.9 (SE=\$23.0) in 2000 to \$816.2 (SE=\$55.5) in 2010. Stimulants accounted for over 70% of total yearly spending on all ADHD medications between 2000 and 2010. From 2002, long-acting stimulants accounted for the majority (>60%) of the total yearly spending on stimulant medications. Furthermore, across the years by demographic sub-groups, younger children ((less-than or equal to)12 years), males, individuals on private health insurance, and low/middle income families had the highest ADHD utilization rates (>37%) and accounted for the highest proportion (>39%) of spending on all ADHD medications.

CONCLUSIONS: A steady growth in ADHD medication use and expenditure was observed across 2000 to 2010 with the key growth drivers being younger children ((less-than or equal to)12 years), males, individuals on private health insurance, and low/middle income families.

Value Health. 2013;16:A62.

ONCE-A-DAY EXTENDED-RELEASE VERSUS TWO-TIMES-DAILY IMMEDIATE-RELEASE METHYLPHENIDATE FOR THE TREATMENT OF ADHD-A COST MINIMIZATION STUDY.

Kachru N, Sansgiry SS.

OBJECTIVES: Attention Deficit/Hyperactivity Disorder (ADHD) is a neurobehavioral disorder and one of the most prevalent chronic health problems affecting school-age children, representing a costly major public health problem. Keeping in view, the substantial economic burden, the objective of this study was to conduct a cost-minimization analysis of once-a-day extended-release (ER) versus two-times-daily immediate-release (IR) methylphenidate for the treatment of ADHD patients.

METHODS: Major literature databases were systematically searched to identify appropriate randomized clinical trials and meta-analyses to obtain costs associated with both the alternative formulations from a payers (third party) perspective. Medical costs included cost of drug, cost of assessments, cost of non-compliance, cost of injuries/accidents and cost of in-school administration and were obtained from published literature. All costs were adjusted to 2012 USD using consumer price index. The expected outcome was considered to be the same for both the formulations and a cost minimization analysis was performed using a decision tree approach. Multiple one-way sensitivity analyses were performed on all cost variables to evaluate the robustness of the results.

RESULTS: The ER regimen of methylphenidate resulted in a total annual cost of \$4685 per patient which was less costly as compared to the IR regimen that resulted in a total annual cost of \$9524 per patient for the treatment of ADHD. One-way sensitivity analyses results were consistent.

CONCLUSIONS: In our study Methylphenidate ER had 50.81% less annual economic burden as compared to the IR regimen for the treatment of ADHD patients.

Z Kinder- Jugendpsychiatr Psychother. 2013;41:133-44.

THE RELATIONSHIP OF THERAPEUTIC ALLIANCE WITH SYMPTOM REDUCTION AND TREATMENT SATISFACTION IN THE THERAPEUTIC TREATMENT OF CHILDREN AND ADOLESCENTS WITH ADHD AND/OR CONDUCT DISORDER.

Kinnen C, Dopfner M.

Abstract. The relationship of therapeutic alliance with symptom reduction and treatment satisfaction in the therapeutic treatment of children and adolescents with ADHD and/or conduct disorder

Objective: The relationship of therapeutic alliance and outcome is investigated in outpatient behavior therapies of children and adolescents with externalizing problem behavior.

Method: Therapist-patient and therapist-parent relationships were evaluated twice during the therapies of N=53 patients using German relationship questionnaires adapted for use in child and adolescent psychotherapy (BeKi). Pre-post symptom reduction in parent and patient rating, treatment satisfaction as rated by therapist, parent and patient as well as child's global functioning by therapist rating are examined as outcome parameters.

Results: The correlations between therapeutic alliance and symptom reduction vary depending on the rater between absence of correlation and high correlation (maximum: $r=.53$). Most correlations are low to moderate. These results are comparable to those reported in recently published meta-analyses and studies of adult psychotherapy. There are moderate correlations between therapist-patient and therapist-parent alliance and treatment satisfaction and low to moderate correlations with improvements in the children's global functioning.

Conclusions: Only few studies have focused on treatment satisfaction and improvements in children's global functioning as outcome variables. Besides symptom reduction, these two variables also correlate significantly with the therapist-patient and therapist-parent alliance. Because correlations highly depend on the rater, future studies should consider the various perspectives.

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Zh Nevrologii Psihiatrii im S S Korsakova. 2011;111:28-32.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER: DETERMINATION OF THE OPTIMAL MEDICAL TREATMENT DURATION.
Zavadenko NN, Suvorinova NY.

Thirty-two patients with attention-deficit hyperactivity disorder (ADHD), 23 boys and 9 girls, aged 6-12 years, were examined in two months intervals during the long-term treatment (up to 6-8 months) with pantogam (homopantothenic acid) in daily dosages of 500-1000 mg. The treatment results were evaluated by the ADHD Rating Scale-DSM-IV and The Weiss Functional Impairment Rating Scale - Parent Report (WFIRS-P). While the core symptoms of ADHD were according ADHD-DSM-IV diminished after 2 months, the improvement of WFIRS-P parameters required the longer duration of medical treatment. Only after 4 months of treatment, the improvement was achieved in selfesteem and social activities, and after 6 months in learning and behavior at school as well as in the level of life skills along with the decrease of risky activities. Thus, getting over psychosocial adaptation problems needs the longer treatment duration than the decrease of ADHD core symptoms.

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Zh Nevrologii Psihiatrii im S S Korsakova. 2013;113:38-40.

CLINICAL AND ENCEPHALOGRAPHIC CHARACTERISTICS OF SLEEP IN CHILDREN WITH THE ATTENTION DEFICIT HYPERACTIVITY SYNDROME.

Kalashnikova TP, Anisimov GV, Kravtsov YI, et al.

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Review article

Epilepsy associated with autism and attention deficit hyperactivity disorder: Is there a genetic link?

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Abstract

Autism Spectrum Disorders (ASDs) and Attention Deficit and Hyperactivity Disorder (ADHD) are the most common comorbid conditions associated with childhood epilepsy. The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, neurotransmission and functional connectivity. Rare clinically relevant chromosomal aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD comorbid with epilepsy. The majority of the candidate genes are involved in synaptic formation/remodeling/maintenance (*NRX1*, *CNTN4*, *DCLK2*, *CNTNAP2*, *TRIM32*, *ASTN2*, *CTNTN5*, *SYN1*), neurotransmission (*SYNGAPI*, *GABRG1*, *CHRNA7*), or DNA methylation/chromatin remodeling (*MBD5*). Two genetic disorders, such as Tuberous sclerosis and Fragile X syndrome may serve as models for understanding the common pathogenic pathways leading to ASDs and ADHD comorbidities in children with epilepsy, offering the potential for new biologically focused treatment options.

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Keywords: Epilepsy; Autism spectrum disorders; ADHD; Comorbidity; Genetics; CNVs; Tuberous sclerosis; Fragile X syndrome

1. Introduction

Epilepsy is one the most common neurological disorders of childhood, occurring in 3.5–6.5 per 1000 children [1], and may be associated with several neurodevelopmental disorders, including intellectual disability (ID), attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs) [2].

ASDs symptoms may occur in 15–35% of children with epilepsy [3–5]. Epilepsy is estimated to affect 7–46% of patients with ASDs [6–8], occurring more frequently in those subjects presenting also an ID [9]. All

seizure types have been reported in ASDs, but focal epilepsy seems to be prevalent [10]. Children and adolescents with epilepsy tend to show an increased risk of ADHD, which is present in 12–70% [11–13]. Overall, these findings suggest a strong interrelationship between the ASDs/ADHD phenotype and childhood epilepsy. Despite current classification systems (ICD-10, DSM-IV) [14] do not allow for a comorbid diagnosis of ASDs and ADHD, in the ASDs population 40–70% of individuals meet full ADHD diagnostic criteria [15,16]. Autistic-like communication and social deficits are evident in 28–62% of ADHD children [17]. These rates of co-occurrence are higher than expected for coincidental findings, making it unlikely that ASDs and ADHD are two independently occurring conditions.

The co-occurrence of an epilepsy/autism phenotype or an epilepsy/ADHD phenotype has a complex and heterogeneous pathogenesis, resulting from several

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2

A. Lo-Castro, P. Curatolo / Brain & Development xxx (2013) xxx–xxx

altered neurobiological mechanisms involved in early brain development, and influencing synaptic plasticity, GABA transmission and functional connectivity [2]. It is likely that rare clinically relevant genetic aberrations, in addition to environmental factors, may confer an increased risk for ASDs/ADHD associated with epilepsy [2,18].

We reviewed the pathogenic mechanisms behind the high rate of comorbidity between epilepsy and ASDs/ADHD and provided an overview of new data from genetic models that have the potential to clarify this co-occurrence.

2. Search strategy and selection criteria

Information in this Review is mainly based on peer-reviewed medical publications from 1974 to 2012 (PubMed). The selection criteria utilized were the novelty and importance of studies, and their relevance to general medical doctors and child neurologists. Only articles published in English were reviewed. The filters included “epilepsy”, “autism”, “autism spectrum disorders”, “attention deficit hyperactivity disorder”, for the identification of studies reporting on a comparison of these neurodevelopmental conditions, and “molecular genetics”, “CNV”, “SNP” for the genetic data.

3. Genetic links

Different alterations of genes involved in neurodevelopment may result in common biological mechanisms that lead to complex neuropsychiatric phenotypes. Conceptually, during intrauterine brain development or at an early stage in life, common molecular pathways may disrupt developmental trajectories leading to abnormalities in neuronal migration, cortical organization and, finally, in synaptic and dendritic functions [19]. An example is represented by the *AUTS2* locus, involved in neurodevelopment, in which nucleotide changes could lead to several neurological diseases, including autism, ADHD, epilepsy, dyslexia, motor delay, language delay, visual impairment, microcephaly, and alcohol consumption [20].

Candidate genes associated with childhood epilepsy and ASDs/ADHD comorbidity are reported in Table 1. The majority of these genes are involved in synaptic formation/remodeling/maintenance (*NRX1* [21–23], *CNTN4* [24], *DCLK2* [25,26], *CNTNAP2* [27–29], *TRIM32* [25], *ASTN2* [25], *CTNTN5* [25,30], *SYN1* [31,32]), neurotransmission (*SYNGAP1* [33], *GABRG1* [34], *CHRNA7* [29,34–36]) or DNA methylation/chromatin remodeling (*MBD5* [37,38]).

GABAergic interneurons are involved in maturation and wiring of proper networks, in the regulation of critical period experience-dependent cortical plasticity, and in the control of minicolumns functions [39–41]. Alter-

ation in neocortical experience-dependent maturation leads to an abnormal plasticity, and may significantly contribute to cognitive and behavioral impairments. This process is severely impaired in *Ube3a* deficient mice models of Angelman syndrome (OMIM #105830), a genetic entity characterized by ID, ASDs in one-half of cases, epilepsy, and ADHD [42,43]. Altered [GABA]/[glutamate] ratio has been evidenced in the frontal lobe of autistic patients, with respect to controls [44]. Moreover, SPECT studies showed a GABAergic system disturbance in the superior and medial frontal cortex, brain regions involved in several aspects of the Theory of Mind [45]. Hyperglutameria and other neurometabolic abnormalities have been demonstrated in pregenual anterior cingulate cortex of pediatric ASDs patients, with possible right-lateralization [46]. Moreover, Dopamine D(4) receptors seem to control the excitatory synaptic strength in local-circuit neurons and GABAergic inhibition in the prefrontal network, underlining the role of D(4) receptors cognitive processes associated with ADHD [47]. Abnormal excitability and disrupted synaptic plasticity in the developing brain may account both for epilepsy and its comorbidities [48,49].

Decreased cortical expression of the two isoforms of glutamic acid decarboxylase (GAD), GAD65 and GAD67, has been observed in autistic brain samples [49,50]. The importance of GAD65 for synthesis of GABA destined for extrasynaptic tonic inhibition, regulating epileptiform activity, was demonstrated in knock-out mice models [51].

Dlx homeobox genes, including *Dlx1* and 2, encode for transcription factors important for specification, maintenance, and migration of interneurons in the adult brain. *Dlx*^{−/−} mice shown a selective alteration in the dendritic morphology of interneurons and their progressive death, with onset of generalized electrographic seizures [52]. *DLX1* and *DLX2* genes are located in 2q32 band, a region associated with autism susceptibility; Single Nucleotide Polymorphisms (SNPs) of these genes have been documented in multiplex ASDs families [53].

ARX mutations, related to ID, epileptic encephalopathies and, rarely, autism [54] is essential for GABAergic interneurons migration, and is a direct downstream target of *Dlx2* [55]. A decreased GABA receptor signaling has been documented in Fragile X syndrome, with a consequent imbalance between excitatory and inhibitory systems [56]. Finally, a selective ablation of MeCP2 from interneurons, causes many features of Rett syndrome and autistic behaviors in mice models [57].

With the advent of whole-genome association studies, several single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) have been associated to ID, ASDs, ADHD, epilepsy and a constellation of other neuropsychiatric disorders. A list of several syndromic conditions associated with chromosomal aberrations are summarized in Table 2. The co-occurrence of

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Table 1
Candidate genes associated with epilepsy, autism and ADHD.

Genes and OMIM entries	Locus	Function(s)	Epilepsy	Autism spectrum	ADHD	References
NRXN1 (+600565)	2p16.3	Cell-surface receptor that binds neuroligins, forming a Ca(2+)-dependent transsynaptic complex required for efficient neurotransmission and involved in the formation of synaptic contacts	Severe early onset epilepsy	+	+	[21–23]
MBD5 (*611472)	2q23.1	Member of a family of genes involved in DNA methylation and/or chromatin remodeling	+	Autistic features	–	[37,38]
CNTN4 (*607280)	3p26-p25	Axon-associated cell adhesion molecule of the contactin subgroup of the Ig superfamily. Important roles in the formation, maintenance, and plasticity of functional neuronal networks	–	+	+	[24]
GABRG1 (*137166)	4p12	Member of the GABA-A receptor gene family involved in mediating responses to benzodiazepines	Neonatal seizures	+	+	[25,95]
DCLK2 (*613166)	4q31.3	In rat brain, DCX domain of Dck2 is required for microtubule binding	+	–	+	[25,26]
SYNGAP1 (*603384)	6p21.32	Encodes a RAS/RAP GTP-activating protein that is a part of N-methyl aspartate receptor (NMDAR) complex	CAE, GTCS, myoclonic seizures, drop attacks, partial complex seizures	+	+	[33]
CNTNAP2 (*604569)	7q35-q36	Member of the neuroligin superfamily, a group of transmembrane proteins that mediate cell–cell interactions in CNS. Highly expressed in prefrontal and anterior temporal cortex, as well as in dorsal thalamus, caudate, putamen, and amygdala. Mutated in Pitt-Hopkins-like syndrome	CDFE generalized seizures	+	+	[27–29]
TRIM32 (*602290)	9q33.1	Encodes a tripartite motif containing E3 ubiquitin ligase protein, involved in deciding the fate of neuronal stem cell lineages. Mutated in Bardet-Biedl syndrome	–	+	+	[25]
ASTN2 (*612856)	9q33.1	Important role in the developing mammalian brain by forming a complex with its paralog astrotactin 1 and regulating its expression on the surface of young cerebellar neuroblasts	–	+	+	[25]
CNTN5 (NB2) (*607219)	11q22.1	Neural adhesion molecule of the contactin subgroup of the Ig superfamily	–	+	+	[25,30]
CHRNA7 (*118511)	15q13.3	Nicotinic acetylcholine receptor, member of a superfamily of ligand-gated ion channels that mediate fast signal transmission at synapses	CAE, JAE, JME, GTCS, Rolandic epilepsy	Classic autism PDD-NOS, Asperger syndrome, Autistic features	+	[29,34–36]
MACROD2 (*611567)	20p12.1	It is expressed in fetal and adult human brain. In embryo and adult mice it is expressed in brain, especially in the ventricular zone. Its function is still unclear	–	+	+	[25,96]
SYN1 (*313440)	Xp11.23	It is associated with membranes of small synaptic vesicles, and may have a role in the regulation of neurotransmitter release in mature synapses and in neuronal development	Complex partial epilepsy, nocturnal epilepsy, GTCS	+	–	[31,32]

Abbreviations: CAE = childhood absence epilepsy; CDFE = cortical dysplasia-focal epilepsy syndrome (reported in homozygous mutation of *CNTNAP2* in Old Order Amish children); CNS = central nervous system; GTCS = generalized tonic-clonic seizures; GABA = gamma-aminobutyric acid; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; PDD-NOS = pervasive developmental disorder – not otherwise specified.

