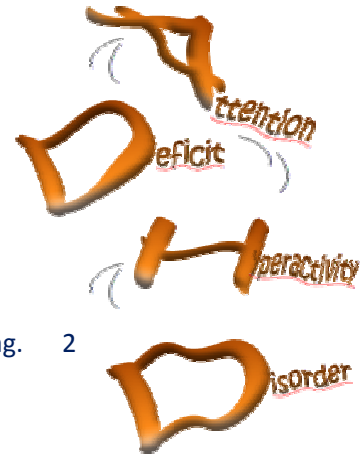
NEWSLETTER



INDICE:

MARIONEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

BIBLIOGRAFIA ADHD OTTOBRE 2012

Aggression Violent Behav. 2012;17:575-80.

THE RELATIVE INFLUENCE OF CONDUCT PROBLEMS AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN THE DEVELOPMENT OF ADOLESCENT PSYCHOPATHY.

Smith CS, Hung LC.

An in depth literature review was conducted into the relative influence of conduct problems and attention-deficit hyperactivity disorder in the development of child/adolescent psychopathy. Lynam (1996) wrote that children/adolescents exhibiting behaviors of both were 'fledgling psychopaths;' however, recent evidence suggests that if youth with comorbid conduct problems and ADHD exhibit a persistent form of antisocial and/or psychopathic behavior, the cause is primarily due to the levels of conduct problems, not the influence of ADHD. This article looks at the three perspectives regarding the development of psychopathy:
(1) Conduct Problem Mediation,
(2) the Independent Position, and
(3) the Comorbid Subtype. The studies examining the three perspectives found that the Conduct Problem Mediation, not the Comorbid Subtype, was the most important in the development of psychopathy.

……

……

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.

Am J Psychiatry. 2012;169:1038-55.

TOWARD SYSTEMS NEUROSCIENCE OF ADHD: A META-ANALYSIS OF 55 FMRI SUDIES.

Cortese S, Kelly C, Chabernaud C, et al.

Objective: The authors performed a comprehensive meta-analysis of task-based functional MRI studies of attention deficit hyperactivity disorder (ADHD).

Method: The authors searched PubMed, Ovid, EMBASE, Web of Science, ERIC, CINAHAL, and NeuroSynth for studies published through June 30, 2011. Significant differences in brain region activation between individuals with ADHD and comparison subjects were detected using activation likelihood estimation meta-analysis. Dysfunctional regions in ADHD were related to seven reference neuronal systems. The authors performed a set of meta-analyses focused on age groups (children and adults), clinical characteristics (history of stimulant treatment and presence of psychiatric comorbidities), and specific neuropsychological tasks (inhibition, working memory, and vigilance/attention).

Results: Fifty-five studies were included (39 for children and 16 for adults). In children, hypoactivation in ADHD relative to comparison subjects was observed mostly in systems involved in executive function (frontoparietal network) and attention (ventral attentional network). Significant hyperactivation in ADHD relative to comparison subjects was observed predominantly in the default, ventral attention, and somatomotor networks. In adults, ADHD-related hypoactivation was predominant in the frontoparietal system, while ADHD-related hyperactivation was present in the visual, dorsal attention, and default networks. Significant ADHD-related dysfunction largely reflected task features and was detected even in the absence of comorbid mental disorders or a history of stimulant treatment.

Conclusions: A growing literature provides evidence of ADHD-related dysfunction in multiple neuronal systems involved in higher-level cognitive functions but also in sensorimotor processes, including the visual system, and in the default network. This meta-analytic evidence extends early models of ADHD pathophysiology that were focused on prefrontal-striatal circuits.

……..

An Pediatr. 2012.

METHYLPHENIDATE IN THE TREATMENT OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: MONITORING IN BIOLOGICAL MATRICES.

Papaseit E, Garcia-Algar O, Simo S, et al.

Attention-deficit hyperactivity disorder (ADHD) has emerged in the last few years as the most commonly diagnosed and treated psychiatric disorder in the paediatric population. In 1980's, methylphenidate (MFD) a psychomotor stimulant drug, was approved in Spain for the symptomatic therapy of ADHD. Since then, MFD has become one of the most extensively prescribed and studied treatment for ADHD both in children and adults. In this paper, the main pharmacological issues of MFD are reviewed, focusing on its pharmacokinetics in conventional (blood and urine) and non-conventional (hair, oral fluid and sweat) biological matrices, its pharmaceutical preparations, therapeutic levels and side effects.

……..

Ann Emerg Med. 2012;60:S124.

INCREASING PREVALENCE OF ADHD DRUG TOXICITY.

Levine M, Ruha A, Froberg BA, et al.

Study Objective: In recent years, the number of children diagnosed with attention Deficit Hyperactivity Disorder (ADHD) has increased. It is not known if the increased prescribing practices of drugs used to treat ADHD is associated with an increased rate of toxicologic admissions following unintentional ingestion of these medications.

Methods: The medical records of patients < 18 years admitted for ADHD drug toxicity from 4 teaching hospitals in different geographical regions in the US were reviewed using standardized data abstraction methods. A list of ADHD drug toxicity was created a priori, and includes amphetamine/dextroamphetamine, clonidine, guanfacine, lisdexamfetamine, and methylphenidate. Subjects were excluded if the ADHD drug was prescribed for a non-ADHD indication (eg, clonidine for hypertension), or if the reason for ingestion was a suicide attempt. Subjects were categorized into 2 cohorts based on admission date (1/1/2001 -

12/31/2003 = group A; 1/1/2009-12/31/2010 = group B). Descriptive statistics were utilized as appropriate. Comparisons of proportions were executed using the Fisher's exact test. Kruskal-Wallis nonparametric analysis was used for comparison of noncategorical data. The pediatric population in each of the 4 metropolitan regions was estimated. For each time frame, the incidence density, or incidence rate (IR) of ADHD drug hospitalization was calculated as the number of incidences/total person-time exposure. A Mantel-Haenszel (MH) test of homogeneity of the IRs was utilized to test the null hypothesis of no association between study region and IR After the MH test failed to reject the null hypothesis, the MH combined IR was calculated to provide a pooled estimate for the overall incident rate ratio (IRR).
Results: A total of 63 subjects were identified (18 group A, 45 group B). Males accounted for the majority (41-63; 65%) of admissions. The median (IQR) age was 3(2-7) years. The median (IQR) length of stay was 2 (1-3) days. These results were similar between the 2 cohorts. The ADHD drug was prescribed for the admitted subject in only 18/63 (29%) of patients and for the subject's sibling in 22/63 (34.9%). The IRR is 3.13 (95% CI 1.80-5.68; p< 0.0001). Combining the data from the 4 regions, the IRR is 3.36 (95% CI 1.97-5.75). The median (IQR) hospital charges in US dollars (adjusted for inflation) per subject was $4,780 ($3,895-$8,287) and $5912 ($3,432-$9,433) for group A and B respectively (p = 0.57).
Conclusion: Comparing the 2 time spans, the incidence of pediatric admissions for toxicity following non-suicidal ingestion of ADHD drugs has increased significantly, and is associated with significant cost. Many of the children developing toxicity were not the ones from whom the drug was prescribed. A further cost-analysis is needed to estimate the full cost to society.

……..

Arch Iran Med. 2012;15:560-63.
ASSOCIATED FACTORS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A CASE-CONTROL STUDY.
Malek A, Amiri S, Sadegfard M, et al.
Background: The current study attempted to investigate factors associated with attention deficit hyperactivity disorder (ADHD) in children without co-morbidities.
Methods: In this case-control study, 164 ADHD children who attended the Child and Adolescent Psychiatric Clinics of Tabriz University of Medical Sciences, Iran were compared with 166 normal children selected in a random-cluster method from primary and secondary schools. Clinical interviews based on DSM-IV-TR using K-SADS were used to diagnose ADHD cases and to select the control group. Participants were matched for age. We used chi-square and binary logistic regression for data analysis.
Results: Among the associated factors with ADHD were gender and maternal employment. Boys (OR 0.54; 95% confidence interval: 0.34 - 0.86) and those children with working mothers (OR 0.16: 95% confidence interval: 0.06 - 0.86) suffered more from ADHD. The birth season, family size, birth order, and parental kinship were not among risk factors for ADHD.
Conclusion: The results of the study show that maternal employment and male gender are among the associated risk factors for ADHD.

……..

Arch Pediatr Adolesc Med. 2012;166:919-25.
TELEVISION VIEWING AND EXTERNALIZING PROBLEMS IN PRESCHOOL CHILDREN: THE GENERATION R STUDY.
Verlinden M, Tiemeier H, Hudziak JJ, et al.
Objective: To determine whether the amount, type, and patterns of television viewing predict the onset or the persistence of externalizing problems in preschool children.
Design: Longitudinal study of a prospective population-based cohort in the Netherlands.
Setting: Parents reported time of television exposure and type of programs watched by children. Externalizing problems were assessed using the Child Behavior Checklist at 18 and 36 months.
Participants: A population-based sample of 3913 children.
Main Exposure: Television viewing time, content, and patterns of exposure (at 24 and 36 months) in children with and without preexisting problems to assess the incidence and persistence of externalizing problems. Main Outcome Measures: Externalizing problems at 36 months.

Results: Program content and time of television exposure assessed at 24 months did not predict the incidence of externalizing problems at 36 months (odds ratio, 2.24; 95% CI, 0.97-5.18). However, the patterns of exposure over time reflecting high levels of television viewing were associated with the incidence of externalizing problems (odds ratio, 2.00; 95% CI, 1.07-3.75) and the persistence of the preexisting externalizing problems (2.59; 1.03-6.55).
Conclusions: Our study showed that high television exposure increases the risk of the incidence and the persistence of externalizing problems in preschool children.

……..

Behav Genet. 2012;42:711-21.

ADDITIONAL EVIDENCE AGAINST SHARED ENVIRONMENTAL CONTRIBUTIONS TO ATTENTION-DEFICIT/HYPERACTIVITY PROBLEMS.

Burt SA, Larsson H, Lichtenstein P, et al.