A. Lo-Castro, P. Curatolo / Brain & Development xxx (2013) xxx–xxx

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3

Table 2
Submicroscopic chromosomal rearrangements associated with syndromic conditions.

Chromosomal segment	Genes potentially involved	Autism	Epilepsy	ADHD	Dysmorphisms and other features	References
Del 1q21.1	PRKAB2, FMO5, CHD1L, BLC9, ACP6, GJA5, GJA8, GPR89B, HYDIN2	ASDs autistic features	GTCS, typical and atypical absence seizures, head drops, drop attacks	+	Variable/subtle dysmorphisms. Microcephaly, mild-moderate ID, MCA, eye abnormalities, short stature. Behavioral problems	[29,97,98]
Dup 1q21.1		ASDs autistic features	+	+	Variable/subtle dysmorphisms. macrocephaly, eye abnormalities. Behavioral problems	
Del 2q23.1	MBD5 [*] , EPC2	ASDs autistic features	FS, absence seizures, atonic seizures, tonic seizures, GTCS	ADHD short attention span hyperactivity impulsiveness	Microcephaly/brachicephaly, craniofacial abnormalities, broad forehead, thick/arched eyebrows, eye, nasal and ear abnormalities, macrostomia. Motor and language impairments, ataxia, behavioral problems	[37,38,99]
Del 15q13.3	CHRNA7 [*] , OTUD7A, KLLF13, TRPM1, MTMR10, MTMR5	Classic autism PDD-NOS Asperger syndrome autistic features	CAE, JAE, JME, Rolandic epilepsy	ADHD short attention span impulsiveness	Subtle dysmorphic features DD, Normal IQ-moderate ID, language impairment, behavioral problems	[36,37,59]
Dup 15q13.3		+	Not significant association	–		
Del 16p11.2	QPRT, DOC2A, SEZ6L2, KCTD13, MAPK3	ASDs autistic features (more common than in dup)	GTCS, MMPSI (more common than in dup)	+	MCA, MRI abnormalities Macrocephaly, broad forehead, flat midface, micrognathia, hypertelorism	[59–62]
Dup 16p11.2		+	+	+(more common than in del)	More severe language impairment, ID and dysmorphic features (but not recognizable) than deletion, microcephaly. Common behavioral problems. MCA, MRI abnormalities	
Del 16p13.11	MYH11, NDE1, ABCC1,	+	CAE, GTCS, JAE, JME	+	Subtle-severe dysmorphic features ID, brain	[59,63]
Dup 16p13.11	ABCC6	+	Generalized epilepsy	+	MRI abnormalities, micro-macrocephaly, congenital heart defects, bone and kidney abnormalities	

Abbreviations: ADHD = Attention Deficit and Hyperactivity Disorder; ASD = Autism Spectrum Disorders; CAE = childhood absence epilepsy; DD = developmental delay; Del = deletion; Dup = duplication; FS = febrile seizures; GTCS = generalized tonic-clonic seizures; ID = intellectual disability; IQ = intelligent quotient; MCA = multiple congenital anomalies; MMPSI = malignant migrating partial seizures of infancy; TC = tonic-clonic seizures; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy.

^{*} See also Table 1 for more information about *MBD5* and *CHRNA7* genes.

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A. Lo-Castro, P. Curatolo / Brain & Development xxx (2013) xxx–xxx

5

epilepsy/ASDs/ADHD varies among different conditions, but ID is present in the majority of aberrations.

Interestingly, de novo CNVs occur in about 7.5% of boys and in about 12% of girls with non-syndromic forms of ASDs. In syndromic patients, the detection of a causal CNV can reach up to 25% [58]. In patients with focal and generalized epilepsies without ID or ASDs comorbidities, CNVs have been found in about 3–9% of cases, with recurrent structural variations at 15q11.2, 15q13.3, 16p13.11 and 16p13.3 [29,35,58,59]. However, these genomic hotspots have been also associated with ID, autism, and other neuropsychiatric phenotypes [60–63]. Patients with epilepsy have a significantly increased burden of larger, gene-rich CNVs respect to controls, in particular when ID of mild-moderate degree or other neuropsychiatric conditions are associated to the epileptic phenotype. However, no significant association between the CNVs frequency or size and the type of epilepsy was found [64]. Also in this case, the only significant difference was represented by the cognitive level of patients [64].

The detection-rates of genome wide techniques in “pure” ADHD varies from 7% to 17% [27,65–67]. The presence of CNVs is not related to an atypical form of the disorder, and no difference has been observed in terms of severity, comorbidity, developmental features, family history or pre-/perinatal markers between patients with ADHD and CNVs and patients with ADHD only. The only significant difference was represented by the cognitive level of patients [27,65–67].

Several large studies have assessed the validity of copy-number changes (CNVs) analysis in the diagnostic workup for intellectual disability and autism, [42,68–71] and, more recently, array CGH has also been proposed in the diagnostic evaluation of patients with complicated epilepsy [72]. Therefore, there is a significant contribution of de novo CNVs recurrence in sporadic ASDs, ADHD, and epilepsy cases, however, the same alterations have also been detected in unaffected individuals and in complex phenotypes, suggesting that rare CNVs predispose to diseases, acting in an additive manner with other genetic or environmental factors [58]. In a recent array CGH study conducted on children known to carry a CNV associated with ID and congenital abnormalities, a second large CNV in addition to the primary genetic lesion has been detected in about 10% of cases [73]. Moreover, syndromic children could be distinguished from children with extreme phenotypic heterogeneity on the basis of the total number of CNVs, and whether the variants are inherited or de novo [73]. These findings support a “two-hit model”, in which a single CNV both increases the risk to have a neuropsychiatric phenotype as a single event, and exacerbates this phenotype in association with other additive large deletions or duplications. [74,75].

However, clinicians should be aware that array-based analysis may not lead to improved health outcomes of children with developmental disorders [76,77].

4. Animal models

Some genetic disorders, such as TSC and FXS, may serve as a model for understanding the common pathogenic pathways leading to epilepsy-associated ASDs and ADHD comorbidities, and offering the potential for new biologically focused treatment possibilities.

TSC is one of the largest identifiable causes of epilepsy, the second major cause of autism [78] and is frequently associated with ADHD-like symptoms, which affect about 30–60% of TSC children [79]. Exact mechanisms of epilepsy and ASDs in TSC are not totally understood, even if it seems clear that alterations in AMPARs and in expression of specific subunits of glutamate and GABA_A receptors, as well as a decreased expression of the glutamate transporter GLT-1 may all contribute to imbalances of excitation and inhibition [80]. mTOR signaling pathway plays a role in regulating neuronal cell morphology, GABAergic interneuron development, white matter connectivity and number and shape of synapses [81]. mTOR overactivation due to TSC1/2 mutation can lead to susceptibility to seizures, ADHD, ASDs and ID. Loss of GABAergic interneurons might be a direct consequence of TSC1 mutation [82]. Interestingly, mouse models of TSC demonstrated that learning and behavioral deficit, as well as impaired synaptic plasticity may be a consequence of mTOR overactivation due to loss of function of TSC1/TSC2 genes, altering the developmental regulation of ionotropic glutamate receptors and enhancing glutamatergic function [83]. In TSC mouse models rapamycin, an mTOR inhibitor, proved efficacy in determining a reversal of learning and behavioral deficits, and reduction of cytomegaly, myelination impairment or neuronal disorganization. Therefore, at least in the TSC mice models, mTOR inhibition could benefit cognitive and behavioral problems associated with epilepsy [84–86].

FXS is one of the most common monogenic cause of autism, responsible for 2–6% of all ASDs cases; cognitive impairment, seizures, hyperactivity, attention deficit, and impulsivity are the other common features of the syndrome [87]. Several molecular mechanisms have been hypothesized to cause the FXS phenotype. However the most relevant finding is the dysregulation between the excitatory mGluR and the inhibitory GABA receptor pathways [87,88]. In FXS, the uncontrolled mGluR activity due to the absence of FMRP, is responsible for disruption of synaptic morphology, cognitive impairment, social deficits, perseverative movements, and enhanced susceptibility to seizures [87]. In addition, significant dysfunctions in production,

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6

A. Lo-Castro, P. Curatolo / Brain & Development xxx (2013) xxx–xxx

metabolism, release, and receptor expression of the GABAergic pathway may alter specific brain regions, such as basolateral amygdala, cerebral cortex, striatum, and hippocampus/subiculum, justifying the neurocognitive and psychiatric phenotypes observed in FXS [89].

In FXS patients, the treatment implications of excessive mGluR activation have been tested using different mGluR antagonists. Treatments with fenobam and acamprosate resulted in reduction of ADHD core symptoms and improved communication skills, respectively [90,91]. In patients with a full methylation at *FMRI* promoter, AFQ056 administration showed a significant improvement on stereotypes, hyperactivity, and inappropriate speech versus placebo [92]. A novel potential therapeutic target is represented by Striatal-Enriched protein tyrosine Phosphatase (STEP), involved in the inappropriate AMPA and NMDA receptors internalization, and ERK1/2 pathway dysregulation observed in FXS animal models. STEP levels are elevated in *Fmr1* KO mice and probably mediate the exaggerated mGluR-dependent LTD, thus contributing to synaptic weakening, consequent cognitive deficits and predisposition to seizures [93].

5. Future directions

Both ASDs and ADHD are common disorders in childhood epilepsy, and this co-occurrence may share a strong genetic basis. Future studies are required to assess the bidirectional relationship between these conditions. Functional genetic studies will shed further light on the biological mechanisms by which genetic variants predispose to ASDs/ADHD comorbidity associated with childhood epilepsy and hopefully may provide new insights for developing biologically tailored treatment options. However, a better knowledge can only be achieved by considering homogeneous populations of patients. Recently, dietary supplementation in Branched Chain Ketoacid Dehydrogenase Kinase (*Bckdk*) knock-out mice showed a significant improvement of neurobehavioral phenotype, providing hope that this form of Mendelian autism associated with ID and epilepsy, may represent a potentially treatable syndrome [94].

While a developmental framework offers a way of understanding the pathogenic complexity of epilepsy and associated comorbidities, the current lack of longitudinal data does not allow to disentangle how different combinations of genetic-environmental risk factors may disrupt developmental trajectories in the brain leading to distinguished neurobiological deficits, and to different clinical endophenotypes.

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A. Lo-Castro, P. Curatolo / Brain & Development xxx (2013) xxx–xxx

7

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8

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9

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Comprehensive Psychiatry xx (2013) xxx–xxx

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On the relationship between retrospective childhood ADHD symptoms and adult BPD features: The mediating role of action-oriented personality traits

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Abstract

A number of studies have reported data suggestive of a significant association between ADHD and BPD, nevertheless, the nature of this relation has not been fully understood yet. In our study, we tried to evaluate if the relationship between retrospectively assessed ADHD symptoms and adult BPD features could be mediated by selected temperament/personality traits. Four hundred forty-seven in- and outpatients consecutively admitted to the Clinical Psychology and Psychotherapy Unit of the Scientific Institute H San Raffaele of Milan, Italy, were administered the Italian versions of the following instruments: Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II), Wender Utah Rating Scale (WURS), Temperament and Character Inventory-Revised (TCI-R), Barratt Impulsiveness Scale-11 (BIS-11), and Aggression Questionnaire (AQ). Our mediation analyses showed that the combination of impulsivity, aggression, novelty seeking, and juvenile conduct problems completely mediate the relationship between retrospectively assessed ADHD symptoms and current BPD features.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by a persistent and developmentally inappropriate pattern of inattention, impulsivity, and hyperactivity [1]. ADHD is thought to affect 3–7% of school-age children, albeit prevalence estimates vary predictably depending on sampling strategies and methods of ascertainment [1]. Although ADHD symptoms, especially restlessness, tend to diminish with age [1,2], it has been consistently reported that ADHD tend to persist into adolescence in 30–80% of affected subjects [3–5], and into adulthood in up to nearly 50% of childhood cases [6–8]. Biederman et al. [9] also found that, in adult life, a large proportion of subjects who had previously received a diagnosis of ADHD, although no longer meeting criteria

for the disorder, continue to show residual symptoms or fail to attain a functional remission. As in the case of childhood ADHD, adult ADHD is associated with an increased risk for comorbid psychopathology. Data collected from a substantial sample of adult respondents ($N = 3199$) in the National Comorbidity Survey Replication [10] indicated that adult ADHD is highly comorbid with many other Axis I DSM-IV disorders (i.e., mood disorders, anxiety disorders, substance use disorders and intermittent explosive disorder) [11]. Moreover, long-term longitudinal studies consistently evidenced a significant association between childhood ADHD and antisocial personality disorder in adulthood [12–14].

The relationships between ADHD and another cluster B personality disorder, namely borderline personality disorder (BPD), have been investigated less thoroughly, this in spite of the several similarities that can be found in the clinical presentation of the two disorders. Indeed, though ADHD patients are not characterized by the intense suicidal preoccupations, self-mutilating behavior or feelings of abandonment often seen in those with BPD, the two disorders share other prominent symptoms, such as impulsivity, affective instability, and difficulty in controlling anger

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2

D. Carlotta et al. / Comprehensive Psychiatry xx (2013) xxx–xxx

[15]. The high degree of similarity between ADHD and BPD may even represent a risk factor for misdiagnosing ADHD patients as if they suffered from BPD (and vice versa). Herpertz [16], for instance, suggested that diagnostic procedure should be supplemented by neuropsychological assessment which includes, in particular, testing of inhibitory functioning. Otherwise, it has to be highlighted that similarities between the disorders also extend to their neuropsychological profile.

In ADHD research, meta-analytic [17,18] reviews have found that deficits in executive functioning, especially in motor inhibition, are among the most robust neuropsychological findings. Since impulsivity is a core aspect of BPD [19], not surprisingly poor inhibitory functioning, particularly poor executive response inhibition [20], has also been consistently found in BPD subjects [21]. However, it has been pointed out that BPD patients generally perform more poorly than control across a wide range of cognitive domains [22,23]. Notably, BPD also shares with ADHD significant impairments in attention [23]. Various studies [24] found significant differences between BPD samples and controls in the performance on the Digit Symbol subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) [25], which is considered a test of attention and visual motor coordination [26]. Carpenter and colleagues [27] reported that individuals with BPD performed poorer than controls on the Trail Making Test A and B [28]. Similar results have been found by Monarch et al. [23], who additionally demonstrated that BPD patients also had worse results than controls on the Continuous Performance Task (CPT) [29]. Posner et al. [30] showed that BPD patients performed worse than controls in the conflict module of the Attentional Network Task (ANT) [31], but displayed no deficit in other attentional networks. More specifically, individuals with BPD exhibited significant difficulties in correctly indicate the direction of a target arrow surrounded by flanker arrows pointed in the opposite direction (incongruent trials). Similar results have also been found with children scoring high on BPD precursors [32] (e.g., emotional lability/negativity, diminished effortful control, interpersonal difficulties, etc.). Notably, Rogosch and Cicchetti [32] found inefficient processing in the conflict attentional network to be relatively unrelated to other forms of childhood disturbance. This result led the authors to suggest it may represent a risk factor for BPD that is less affected by experience, probably linked to neuronal loss in the anterior cingulate cortex (ACC). ACC is a brain region which is essential to executive control [33,34], particularly to conflict monitoring [35], and attention [36], but also plays an important role in emotional processing [37]. Interestingly, functional and volumetric abnormalities of the ACC have been found in both ADHD [38] and BPD [39,40] patients. More generally, ADHD and BPD have been associated with dysfunctions in various prefrontal areas [38,40] related to attentional mechanisms, decision-making, impulse control, etc.

These similarities in the neuropsychology of the disorders could maybe explain the high rates of comorbidity between them. A recent cross-sectional study [41] reports that of 181 participants who were diagnosed as BPD, 69 (38.1%) were diagnosed as suffering a comorbid adult ADHD. Moreover, the BPD-ADHD group was found to be associated with higher rate of substance abuse disorder and suicidal behavior and to score higher on self-reported impulsivity, showing a more impulsive profile than BPD patients without ADHD comorbidity, which, by contrast, reports more anxiety and depressive disorders. Another study [42], examining a group of women with BPD, found a prevalence of adult ADHD of approximately 16%, a value significantly lower than that reported by Ferrer and colleagues [41]. However, as argued by these last authors [41], this difference may be explained by the fact that, in Philipsen et al.'s study [42], men were not included in the sample (ADHD is more common among males than females [1]) and that only the combined ADHD type was studied, which could have led to an underestimation of comorbidity rates. Various studies also examined the prevalence of BPD among adults with ADHD: comorbidity rates ranged from 19% to 37% [43–45,20]. Miller et al. [43], in particular, subdivided a group of older adolescents/young adults (aged 16–26 years) previously diagnosed with childhood ADHD into those who continued to meet diagnostic criteria for ADHD (“persisters”) and those that did not (“remitters”) and compared them to a never-ADHD comparison group. Interestingly, although persisters were significantly more likely than controls to be diagnosed with paranoid, narcissistic, borderline and antisocial personality disorders, they were separable from remitters only for antisocial personality disorder and paranoid personality disorder.

With regard to the relationship between childhood ADHD and BPD, retrospective studies report prevalence estimates of childhood ADHD in adult BPD patients ranging from 25.5% up to 59.5% [42,46–51]. In particular, Philipsen et al. [42] found that, among women with BPD, childhood ADHD was associated with greater emotional abuse in childhood as well as more severe BPD psychopathology in adulthood. Among the major controlled prospective studies on childhood ADHD, only the Milwaukee follow-up study [52] reported data regarding BPD. Its results indicated that 14% of the hyperactive children met the criteria for BPD diagnosis as adults, and that the presence of adolescence CD increased the likelihood of BPD diagnosis in adulthood. Using a prospective follow-up design, Miller et al. [43] found a similar percentage (13.5%) of childhood ADHD-diagnosed subjects with BPD but it did not confirm Fischer et al.'s evidence [52] on the relationship between ADHD, CD and BPD. In fact, Miller et al.'s results [43] showed that externalizing childhood comorbidity marginally predicted antisocial personality disorder but not BPD. In a recent prospective longitudinal study [53], Stepp and colleagues examined ADHD and Oppositional Defiant Disorder (ODD) severity as childhood psychopathology precursors of BPD

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D. Carlotta et al. / *Comprehensive Psychiatry* xx (2013) xxx–xxx

3

symptoms in adolescence. The authors used data collected in a large sample of girls, followed annually from late childhood to early adolescence, finding that ADHD and ODD at age 8 predicted BPD symptoms at age 14. Furthermore, the effects of ADHD and ODD were independent from Conduct Disorder (CD) and depression at baseline. Similar evidences were found in another prospective study [54] conducted on a clinical sample of males, initially aged between 7 and 12, and reassessed on multiple occasions through to age 24. Again, ADHD and ODD were the only childhood psychiatric disorders to predict BPD symptoms.

Although various studies have reported data suggestive of a significant association between ADHD and BPD, this relation has not been fully understood yet. One hypothesis is that the overlap of phenomenological features between ADHD and BPD may indicate that the two disorders belong to a common liability spectrum [55]. In particular, following Hollander's [55] suggestion, ADHD, BPD and other psychiatric disorders (e.g., impulse control disorders, cluster B personality disorders, substance use, etc.) may belong to a shared group lying at one end of a spectrum of compulsive-impulsive disorders related to risk taking or avoidance. Other researchers have proposed that ADHD could be a childhood precursor of BPD [43,56]. For example, it has been suggested that impulsivity and impulse control disorders, such as ADHD, may predispose individuals to the development of BPD [57]. In particular, Crowell et al. [56,57], extending Linehan's biosocial theory of BPD [58] suggested that impulsivity is among the earliest emerging traits among those who later receive a BPD diagnosis. According to Linehan [58], BPD's core problem is emotion dysregulation, resulting from the interaction between biological vulnerabilities and an invalidating developmental context. Crowell et al.'s model [57] posit that impulsivity has a primary role in generating escalating transactions between the child and the caregiver which increase risk for emotion dysregulation. According to another hypothesis [59], ADHD may represent a risk factor that may interact with the social environment of the child so as to aggravate and amplify his/her neurobehavioral vulnerabilities through poor affective fit and/or maltreatment. These transactions may contribute to an insecure/disorganized attachment model and dissociation, which, in turn, would contribute to impaired metacognition and difficulties in the cognitive processing of interpersonal information. This would lead to various manifestations of BPD, including splitting, paranoia, transient psychoses, etc.

In this study, we tried to evaluate if the relationship between retrospectively assessed childhood history of ADHD symptoms and adult BPD features could be mediated by selected temperament/personality traits. In particular, we focused our attention on the mediating role of action-oriented personality traits [60,61], a cluster of personality features (including extraversion, sensation seeking, and lack of inhibition) considered orthogonal to anxiety proneness

and associated to risk taking, acting without thinking, and lack of planning.

2. Method

2.1. Participants

The subjects in this study were 447 in- and outpatients (193 [43.2%] males, 254 [56.8%] females; mean age = 39.21 years [SD = 11.41]) consecutively admitted, from January 2008 to May 2011, to the Clinical Psychology and Psychotherapy Unit of the Scientific Institute H San Raffaele of Milan, Italy. None of the subjects met any of the following exclusion criteria: (1) age less than 18 years; (2) IQ less than 75; (3) diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder according to DSM-IV diagnostic criteria; (4) diagnosis of dementia or organic mental disorder according to DSM-IV diagnostic criteria; and (5) education level lower than elementary school. Subjects with Axis I diagnoses were administered the SCID-II at acute symptom remission, according to the judgment of the clinicians who were following them in treatment, by expert trained raters to avoid confounding effects of Axis I disorders on Axis II diagnoses [62]. The absence of acute symptom remission was considered an exclusion criterion from the study.

2.2. Measures

Participants were administered the Italian versions of the following instruments: a) Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II) [63]; b) Wender Utah Rating Scale (WURS) [64]; Temperament and Character Inventory-Revised (TCI-R) [65]; Barratt Impulsiveness Scale-11 (BIS-11) [66]; Aggression Questionnaire (AQ) [67].

2.2.1. SCID-II

The SCID-II [63] is a semi structured interview of 140 items organized by diagnosis, which provides both a categorical and a dimensional (i.e., the number of criteria found) assessment of ten DSM-IV axis II personality disorders as well as depressive personality disorder, passive-aggressive personality disorder, and personality disorder not otherwise specified (NOS). The SCID-II was administered approximately one week after questionnaire completion by trained raters who were blind to the aims of the study and also to the personality traits data. Although DSM-IV conceptualizes mental disorders as distinct categories, several studies have provided data suggesting that personality disorders can be best described as dimensional constructs, rather than as discrete categories [68–74]. The DSM-IV's categorical approach to diagnosis has been criticized for inadequate coverage and for the use of arbitrary diagnostic thresholds [75], whereas dimensional scores are thought to approximate more closely the continuous distribution of cognitive and social features associated with

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4

D. Carlotta et al. / *Comprehensive Psychiatry* xx (2013) xxx–xxx

personality disorders [76]. In light of these considerations, we used dimensional scores of personality disorders (i.e., the number of criteria rated as present for each disorder) in most of our analyses; a categorical measure of BPD was used only to provide a prevalence rate of childhood ADHD comparable to those reported in prior studies.

In the current study, the inter-rater reliability of the SCID-II diagnoses was assessed in the first 67 consecutively admitted outpatients, using a pairwise interview design. Interclass correlation coefficients (ICCs), based on a one-way random effects ANOVA, were computed to evaluate the inter-rater reliability of dimensionally assessed SCID-II personality disorders. As a whole, the inter-rater reliability of the dimensional SCID-II diagnoses was acceptable, median ICC value = .84, SD = .15; in particular, the ICC value for the dimensional BPD diagnosis was .88. The inter-rater reliability of the number of personality disorder diagnoses based on SCID-II was adequate, ICC = .88. The inter-rater reliability of the categorical SCID-II personality disorder diagnoses was assessed computing Cohen κ coefficient. The Cohen κ value for BPD diagnosis was .90; the inter-rater reliability of any PD diagnosis was adequate, κ = .88.

2.2.2. WURS

The WURS [64] is a self-report questionnaire designed to retrospectively assess the severity of ADHD symptoms during childhood. Ward et al. [64] reported adequate split-half reliability of the WURS; the scale also showed a moderate convergence with parent retrospective reports and demonstrated to efficiently discriminate subjects with adult ADHD from controls. Moreover, the WURS significantly predicted the treatment outcome of subjects with adult ADHD. In Ward et al.'s study [64], a cut-off score of 46 was proposed. A recent review of the currently available adult ADHD rating scales cited the WURS, together with the CAARS, as having the best psychometric properties among the fourteen scales identified; it also reported for the WURS a 85% sensitivity and a >90% specificity at its given cut off [77]. The Italian translation of the WURS showed adequate reliability and validity [78]. In the present study, the Cronbach α value of the WURS total score was .89.

2.2.3. TCI-R

The TCI-R [65] is a 240-item self-report questionnaire, with responses in a five point Likert-type scale questionnaire, measuring the four dimensions of temperament (novelty seeking, harm avoidance, reward dependence, and persistence) and three dimensions of character (self-directedness, cooperativeness, and self-transcendence). The scales of the Italian version of the TCI-R showed adequate internal consistency and 1-month test-retest reliability [79]; moreover, the factor analysis results have been found to be consistent with the 7-factor structure of the TCI-R scales. In the present study, the Cronbach α values of the TCI scales were .69, .87, .78, .89, .87, .85 and .85, respectively.

2.2.4. BIS-11

The BIS-11 [66] is a 30-item self-report questionnaire with responses in a four point Likert-type scale. It measures three subtypes of impulsivity: motor impulsivity, attention impulsivity, and nonplanning impulsivity. The three scores are summed to produce a total impulsivity score. The Italian version showed internal consistency reliability, test-retest reliability, and construct validity data almost identical to those reported for the English version in both nonclinical [80] and clinical samples [81]. In the present study, we have taken into account only the BIS-11 total score, the Cronbach α value was .69.

2.2.5. AQ

The AQ [67] is a 29-item, Likert type, self-report questionnaire, which measures four components of aggression: physical aggression, verbal aggression, anger, and hostility. The four components are summed to produce a total aggression score. Evidence of reliability and construct validity for both English [67] and Italian [82] versions of the scale was reported in previous studies. In the present study, we have taken into account only the AQ total score, the Cronbach α value was .90.

2.3. Mediation analyses

Mediation models of psychological processes are popular because they allow interesting associations to be decomposed into components that may be useful for theory development and identification of possible points of intervention in applied work [83].

Fig. 1 shows the elements of the mediation analysis. Part 1 of Fig. 1 implies that a unit change in X is associated with a change of c units in Y , when only X and Y are considered (i.e., c represents the ordinary least square regression coefficient). Part 2 of Fig. 1 shows a model that includes variable I , the proposed mediator. The mediation model assumes that I is affected by changes in X ; one unit change in X is associated with a change of a units in I . The model also assumes that changes in I are associated with changes in Y , above and beyond the direct affect of X on Y . A unit change of I is associated with a change of b units in Y , when X is held constant. As a result, X is said to have an indirect effect on Y through the mediator I [83].

In order to assess the intervening variable effect, we estimated, following Shrout and Bolger's [83] recommendations, indirect path coefficients ($a \times b$ coefficients). In the case of multiple intervening variables, the method of $a \times b$ products provides both an overall significance test and separate significance tests for the individual mediating variables, it allows also to statistically evaluate the existence of significant differences between the mediating variables [83]. In order to evaluate not only the significance of the mediation effect, but also the strength of mediation, we computed the effect proportion mediated measure (P_M) [83]. P_M is the ratio of the indirect effect to the total effect of the independent variable in predicting the dependent variable.