A recent meta-analysis "Burt (Psychol Bull 135:608-637, 2009)" indicated that shared environmental influences (C) do not contribute to Attention-Deficit/ Hyperactivity Disorder (ADHD). Unfortunately, the metaanalysis relied almost exclusively on classical twin studies. Although useful in many ways, some of the assumptions of the classical twin model (e.g., dominant genetic and shared environmental influences do not simultaneously influence the phenotype) can artifactually decrease estimates of C. There is thus a need to confirm that dominant genetic influences are not suppressing estimates of C on ADHD. The current study sought to do just this via the use of a nuclear twin family model, which allows researchers to simultaneously model and estimate dominant genetic and shared environmental influences. We examined two independent samples of child twins: 312 pairs from the Michigan State University Twin Registry and 854 pairs from the PrE School Twin Study in Sweden. Shared environmental influences were found to be statistically indistinguishable from zero and to account for less than 5 % of the variance.We conclude that the presence of dominant genetic influences does not account for the absence of C on ADHD.

……..

Behav Genet. 2012;42:924.

EARLY MATERNAL AGE AT CHILDBEARING AND RISK FOR ADHD IN OFFSPRING.

Chang Z, Lichtenstein P, D'Onofrio B, et al.

Background: Women who give birth at younger ages (e.g., teenage mothers) are more likely to have children who exhibit behaviors problems, in particular antisocial behaviors. However, the link between early maternal age and offspring ADHD has not been established. In addition, it is not clear whether early maternal age at childbearing is causally associated with poor offspring outcomes or confounded by familial factors.
Methods: We used a population-based cohort of children born in Sweden between 1992 and 1998 (N=720,764), using linkage of national registries. Children and their mother were identified from the Multi-generation Registry. Offspring ADHD (n=13,963) were identified from the National Patient Registry (NPR) and the Prescribed Drug Registry (PDR). First, survival models were used to analyze the association between early maternal age and offspring ADHD among unrelated individuals. Second, we compared the risk of ADHD among differentially exposed siblings within nuclear families to control for familial background factors.
Results: Results showed that early maternal age at childbearing (maternal Age<20) was significantly associated with the risk of ADHD in offspring (Hazard ratio = 2.22, 95 % CI 2.06-2.38). Comparison of differentially exposed siblings indicated no within family association. Adjusted model showed that maternal age at first birth (MAFB) accounted for the observed association.
Conclusions: Early maternal age increased the risk of offspring ADHD. However, the absence of within-family association suggests that familial factors shared by siblings account for the association. Interventions for reducing ADHD should target risk factors that shared in a teenage-mother family.

……..

Behav Genet. 2012;42:920.

COMMON AND SPECIFIC GENETIC EFFECTS ON ADHD AND INITIAL SENSITIVITY TO CIGARETTES IN FEMALE ADOLESCENT TWINS.

Bidwell C, Palmer R, Heath A, et al.

Background: Attention-Deficit Hyperactivity Disorder (ADHD) is highly heritable and a robust predictor of adolescent smoking initiation, even after controlling for comorbid Conduct Disorder (CD) (e.g. B.F. Fuemmeler et al. 2007, J Pediatr Psychol 32:1203-1213). There is also evidence that ADHD symptoms may qualify genetic influences on initial sensitivity (IS) to cigarettes (Bidwell et al. 2011, Nicotine & Tob Res 14:229-233). This study aimed to examine common and specific genetic effects among ADHD symptom dimensions and IS to cigarettes while accounting for CD in female adolescent twins.

Methods: We examined age-adjusted rank normalized scores for DSM-IV Inattentive (IN) and Hyperactive-Impulsive (HI) subtypes of ADHD, CD, and IS to cigarettes in 3,753 respondents from the Missouri Adolescent Female Twin Study. DSM-IV ADHD was assessed via parent interview when the twins were adolescents. DSM-IV CD and IS (i.e. 7 items reflecting subjective responses to first experiences with cigarettes) were assessed by twin self-report. A multivariate Cholesky was used to partition the variance and covariance among the traits.

Results: Based on the results of the full Cholesky, each phenotype was at least moderately heritable (46, 76, 87, 29 % for CD, IN, HI, and IS, respectively), with modest shared environmental effects. The genetic relationship between ADHD and IS was driven by common and traitspecific genetic factors (a common genetic factor accounted for 54 % of the genetic covariance between IN and IS and 30 % of the covariance between HI and IS). There was also evidence for ADHDsubscale- specific genetic factors and tobacco sensitivity specific genetic effects. Common genetic effects on CD and ADHD accounted for only 11 % of the genetic effect on IS.

Conclusion: The covariation between ADHD subtypes and initial sensitivity to tobacco is primarily explained through a genetic factor common with CD. In addition, ADHD-specific and tobacco specific genetic effects are significant contributors.

……..

Behav Genet. 2012;42:931.

HERITABILITY OF SWAN-MEASURED ADHD IN ADOLESCENTS AND ADULTS.

Ebejer J, Medland S, Eldridge A, et al.

The heritability of ADHD for adolescents when measured using the Strengths and Weaknesses of ADHD symptoms and Normal Behaviour (SWAN) scale is lower than when scales of severity (for example, the Australian Twin Behaviour Rating Scale; ATBRS) are used. This is essentially due to a higher DZ correlation for SWAN rated behaviours. This study will examine data from 1,187 (621 female and 566 male) adolescent twins and their siblings aged from 10 to 18 to determine whether this result can be replicated. The heritability of the inattentive and hyperactive-impulsive subtypes of ADHD will also be estimated in a sample of 2,179 (1,094 female and 1,085 male) adult twins and their siblings aged from 19 to 46 as only one other study has examined the heritability of ADHD in adults and this was as a total score. This study has three aims; first to estimate the heritability of ADHD using the SWAN scale for both adolescents and adults. The second is to infer developmental changes in genetic and environmental variance components contributing to symptom expression across age groups. A third aim is to explore how these effects may vary across sex. A non-scalar sex limitation model will be used to test sex specific genetic and environmental effects in both age cohorts. Additionally, standard ACE, ADE and sub-models will be fitted to find the most parsimonious and essentially the most appropriate description of the genetic and environmental effects influencing the variation of ADHD symptoms within our sample. Results to be presented.

……..

Behav Genet. 2012;42:945-46.

THE SEPARATION OF ADHD INATTENTION AND HYPERACTIVITY-IMPULSIVITY SYMPTOMS: PATHWAYS FROM GENETIC EFFECTS TO COGNITIVE IMPAIRMENTS AND SYMPTOMS.

Kuntsi J, Pinto R, Price T, et al.

Both shared and unique genetic risk factors underlie the two symptom domains of attention deficit hyperactivity disorder (ADHD): inattention and hyperactivity-impulsivity. The developmental course and relationship to co-occurring disorders differs across the two symptom domains, highlighting the importance of their partially distinct etiologies. Familial cognitive impairment factors have been identified in ADHD, but whether they show specificity in relation to the two ADHD symptom domains remains poorly understood. A better understanding of the underlying risk pathways is required for the development of targeted interventions. We aimed to determine, using a multivariate genetic model fitting approach, whether different cognitive impairments are genetically linked to the ADHD symptom domains of inattention versus hyperactivity- impulsivity. A population twin sample of 1,314 children, ages 7-10, was individually assessed on a 4-choice reaction time task and a go/no-go inhibition task. Reaction time variability (RTV) showed substantial genetic overlap with inattention, as observed in a genetic correlation of 0.68, compared to a genetic correlation of 0.34 with hyperactivity-impulsivity. Commission errors (CE) showed low genetic correlations with both hyperactivity-impulsivity and inattention (genetic correlations of 0.18 and 0.10, respectively). The genetic correlation between RTV and CE was also low and non-significant at -0.13, consistent with the etiological separation between the two indices of cognitive impairments. Two key cognitive impairments phenotypically associated with ADHD symptoms, captured by reaction time variability (RTV) and commission errors (CE), showed different genetic relationships to the two ADHD symptom domains. Overall, the findings extend a previous model of two familial cognitive impairment factors in combined subtype ADHD by separating pathways underlying inattention and hyperactivity-impulsivity symptoms.

……..

Behav Genet. 2012;42:875-85.

BIGGER FAMILIES FARE BETTER: A NOVEL METHOD TO ESTIMATE RATER CONTRAST EFFECTS IN PARENTAL RATINGS ON ADHD SYMPTOMS.

Pinto R, Rijsdijk F, Frazier-Wood AC, et al.

Many twin studies on parental ratings of attention deficit hyperactivity disorder (ADHD) symptoms report low or negative DZ correlations. The observed differences in MZand DZvariances indicate sibling contrast effects, which appear to reflect a bias in parent ratings. Knowledge of the factors that contribute to this rater contrast effect is, however, limited. Using parent-rated ADHD symptoms from the Twins' Early Development Study and a novel application of a twin model, we explored a range of socio-demographic variables (ethnicity, socio-economic status, and family size), as potential contributors to contrast effects and their interactive effect with gender composition of twin pairs. Gender did moderate contrast effects but only in DZ opposite-sex twin pairs. Family size also showed a moderating effect on rater contrast effects, which was further modified by gender. We further observed an effect of rating scale, with the DSMIV ADHD subscale of the Revised Conners' Parent Rating Scale more resistant to contrast effects than shorter scales of ADHD symptoms. The improved identification of situations where the accuracy of the most common informant of childhood ADHD symptoms-parents-is compromised as a result of rater bias, might have implications for future research on ADHD.

……..

Behav Genet. 2012;42:936.

THE INFLUENCE OF EARLY ANESTHESIA EXPOSURE ON ADHD.

Groen-Blokhuis M, De Graaff J, Bartels M, et al.