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D. Carlotta et al. / Comprehensive Psychiatry xx (2013) xxx–xxx

5

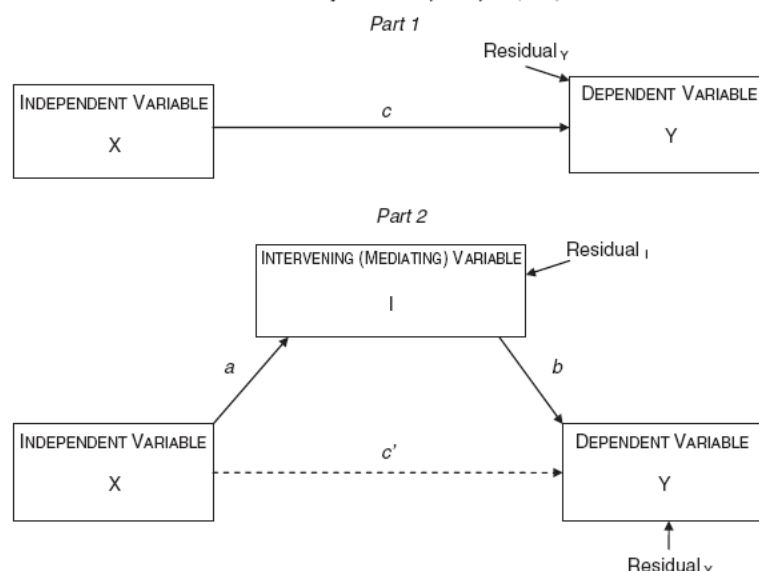


Fig. 1. Path diagrams showing total effect (Part 1) and mediated effect (Part 2) of the independent variable (X) on the dependent variable (Y).

Normal-theory significance tests were used to test the significance of all path coefficients, with the exception of indirect effect (ab) path coefficients. Following recommendations by Bollen and Stine [84] and Shrout and Bolger [83], the significance of indirect effect coefficients was tested by computing confidence intervals (CIs) using bootstrap simulations; in particular, 95% bias corrected accelerated CIs were computed based on 5,000 bootstrap replications. Mediation and bootstrap analyses were carried out using Preacher and Hayes's [85] computer program. In all regression models collinearity diagnostics were based on condition index values and on regression coefficient variance decomposition [86].

3. Results

Roughly 75% of the participants (74.9%, $n = 335$) had a personality disorder (PD); the most frequently diagnosed personality disorders were narcissistic PD (21.5%, $n = 96$), PD NOS (17.7%, $n = 79$) and BPD (14.5%, $n = 65$). In this sample, gender was not significantly associated with both categorical, $\chi^2 = .19$, $p > .50$, and dimensional, $t(445) = .64$, $p > .50$, BPD diagnoses. With regard to Axis I diagnoses, 162 (36.2%) of participants had an Axis I disorder; the most frequently diagnosed Axis I disorders were mood disorders (22.0%, $n = 105$).

Descriptive statistics and gender comparisons for all measures used in this study are listed in Table 1. Participants' gender showed a significant correlation only with novelty seeking scores, $r_{p-b} = .14$, $p < .005$, with males reporting

higher levels of novelty seeking than females. The percentage of participants scoring over the WURS cut-off point of 46 was 12.8% ($n = 57$). Among BPD participants, the percentage of subjects scoring 46 or more on the WURS (30.8%, $n = 20$) was significantly higher than that of non-BPD participants (9.7%), $\chi^2 = 20.34$, $p < .001$, $\phi = .22$.

In Table 2 are listed the correlation coefficients of the WURS scores and the SCID-II BPD dimensional scores with the other measures used in this study. As regards the correlations with other dimensionally assessed psychopa-

Table 1

Wender Utah Rating Scale, Temperament and Character Inventory-Revised, Barratt Impulsiveness Scale-11, and Aggression Questionnaire descriptive statistics and gender comparisons.

	Whole sample ($N = 447$)		Male participants ($N = 193$)		Female participants ($N = 254$)	
	M	SD	M	SD	M	SD
WURS	23.15	18.63	24.93	19.34	21.83	18.02
NS	102.08	13.61	104.24	13.64	100.47	13.41
HA	103.94	19.39	102.25	18.91	105.33	19.56
RD	98.12	14.48	95.97	13.75	99.61	14.80
P	108.31	19.75	107.73	18.55	108.60	20.55
SD	122.68	22.09	121.93	22.36	123.07	21.81
C	122.41	18.50	119.89	17.83	124.12	18.72
ST	66.25	15.61	65.20	15.02	66.98	16.03
BIST	66.62	11.46	66.75	11.16	66.55	11.71
AQT	76.50	19.92	78.36	19.66	75.15	20.06

WURS: Wender Utah Rating Scale; NS: Novelty Seeking; HA: Harm Avoidance; RD: Reward Dependence; P: Persistence; SD: Self-Directedness; C: Cooperativeness; ST: Self-Transcendence; BIST: Barratt Impulsiveness Scale-11 Total score; AQT: Aggression Questionnaire Total score.

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6

D. Carlotta et al. / *Comprehensive Psychiatry* xx (2013) xxx–xxx

Table 2

Correlations of Wender Utah Rating Scale scores and SCID-II BPD dimensional scores with Temperament and Character Inventory-Revised, Barratt Impulsiveness Scale-11, and Aggression Questionnaire Scores (N = 447).

	NS	HA	RD	P	SD	C	ST	BIST	AQT
WURS	.32*	.20*	-.00	-.09	-.21*	-.17*	.23*	.46*	.52*
BPD	.31*	.06	.05	-.09	-.14*	-.13	.12	.39*	.37*

BPD: SCID-II BPD Dimensional Score. * Significant after Bonferroni correction ($p < .004$).

thology, even after Bonferroni correction for multiple testing (Bonferroni-corrected significance level: $p = .004$), BPD diagnosis correlated significantly with histrionic PD, $r = .30$, $p < .001$, antisocial PD, $r = .21$, $p < .001$, and dimensionally assessed CD – i.e., the number of DSM-IV criteria for conduct disorder based on SCID-II interview – $r = .38$, $p < .001$. After Bonferroni correction (Bonferroni-corrected significance level: $p = .004$), the WURS correlated significantly with dimensionally assessed BPD, $r = .35$, $p < .001$, CD, $r = .31$, $p < .001$, antisocial PD, $r = .21$, $p < .001$, narcissistic PD, $r = .19$, $p < .001$, and passive-aggressive PD, $r = .14$, $p < .004$. However, no significant association was observed between the WURS and antisocial PD when the effect of CD was held constant, partial $r = .07$, $p > 0$.

Participant's gender did not show a significant moderator effect on the association between WURS and BPD, gender-by-WURS $\beta = -.12$, $p > .10$ (Bonferroni-corrected significance level: $p = .017$), but it has been found to moderate the relationships between the WURS and CD, gender-by-WURS $\beta = -.36$, $p < .001$, and adult antisocial PD, gender-by-WURS $\beta = -.36$, $p < .001$. Interestingly, the WURS significantly predicted the number of adult antisocial PD traits only in male participants, $\beta = .32$, $p < .001$ (female participants: $\beta = .01$, $p > .90$). On the other hand, despite the gender-by-WURS effect, the WURS significantly predicted CD both in men, $\beta = .39$, $p < .001$, and women, $\beta = .19$, $p < .005$.

The variables we have chosen as possible mediators in the relation between childhood ADHD symptoms and adult BPD features were those which showed significant correlation with both WURS scores and SCID-II BPD dimensional scores (namely, CD, novelty seeking, self-directedness, BIS-11 total score, and AQ total score). In all mediation models participants' gender were entered as control variable.

For the first five models, The Bonferroni-corrected significance threshold was set to $p = .017$. In the first mediation model, we tested the mediation effect of CD on the relation between WURS scores and BPD dimensional scores. The WURS significantly predicted conduct disorder, standardized path coefficient = .31, $p < .001$; in turn, the conduct disorder significantly predicted BPD, standardized path coefficient = .30, $p < .001$. The total standardized effect of the WURS on BPD was .35, $p < .001$. Conduct disorder significantly mediated the relationship between WURS scores and BPD dimensional scores, $a \times b = .09$, 95% CI:

.05–.14, although the direct effect of the WURS remained significant, standardized path coefficient = .26, $p < .001$. The P_M effect size measure for this partial mediation effect was .26, i.e., 26% of the association between WURS scores and SCID-II BPD dimensional scores was mediated by conduct disorder.

In the second mediation model, WURS scores significantly predicted the mediator, that is, novelty seeking scores, standardized path coefficient = .32, $p < .001$; in turn, novelty seeking scores significantly predicted BPD dimensional scores, standardized path coefficient = .21, $p < .001$. The total standardized effect of the WURS on BPD was .36, $p < .001$. The mediator effect was significant, $a \times b = .07$, 95% CI: .03–.12, nevertheless, as above, the direct effect of the WURS remained significant, standardized path coefficient = .29, $p < .001$. The P_M effect size measure for this mediation model was .19.

In the third model, the mediator role of self-directedness was tested. WURS scores significantly predicted self-directedness scores, standardized path coefficient = -.21, $p < .001$; on the contrary, self-directedness scores did not significantly predict BPD, standardized path coefficient = -.07, $p > .05$. The total standardized effect of the WURS on BPD dimensional scores was .36, $p < .001$. The mediator effect was not significant, $a \times b = .01$, 95% CI: -.00–.04; the direct effect of the WURS total score remained significant, standardized path coefficient = .35, $p < .001$. The P_M effect size measure was .03.

In the fourth mediation model, we tested the mediation effect of BIS-11 total scores. The WURS significantly predicted the mediator, standardized path coefficient = .46, $p < .001$; in turn, the BIS-11 significantly predicted BPD, standardized path coefficient = .29, $p < .001$. The total standardized effect of the WURS on BPD was .35, $p < .001$. BIS-11 total scores significantly mediated the relationship between WURS scores and BPD dimensional scores, $a \times b = .14$, 95% CI: .09–.19, but the direct effect of the WURS remained significant, standardized path coefficient = .21, $p < .001$. The P_M effect size measure for this partial mediation effect was .40.

In the fifth model, the mediator role of AQ total scores was analyzed. The WURS significantly predicted AQ total scores, standardized path coefficient = .52, $p < .001$; in turn, the AQ significantly predicted BPD, standardized path coefficient = .27, $p < .001$. The total standardized effect of the WURS on BPD dimensional scores was .34, $p < .001$. The mediator effect was significant, $a \times b = .14$, 95% CI: .08–.20; also the direct effect of the WURS total score remained significant, standardized path coefficient = .20, $p < .001$. The P_M effect size measure for this mediation model was .40.

Lastly, we tested the combined mediation effect of CD, novelty seeking, BIS-11, and AQ; self-directedness was excluded from the model because, as indicated by the previous mediation analysis, it did not result a significant mediator of the relation between the WURS and BPD. In this last model, the significance level, according to Bonferroni

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D. Carlotta et al. / Comprehensive Psychiatry xx (2013) xxx–xxx

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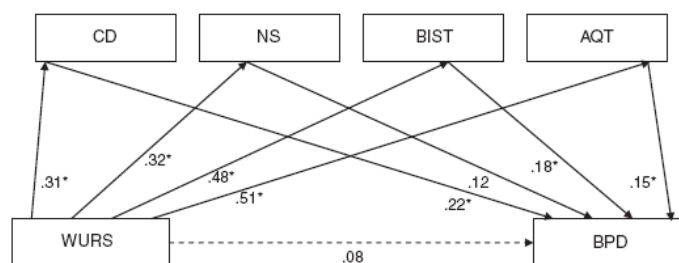


Fig. 2. Path diagram showing mediated effect (through Conduct Disorder, Novelty Seeking, Barratt Impulsiveness Scale-11, and Aggression Questionnaire) and direct effect of the Wender Utah Rating Scale on SCID-II BPD Dimensional Scores. The model included participants' gender as control variable. For ease of presentation residual terms were omitted. Note. *Significant after Bonferroni correction ($p < .008$).

correction, was set to $p = .008$. Standardized path coefficients for this model are presented in Fig. 2. The total mediation effect was significant, $a \times b = .27$, 95% CI: .18–.36, while the direct effect of the WURS resulted no longer significant, standardized path coefficient = .08, $p > .05$, suggesting complete mediation. The P_M effect size measure for this mediation model was .76.

4. Discussion

The relationship between ADHD and BPD has been documented by a number of studies, however has not yet been fully understood. The two disorder share diverse clinical features [15] and show several overlapping functional and structural neuroanatomical abnormalities [87]. Further, cross-sectional and longitudinal studies (for references, see Introduction) reported evidences suggesting that childhood ADHD may be a serious risk factor for adult BPD. However, as discussed by Philipsen [87], BPD patients present some symptoms, such as suicidal and self-injurious behaviors, which are not characteristic of ADHD. Moreover, the interpersonal correlates of the two disorders are quite different. Therefore, the emergence of BPD symptoms in ADHD individuals might depend on additional developmental antecedents. Following Philipsen's suggestions, the present study investigated if temperament/personality traits could mediate the relation between childhood ADHD symptoms and adult BPD features.

The main finding of our study is that this relation seems to be mediated by action-oriented personality traits. Indeed, impulsivity, aggression, novelty seeking, and juvenile conduct problems altogether completely mediated the relationship between retrospective ADHD symptoms and current BPD features. These evidences suggest that the developmental relationships between ADHD and BPD are likely to be complex and to involve the impact of childhood ADHD on extreme manifestations of a selected personality profile. Following Judd's [59] hypothesis, it could be argued that the early parent–child relationship may be negatively influenced by transactions between neurocognitive difficulties associated to ADHD and an extreme temperament

profile, leading to insecure attachment patterns, which are thought to play a role in BPD development [88]. However, our results also support alternative propositions within the literature on BPD and its developmental antecedents. Hollander [55], for example, formulated the hypothesis of common neurobiological liability factors underlying ADHD and BPD. According to the author, ADHD and BPD share structural and neurotransmitter alterations in the brain which result into impulsive decision-making and risky behaviors. Action-oriented personality traits have been similarly linked to risk taking and impulse control/dyscontrol [60,61], thus our results could suggest a possible overlap in the neurobiological substrates underlying ADHD and BPD.

The results of our mediation analyses show that, taken individually, impulsivity and aggression explain about 40% of the association between ADHD and BPD. This results are consistent with the notion of impulsivity and impulsive aggression as major underlying dimensions of BPD [19,89] and provide support to the biosocial developmental model proposed by Crowell and colleagues [57]. According to this model, early biological vulnerabilities, initially expressed as impulsivity, affects nurturing contexts, which in turn affect the child's biological functioning, in an escalating process. These transactions would lead to emotional, behavioral, and cognitive dysregulation, and thereby contribute to the genesis of a borderline personality. Starting from this theory, the developmental link between ADHD and BPD could be explained as primarily due to the child's impulsivity and its interaction with an invalidating family environment. The results of the present study do highlight the prominent role of impulsivity in mediating the relation between ADHD and BPD, but also draw attention to the contribution of other personality features, particularly aggression.

The main limitation of the present study is that it is retrospective in nature. Following Brewin et al.'s [90] recommendations, we used a structured method of assessment that could enhance recall of childhood ADHD symptoms (i.e., the WURS). However, the risk of a memory bias cannot be completely ruled out, and our results should be considered in the light of the questions raised about the accuracy of adult

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8

D. Carlotta et al. / *Comprehensive Psychiatry* xx (2013) xxx–xxx

recall of childhood ADHD symptoms [91]. A second major limitation of this study is its cross-sectional design. In this case, mediation analyses need to be considered with caution, because alternative directions of causality cannot be excluded. Although it was based on a large number of participants, our sample was not actually randomly selected. In other words, it represented a convenient study group of clinical adults rather than a representative sample. This sampling procedure raises questions about the generalizability of our findings to different clinical samples, and to nonreferred samples; we emphasize the need for further studies that replicate our findings. Finally, no measures of general psychiatric severity were gathered, hence our analyses could not be controlled for the potential confounding effect of this variable.

Even with these limitations, the present study contributes to increase the existing body of evidences regarding the developmental antecedents of BPD and, in particular, offers insights on the role played by action-oriented personality traits. Otherwise, further studies, especially prospective ones, are needed to elucidate the association between ADHD in childhood and later BPD, and the effect of temperament/personality traits on this relation. Indeed, although recent longitudinal studies [53,54] have provided initial support for the notion that BPD symptoms may emerge as the result of previous ADHD symptoms, little is known about the process (or processes) underlying this progression.

A promising research line is that concerning the role of the interaction between the child's personality profile and his/her family environment in the transition from ADHD to BPD. In the present study, we focused primarily on the part played by personality features, but other researchers have highlighted the critical role of the parent–child relationship in the genesis of BPD (e.g., Crowell et al. [57]; Judd [59]). It would be of great interest to conduct longitudinal studies following ADHD children into adulthood, evaluating the different contribution of individual temperamental characteristics and parent's rearing attitudes to the later emergence of PDs, particularly BPD. Considering the importance ascribed to attachment relations in the development of BPD [88], longitudinal studies could also provide data on how ADHD symptomatology and extreme temperamental traits impact on attachment patterns, and whether, and in what ways, this influence may account for the development of BPD features. An alternative approach might be to specifically select “at-risk” samples on the basis of extreme temperamental characteristics. These subjects may be followed longitudinally and compared with “normal” controls in respect to rates of ADHD and BPD symptoms, testing the possible differences in the correlations between the two disorders. The results from such studies may help to confirm and to extend our findings, shedding light on the developmental pathways linking childhood ADHD to later BPD.

From a clinical perspective, our results lend support to the utility of a temperament/personality testing in the assessment of ADHD in children, in order to identify potential risk factors for developing later personality problems and to

arrange early preventive interventions. In addition, evaluating the presence of childhood and adult ADHD in BPD patients could aid case formulation, informing clinical decisions on choice and course of treatment. Moreover, the integration of neurobehavioral testing into ADHD and BPD assessment procedures might help to identify potential targets of preventive interventions and could serve to improve diagnostic accuracy, to guide prognostic judgments and to suggest intervention priorities.

Taking into account the overlapping clinical features of adult ADHD and BPD, Hesslinger et al. [92] have presented a structured skills training program for adult patients with ADHD based on the principles of Dialectical Behavioral Therapy (DBT) for BPD developed by Linehan [58]. This treatment resulted in positive outcomes, with patients significantly improving on measures of ADHD and depressive symptoms, and overall personal health status. However, the current literature on psychotherapy research lacks empirical data on the effect of psychotherapy in BPD patients with current or childhood ADHD. Hence, in line with Philipson's suggestions [42], we recommend further research to evaluate whether these subgroups of patients would benefit from specific interventions.

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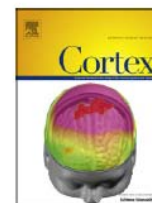
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Research report

Zoom-out attentional impairment in children with autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) has long been associated with an inability to experience wholes without full attention to the constituent parts. A zoom-out attentional dysfunction might be partially responsible for this perceptual integration deficit in ASD. In the present study, the efficiency of attentional focusing mechanisms was investigated in children affected by ASD. We measured response latencies to a visual target onset displayed at three eccentricities from the fixation. Attentional resources were focused (zoom-in) or distributed (zoom-out) in the visual field presenting a small (containing only the nearest target eccentricity) or large (containing also the farthest target eccentricity) cue, 100 or 800 msec, before the target onset. Typically developing children, at the short cue-target interval, showed a gradient effect (i.e., latencies are slower at the farthest eccentricity) in the small focusing cue, but not in the large focusing cue condition. These results indicate an efficient zoom-in and zoom-out attentional mechanism. In contrast, children with ASD showed a gradient effect also in the large focusing cue condition, suggesting a specific zoom-out attentional impairment. In addition, the ASD group showed an atypical gradient effect at the long cue-target interval only in the small cue condition, suggesting a prolonged zoom-in and sluggish zoom-out attentional mechanism. This abnormal attentional focusing – probably linked to a dysfunctional top-down feedback from fronto-parietal network to the early visual areas – could contribute to the atypical visual perception associated to individuals with ASD which, in turn, could have consequences in their social-communicative development.

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1. Introduction

Autism Spectrum Disorder (ASD) is a complex neuro-developmental disorder characterized by abnormalities in communication, social interaction and presence of markedly

restricted interests and stereotyped behaviours (American Psychiatric Association, 1994).

Although the dysfunctions in social cognition and communication are typically considered the “core” deficits in individuals with ASD, there is growing evidence of abnormalities in

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their visual perception and attention (e.g., Grandin, 2009; Vlamings et al., 2010; see Dakin and Frith, 2005; Happé, 1999; Mottron et al., 2006 for reviews). The idea that individuals with ASD pay attention to the world differently, and that the consequent atypical perception might contribute to abnormalities in both social and “non-social” (e.g., repetitive behaviours, insistence on sameness and preoccupation with parts of objects) domains, is perhaps one of the most intriguing aspects of the current ASD research (see Mazer, 2011 for a recent review). According to the neuro-constructivist approach (see Karmiloff-Smith, 1998; Johnson, 2011 for reviews) low-level attentional and perception abnormalities could, indeed, cause impairments in the higher level cognitive modules (e.g., Elsabbagh et al., 2011).

It is well known that perception of relevant information is mediated by attention orienting (see Reynolds and Chelazzi, 2004 for a review). Attention orienting is often compared with a “spotlight” that moves to a specific region in the visual space, improving information processing in the attended area at the expense of other locations (see Posner and Petersen, 1990; Corbetta and Shulman, 2002 for reviews). However, the attention spotlight is not only oriented in a specific location, but has also to be adjusted in its size. This ability allows to process visual stimuli from a narrow (zoom-in) or a broad visual region (zoom-out). Eriksen and St. James (1986) suggested a “zoom-lens” model, in which the attentional spotlight size can be varied continuously (see also the attentional scaling by Luo et al., 2001). In particular, the zoom-lens model explicitly predicts an increase of processing efficiency within the focus when the attentional spotlight is decreased in size. This prediction has been supported by behavioural, neuro-imaging and neurophysiological data demonstrating a partial independence between the focusing and the orienting mechanisms (e.g., Castiello and Umiltà, 1990; Müller et al., 2003; Fu et al., 2005; Turatto et al., 2000).

Although several studies investigated the attentional orienting in ASD (e.g., Townsend et al., 1996a, 1996b), only a few of them are related to the ability to adjust the size of the attentional spotlight (hereafter, attentional focusing). In a recent review Ames and Fletcher-Watson (2010) reported that only two studies attempted to explore the attentional focusing mechanisms in ASD (Burack, 1994; Mann and Walker, 2003). In the Burack’s study (1994) participants (four mental-age matched groups composed by subjects: with autism, with organic mental retardation, with familial mental retardation, and with no handicap) performed a forced-choice reaction time (RT) task to assess the filtering component of selective attention. The independent variables were the presence/absence of a window which narrowed the attentional spotlight (zoom-in), the number (zero, two, or four) and the location of distractors. The RTs of the subjects with autism improved relative to the other groups in the presence of the window without distractors, but this effect was negated when distractors were also presented. Performance of the autism group was, indeed, the most impaired in the presence of distractors. These findings represent a behavioural evidence of an inefficient broad attentional lens among persons with autism. In the second study, Mann and Walker (2003) employed a paradigm requiring participants to make a judgement about which one of the two pairs of cross-hairs was the

longer. ASD participants were less able than comparison group in making this judgement when the previous pair of cross-hairs was smaller than the one to be judged. The authors argued that individuals with ASD have a difficulty in the zoom-out of the attentional spotlight, even if they speculated that this deficit could arise from a general difficult in orienting attention to a target in the periphery.

We hypothesise that the “inability to experience wholes without full attention to the constituent parts” (Kanner, 1943, p. 246) in ASD could be related to an abnormal attentional focusing mechanism. Precisely, we suppose that children with ASD present a poorer ability to enlarge the size of their attentional spotlight: i.e., a specific zoom-out attentional impairment. This deficit in the zoom-out of the attentional spotlight, although it could lead to superior performances in several perceptual tasks (see Dakin and Frith, 2005; Mottron and Burack, 2001 for reviews), it could also result in poor performance in other visual paradigms. For example, in coherent dots motion detection paradigm (Newsome and Pare, 1988), observers with ASD require about 10% more of coherent motion to correctly report direction (e.g., Milne et al., 2002; Pellicano and Gibson, 2008; Ronconi et al., under review; Spencer et al., 2000; but see De Jonge et al., 2007; see Grinter et al., 2010 for a recent review). A narrow attentional spotlight could contribute to worsen the coherent motion performance because it would filter the information outside the attentional focus, leading individuals with ASD to base their judgement on a restricted portion of moving dots. Moreover, Navon Task (Navon, 1977) performance in ASD indicates a preference for the local level of hierarchical stimulus analysis – maybe due to a deficit in the zoom-out of the attentional spotlight (e.g., Milne et al., 2002; Rinehart et al., 2000). These findings suggest that a detail-oriented visual perception could be a possible mechanism for the “weak central coherence” (Frith and Happé, 1994; Happé and Frith, 2006; see Happé, 1999 for a review).

In the present study, we investigated the attentional focusing mechanisms (i.e., zoom-in and zoom-out) in children with and without ASD, to verify the hypothesis for which children with ASD present a specific deficit in zooming-out their attentional spotlight. We employed a simple RTs task to measure the target detection – presented at three eccentricities from the fixation point – when a non-informative small or large focusing cue guided participants to scale the attentional processing in a restricted or enlarged visual field area, respectively. The “attentional gradient” is defined as the specific RTs pattern evoked in presence of a small cue-size that focuses the attentional spotlight (i.e., zoom-in mechanism); it predicts that the RTs to the target are slower at the farthest in comparison with the nearest eccentricity. In contrast, when a large cue-size enlarges the attention spotlight this gradient should be reduced or nullified because the target is presented inside the focus regardless target eccentricity (i.e., zoom-out mechanism; e.g., LaBerge, 1983; see LaBerge and Brown, 1989 for a review).

We predict that typically developing (TD) participants will be able to zoom-in their attention, generating a gradient effect, only when a small cue anticipates the target onset. On the other hand, with a large cue, they should be able to zoom-out their attention, nulling the gradient effect of the target

eccentricity. This prediction should be valid only at the shorter stimulus-onset-asynchrony (SOA, i.e., 100 msec), because when a longer SOA is employed (i.e., 800 msec) the time between the cue and the target will be too long to sustain the zoom-in of the attentional focus (Turatto et al., 2000). Thus, our prediction is that if the zoom-out attentional mechanism is specifically impaired in children with ASD, these children will show an abnormal gradient effect in the large focusing cue only at short cue-target SOA.

The comparison between the target RTs at the two SOAs (across the cue-sizes and target eccentricity) will be a good control to test whether children with ASD were able to process the cues or they simply ignored them. The presence of a SOA effect (i.e., faster target RTs at the long SOA compared to the short SOA) should, indeed, suggest that the observers processed the cues.

2. Methods

2.1. Participants

Twenty-three children took part of the experiment. The ASD group comprised 11 children. All the participants with ASD were included according to the following criteria: (i) full scale IQ > 70 as measured by the Italian version of Wechsler Intelligence Scale for Children-Revised (WISC-R, Wechsler, 1993); (ii) absence of gross behavioural problems; (iii) normal or corrected-to-normal vision and hearing; (iv) absence of drug therapy; and (v) absence of attention deficit hyperactivity disorder on the basis of DSM-IV criteria (American Psychiatric Association, 1994). Children with ASD were recruited at the Developmental Neuropsychology Units of Scientific Institute “E. Medea”. Diagnosis of ASD was made by licensed clinicians experienced in the assessment of ASD in respect to DSM-IV diagnostic criteria and to the Autism Diagnostic Observation Scale (ADOS; Lord et al., 2002). The control group comprised 12 TD children randomly sampled in Padua public schools. According to the parents' report, TD children did not have prior history of any psychiatric disorders. Both groups were matched for chronological age [$t_{(21)} = -.19, p > .05$] and gender [$\chi^2 = 1.54, p > .05$]. Cognitive level in TD children was estimated with two Verbal (Vocabulary and Similarities) and two Performance (Block Design and Pictures Completion) subtests of the WISC-R (Wechsler, 1993). ASD and TD group differed only in the Vocabulary subtest [mean ASD: 9.09, mean TD: 12.27; $t_{(21)} = -2.7, p < .05$], while they did not differ in the other three subtests (Similarities: mean ASD = 11.27, mean TD = 12.43; Block Design: mean ASD = 11.18, mean TD = 11.9; Pictures Completion: mean ASD = 11.45, mean TD = 10.83; all $ps > .05$). Informed consent was obtained from each child and their parents. For details about participants' characterization see Table 1.

2.2. Material and stimuli

The experiment was conducted in a dimly lit and quiet room. Participants were seated 40 cm far from an LCD screen (20 inch, 75 Hz). A chinrest was used to stabilize the head. Stimulus presentation and data acquisition were performed with E-Prime 1.1 (Schneider et al., 2002). All stimuli were middle

Table 1 – Descriptive statistics for ASD and TD groups (VIQ = verbal intelligence quotient, PIQ = performance intelligence quotient, TIQ = total intelligence quotient). Vocabulary, Similarities, Picture Completion, Block Design are subtests from WISC-R.

Measure	Group	
	ASD (n = 11)	TD (n = 12)
Mean age (\pm SD)	13.2 (\pm 2.9)	13.4 (\pm 2.8)
Gender	11 M	9 M
VIQ	107 (\pm 16.4)	–
PIQ	103.2 (\pm 14.4)	–
TIQ	105.9 (\pm 16.8)	–
Vocabulary	9.09 (\pm 3.42)	12.27 (\pm 2.13)
Similarities	11.27 (\pm 2.45)	12.43 (\pm 1.4)
Picture Completion	11.45 (\pm 3.36)	10.83 (\pm .9)
Block Design	11.18 (\pm 3.68)	11.9 (\pm 2.06)
ADOS		
– Communication	3.5 (\pm 1.27)	–
– Social interaction	5 (\pm 2.45)	–

grey displayed on a black background. The fixation point consisted of a cross (.5 deg) presented in the centre of the screen. In the Small cue condition (see Fig. 1 panel A) a circle with a ray of 4 deg was presented concentrically to the fixation point. In the Large cue condition (see Fig. 1 panel B) a circle with a ray of 12.5 deg was presented concentrically to the fixation point. The target stimulus was a dot of .5 deg which could appear at one of the three possible distances from the fixation point on the horizontal axis (i.e., 2, 6 and 12 deg, named: Eccentricity 1, Eccentricity 2, Eccentricity 3, respectively). In the Small cue condition, the target was displayed inside the focusing cue at the Eccentricity 1, whereas at Eccentricity 2 and at Eccentricity 3 it fell outside. In the Large cue condition the target was always displayed inside the focusing cue. The target was randomly presented in the left and in the right visual hemi-field.