Recent retrospective studies have shown an association between anesthesia exposure early in life and later learning and behavioral problems, in particular Attention Deficit Hyperactivity Disorder (ADHD). A previous study by the Netherlands Twin Register (NTR) confirmed the association between anesthesia exposure and Educational Achievement (EA) and Learning Problems (LP), but showed that undergoing

anesthesia at an early age may be considered an indicator of a genetic vulnerability rather than a causal factor for LP and EA. The aim of the current study was to attempt to replicate the association between anesthesia and ADHD and establish whether the association can be explained by a shared (genetic) vulnerability. Within the NTR, data on anesthesia exposure under age 3 were available from maternal reports at age 2 and 3. ASEBA and Conners' ADHDassociated phenotypes as rated by mothers, fathers and teachers were available for twins at age 7, 10 and 12 (n = 12,103). A significant higher score on all ADHD-related scales was observed for children exposed to anesthesia under age 3. However, in twin pairs discordant for early anesthesia exposure, the unexposed twin had similar scores as the exposed twin. Therefore, the association between early anesthesia exposure does not appear to be causal, but rather due to a shared vulnerability that puts children at risk for both early anesthesia and ADHD. A follow-up study in which detailed information about the type of surgery and duration of anesthesia is collected will address the question whether this conclusion also holds for severe exposures.

……..

Biol Psychiatry. 2012.

A META-ANALYTIC STUDY OF EVENT RATE EFFECTS ON GO/NO-GO PERFORMANCE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Metin B, Roeyers H, Wiersema JR, et al.

Background: According to the state regulation deficit model, event rate (ER) is an important determinant of performance of children with attention-deficit/hyperactivity disorder (ADHD). Fast ER is predicted to create overactivation and produce errors of commission, whereas slow ER is thought to create underactivation marked by slow and variable reaction times (RT) and errors of omission.

Methods: To test these predictions, we conducted a systematic search of the literature to identify all reports of comparisons of ADHD and control individuals' performance on Go/No-Go tasks published between 2000 and 2011. In one analysis, we included all trials with at least two event rates and calculated the difference between ER conditions. In a second analysis, we used metaregression to test for the moderating role of ER on ADHD versus control differences seen across Go/No-Go studies.

Results: There was a significant and disproportionate slowing of reaction time in ADHD relative to controls on trials with slow event rates in both meta-analyses. For commission errors, the effect sizes were larger on trials with fast event rates. No ER effects were seen for RT variability. There were also general effects of ADHD on performance for all variables that persisted after effects of ER were taken into account.

Conclusions: The results provide support for the state regulation deficit model of ADHD by showing the differential effects of fast and slow ER. The lack of an effect of ER on RT variability suggests that this behavioral characteristic may not be a marker of cognitive energetic effects in ADHD.

……..

Biol Psychiatry. 2012;72:684-91.

ALTERED DEVELOPMENT OF THE DORSOLATERAL PREFRONTAL CORTEX IN CHROMOSOME 22Q11.2 DELETION SYNDROME: AN IN VIVO PROTON SPECTROSCOPY STUDY.

Shashi V, Veerapandiyan A, Keshavan MS, et al.

Background: Chromosome 22q11.2 deletion syndrome (22q11DS), the most common microdeletion in humans, is associated with multiple medical features, almost universal cognitive deficits, and a high risk of schizophrenia. The metabolic basis of the psychological/psychiatric features is not well understood. Volumetric brain imaging studies have shown that gray matter abnormalities in the dorsolateral prefrontal cortex (DLPFC), an area that is believed to be integral for higher neurocognition, as well as being involved in schizophrenia, are associated with the psychological manifestations. However, studies have not characterized any possible metabolite alterations within the DLPFC of children with 22q11DS and their correlations with the psychological findings.

Methods: We conducted a short echo time, single-voxel, in vivo proton spectroscopy study involving children with 22q11DS (n=26) and matched control subjects (n=23).

Results: Absolute N-acetylaspartate (NAA) levels from the DLPFC were significantly elevated in children with 22q11DS compared with control subjects and the elevations were associated with poor global

functioning and higher rates of comorbid attention-deficit/hyperactivity disorder. Children with 22q11DS had a lack of an age-associated decrease in NAA levels, a trend seen in the control subjects. However, the results did not remain statistically significant after corrections for multiple comparisons were made.
Conclusions: These findings represent the first report of proton spectroscopy in children with 22q11DS. The elevated DLPFC NAA levels and the lack of decreasing trends in NAA with age in the 22q11DS group relative to control subjects suggest an alteration in cortical development. Also, such neuronal dysmaturation is associated with psychopathology in children with 22q11DS.

……..

BMC Pediatr. 2012;12.

THE EPIDEMIOLOGY OF PHARMACOLOGICALLY TREATED ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN, ADOLESCENTS AND ADULTS IN UK PRIMARY CARE.

McCarthy S, Wilton L, Murray ML, et al.

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterised by the symptoms of inattention, impulsivity and hyperactivity. ADHD was once perceived as a condition of childhood only; however increasing evidence has highlighted the existence of ADHD in older adolescents and adults. Estimates for the prevalence of ADHD in adults range from 2.5-4%. Few data exist on the prescribing trends of the stimulants methylphenidate and dexamfetamine, and the non-stimulant atomoxetine in the UK. The aim of this study was to investigate the annual prevalence and incidence of pharmacologically treated ADHD in children, adolescents and adults in UK primary care.
Methods: The Health Improvement Network (THIN) database was used to identify all patients aged over 6 years with a diagnosis of ADHD/hyperkinetic disorder and a prescription for methylphenidate, dexamfetamine or atomoxetine from 2003-2008. Annual prevalence and incidence of pharmacologically treated ADHD were calculated by age category and sex.
Results: The source population comprised 3,529,615 patients (48.9% male). A total of 118,929 prescriptions were recorded for the 4,530 patients in the pharmacologically treated ADHD cohort during the 6-year study. Prevalence (per 1000 persons in the mid-year THIN population) increased within each age category from 2003 to 2008 [6-12 years: from 4.8 (95% CI: 4.5-5.1) to 9.2 (95% CI: 8.8-9.6); 13-17 years: from 3.6 (95% CI: 3.3-3.9) to 7.4 (95% CI: 7.0-7.8); 18-24 years: from 0.3 (95% CI: 0.2-0.3) to 1.1 (95% CI: 1.0-1.3); 25-45 years: from 0.02 (95% CI: 0.01-0.03) to 0.08 (95% CI: 0.06-0.10); >45 years: from 0.01 (95% CI: 0.00-0.01) to 0.02 (95% CI: 0.01-0.03). Whilst male patients aged 6-12 years had the highest prevalence; the relative increase in prescribing was higher amongst female patients of the same age - the increase in prevalence in females aged 6-12 years was 2.1 fold compared to an increase of 1.9 fold for their male counterparts. Prevalence of treated ADHD decreased with increasing age. Incidence (per 1000 persons at risk in the mid-year THIN population) was highest for children aged 6-12 years.
Conclusions: A trend of increasing prescribing prevalence of ADHD drug treatment was observed over the period 2003-2008. Prevalence of prescribing to adult patients increased; however the numbers treated are much lower than published estimates of the prevalence of ADHD. This study has added to the limited knowledge on ADHD prescribing in primary care, particularly in the area of drug treatment in adulthood.

……..

BMC Psychiatry. 2012;168.

PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN AND ADOLESCENTS IN SPAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EPIDEMIOLOGICAL STUDIES.

Catala-Lopez F, Peiro S, Ridao M, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is a commonly diagnosed neuropsychiatric disorder in childhood, but the frequency of the condition is not well established in many countries. The aim of the present study was to quantify the overall prevalence of ADHD among children and adolescents in Spain by means of a systematic review and meta-analysis.
Methods: PubMed/MEDLINE, IME, IBECS and TESEO were comprehensively searched. Original reports were selected if they provided data on prevalence estimates of ADHD among people under 18 years old in Spain and were cross-sectional, observational epidemiological studies. Information from included studies

was systematically extracted and evaluated. Overall pooled-prevalence estimates of ADHD were calculated using random-effects models. Sources of heterogeneity were explored by means sub-groups analyses and univariate meta-regressions.
Results: Fourteen epidemiological studies (13,026 subjects) were selected. The overall pooled-prevalence of ADHD was estimated at 6.8% [95% confidence interval (CI) 4.9 -- 8.8%] representing 361,580 (95% CI 260,550 -- 467,927) children and adolescents in the community. There was significant heterogeneity (P < 0.001), which was incompletely explained by subgroup analyses and meta-regressions.
Conclusions: Our findings suggest that the prevalence of ADHD among children and adolescents in Spain is consistent with previous studies conducted in other countries and regions. This study represents a first step in estimating the national burden of ADHD that will be essential to building evidence-based programs and services.

……..

BMC Psychiatry. 2012;174.

THE IMPACT OF ADHD SYMPTOMS AND GLOBAL IMPAIRMENT IN CHILDHOOD ON WORKING DISABILITY IN MID-ADULTHOOD: A 28-YEAR FOLLOW-UP STUDY USING OFFICIAL DISABILITY PENSION RECORDS IN A HIGH-RISK IN-PATIENT POPULATION.

Mordre M, Groholt B, Sandstad B, et al.

Background: Individuals with ADHD have been associated with more employment difficulties in early adulthood than healthy community controls. To examine whether this association is attributable specifically to disturbance of activity and attention (ADHD) or to psychopathology in general, we wanted to extend existing research by comparing the rate of mid-adulthood working disabilities for individuals diagnosed with ADHD as children with the rate for clinical controls diagnosed with either conduct disorder, emotional disorder or mixed disorder of conduct and emotions.
Methods: Former Norwegian child-psychiatric in-patients (n=257) were followed up 17--39 years after hospitalization by record linkage to the Norwegian national registry of disability pension (DP) awards. Based on the hospital records, the patients were re-diagnosed according to ICD-10. Associations between the diagnoses, other baseline factors and subsequent DP were investigated using Kaplan--Meier survival analyses and logrank testing.
Results: At follow-up, 19% of the participants had received a DP award. In the logrank testing, ADHD was the only disorder associated with a subsequent DP, with 30% being disabled at follow-up (p=0.01). Low psychosocial functioning (assessed by the Children's Global Assessment Scale) at admission uniquely predicted future DP (p=0.04).
Conclusions: ADHD in childhood was highly associated with later receiving a DP. Our finding of worse prognosis in ADHD compared with other internalizing and externalizing disorders in mid-adulthood supports the assumption of ADHD being specifically linked to working disability. Assessment of psychosocial functioning in addition to diagnostic features could enhance prediction of children who are most at risk of future disability.

……..

Brain Connectivity. 2012;2:A128.

RESTING-STATE FUNCTIONAL CONNECTIVITY ANOMALIES IN ADHD AND RESPONSES TO METHYLPHENIDATE MEDICATION.

Silk T.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood and is associated with multiple, significant impairments persisting into adulthood. The most commonly prescribed treatment for ADHD is the stimulant medication, methylphenidate (MPH). While it is well-established that not all children with ADHD achieve equal benefit from MPH, there is a poor understanding of the mechanisms that underpin their neural response. The advantage of resting-state approaches has recently demonstrated clinical utility and is hypothesized to be able to predict individual responsiveness to medication based on patterns of resting-state functional connectivity. Methods: This study employed a placebo-controlled, doubleblind, randomised, cross-over design of the influence of

methylphenidate vs placebo on the neural substrates in participants with ADHD. Children with ADHD perform two fMRI measurement sessions, separated by a minimum of 2 weeks. One session was performed under placebo and the other session under an acute standard clinical dose of MPH (20 mg). The two sessions were counterbalanced to avoid practice effects. Data were acquired used a 3-Tesla Siemens TIM Trio scanner at the Royal Children's Hospital, Melbourne. 180 whole-brain volumes of Resting state EPI were acquired over the 6 min sequence. Pre-processing and data analysis will be performed using the methods described for the 1000 Functional Connectomes Project and International Neuroimaging Data-sharing Initiative. ROIs were selected in inferior frontal, caudate and parietal regions. Results: The follow results are an initial pilot analysis within a small group, seeding key front0-striatal and parietal regions. When caudate was seeded, repeated measures analysis showed significantly greater functional connectivity when under MPH compare to placebo, in the supramarginal gyrus. Further analysis with greater numbers may reveal that the striatalparietal connectivitymay be a better indicator of responsiveness to medication than fronto-striatal connectivity based on patterns of resting-state functional connectivity.

……..

Brain Connectivity. 2012;2:A97.

INTRINSIC FUNCTIONAL CONNECTIVITY NETWORKS IN ADULTS WITH CHILDHOOD ATTENTION-DEFICIT HYPERACTIVITY DISORDER AT 33-YEAR FOLLOW-UP.

Proal E, Castellanos FX, Rojas G, et al.

Background and Objectives: Most imaging studies of Attention- Deficit/Hyperactivity Disorder (ADHD) in adults have relied on retrospective recall of childhood ADHD status. In the longest longitudinal study of ADHD, from which this report is drawn, children with impairing symptoms of hyperactivity, impulsivity, and inattention were recruited between ages 6 and 12. They were followed-up at mean ages 18, 25, and 41 along with comparisons free of such childhood symptoms enrolled at mean age 18. At age 41 they underwent an MRI study. Our objective here was to examine intrinsic functional connectivity (iFC), by contrasting individuals with a documented history of childhood ADHDto non- ADHD comparisons.

Methods: **Participants**: We analyzed resting fMRI data in a subset from the NY Longitudinal Study of ADHD (N = 45; 20 Probands, mean age, 42.6; and 25 Comparisons mean age, 40.6) who underwent MRI scans. Seed based analyseswere performed with26 seeds selected froman ADHD meta-analysis of 55 fMRI studies. Subject level analyses of correlations between seed time-series and every other voxel in the brain were obtained; group-level analyses were carried out using random-effects ordinary least squares, whole-brain corrected.

Results: Comparisons had greateriFC between left putamen and widespread dorsomedial frontal regions. Left inferior frontal gyrus (BA44) exhibited greater iFC in ventral frontal striatal regions. In the right hemisphere, group differences for inferior frontal gyrus included frontal pole and caudate. Differences in postcentral gyrus iFC were seen in frontal and insular regions. ADHD showed greateriFC in both Inferior frontal gyri with pre and postcentral regions and parietal lobe. Lack of IFC in probands and negative iFC in comparisons was found for left putamen, right posterior cingulate cortex, and left inferior frontal gyrus (BA45) seeds with regions located mostly in occipital and temporal regions.

Conclusions: Overall we found decreased iFC in probands in frontoparietal and limbic networks, and increased iFC in visual and somatomotor networks that persisted into adulthood. We note that decreased iFC in probands was seen mostly in frontal and striatal circuits related to motivation and executive function and lack of negative iFC was observed posteriorly in visual and parietal networks related to attentional tasks.

……..

Can Pharm J. 2012;145:226-30.

ATOMOXETINE AND STIMULANT MEDICATIONS IN CHILDREN AND ADOLESCENTS WITH PERSISTENT SYMPTOMS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER DESPITE MONOTHERAPY.

Jacques A.

……..

Child Adolesc Psychiatry Ment Health. 2012;33.

SOCIAL AND EMOTIONAL DIFFICULTIES IN CHILDREN WITH ADHD AND THE IMPACT ON SCHOOL ATTENDANCE AND HEALTHCARE UTILIZATION.

Classi P, Milton D, Ward S, et al.

Background: The objective of this study was to examine the impact of co-occurring social and emotional difficulties on missed school days and healthcare utilization among children with attention deficit/hyperactivity disorder (ADHD).

Methods: Data were from the 2007 U.S. National Health Interview Survey (NHIS) and were based on parental proxy responses to questions in the Sample Child Core, which includes questions on demographics, health, healthcare treatment, and social and emotional status as measured by questions about depression, anxiety, and phobias, as well as items from the brief version of the Strength and Difficulties Questionnaire (SDQ). Logistic regression was used to assess the association between co-occurring social and emotional difficulties with missed school days and healthcare utilization, adjusting for demographics.

Results: Of the 5896 children aged 6--17 years in the 2007 NHIS, 432 (7.3%) had ADHD, based on parental report. Children with ADHD and comorbid depression, anxiety, or phobias had significantly greater odds of experiencing > 2 weeks of missed school days, >= 6 visits to a healthcare provider (HCP), and >= 2 visits to the ER, compared with ADHD children without those comorbidities (OR range: 2.1 to 10.4). Significantly greater odds of missed school days, HCP visits, and ER visits were also experienced by children with ADHD who were worried, unhappy/depressed, or having emotional difficulties as assessed by the SDQ, compared with ADHD children without those difficulties (OR range: 2.2 to 4.4).

Conclusions: In children with ADHD, the presence of social and emotional problems resulted in greater odds of missed school days and healthcare utilization. These findings should be viewed in light of the limited nature of the parent-report measures used to assess social and emotional problems.

……..

Clin Case Stud. 2012;11:312-25.

INATTENTION AND HYPERACTIVITY BEHAVIORAL PATTERN OF A CHILD WITH WILLIAMS SYNDROME: COMPARISONS OF REGULAR AND EXPERIMENTAL CLASS SETTING.

Lima SDFB, Carreiro LRR, Seraceni MFF, et al.

Children and adolescents with Williams syndrome (WS) frequently present inattention and hyperactivity. This study aims to compare the number of behaviors of inattention and hyperactivity/impulsivity in one child with WS in two school settings: a regular class setting and an experimental class setting with the introduction of strategies for behavioral management. A case study was conducted with a child with WS, his regular teacher at school, his mother, and a teacher of the experimental class setting. A protocol was used to observe behavioral patterns of inattention, hyperactivity, and impulsivity. Behavioral strategies of stimulus control and reinforcement were also used. Results indicated a significant improvement in the rates of inattention and hyperactivity responses for the experimental class condition. Behavioral strategies, if adapted to the needs of students with WS, may optimize an effective school inclusion and contribute to the child's adaptation to classroom setting.

……..

Dev Med Child Neurol. 2012 Oct;54:898-904.

DOES ATTENTION-DEFICIT-HYPERACTIVITY DISORDER EXACERBATE EXECUTIVE DYSFUNCTION IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1?

Payne JM, Arnold SS, Pride NA, et al.

AIM: Although approximately 40% of children with neurofibromatosis type 1 (NF1) meet diagnostic criteria for attention-deficit-hyperactivity disorder (ADHD), the impact of ADHD on the executive functioning of children with NF1 is not understood. We investigated whether spatial working memory and response inhibition are impaired in children with NF1 without a diagnosis of ADHD and whether executive deficits are exacerbated in children with a comorbid diagnosis.

METHOD: Forty-nine children aged 7 to 15 years with NF1 only (31 males, 18 females; mean age 11y, SD 2y 4mo) or 35 with NF1 and ADHD (18 males, 17 females; mean age 10y 8mo, SD 2y 4mo) and 30 typically developing comparison children (16 males, 14 females; mean age 10y, SD 2y 8mo) were compared on measures of spatial working memory and response inhibition. Group differences in IQ and visuospatial ability were controlled for as required.
RESULTS: Compared with typically developing children, children with NF1 with or without comorbid ADHD demonstrated significant impairment of both spatial working memory (both $p<0.004$) and inhibitory control (both $p<0.010$). There were, however, no differences between the two NF1 groups in spatial working memory ($p=0.91$) or response inhibition ($p=0.78$).
INTERPRETATION: Executive dysfunction occurs with the same severity in children with NF1, whether or not they have a comorbid diagnosis of ADHD, suggesting that executive impairments are not unique contributors to ADHD symptomatology in NF1. The findings are discussed within the context of recent evidence in Nf1 optic glioma (OPG) mice, in which a mechanistic connection between NF1 gene expression, executive system failure, and dopaminergic pathway integrity has been established.

……..

Dev Med Child Neurol. 2012 Oct;54:905-11.

PSYCHIATRIC AND COGNITIVE PHENOTYPE OF CHILDHOOD MYOTONIC DYSTROPHY TYPE 1 .

Douniol M, Jacquette A, Cohen D, et al.