2.3. Procedure

Participants were instructed to keep their eyes on the fixation point throughout the duration of the trial. Each trial started with the onset of the fixation point. After 500 msec, a non-informative (i.e., the probability of the target location was equal in the two focusing cue condition) small or large focusing cue was presented. The target was displayed for 20 msec. In order to measure the time-course of attentional focusing the cue-target SOA was manipulated (i.e., 100 or 800 msec). Participants were instructed to press the space bar on the keyboard as fast as possible at the target onset, and the computer recorded RTs and accuracy. Response was recorded within 2 sec from the stimulus onset. If any response was given, participants were advised with a 800 Hz sound played for 500 msec. Catch trials, in which the stimulus was not presented and the participant did not have to respond, were intermixed with response trials. The experimental session consisted of 132 randomised trials. Precisely, 120 response trials (2 focusing cue-sizes \times 2 SOAs \times 3 Eccentricities \times 10 times) and 12 catch trials. At the end of each trial a blank screen was presented until the experimenter pressed the mouse button to start the next trial.

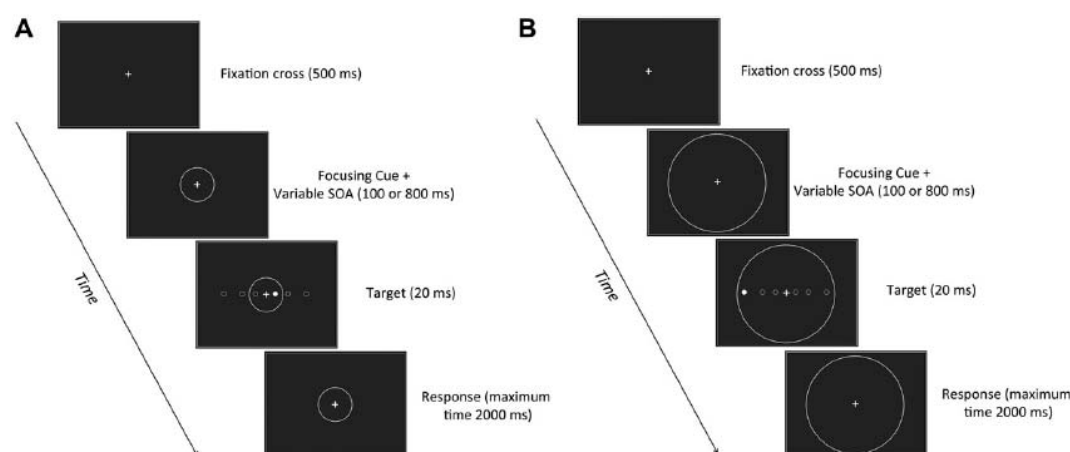


Fig. 1 – Representation for an experimental sequence in the Small (A) and in the Large (B) focusing cue condition. Target could appear in one of the six locations depicted along the horizontal axis.

3. Results

The two groups (TD and ASD children) did not differ significantly in the overall response accuracy as revealed by the error analysis. Precisely, we counted as errors the omissions in the response trials and the false alarms in the catch trials. Mean accuracy for the response trials was 98.3% (± 2.3) for the children with ASD and 98.9% (± 1.2) for the TD children [$t_{(21)} = -.82, p > .05$], while for the catch trials mean accuracy was 87.2% (± 27.8) for children with ASD and 95.9% (± 6.5) for the TD children [$t_{(21)} = -1.06, p > .05$]. RTs faster than 150 msec and slower than 1500 msec were filtered-out from the statistical analysis. The two groups did not significantly differ for the number of trials excluded by this procedure [ASD group mean = 6.7 ± 2.6 , TD group mean = $6.1 \pm .8$, $t_{(21)} = 1.16, p > .05$].

RTs mean of corrected trials was computed by a mixed analysis of variance (ANOVA) with $2 \times 3 \times 2$ design in which within-subject factors were the focusing cue-size (Small and Large) and Eccentricity (2, 6 and 12 deg), while the between-subject factor was the Group (ASD and TD). ANOVA was performed separately for the two SOAs (100 and 800 msec).

ANOVA on the first SOA (100 msec) presented a significant main effect of Eccentricity [$F_{(2,42)} = 8.72, p < .05, \eta_p^2 = .29$], showing that RTs were modulated by target eccentricity (mean RTs was 393 ± 62 msec at Eccentricity 1, 402 ± 76 msec at Eccentricity 2, and 423 ± 66 msec at Eccentricity 3). Importantly, focusing cue-size by Eccentricity by Group interaction (see Fig. 2, panels A and B) was significant [$F_{(1,21)} = 4.96, p < .05, \eta_p^2 = .19$], suggesting that the two groups presented a different Eccentricity effect as a function of the focusing cue-size. In the Small cue condition both ASD [mean RTs at Eccentricity 1 was 400 ± 44 msec while at Eccentricity 3 it was 432 ± 68 msec; $F_{(1,10)} = 5.34, p < .05, \eta_p^2 = .35$] and TD children [mean RTs at Eccentricity 1 was 382 ± 66 msec while at Eccentricity 3 it was 423 ± 69 msec; $F_{(1,10)} = 16.57, p < .05, \eta_p^2 = .60$] showed the typical attentional gradient effect (i.e., faster RTs for stimuli displayed at Eccentricity 1 and slower RTs for stimuli

displayed at Eccentricity 3, i.e., inside and outside the small focus, respectively). In contrast, in the Large cue condition, the gradient effect disappeared in the TD group, as predicted by the attentional zoom-lens model: i.e., no significant differences in the target RTs at two different eccentricities ($F < 1$) were observed. In contrast, children with ASD still presented an abnormal gradient effect, showing a significant difference [$F_{(1,21)} = 5.09, p < .05, \eta_p^2 = .34$] between target RTs at Eccentricity 1 (mean RTs was 404 ± 61 msec) and Eccentricity 3 (mean RTs was 452 ± 86 msec). No other main effects and interactions were significant (all $ps > .05$).

ANOVA at the second SOA (800 msec, see Fig. 2, panels C and D) showed a significant main effect for Eccentricity [$F_{(2,42)} = 4.05, p < .05, \eta_p^2 = .16$; mean RTs was 375 ± 15 msec at Eccentricity 1, 375 ± 15 msec at Eccentricity 2, and 398 ± 17 msec at Eccentricity 3]. No other main effects and interactions were significant (all $ps > .05$).

To rule-out that children with ASD were simply ignoring uninformative spatial cue, mean RTs of corrected trials was computed by a mixed ANOVA 2 (the within-subject factor was the SOA) \times 2 (the between-subject factor was the Group) design. In particular, if children with ASD process the spatial cue, faster target RTs should be shown at long SOA in comparison with the short one. On the other hand, if children with ASD ignored the spatial cue, no target RTs difference between long and short SOA should be present. The ANOVA showed a significant main effect of the SOA [$F_{(1,21)} = 8.07, p < .05, \eta_p^2 = .28$], demonstrating that target RTs were affected by the SOA (RTs mean at 100 msec SOA was 407 ± 65 msec, while RTs mean at 800 msec SOA was 383 ± 72 msec). The SOA by Group interaction was not significant ($F < 1$), highlighting that the SOA effect did not differ in the two groups. Planned comparisons reveal that the SOA effect was significant for both ASD [$F_{(1,10)} = 3.28, p < .05, \eta_p^2 = .25$; RTs mean at 100 msec SOA was 421 ± 61 msec, while RT mean at 800 msec SOA was 401 ± 84 msec] and TD group [$F_{(1,11)} = 4.95, p < .05, \eta_p^2 = .31$; RTs mean at 100 msec SOA was 393 ± 68 msec, while RTs mean at 800 msec SOA was 364 ± 57 msec], ruling-out that children

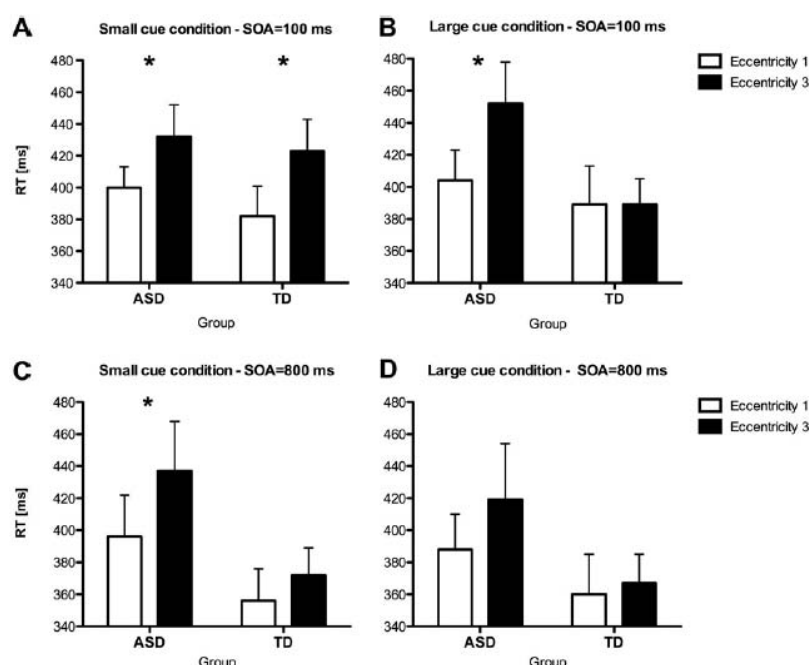


Fig. 2 – Bars represent the mean RTs reported by the two groups at the Eccentricity 1 and 3 as a function of the focusing cue-size, at 100 msec SOA (panels A and B) and at 800 msec SOA (panels C and D). Error bars represent mean standard errors and * indicates a significant difference revealed by planned comparisons. Regarding the 800 msec SOA, the TD group did not show any significant gradient effect neither in the small (mean RTs was 356 ± 68 msec and mean RTs was 372 ± 60 msec, respectively; $F < 1$). In contrast, the ASD group still showed a significant gradient effect in the small cue-size [mean RTs was 396 ± 85 msec and mean RTs was 437 ± 103 msec, respectively; $F_{(1,10)} = 5.25$, $p < .05$, $\eta_p^2 = .34$], while the gradient effect in the large cue-size (mean RTs was 388 ± 74 msec and mean RTs was 419 ± 117 msec, respectively) was not significant [$F_{(1,10)} = 2.75$, $p > .05$, $\eta_p^2 = .22$].

with ASD were simply ignoring the cue during the attentional focusing task.

This last result, however, is not informative regarding the spatial effect of the large and small cue-size in children with ASD. Thus, a 2 (focusing cue-size) \times 2 (SOA) ANOVA in the ASD group, was performed to investigate whether children with ASD processed the large and small cue. Focusing cue-size \times SOA interaction was significant [$F_{(1,10)} = 5.18$, $p < .05$, $\eta_p^2 = .34$], showing that the large versus small focusing cue were differently processed at the two SOAs. In particular, target RTs (across the three eccentricities) were faster in presence of the small cue-size than with the large one at the short SOA (415 ± 19 msec and 427 ± 20 msec, respectively), whereas they were slower in presence of the small cue-size than with the large one at the long SOA (409 ± 26 msec and 394 ± 26 msec, respectively).

4. Discussion

In the present study, we investigated the visual spatial attentional focusing mechanism (see Reynolds and Heeger,

2009 for a recent neuro-computational review) in a group of children affected by ASD using a simple target-detection task. Our aim was to verify a possible deficit in adjusting the size of the attentional focus in ASD. We manipulated the allocation of attentional resources in the visual field presenting a small or large spatial cue (e.g., Ericksen and St. James, 1986; Castiello and Umiltà, 1990; Turatto et al., 2000). In addition, in order to measure the spatial distribution of the “attentional gradient”, participants were asked to respond as fast as possible to a visual target, which could appear at three eccentricities from the fixation point along the horizontal axis (e.g., Facoetti and Molteni, 2001; see LaBerge and Brown, 1989 for a review). When a small focusing cue (a circle that included only the first target eccentricity) is presented, it is expected to induce in participants a specific attentional gradient (i.e., zoom-in mechanism). RTs should increase with target eccentricity (gradient effect). On the contrary, when a large cue is presented, it is not expected a gradient effect because attentional processing resources spread on the entire cue-delimited visual space (i.e., zoom-out mechanism; e.g., LaBerge, 1983). These results are expected only in presence of a short cue-target SOA (i.e., 100 msec), because of the

specific time-course of attentional focusing (Turatto et al., 2000).

RTs pattern of TD children was consistent with these predictions, showing an attentional gradient when a small focusing cue preceded by 100 msec the target onset, whereas no attentional gradient emerged when a large focusing cue was displayed. Thus, the presence of a gradient effect in the small focusing cue condition only at 100 msec SOA, indicates that our experimental manipulation was appropriated.

Children with ASD, in contrast, showed narrowly focused attention not only in the small but also in the large attentional cue condition at 100 msec SOA. Thus, we find a deficit in the distribution of the attentional resources in ASD. In particular, children with ASD show an impairment in zooming-out the spotlight of visual attention. The cue-target SOA effect was similar in both groups, showing that the participants with ASD did not ignore the temporal feature of the spatial cue. Moreover, the different effect of the cue-size at the two cue-target SOAs confirmed that the children with ASD processed the size of the attentional cue as well. Interestingly, the attentional gradient abnormally present in the ASD group with a large cue at the short cue-target SOA disappeared at the long SOA (Fig. 2, Panel D), suggesting a specific sluggish zoom-out attentional mechanism. Thus, the zoom-out attentional deficit seems to be the more appropriate explanation for our findings. Finally, the ASD group, unlike the TD children, showed, in the Small cue condition, an atypical gradient effect also at the long cue-target SOA (Fig. 2, Panel C), suggesting a prolonged zoom-in attentional mechanism.