AIM: To investigate the psychiatric and cognitive phenotype in young individuals with the childhood form of myotonic dystrophy type 1 (DM1).
METHOD: Twenty-eight individuals (15 females, 13 males) with childhood DM1 (mean age 17y, SD 4.6, range 7-24y) were assessed using standardized instruments and cognitive testing of general intelligence, visual attention, and visual-spatial construction abilities.
RESULTS: Nineteen patients had repeated a school grade. The mean (SD) Full-scale IQ was 73.6 (17.5) and mean Verbal IQ was significantly higher than the mean Performance IQ: 80.2 (19.22) versus 72.95 (15.58), $p=0.01$. Fifteen patients had one or more diagnoses on the DSM-IV axis 1, including internalizing disorders (phobia, n=7; mood disorder, n=6; other anxiety disorders, n=5) and attention-deficit-hyperactivity disorder, inattentive subtype (n=8). Twelve out of 22 patients had alexithymia (inability to express feelings with words and to recognize and share emotional states). Cognitive testing found severe impairments in visual attention and visual-spatial construction abilities in four out of 18, and 14 out of 24 patients respectively. No diagnosis was correlated with the transmitting parent's sex or with cytosine-thymine-guanine (CTG) repeat numbers. Patients with severe visual-spatial construction disabilities had a significantly longer CTG expansion size than those with normal visual-spatial abilities ($p=0.04$).
INTERPRETATION: Children and adolescents with childhood DM1 have frequent diagnoses on DSM-IV axis 1, with internalizing disorders being the most common type of disorder. They also have borderline low intelligence and frequent impairments in attention and visual-spatial construction abilities.

……..

Dev Med Child Neurol. 2012 Oct;54:912-17.

DO SEQUENTIAL EEG CHANGES PREDICT ATYPICAL CLINICAL FEATURES IN ROLANDIC EPILEPSY?

Kanemura H, Sano F, Aoyagi K, et al.

AIM: Although the prognosis for rolandic epilepsy is regarded to be favourable, a small proportion of cases that initially present as rolandic epilepsy evolve into atypical benign partial epilepsy (ABPE) of childhood. The purpose of our study was to determine electroencephalogram (EEG) criteria in relation to atypical seizure manifestations, and cognitive and behavioural problems in rolandic epilepsy.
METHODS: The rolandic epilepsy group consisted of 10 children (mean age 5y 6mo, SD 1y 1mo, median age 5y 5mo; six males, four females). The ABPE group comprised five children (mean age 5y, SD 1y 2mo, median age 4y 5mo; three males, two females). We recorded the number of spikes, the locations of spikes, and the duration of the spike activity. The Wechsler Intelligence Scale for Children-Third Edition or the Wechsler Preschool and Primary Scale of Intelligence, depending on age, was administered to all children

at the onset of seizures and every year thereafter. The diagnosis of attention-deficit-hyperactivity disorder was made according to the DSM-IV.
RESULTS: Significant correlations were found between atypical clinical features and extended periods of high-frequency paroxysmal EEG abnormalities (>24mo after onset; p<0.01) and frontal EEG focus (>10mo after onset; p<0.003).
INTERPRETATION: A combination of spike rate and extended periods of high-frequency paroxysmal EEG abnormalities may predict the evolution of atypical rolandic epilepsy.

……..

Dev Med Child Neurol. 2012;54:874-75.
THE IMPORTANCE OF SCREENING FOR INTERNALIZING SYMPTOMS, INATTENTION, AND COGNITIVE DIFFICULTIES IN CHILDHOOD-ONSET MYOTONIC DYSTROPHY.
Kledzik AM, Dunn DW.

……..

Encephale. 2012;38:418-25.
A STUDY OF TEMPERAMENT AND PERSONALITY IN CHILDREN DIAGNOSED WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).
Bouvard M, Sigel L, Laurent A.
Background: The study of children's personality and its development has generated several theoretical models in psychology. In a developmental approach, Buss and Plomin elaborated a genetic model of temperament that involves four dimensions: emotionality (refers to the negative quality of the emotion and the intensity of the emotional reactions), activity (intensity and frequency of a person's energy output in motor movements and speech), sociability (search for social relationships and preference for activities with others) and shyness (behavioural inhibition and feelings of distress when in interaction with strangers). The psychobiological approach postulates a biological model of personality. Thus, in Gray's first model, there are two brain systems that explain behaviours: the Bbehavioural Activation System (BAS) related to impulsivity and the Behavioural Inhibition System (BIS) linked to anxiety. Finally, dispositional theories seek to identify functional units of the normal personality from the factorial approach. Accordingly, Barbaranelli et al. build a questionnaire, the big five questionnaire for children (BFQ-C), which is intended to estimate the emergence of five fundamental dimensions (energy/extraversion, agreeableness, conscientiousness, emotional instability and intellect/openness) in children from 8 to 18 years. The clinical study we will present concerns the personality of children suffering from attention-deficit hyperactivity disorder (ADHD).
Study 1: methods and results: In a first study, we compared the ratings of 33 children with ADHD regarding their personality, as well as the ratings of their parents, over a one-year interval. The EAS questionnaire tapping into the genetic model put forth by Buss and Plomin evaluates four dimensions: emotionality, activity, sociability and shyness. The BIS/BAS scales for children correspond to Gray's first psychobiological model of personality. The BIS scale is unidimensional and the BAS scale is divided into three subscales (drive, fun-seeking and reward responsiveness). The answers collected from parents at the two moments of completion of the EAS were comparable and the correlations were all higher than 0.70. Concerning the children, there were no significant differences between the two time periods but the correlations were rather low. On the BIS/BAS scales, they varied from 0.22 (fun-seeking BAS scale) to 0.51 (BIS scale), whereas the obtained correlations on the EAS ranged from 0.32 (emotionality) to 0.58 (activity and shyness). Finally, to compare the answers of the children with their parents on the EAS questionnaire, we used a correlation coefficient test. For time 1, the correlations varied from 0.54 (emotionality) to 0.69 (sociability), and for time 2, they varied from 0.18 (sociability) to 0.50 (shyness). The concordance between the parents' and children' answers was thus higher than in a group from the general population.
Study 2: methods and results: In the second study, we compared the personality of children with ADHD (n = 35) with a sample from the general population (n = 35). The two groups of subjects were matched on age (mean: 12.7 years) and made comparable for gender. Participants with ADHD were comparable with control participants on the BIS, as well as on the reward responsiveness subscale of the BAS. Furthermore, participants with ADHD and controls were comparable concerning the tendency to avoid and

the anxiety. However, as expected, those with ADHD obtained higher scores on two subscales of the BAS. Concerning the traits of temperament, participants with ADHD reported being more active and having greater emotionality than did control subjects. On the other hand, there were no group differences for the two other aspects of temperament (sociability and shyness). Finally, participants with ADHD obtained higher scores on the BFQ-C than did control participants. It is interesting to note that children with ADHD obtained higher scores on the extraversion scale of the BFQ-C and the activity scale of the EAS. Our findings parallel the existing literature concerning the neuroticism scale of the BFQ-C and the BAS, but not the agreeableness and conscientiousness scales of the BFQ-C.
Discussion: It is interesting to note that children have a less stable representation of their own temperament as compared to the evaluation of their parents. This study replicates the findings of previous research on adults with ADHD regarding neuroticism (emotional instability), but contrary to findings in adults with ADHD, children obtained elevated scores on the conscientiousness and agreeableness subscales. In accordance with our hypotheses, children with ADHD could be distinguished from control participants on the BAS, particularly for the drive and reward responsiveness subscales. Furthermore, they also obtained higher scores on the extraversion subscale of the BFQ-C and the on the EAS activity subscale.

……..

Environ Res. 2012 Oct;118:65-71.
INVERSE ASSOCIATION OF INTELLECTUAL FUNCTION WITH VERY LOW BLOOD LEAD BUT NOT WITH MANGANESE EXPOSURE IN ITALIAN ADOLESCENTS.
Lucchini RG, Zoni S, Guazzetti S, et al.
BACKGROUND: Pediatric lead (Pb) exposure impacts cognitive function and behavior and co-exposure to manganese (Mn) may enhance neurotoxicity.
OBJECTIVES: To assess cognitive and behavioral function in adolescents with environmental exposure to Pb and Mn.
METHODS: In this cross sectional study, cognitive function and behavior were examined in healthy adolescents with environmental exposure to metals. The Wechsler Intelligence Scale for Children (WISC) and the Conners-Wells' Adolescent Self-Report Scale Long Form (CASS:L) were used to assess cognitive and behavioral function, respectively. ALAD polymorphisms rs1800435 and rs1139488 were measured as potential modifiers.
RESULTS: We examined 299 adolescents (49.2% females) aged 11-14 years. Blood lead (BPb) averaged 1.71 mug/dL (median 1.5, range 0.44-10.2), mean Blood Manganese (BMn) was 11.1 mug/dL (median 10.9, range 4.00-24.1). Average total IQ was 106.3 (verbal IQ=102, performance IQ=109.3). According to a multiple regression model considering the effect of other covariates, a reduction of about 2.4 IQ points resulted from a two-fold increase of BPb. The Benchmark Level of BPb associated with a loss of 1 IQ-point (BML01) was 0.19 mug/dL, with a lower 95% confidence limit (BMLL01) of 0.11 mug/dL. A very weak correlation resulted between BPb and the ADHD-like behavior (Kendall's tau rank correlation=0.074, p=0.07). No influence of ALAD genotype was observed on any outcome. Manganese was not associated with cognitive and behavioral outcomes, nor was there any interaction with lead.
CONCLUSIONS: These findings demonstrate that very low level of lead exposure has a significant negative impact on cognitive function in adolescent children. Being an essential micro-nutrient, manganese may not cause cognitive effects at these low exposure levels.

……..

Epilepsia. 2012;53:161.
NATURAL PROGNOSIS OF EEG ABNORMALITIES AND INTELLECTUAL FUNCTIONS IN CHILDREN WITH ADHD AND/OR LD.
Turkdogan D, Zaimoglu S.
Purpose: We aimed to study evolution of EEG abnormalities in children with ADHD and/or LD.
Method: In 30 (aged 7-14, mean: 8.2(plus or minus)1.9 years, 7% female) patients with ADHD and/or LD and an abnormal EEG, serial EEG examinations were done in an interval of 3 to 42 months.