According to the “weak central coherence” hypothesis (Happé and Frith, 2006; Frith and Happé, 1994), our results suggest that in children with ASD attentional resources appear to be rigidly allocated in a narrow region of the visual field. These results could provide a better understanding of the detail-oriented perception exhibited by individuals with ASD. There is a large experimental literature describing this detail-oriented perception in visual domain in ASD (Happé and Frith, 2006; Mottron et al., 2006), which results, sometimes, in superior performances compared to typical developing children (see Dakin and Frith, 2005; Mottron and Burack, 2001 for reviews). Superior detail-oriented visual perception in ASD was found, for example, in serial search tasks, in which a target stimulus has to be discriminated from distractors (e.g., Joseph et al., 2009; O’Riordan et al., 2001). Superior search performances were confirmed also in typical individuals with high autistic traits (Almeida et al., 2010), and in the embedded figure test, in which a shape has to be found within a larger design (e.g., Jolliffe and Baron-Cohen, 1997; Manjaly et al., 2007). However, the findings by Joseph et al. (2009) and O’Riordan et al. (2001) can not be fully explained by “weak central coherence” because they showed that the superiorities were most prominent in a conjunctive search condition, where the targets shared features with both of the distractors, and which thus requires some integration process. Recently, Baldassi et al. (2009) showed that children with ASD present reduced interference effect in visual crowding. Remington et al. (2009) reported similar results for the visual perceptual load, confirming detail-oriented visual perception in ASD. This large body of literature could be plausibly related to this prolonged zoom-in attentional mechanism. In particular, it is

demonstrated that orienting of attention improves performance in several visual task, such as serial visual search and crowding, by diminishing the noise effect outside the spotlight while intensifying the signal processing inside the attentional focus (e.g., Montagna et al., 2009; Yeshurun and Rashal, 2010; see Reynolds and Heeger, 2009 for a recent review).

Thus, our results suggest that the sluggish attentional zoom-out combined with prolonged zoom-in of the attentional spotlight in ASD could be linked to the superior performances in several visual tasks requiring efficient perceptual noise-exclusion mechanisms. Joseph et al. (2009) reported, indeed, that the ASD advantage in a visual search task derived from an enhanced ability to discriminate between targets and distractors at the locus of attention. The attentional focusing impairments, suggested by our findings, could allow individuals with ASD to better inhibit distractors in a visual search display (Baldassi et al., 2009; Remington et al., 2009).

On the other hand, these attentional focusing deficits, reducing the global spatio-temporal integration processing, could be related to the characteristic social domain impairments associated to ASD. For example, the efficient faces and emotions processing development, as well as the biological motion detection (Klin et al., 2009; Simion et al., 2008), could be impaired when the size of attentional focus is not spread to integrate local elements of the global visual scene. Accordingly, previous studies have found a relation between basic abnormal visual perceptual skills and autism symptomatology. In particular, visual search performance (Joseph et al., 2009), biological motion processing (Koldewyn et al., 2010), and visual fixation pattern (Klin et al., 2002) predicted communication and social interaction impairments in individuals with ASD.

According to the neuro-constructivist approach (see Karmiloff-Smith, 1998 for the original review), development itself is the key to understand developmental disorders. ASD characteristic features include impaired social-communication skills and atypical visual attention. A recent debate focused on whether the later emergence of atypical communicative skills is a consequence of attention problems during early life (see Johnson, 2011 for a recent review). For example, 9 months infants at familial-risk for a later diagnosis of ASD, differed from controls, both in measures of social perception and attentional disengagement. Preliminary data from an ongoing longitudinal research program, suggest an associations between attentional measures and autism-related characteristics in children of 3 years old. The emergent nature of ASD could be the result of a complex developmental interactions among attentional- and social-brain networks (Elsabbagh et al., 2011). Thus, low-level attentional and perception abnormalities could cause impairments in the high-level communication and language modules (e.g., Mundy et al., 1987; Lum et al., 2007). In particular, a specific zoom-out attentional dysfunction in ASD – hampering the integration of distributed communication cues – might be partially responsible for the typical social “core” deficit.

However, as found by Ronconi et al. (under review) by using central and peripheral coherent dots motion tasks, the inability to enlarge the focus could be overcome. When the

information relevant to the task is, indeed, completely absent inside the attentional focus children with ASD seem to be able to zoom-out the focus of attention in the same way the TD group do. In contrast, when a small amount of relevant information fall into the attentional focus, the ASD group is unable to enlarge the focus even if it would be beneficial for the task performance.

4.1. What could be the neural correlate of these attentional focusing deficits in children with ASD?

Neuroimaging studies in non-clinical population could suggest a plausible physiological explanation of zoom-out attentional deficit found in children with ASD. It has been demonstrated that the neural activity preceding the object presentation was finely modulated by the size of attended region in the early visual areas (Müller et al., 2003). The increasing size of the attended region causes a reduction in the blood oxygen level-dependent response in early visual areas (Müller et al., 2003; see also Brefczynski and DeYoe, 1999). In addition, the temporal dynamics of the attentional focusing has been examined by recording event-related potentials. In particular, the attentional zoom-out was associated to a decreased in N1 amplitude (Luo et al., 2001; Fu et al., 2005). Recent studies shed some lights on the influence of top-down fronto-parietal attention network (e.g., Saalmann et al., 2007; see Corbetta and Shulman, 2002 for a review) on the early visual processing. Combining transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI), Ruff et al. (2006, 2008) found that the TMS application on the right prefrontal cortex (frontal eye fields – FEF) and on the right parietal cortex (intra-parietal sulcus – IPS), increased fMRI activity for representations of the peripheral visual field, and reduced activity for the central field in all retinotopic visual areas.

One possible explanation for the children with ASD inability to zoom-out the attentional spotlight size in response to a large visual cue could arise from a dysfunction in the connectivity between top-down fronto-parietal attention network and early visual areas, where the “zoom-lens” of the spatial attention is modulated (Müller et al., 2003; see also Brefczynski and DeYoe, 1999). A large number of recent studies suggest a possible under-connectivity between frontal and occipital areas in ASD (e.g., Barttfeld et al., 2010; Courchesne and Pierce, 2005; see Belmonte et al., 2004 for a review). Accordingly, two fMRI studies have shown, in individuals with ASD, a dysfunction of the dorso-lateral prefrontal and the intra-parietal cortex during visual attention task (Manjaly et al., 2007; Ring et al., 1999). A recent study showed that atypical prefrontal activations seem to be present also in unaffected sibs (Belmonte et al., 2010). Thus, both the impaired zoom-out as well as the prolonged zoom-in attentional focusing here shown in children with ASD could be probably linked to a sluggish top-down feedback from fronto-parietal network to the early visual areas.

We conclude that if this attentional focusing deficit will be confirmed also in infants at familial-risk for ASD, the zoom-out attentional impairment could be considered an important neuropsychological marker for the early identification of ASD.

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Letter to the Editor

Drugs for attention deficit–hyperactivity disorder do not increase the mid-term risk of sudden death in children: A meta-analysis of observational studies

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Attention-deficit/hyperactivity disorder (ADHD) is a chronic neuro-behavioral condition that typically manifests in childhood and is characterized by a wide range of emotional, functional, and neurocognitive impairments that interfere with social and emotional quality of life. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the diagnosis is made by confirming numerous symptoms in the inattention domain or the hyperactivity–impulsivity domain or both.

Stimulant medications have been demonstrated to be efficacious and are considered the first-line pharmacological therapy for ADHD [1]. Because of the increasing recognition of ADHD as a chronic disorder, the use of medications for the treatment of this disease has considerably expanded over the last decade, becoming common also among adolescents and adults in addition to prepubertal children [2].

Both stimulants and atomoxetine have cardiovascular effects with increase in heart rate and blood pressure. It has been calculated that these agents can increase systolic and diastolic blood pressures (on average 1–4 mm Hg) and heart rate (on average 3–8 bpm) [3]. These changes are not usually clinically significant in the short-term, but their possible significance for the long-term deserves further investigation. Besides, while a causal link between therapeutic stimulant use and sudden cardiac death has not been established, there are concerns that treatment

may increase the risk for sudden death in patients with structural cardiac abnormalities [2]. Consequently there is still a lively debate about the safety of these medications in order to assess risk in the context of the evolving clinical practice [2]. Thus, there is a compelling need to obtain better safety data for these drugs.

This letter was reported according to established methods: 3 independent reviewers (GBZ; MM, FDA) independently searched Medline, Cochrane Library and Biomed Central with the following high sensitive strategy “(cardiovascular OR cardio-vascular OR cardiac OR vascular OR coronary OR ischemic OR vascular OR infarction OR ischemia OR ischemia OR thrombosis OR angina OR stroke OR sudden death OR arrhythmia*) AND (adhd OR (attention AND deficit AND hyperactivity)) AND (therapy OR treatment OR drug* OR medicine* OR methylphenidate* OR dexamethylphenidate* OR dextroamphetamine* OR amphetamine* OR atomoxetine* OR pemoline*)”.

Inclusion criteria were: (a) patients with ADHD disorders (b) including at least 100 patients (c) reporting clinical cardiovascular outcomes (d) exploring the adjusted effect of ADHD drugs on cardiovascular outcomes and (e) follow up longer than 1 year. Rates of sudden cardiac death were the primary outcome, while rates of myocardial infarction and of stroke the secondary.

Continuous variables have been reported as mean (SD) or median (range) and categorical variables as n (%). Pooling was performed according to random-effect models with generic inverse variance weighting with RevMan 5 (The Nordic Cochrane Center, København, Denmark) for computing incidence estimates with their relative 99% Confidence Intervals (CI).

A total of 476 results were evaluated at abstract level and finally 3 [3–5] studies were included in the analysis with 1,884,963 patients and of them 766,343 (41%) were on current ADHD therapy. Methylphenidate and amphetamine were the most frequently used drugs. After a median follow up of 806,162 person-years (498,556–1,663,560), pooled analysis among patients with current use of ADHD drugs showed rates of 10.5% of sudden death/100,000 person-years (4.4–16.5) and of 14.13%/100,000 person-years (5.88–22.37) of stroke.

Pooled analysis of adjusted Odds Ratio (Figs. 1–2) showed that current use of ADHD did not increase risk of sudden death, 0.93 [0.73, 1.17], and of stroke 0.93 [0.90, 0.96]. The study of Habel et al. was the only

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M. Mazza et al. / International Journal of Cardiology xxx (2013) xxx–xxx

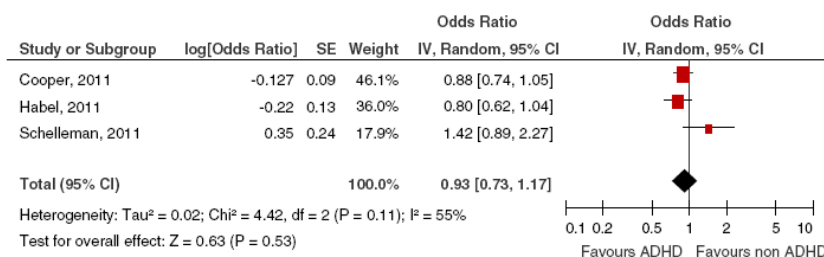


Fig. 1. Logarithmic transformation for adjusted Odds Ratio for sudden death for current users.

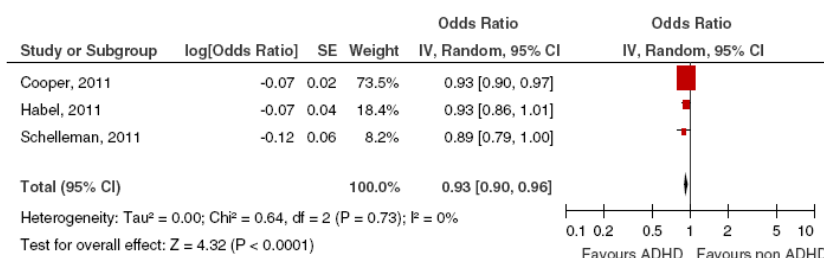


Fig. 2. Logarithmic transformation for adjusted Odds Ratio for stroke.

study to include middle aged patients, and after excluding it, with a median follow up of 498,557 person-years (344,743–652,369) rates of sudden death were 0.83%/100,000 person-years (0.68, 0.97) and of stroke 0.92%/100,000 person-years (0.00, 1.84). Moreover risk for sudden and for stroke was not increased among current users of ADHD medications (1.06 [0.67, 1.68] and 0.93 [0.89, 0.96] respectively; all CI 95%). Additional details on included studies are available from the corresponding author upon request.

To the best of our knowledge, this is the largest study appraising the incidence of adverse cardiac events in patients assuming ADHD drugs, showing that a) sudden death and cardiovascular adverse events are un-frequent among young patients assuming ADHD and b) absence of influence of ADHD drugs on adverse cardiovascular outcomes.

Because of the widespread use of stimulants and other ADHD drugs it is crucial to assess the cardiovascular effects associated with both short and long-term administration. In 2006, the U.S. Food and Drug Administration (FDA) investigated cardiac risks associated with ADHD medication use, because of the review of adverse-event reports of serious cardiovascular events associated with the use of ADHD drugs in Canada and the United States. Anyway, no declines in medication use following FDA safety warnings were observed [6].

With the present study we demonstrated that ADHD drugs do not increase risk of adverse cardiac events, both arrhythmic and both ischemic. Cardiovascular effects of ADHD drug are known and are part of their pharmacological activity. This is slightly different for each class of ADHD drugs. Methylphenidate and amphetamines are sympathomimetic agents that increase noradrenergic and dopaminergic transmission: an effect on heart rate and blood pressure can be considered an intrinsic feature of their pharmacological activity [7]. A similar analysis can be

done for atomoxetine, a selective norepinephrine reuptake inhibitor that is used for ADHD therapy since 2003. Also atomoxetine, as stimulant medications, has an effect on cardiovascular function: placebo-controlled clinical trials show that atomoxetine produces an increase of 5–9 bpm in heart rate, an increase in systolic blood pressure in adults but not in children and an increase in diastolic blood pressure in children and adolescents but not in adults, in the few weeks of treatment without further increase in long term treatment. No electrocardiographic changes are documented and no QT interval prolongation was seen [8].

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COMUNICATO STAMPA

**Un affollatissimo convegno all'Istituto Mario Negri con circa 500 partecipanti
L'iperattività e il deficit di attenzione infantili (ADHD)
andrebbero diagnosticati più precocemente prima che diventino
una patologia da trattare anche farmacologicamente**

In Lombardia, anche grazie a un progetto, unico a livello internazionale, sostenuto dalla Regione, questo disturbo infantile presenta una diffusione contenuta, così come l'utilizzo di psicofarmaci, purtroppo però spesso non prescritti dai medici specialistici

Milano, 30 Maggio 2013. In Regione Lombardia sono 18 i Centri di riferimento per l'ADHD, il disturbo da deficit di attenzione e iperattività, che è una delle più frequenti sindromi neuropsichiatriche infantili.

Nel corso del 2012, vi sono stati 55.093 accessi alle 18 Unità Operative di Neuropsichiatria dell'Infanzia e dell'Adolescenza da cui dipendono i Centri, ovvero il 73% dell'intera popolazione regionale di 6-17 anni che si è rivolta ai servizi regionali di neuropsichiatria. **1.635 (3%) sono stati gli accessi ai Centri stessi per ADHD.** Dei 510 nuovi casi di sospetta ADHD (31% degli accessi) la diagnosi è stata confermata in 339 (66%) e solo per 48 (14%) è stata intrapresa una terapia con psicostimolanti in associazione con una terapia psicologica spesso rivolta anche alla famiglia.