Comprehensive battery of cognitive tests assessing Full Scale Intelligence Quotient-FSIQ, attention and executive functions (Wisconsin Card Sorting Test; Visual Memory Span, subtest of Wechsler Memory Scale-Revised; Stroop Task; Category Fluency) and verbal learning and memory functions (California Verbal Learning Test) were done in all patients within 2 weeks of EEG recordings.
Result: The initial EEG demonstrated epileptiform abnormalities in 26, focal slowing in 1 and both in 3 patients. The localization of abnormality was frontal in 10, centro-temporal in 9, occipital in 4, central in 2, temporal in 1, parietal in 1, and generalized in 3 patients. Epileptiform potentials were activated by sleep in 12 patients. Epileptiform activity was frequent in 13, moderate in 2 and rare in 14 patients. The characteristics of EEG abnormality persisted in consecutive recordings of 15 patients after 9 to 24 (mean: 15.4(plus or minus)4.7) months. Initial EEG abnormality (focal in 13 patients and generalized in 1 patient) normalized after 3 to 42 (mean 14.1(plus or minus)9.9) months. Comparison of consecutive intellectual functioning parameters in patients with persisting epileptiform potentials and patients with normalized EEG did not demonstrate a significant change.
Conclusion: The intellectual functions in patients with ADHD and/or LD seems not to be affected by the presence of EEG abnormalities.

……..

Eur Child Adolesc Psychiatry. 2012;1-10.
COMORBID ANXIETY AND NEUROCOGNITIVE DYSFUNCTIONS IN CHILDREN WITH ADHD.
Bloemsma JM, Boer F, Arnold R, et al.
Previous research established that children with ADHD and comorbid anxiety have a later age of ADHD onset, show less off-task and hyperactive behavior, and have more school problems than children with ADHD alone. Comorbid anxiety appears to ameliorate behavioral inhibition deficits, worsen working memory problems, and lengthen reaction times in ADHD. This study investigated the effect of comorbid anxiety on a broad range of neurocognitive functions and includes child-, parent- and teacher reports of anxiety. The sample consisted of 509 children in the age range 5-19 years, including 238 children with a diagnosis of ADHD combined subtype and 271 normal control children. Children were tested on a broad battery of neurocognitive tasks that proved highly sensitive to ADHD in previous work. Linear Structural Equation Modeling (SEM) was used to estimate the effect of comorbid anxiety on the neurocognitive functions. Child reported anxiety was associated with slower motor speed and response speed and better behavioral inhibition. Teacher reported anxiety was related to worse time production. Parent reported anxiety was not significantly associated with any of the neurocognitive functions. Compared to parent and teacher reports of anxiety, child reported comorbid anxiety shows foremost the largest associations with the neurocognitive dysfunctions observed in children with ADHD. This stresses the importance of including child self-reported anxiety assessments in clinical and research practice.

……..

Eur Child Adolesc Psychiatry. 2012;1-12.
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.

……..

Eur J Clin Pharmacol. 2012;68:1443-50.

THE USE OF MEDICATION AGAINST ATTENTION DEFICIT HYPERACTIVITY DISORDER IN DENMARK: A DRUG USE STUDY FROM A NATIONAL PERSPECTIVE.

Pottegard A, Bjerregaard BK, Glintborg D, et al.

Purpose The purpose of the study was to characterize the utilization of medication against attention deficit hyperactivity disorder (ADHD) in Denmark between 1995 and 2011 from a national perspective, by using population-based prescription data.

Methods National data on drug use in Denmark between 1 January 1995 and 30 September 2011 were extracted from the Registry of Medicinal Product Statistics (RMPS). Drug utilization was characterized using descriptive statistics.

Results A total of 1,085,090 prescriptions issued to 54,020 persons were identified. The incidence rate was stable in the last 3 years of the study period, and a slightly decreasing incidence rate and a stabilizing prevalence were observed towards the end of this period. The therapeutic intensity was 6.7 defined daily dose/person/day, with large regional differences that ranged from 64 to 145 % of the national average. Methylphenidate accounted for 92.6 % of DDDs used. The general practitioner (GP) rarely initiated treatment, although treatment initiation based on the GP's advice increased with older age of the patient. Maintenance treatment was found to be distributed roughly equally between prescriber types. For methylphenidate, 1%of users accounted for 6.1%of the drug volume and 50 % of users accounted for 84.4 %. The data therefore do not suggest a high proportion of heavy users.

Conclusion The findings of this analysis are mostly reassuring, with the data indicating a seemingly stagnant incidence and prevalence rate and lacking evidence of heavy users. However, the prescriber profile for incident users and the large regional variances raise concerns. It is therefore vital that the use of ADHD drugs is closely monitored.

……..

Front Syst Neurosci. 2012;1-22.

ADHD-200 GLOBAL COMPETITION: DIAGNOSING ADHD USING PERSONAL CHARACTERISTIC DATA CAN OUTPERFORM RESTING STATE FMRI MEASUREMENTS.

Brown MRG, Sidhu GS, Greiner R, et al.

Neuroimaging-based diagnostics could potentially assist clinicians to make more accurate diagnoses resulting in faster, more effective treatment. We participated in the 2011 ADHD-200 Global Competition which involved analyzing a large dataset of 973 participants including Attention deficit hyperactivity disorder (ADHD) patients and healthy controls. Each participant's data included a resting state functional magnetic resonance imaging (fMRI) scan as well as personal characteristic and diagnostic data. The goal was to learn a machine learning classifier that used a participant's resting state fMRI scan to diagnose (classify) that individual into one of three categories: healthy control, ADHD combined (ADHD-C) type, or ADHD inattentive (ADHD-I) type. We used participants' personal characteristic data (site of data collection, age, gender, handedness, performance IQ, verbal IQ, and full scale IQ), without any fMRI data, as input to a logistic classifier to generate diagnostic predictions. Surprisingly, this approach achieved the highest diagnostic accuracy (62.52%) as well as the highest score (124 of 195) of any of the 21 teams participating in the competition. These results demonstrate the importance of accounting for differences in age, gender, and other personal characteristics in imaging diagnostics research. We discuss further implications of these results for fMRI-based diagnosis as well as fMRI-based clinical research. We also document our tests with a variety of imaging-based diagnostic methods, none of which performed as well as the logistic classifier using only personal characteristic data.

……..

Genes Brain Behav. 2012;11:864-68.

ASSOCIATION STUDY OF GIT1 GENE WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN BRAZILIAN CHILDREN AND ADOLESCENTS.

Salatino-Oliveira A, Genro JP, Chazan R, et al.

This paper reports that the association of the GIT1 gene with attention-deficit hyperactivity disorder previously reported was not observed in Brazilian youths. Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in children with a worldwide prevalence of 5.3%. Recently, a Korean group assessed the G-protein-coupled receptor kinase-interacting protein 1 (GIT1) gene that had previously been associated with ADHD. In their work, 27 single nucleotide polymorphisms SNPs in the GIT1 gene were tested; however, only the rs550818 SNP was associated with ADHD susceptibility. Moreover, the presence of the risk-associated allele determined reduced GIT1 expression, and Git1-deficient mice exhibit ADHD-like phenotypes. The aim of this study was to determine if this association also occurs in a sample of Brazilian children with ADHD. No effect of GIT1 genotypes on ADHD susceptibility was observed in the case-control analysis. The odds ratios (ORs) were 0.75 (P = 0.184) for the CT genotype and 1.09 (P = 0.862) for the TT genotype. In addition, the adjusted OR of the CT+TT genotypes vs. the CC genotype was also estimated (P = 0.245). There were no dimensional associations between the GIT1 genotypes and both hyperactivity and impulsivity, and only hyperactivity Swanson, Nolan and Pelham Scale-Version IV (SNAP-IV) scores (P=0.609 and P=0.247, respectively). The transmission/disequilibrium test indicated that there was no over-transmission of rs550818 alleles from parents to ADHD children (z=0.305; P=0.761). We conclude that rs550818 is not associated with ADHD in this Brazilian sample. More studies are required before concluding that this polymorphism plays a role in ADHD susceptibility.

……..

Health Serv Outcomes Res Methodol. 2012;1-14.

EVALUATING LONG-TERM EFFECTS OF A PSYCHIATRIC TREATMENT USING INSTRUMENTAL VARIABLE AND MATCHING APPROACHES.

Lu B, Marcus S.

Evaluating treatment effects in non-randomized studies is challenging due to the potential unmeasured confounding and complex form of observed confounding. Propensity score based approaches, such as matching or weighting, are commonly used to handle observed confounding variables. The instrumental variable (IV) method is known to guard against unmeasured confounding if a good instrument can be identified. We propose to combine both methods to estimate the long-term treatment effect in a longitudinal psychiatric study. The NIMH collaborative Multi-site Treatment study of children with Attention-deficit/hyperactivity disorder (ADHD) compared different treatment strategies for children diagnosed with ADHD (known as MTA study). The first 14 months is a randomized study and the participants are allowed to choose their desired treatment strategies afterwards. Follow-up measurements are taken at 24, 36 and 72 months. Randomization is often considered as a good instrument since it is not associated with any covariate, observed or unobserved. We first apply a randomization based IV method to estimate the self-selected medication effect on outcome at the end of 72 months. However this approach yields results with huge standard errors due to randomization's weak relationship with later treatment selection. We then consider the self-selection right after the randomization as an instrument, because it is associated with later treatment selection and it is unlikely to affect the outcome directly given the 5-year time lapse. To better control the confounding due to observed factors, propensity score matching is used to create a subpopulation with comparable covariate distributions across different self-selected treatments. Using MTA data, matching-enhanced IV estimation yields the most sensible result, while other estimation strategies tend to imply a spurious significant effect. Also, our simulation study shows that the matching-enhanced IV estimation outperforms non-matched methods in terms of relative bias.

……..

Innov Clin Neurosci. 2012;9:22-30.

ATTENTION DEFICIT HYPERACTIVITY DISORDER SUBTYPES AND SYMPTOM RESPONSE IN ADULTS TREATED WITH LISDEXAMFETAMINE DIMESYLATE.

Mattingly G, Weisler R, Dirks B, et al.

Objective: To evaluate the efficacy of lisdexamfetamine dimesylate in adults with attention deficit hyperactivity disorder symptom subtypes who exhibit predominantly inattention, hyperactivity/ impulsivity, or combined symptom clusters.

Design/Setting/Participants: This is a post-hoc analysis from a multicenter, one-year, open-label lisdexamfetamine dimesylate study in adults with attention deficit hyperactivity disorder previously completing two weeks or more in a four-week, randomized, placebo controlled lisdexamfetamine dimesylate study, using Attention Deficit Hyperactivity Disorder Rating Scale IV symptom ratings as an attention deficit hyperactivity disorder subtype proxy (N=349).

Measurements: Attention Deficit Hyperactivity Disorder Rating Scale IV was measured at baseline of prior study and throughout the open-label study. Proxy subtypes were based on item scores of 2 (moderate) or 3 (severe), representing endorsement of at least six of nine symptoms on respective subscales; predominantly combined type endorsed at least six of nine symptoms on each subscale. Overall safety evaluations included treatment-emergent adverse events.

Results: At baseline, 93 of 345 participants exhibited predominantly inattention, 13 predominantly hyperactivity/ impulsivity, 236 combined symptom clusters, and three were unassigned. For the three subgroups, respectively, mean (standard deviation) Attention Deficit Hyperactivity Disorder Rating Scale IV total scores at baseline were 34.5 (4.02), 33.8 (3.27), and 43.6 (5.24); change from baseline to endpoint scores were -19.3 (9.48), -24.0 (7.22), and -27.3 (11.78). Mean (standard deviation) end-of-study lisdexamfetamine dimesylate dose was 57.7 (14.75), 53.1 (16.01), and 56.9 (14.94)mg/day, respectively. Treatment-emergent adverse events (<5%) were upper respiratory tract infection (21.8%), insomnia (19.5%), headache (17.2%), dry mouth (16.6%), decreased appetite (14.3%), irritability (11.2%), anxiety (8.3%), nasopharyngitis (7.4%), sinusitis (6.6%), decreased weight (6.0%), back pain (5.4%), and muscle spasms (5.2%).

Conclusions: Lisdexamfetamine dimesylate was effective in participants with predominantly inattention, hyperactivity/ impulsivity, and combined attention deficit hyperactivity disorder symptom clusters. Groups exhibiting specific predominant subtype symptoms did not differ in clinical response to lisdexamfetamine dimesylate.

……..

Iran J Psychiatr Behav Sci. 2012;6:26-32.

COMPARISON OF TWO BRANDS OF METHYLPHENIDATE (STIMDATE(REGISTERED TRADEMARK) VS. RITALIN(REGISTERED TRADEMARK)) IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL.

Khodadust N, Jalali AH, Ahmadzad-Asl M, et al.

Objective: To compare the effectiveness and safety of the methylphenidate produced in Iran (Stimdate(registered trademark)) with its original brand (Ritalin(registered trademark)) in children with Attention deficit hyperactivity disorder (ADHD).

Methods: In this double-blinded randomized clinical trial, 30 patients with ADHD who were 6 to 16 years old, were divided into two groups: 15 in Stimdate(registered trademark) and 15 in Ritalin(registered trademark) group. The two groups were compared for side effects profile, Conner's Parent's Rating Scale-Persion version (CPRS-R), Child Symptom Inventory-4 (CSI-4), Clinical Global Impressions (CGI), and Children's Global Assessment Scale (CGAS), at baseline and at the 4th and 6th weeks.

Results: The subjects showed significant decreases in the CPRS-Rand CSI-4 scores and significant increase of CGAS scores during the follow-up, but there were no significant difference between Stimdate(registered trademark) and Ritalin(registered trademark) group, regarding the pattern of changes observed. The mean therapeutic dose and the number of side effects were not significantly different between the two studied groups.

Conclusions: Both Stimdate (registered trademark) and Ritalin(registered trademark) had comparable clinical efficacy and safety in children with ADHD.

……..

J Affective Disord. 2012;141:382-89.

PEDIATRIC BIPOLAR DISORDER AND ADHD: FAMILY HISTORY COMPARISON IN THE LAMS CLINICAL SAMPLE.

Arnold LE, Mount K, Frazier T, et al.

Background: Transgenerational association of bipolar spectrum disorder (BPSD) and attention deficit/hyperactivity disorder (ADHD) has been reported, but inconclusively.

Method: Children ages 6-12 were systematically recruited at first outpatient visit at 9 clinics at four universities and reliably diagnosed; 621 had elevated symptoms of mania (>12 on the Parent General Behavior Inventory 10-Item Mania Scale); 86 had scores below 12. We analyzed baseline data to test a familial association hypothesis: compared to children with neither BPSD nor ADHD, those with either BPSD or ADHD would have parents with higher rates of both bipolar and ADHD symptoms, and parents of comorbid children would have even higher rates of both.

Results: Of 707 children, 421 had ADHD without BPSD, 45 BPSD without ADHD, 117 comorbid ADHD + BPSD, and 124 neither. The rate of parental manic symptoms was similar for the comorbid and BPSD-alone groups, significantly greater than for ADHD alone and neither groups, which had similar rates. ADHD symptoms in parents of children with BPSD alone were significantly less frequent than in parents of children with ADHD (alone or comorbid), and no greater than for children with neither diagnosis. Family history of manic symptoms, but not ADHD symptoms, was associated with parent-rated child manic-symptom severity over and above child diagnosis.

Limitations: The sample was not epidemiologic, parent symptoms were based on family history questions, and alpha was 0.05 despite multiple tests.

Conclusions: These results do not support familial linkage of BPSD and ADHD; they are compatible with heritability of each disorder separately with coincidental overlap.

……..

J Autism Dev Disord. 2012;1-6.

BRIEF REPORT: PREVALENCE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER AMONG INDIVIDUALS WITH AN AUTISM SPECTRUM DISORDER.

Hanson E, Cerban BM, Slater CM, et al.

Currently, both the DSM-IV-TR and ICD-10 preclude the diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) in cases that present with an Autism Spectrum Disorder (ASD). This criterion will be removed in the upcoming DSM-V, but the relationship between ASD and ADHD, and in particular the prevalence of ADHD among the ASD population, remains controversial. Previous studies have reported clinically significant ADHD symptoms in one-third to three-quarters of ASD-affected individuals (probands). In our sample of 1,838 simplex children and adolescents with ASD, we found that less than 16 % met clinically significant levels of ADHD symptoms, per parent report. When both parent and teacher reports were considered, the comorbidity rate was even lower, at 2 %.

……..

J Autism Dev Disord. 2012;42:1790-98.

JUST ANOTHER SOCIAL SCENE: EVIDENCE FOR DECREASED ATTENTION TO NEGATIVE SOCIAL SCENES IN HIGH-FUNCTIONING AUTISM.

Santos A, Chaminade T, Da Fonseca D, et al.

The adaptive threat-detection advantage takes the form of a preferential orienting of attentionto threatening scenes. In this study, we compared attention to social scenes in 15 high-functioning individuals with autism (ASD) and matched typically developing (TD) individuals. Eye-tracking was recorded while participants were presented with pairs of scenes, either emotional positive-neutral, emotional negative-neutral or

neutral-neutral scenes. Early allocation of attention, the first image fixated in each pair, differed between groups: contrary to TD individuals who showed the typical threat-detection advantage towards negative images, the ASD group failed to show a bias toward threat-related scenes. Later processing of stimuli, indicated by the total fixation to the images during the 3-s presentation, was found unaffected in the ASD group. These results support the hypothesis of an early atypical allocation of attention towards natural social scenes in ASD, that is compensated in later stages of visual processing.

……..

J Autism Dev Disord. 2012;1-6.

BRIEF REPORT: CHILDREN WITH ADHD WITHOUT CO-MORBID AUTISM DO NOT HAVE IMPAIRED MOTOR PROFICIENCY ON THE MOVEMENT ASSESSMENT BATTERY FOR CHILDREN.

Papadopoulos N, Rinehart N, Bradshaw JL, et al.

Motor proficiency was investigated in a sample of children with Attention Deficit Hyperactivity Disorder-Combined type (ADHD-CT) without autism. Accounting for the influence of co-morbid autistic symptoms in ADHD motor studies is vital given that motor impairment has been linked to social-communication symptoms in children who have co-morbid ADHD and autistic-like symptoms. Two groups of children aged between 7-14 years were recruited; children with ADHD-CT (n = 16; mean age 10 years, 7 months [SD = 1 year, 10 months]) and a typically developing (n = 16; mean age 10 years, 6 months [SD = 2 years, 6 months]) group. Motor proficiency was measured using the Movement Assessment Battery for Children-2nd Edition, ADHD symptoms were measured using the Conner's Parent Rating Scale. Children with ADHD-CT who had been screened for co-morbid autism did not display motor difficulties on the MABC-2. Higher levels of inattention, but not hyperactivity or impulsivity were associated with poorer motor performance. These findings provide indirect evidence that the motor problems that children with ADHD experience may be related to co-occurring social responsiveness impairments.

……..

J Indian Assoc Child Adolesc Ment Health. 2012;8:6-11.

A CLINICAL COMPARISON STUDY OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER (DSM-IV) AND HYPERKINETIC DISORDER (ICD-10) IN INDIAN CHILDREN AND ADOLESCENTS.

Sitholey P, Agarwal V, Bharti V.

Aims: To compare the usefulness of DSM IV and ICD-10 DCR criteria in clinic children presenting with the symptoms of inattention and hyperactivity- impulsivity.

Methods: 62 children (54 boys and 8 girls) participated in the study. Children were assessed on Kiddie schedule for affective disorders and schizophrenia - present and lifetime version and then diagnosed as attention deficit/hyperactivity disorder (ADHD) or hyperkinetic disorder (HKD) as per DSM IV or ICD-10 DCR criteria. Comorbidities were diagnosed as per DSM IV criteria. Severity of symptoms was rated using Hillside Behavior Rating Scale (HBRS) while global assessment of functioning was assessed on Children's Global assessment Scale (CGAS).

Results: All could be diagnosed with ADHD however, only 44 (71%) could be diagnosed as HKD. There was no statistically significant difference in most sociodemographic variables, severity of illness on HBRS and impairment on CGAS of the subjects diagnosed with ADHD and HKD and subjects with ADHD but not HKD (non-HKD-ADHD).

Conclusions: DSM IV should be used because it diagnoses more children with impairing symptoms of inattention and hyperactivity-impulsivity as compared to ICD-10 DCR. Also, there is a significant overlap in between ADHD and HKD.