*“L'ADHD in Regione Lombardia rappresenta un disturbo molto meno frequente di quello ipotizzato da più parti - afferma **Maurizio Bonati** dell'Istituto Mario Negri, promotore insieme alla UONPIA della Azienda Ospedaliera “Spedali Civili” di Brescia del Congresso svoltosi il 28/29 Maggio che ha visto la partecipazione di circa 500 persone tra genitori, insegnanti, psicologi, neuropsichiatri infantili e altri addetti ai lavori -. Infatti contrariamente all'1-8% riportato per altri contesti nazionali e internazionali, i pazienti con ADHD sono solo il 2 per mille della popolazione lombarda di 6-17 anni. Come pure la prescrizione di psicofarmaci è considerevolmente inferiore rispetto ad altre realtà”.*

Sono questi i risultati evidenti, frutto di uno specifico progetto (a tutt'oggi unico anche a livello internazionale) sostenuto dall'Assessorato regionale alla Sanità che ha previsto: 1) La costruzione e l'aggiornamento continuo di un Registro regionale per l'ADHD che ha consentito di raccogliere informazioni approfondite relative ai bisogni assistenziali del paziente e i percorsi di cura ricevuta; 2) La formazione degli operatori sanitari e la sensibilizzazione della popolazione per una diagnosi e interventi più tempestivi e appropriati; 3) La condivisione di percorsi di riferimento comuni, volti a garantire approcci e gestioni più omogenei da parte di tutti i Centri di riferimento della Regione Lombardia.

*“Sono state individuate alcune criticità, tra cui quelle relative alle risorse e all'organizzazione dei servizi, che necessitano di una soluzione in un prossimo futuro - aggiunge la dottoressa **Antonella Costantino** vice presidente della Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza -. Per esempio, i tempi di attesa tra la richiesta di cura e la diagnosi di ADHD variano considerevolmente tra i Centri di riferimento, superando in alcuni casi anche l'anno”.*

Dopo tre anni di lavoro, il progetto è alla sua conclusione. In considerazione dei risultati raggiunti il progetto dovrebbe essere rinnovato e implementato da parte della Regione Lombardia: nell'interesse dei pazienti con ADHD (e delle loro famiglie), dell'aggiornamento degli operatori dei servizi sanitari preposti e degli insegnanti coinvolti, e delle criticità organizzative dei percorsi di cura individuate.

*“Maggiore attenzione e risorse – commenta **Silvio Garattini**, Direttore dell'Istituto Mario Negri - dovrebbero essere rivolte alla diagnosi precoce dell'ADHD, prima che il bambino entri nella scuola primaria così da ridurre anche il rischio di medicalizzazione per ritardata diagnosi come attualmente succede per troppi pazienti”.*

Per ulteriori informazioni:

Ufficio Stampa

IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri'

Sergio Vicario (348 98 95 170)

COMUNICATO STAMPA**L'USO DEGLI PSICOFARMACI IN ETÀ EVOLUTIVA
NECESSITA DI ULTERIORI INDAGINI ACCURATE
E PROTRATTE NEL TEMPO**

Milano/Roma, 10 Giugno 2013 - Nei giorni scorsi è stato dato ampio rilievo, da parte degli organi di informazione, ai risultati del **15° rapporto italiano del progetto europeo ESPAD (European school project on alcohol and other drugs)**, indagine campionaria condotta nel 2012 sull'uso di alcol, droga e sostanze psicoattive da parte degli adolescenti di 15-16 anni di età. Il Rapporto è stato curato per l'Italia dall'Istituto di fisiologia clinica del CNR di Pisa.

L'8% degli studenti intervistati ha dichiarato di avere utilizzato almeno una volta nella vita psicofarmaci dopo prescrizione medica, mentre il 15% ha dichiarato di averli assunti almeno una volta senza la prescrizione del medico. **Questi risultati contrastano con quelli relativi alle prescrizioni effettuate dai medici che vengono aggiornate annualmente e che indicano nell'1,5% la percentuale di adolescenti di età 15-16 anni che hanno ricevuto una o più prescrizioni di psicofarmaci nel corso della loro vita.**

*“Questa stima – spiega **Maurizio Bonati**, Capo del Dipartimento Igiene Pubblica dell'IRCCS Istituto di Ricerche Farmacologiche ‘Mario Negri’ - è pressoché costante nel corso degli ultimi anni. Il tasso dell'1,5% è considerevolmente inferiore all'8% del Rapporto. Sebbene l'1,5% possa essere considerato come sottostimato, poiché alcune classi di psicofarmaci (p. es. gli ansiolitici) non sono rimborsati dal Servizio Sanitario Nazionale e quindi non sono contemplati nelle analisi, è tuttavia difficile giustificare tale divario tra quanto prescritto e quanto dichiarato dagli studenti”.*

I dati di prescrizione e le indagini campionarie costituiscono due punti di osservazioni differenti, ciascuno con proprie finalità, potenzialità e limiti. Le banche dati di prescrizione forniscono dati solidi sul numero di farmaci prescritti dal medico sul ricettario del Servizio Sanitario Nazionale (ricetta rossa) e di pazienti che hanno acquistato il farmaco prescritto. Che un farmaco sia stato prescritto non significa automaticamente che sia stato anche assunto. Quindi, quell'8% del Rapporto sarebbe da considerare inferiore al prescritto e ulteriormente in contrasto con i dati dei flussi correnti amministrativi (1,5%).

*“L'indagine campionaria – aggiunge **Bernardo Dalla Bernardina**, Presidente della Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza (SINPIA) - fornisce informazioni sul consumo dei farmaci, anche di quelli assunti senza il consiglio del medico. Questo tipo di studi sono però gravati da alcuni limiti, tra cui la capacità della persona intervistata di ricordare che cosa ha assunto, e la comprensione e interpretazione delle domande poste. Ad esempio, nel caso*

della versione italiana del questionario ESPAD non è chiaro quale possa essere l'interpretazione di un adolescente della domanda "In quante occasioni hai fatto uso di farmaci per dormire e/o rilassarsi?".

Il 6% degli intervistati ha dichiarato di averli usati senza prescrizione medica, ma è possibile che alcuni studenti abbiano considerato "farmaci per dormire" anche prodotti fitoterapici (p. es. camomilla, valeriana) o integratori (p. es. melatonina): medicinali ben diversi dagli ansiolitici (p. es. alprazolam o lorazepam). A questo proposito il questionario originale in lingua inglese era più specifico perché chiedendo di "sedativi o tranquillanti si riferiva in modo preciso ad alcune classi di farmaci.

Appare anche discutibile, almeno per il contesto italiano, considerare i "farmaci per dimagrire" (seconda classe di farmaci più utilizzata, in base al rapporto ESPAD, con una percentuale di utilizzatori pari al 3%) come psicofarmaci; contribuendo quindi alla stima del 15% di adolescenti che si autoprescrive questo tipo di medicinali.

In Italia, infatti, non sono in commercio psicofarmaci con questa indicazione e quindi l'uso, se fosse vero, rimanderebbe ad un acquisto illegale di farmaci e/o ad un impiego equiparabile a quello di una sostanza d'abuso. Non è da escludere, quindi, che molte delle risposte affermative alla domanda "In quante occasioni hai fatto uso di farmaci per dimagrire?" si riferissero all'utilizzo di integratori alimentari.

Da ultimo, poiché nel questionario non era previsto che si indicasse anche il nome del farmaco utilizzato, non è possibile valutare con maggiore accuratezza e precisione le risposte di quel 15% di adolescenti che riferiscono di essersi autoprescritti psicofarmaci.

Occorre maggiore cautela nell'interpretazione dei risultati pur sostenendo la necessità che il Ministero della Salute e l'Agenzia Italiana del Farmaco promuovano sistemi di sorveglianza attiva e di programmi finalizzati al monitoraggio della prescrizione di psicofarmaci a bambini e adolescenti, come fatto in passato per l'uso degli psicostimolanti per la terapia del deficit di attenzione e iperattività. Solo disponendo di stime attendibili circa l'uso razionale dei farmaci (e tra questi gli psicofarmaci) sarà possibile migliorare, in termini di efficacia e sicurezza, i percorsi terapeutici volti a rispondere ai bisogni di salute dei bambini e degli adolescenti (e delle loro famiglie).

Maurizio Bonati

Antonio Clavenna

IRCCS

Istituto di Ricerche

Farmacologiche Mario Negri

Bernardo Dalla Bernardina

SINPIA

Società Italiana di Neuropsichiatria
dell'Infanzia e dell'Adolescenza

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del 10 Giugno 2013

viversani
SONO

estratto da pag. 15



ai ragazzi vengono dati troppi psicofarmaci?

Recenti studi evidenziano un aumento nel consumo di questi medicinali tra i minori. Secondo qualcuno è un dato allarmante, mentre per altri la situazione è tenuta sotto controllo dagli psichiatri

no

I MEDICI LI PRESCRIVONO SOLAMENTE SE NECESSARI

I ragazzini consumano troppi psicofarmaci?

Non ci risulta che sia esattamente così. Di sicuro non è aumentata la prescrizione da parte degli specialisti. Psichiatri e neuropsichiatri prescrivono gli psicofarmaci ai bambini e ai ragazzi soltanto in caso di estrema necessità, quando altri tipi di interventi messi in atto prima non hanno dato risultati. In questo caso, è elevato il controllo da parte dello specialista curante e di sicuro non c'è un abuso.

Perché i dati dicono che il consumo è in aumento?

Prima di tutto bisogna valutare in quale modo sono state svolte queste indagini sui ragazzi intervistati. A domande troppo vaghe possono corrispondere risposte ambigue. I ragazzi, per esempio, non hanno idee chiare su che cosa siano gli psicofarmaci. Una domanda del tipo "Prendi qualche sostanza per dormire?" può indurre un ragazzo a dire di sì anche se si tratta di una camomilla o di un integratore alle erbe. Uno psicofarmaco è una questione ben diversa, ma in questo caso la distinzione non emerge.

I ragazzi di oggi hanno più problemi psichiatrici rispetto a una volta?

Sicuramente c'è una maggiore attenzione nella diagnosi e si può contare su un più ampio ventaglio di strategie di cura. Tra queste ci sono anche gli psicofarmaci che, però, vengono prescritti solo in casi molto rari. Prescritti, appunto: perché nonostante questo



dottor Maurizio Bonati, capo dipartimento di Salute pubblica, Istituto di ricerche farmacologiche Mario Negri, Milano.

suggerimento, spesso il farmaco non viene neppure acquistato dai genitori, che decidono di seguire altre strade. Quindi, se possibile, la vendita di psicofarmaci per bambini e ragazzi è ancora inferiore alla già bassa prescrizione.

È vero che i ragazzi acquistano gli psicofarmaci in Rete?

Sì, questo fenomeno esiste, ma non ha nulla a che vedere con la prescrizione terapeutica fatta dagli psichiatri. È un fenomeno che attiene più a comportamenti trasgressivi o ai problemi delle dipendenze, esattamente come succede con gli alcolici e gli stupefacenti. Va sicuramente messa in atto una strategia di prevenzione, perché qualsiasi tipo di farmaco acquistato in Rete espone a una serie di problemi, non solo gli psicofarmaci.

Ci sono effetti collaterali?

Sì, i rischi esistono come per tutti farmaci, quindi si deve stare attenti a demonizzare, anche laddove gli psicofarmaci possono essere davvero utili, come nei casi estremi di ADHD (disturbo da deficit di attenzione con iperattività). Gli psicofarmaci sono assunti solo da una piccolissima parte dei bambini con questo problema e, comunque, sempre sotto controllo medico e dovrebbero essere sempre associati a una cura psicologica.



Luca Poma, portavoce nazionale di "Giù le mani dai bambini", comitato indipendente per la farmacovigilanza pediatrica in Italia.

I bambini e i ragazzi assumono davvero troppi psicofarmaci?

Lo dicono indagini più che serie. L'Istituto di Fisiologia clinica del Cnr di Pisa, nel suo 15° rapporto relativo all'anno 2012, conferma che il 15,4% dei giovani italiani assume psicofarmaci senza prescrizione medica e più del 52% di coloro a cui sono stati prescritti continua ad assumerli successivamente, anche senza alcun controllo sanitario. L'indagine è stata condotta su un campione di 45mila studenti delle scuole medie superiori in 516 istituti scolastici e ha mostrato dati sull'aumento dell'uso improprio di sostanze stimolanti, in particolare amfetamine e loro derivati e allucinogeni.

Quali rischi si corrono?

Gli effetti collaterali vanno da problemi di carattere psicologico e pedagogico, a complicazioni cardiache anche serie e alla stimolazione di idee suicidarie, a seconda della classe farmacologica utilizzata. Non va trascurato l'aspetto della diseducazione: stiamo permettendo la trasmissione ai nostri figli di un modello sbagliato, ovvero che basta una pillola per risolvere qualsiasi problema.

Non c'è una sorveglianza adeguata?

Nonostante le norme stabilite dagli enti sanitari di controllo, questi prodotti si reperiscono con estrema

sì

ALCUNI DATI DENUNCIANO UN CONSUMO SENZA CONTROLLI

facilità su internet, pagando con una comune carta PayPal. Da anni il nostro comitato si è messo gratuitamente a disposizione dell'Agenzia del farmaco e dell'Istituto superiore di sanità per organizzare una campagna seria di sensibilizzazione su questo tema, ma il problema continua a essere colpevolmente sottovalutato. Per questo abbiamo fatto appello al ministro della Salute.

Si dovrebbero imporre maggiori divieti?

Vietare serve a poco, perché il problema è culturale: genitori e medici devono capire che con un farmaco si tengono sotto controllo soltanto i sintomi, ma non si risolve il problema alla base e che questo è destinato a ripresentarsi non appena si sospende l'assunzione. La strada è, quindi, quella dell'accesso a informazioni indipendenti dagli interessi del marketing, scientificamente serie, tali da far comprendere a genitori e insegnanti il prezzo che si paga sul medio-lungo termine per queste "scorciatoie".

La nostra società è sempre più "medicalizzata"?

Sì, e anche la vigilanza degli enti regolatori rispetto a questi trend è insufficiente, non dobbiamo aspettare che la situazione vada completamente fuori controllo, come già successo in Usa e in altre nazioni, come la vicina Germania, dove in pochi anni si è arrivati a 750mila bambini definiti iperattivi, perché qui è in gioco il futuro delle nuove generazioni del nostro Paese.

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

Iniziativa nell'ambito del Progetto di Neuropsichiatria dell'Infanzia e dell'Adolescenza
Il Progetto è realizzato con il contributo, parziale, della Regione Lombardia
(in attuazione della D.G. sanità n. 3250 del 11/04/2011)
Capofila Progetto: UONPIA Azienda Ospedaliera "Spedali Civili di Brescia"
"Condivisione dei percorsi diagnostico-terapeutici per l'ADHD in Lombardia".

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