……..

J Isfahan Med Sch. 2012;30.

THE CORRELATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND ENURESIS IN CHILDREN WITH NOCTURNAL ENURESIS.

Yousefi P, Salehi B, Firouzifar MR, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is the most common childhood psychiatric disorder which affects 5-10% of children in school age. It seems that the disorder is more common among children with enuresis. The aim of this study was to investigate ADHD in children with enuresis and compare it with a control group in patients referring to Amir Kabir Hospital (Arak, Iran).
Methods: This case-control study was performed on 100 children with enuresis and 100 children without enuresis in the age bracket of 5-16 years old. In all patients, Conners questionnaire [based on the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV)] and a demographic checklist about age, gender, history of maternal disease during pregnancy, birth weight, and head trauma were filled. The subjects were interviewed by a psychiatrist to confirm the diagnoses. The data was analyzed using descriptive and analytical statistics in SPSS15.
Findings: Attention deficit was observed in 16 cases (16%) with enuresis and 5 controls (5%) (P=0.01). Moreover, while 25 children with enuresis (25%) were affected by hyperactivity/impulsive behavior, only 16 controls (16%) were affected by this behavior. However, this important difference was not significant between the 2 groups (P=0.08).
Conclusion: ADHD in children with enuresis is significantly more common than non-enuretic children. The observed correlation between ADHD and enuresis makes psychological counseling mandatory in children with enuresis.

……..

J Pediatr. 2012;161:705-09.

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND COGNITIVE FUNCTION IN DUCHENNE MUSCULAR DYSTROPHY: PHENOTYPE-GENOTYPE CORRELATION.

Pane M, Lombardo ME, Alfieri P, et al.

Objectives: To assess attention deficit hyperactivity disorder (ADHD) in boys affected by Duchenne muscular dystrophy (DMD) and to explore the relationship with cognitive abilities and genetic findings.
Study design: Boys with DMD (n=103; 4-17 years of age, mean:12.6) were assessed using a cognitive test (Wechsler scales). Assessment of ADHD was based on the Diagnostic Statistical Manual, Fourth Edition, Text Revision criteria and on the long version of the Conners Parents and Teachers Rating Scales.
Results: ADHD was found in 33 of the 103 boys with DMD. Attention problems together with hyperactivity (17/33) or in isolation (15/33) were more frequent than hyperactivity alone, which was found in 1 patient. Intellectual disability (ID) was found in 27/103 (24.6%). Sixty-two of the 103 boys had no ID and no ADHD, 9 had ID but no ADHD, 14 had ADHD but no ID, and 18 had both. ADHD occurred more frequently in association with mutations predicted to affect Dp140 expression (exon 45-55) and in those with mutations predicted to affect all dystrophin product, including Dp71 (ie, those that have promoter region and specific first exon between exons 62 and 63 but were also relatively frequent).
Conclusions: Our results suggest that ADHD is a frequent feature in DMD. The risk of ADHD appears to be higher in patients carrying mutations predicted to affect dystrophin isoforms expressed in the brain and are known to be associated with higher risk of cognitive impairment.

……..

J Psychiatr Res. 2012.

METHYLPHENIDATE EFFECTS ON BLOOD SEROTONIN AND MELATONIN LEVELS MAY HELP TO SYNCHRONISE BIOLOGICAL RHYTHMS IN CHILDREN WITH ADHD.

Molina-Carballo A, Naranjo-Gomez A, Uberos J, et al.

The neuroendocrine mediators that may contribute to ADHD (Attention deficit and hyperactivity disorder), serotonin and melatonin, are both thought to regulate circadian rhythms, neurological function and stress response.

The objective of this study was to determine the effect of the chronic administration of prolonged release methylphenidate (PRMPH) on daily variations in blood serotonin and melatonin and on the excretion of 6-sulphatoxy-melatonin. A total of 179 children (136 males, 42 females) between the ages of 5 and 14 (9.70 (plus or minus) 2.55) years were enrolled in a controlled quasi-experimental open clinical study. Of the sample, there were 136 Children with ADHD (based on DSM-IV-TR criteria), who were further grouped into subtypes, and the 42 siblings of the participants who did not ADHD patients. Blood samples were taken at 20:00 and 09:00; urine was collected between 21:00 and 09:00. In the ADHD group, the study protocol was repeated after 4.61 (plus or minus) 2.3 months of treatment. Measurements included melatonin and serotonin by RIA and urine 6-S-aMT by ELISA. Factorial analyses were conducted by STATA 12.0.
Results: ADHD patients showed reduced morning serotonin with a daily profile that was different than the control group due to the predominance of nocturnal concentrations. PRMPH did not result in any significant changes. Melatonin and its daily profile did not differ between controls and the ADHD group with a diurnal rhythm showing higher morning levels that disappear after PRMPH administration. Melatonin was higher in children with predominantly hyperactive-impulsive/conduct disorder subtype. PRMPH resulted in a decrease in 6-S-aMT excretion for both ADHD subtypes.
Conclusion: Chronic treatment with prolonged release methylphenidate induces subtle changes in the daily fluctuations and concentrations of both serotonin and melatonin. Improvement in Children's Depression Inventory (CDI) scores was not related to a morning increase in serotonin.

……..

J Sleep Res. 2012.

SLEEP PATTERNS IN CHILDREN WITH ADHD: A POPULATION-BASED COHORT STUDY FROM BIRTH TO 11 YEARS.

Scott N, Blair PS, Emond AM, et al.

Associations between sleep duration and disturbance in infancy and early childhood and attention deficit hyperactivity disorder diagnoses were investigated. Data from the Avon Longitudinal Study of Parents and Children, a population-based prospective longitudinal birth-cohort study of children born in 1991-1992 in South-West England, were employed. Eight thousand, one hundred and ninety-five children were assessed using the Development and Well-Being Assessment. One hundred and seventy-three cases (2.1%) met criteria for attention deficit hyperactivity disorder. Parental report at eight time points showed children with attention deficit hyperactivity disorder slept less than peers. Absolute differences were small and mainly restricted to night-time sleep, with no strong evidence of differences from controls, except at 69 months [5 years 9 months; 12 min (95% CI:5-19), P = 0.001], at 81 months [6 years 9 months; 15 min (95% CI: 8-22), P<0.001] and at 115 months [9 years 7 months; 11 min (95% CI:4-18), P = 0.001]. The attention deficit hyperactivity disorder group had more night-waking at every age, significant from about 5 years. When tracking children's sleep along a normative centiles chart, a shift in sleep duration from one centile to a lower centile was a useful predictor of attention deficit hyperactivity disorder. Age-specific decreases of >1SD in sleep duration across adjacent time points was a significant predictor of attention deficit hyperactivity disorder at 3-5 years (P=0.047). In children with attention deficit hyperactivity disorder, shorter sleep duration and sleep disturbances appear early and predate the usual age of clinical diagnosis. The rate of change of sleep duration relative to an individual, rather than absolute sleep duration at any stage, may prove beneficial in identifying increased risk of attention deficit hyperactivity disorder.

……..

J Am Acad Child Adolesc Psychiatry. 2012;51:1076-84.

SCHIZOPHRENIA SPECTRUM AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS IN AUTISM SPECTRUM DISORDER AND CONTROLS.

Gadow KD.

Objective: This study compared the differential severity of specific symptoms of schizophrenia spectrum disorder (SSD) in children with autism spectrum disorder (ASD) and child psychiatry outpatient referrals (controls). Each group was further subdivided into subgroups with and without co-occurring attention-deficit/hyperactivity disorder (ADHD).

Method: Children with ASD (n=147) and controls (n=335) were evaluated with parent and teacher versions of a psychometrically established DSM-IV-referenced rating scale.
Results: The two ASD groups (with and without ADHD) had a larger number of more severe SSD symptoms than their respective control groups (with and without ADHD), extending the observation of an association between ASD and SSD to subgroups with and without co-occurring ADHD. The ASD groups exhibited more severe schizoid personality symptoms than controls, but findings for schizophrenia symptoms were mixed. The ASD + ADHD group generally had more severe disorganized thought, disorganized behavior, and negative schizophrenia symptoms than controls (with and without ADHD); nevertheless, findings varied according to ADHD status (present versus absent), individual symptom (symptom specificity), and informant (informant specificity). Ratings of hallucinations and delusions indicated mild severity and few group differences. Negative symptoms such as inappropriate emotional reactions evidenced considerable group divergence.
Conclusion: Findings provide additional support for an interrelation between ASD and SSD symptoms and the differential influence of neurobehavioral syndromes on co-occurring symptom severity, underscore the multidimensionality of SSD in children with ASD, and suggest how symptom phenotypes may contribute to a better understanding of the etiology, nosology, and possibly clinical management.

……..

Med Eng Phys. 2012;34:1317-29.

NONLINEAR ANALYSIS OF ACTIGRAPHIC SIGNALS FOR THE ASSESSMENT OF THE ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Martin-Martinez D, Casaseca-de-la-Higuera P, Alberola-Lopez S, et al.

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children and adolescents; however, its etiology is still unknown, which hinders the existence of reliable, fast and inexpensive standard diagnostic methods. In this paper, we propose a novel methodology for automatic diagnosis of the combined type of ADHD based on nonlinear signal processing of 24. h-long actigraphic registries. Since it relies on actigraphy measurements, it constitutes an inexpensive and non-invasive objective diagnostic method. Our results on real data reach 96.77% sensitivity and 84.38% specificity by means of multidimensional classifiers driven by combined features from different time intervals. Our analysis also reveals that, if features from a single time interval are used, the whole 24-h interval is the only one that yields classification figures with practical diagnostic capabilities. Overall, our figures overcome those obtained by actigraphy-based methods reported and are comparable with others based on more expensive (and not so convenient) adquisition methods.

……..

Mol Med Rep. 2012;6:1093-98.

ASSOCIATION OF DOPAMINERGIC/GABAERGIC GENES WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Wang GX, Ma YH, Wang SF, et al.

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder in children and adolescents; however, its etiology is unknown. In this study, we investigated the association of five polymorphisms in dopaminergic/GABAergic genes with ADHD using polymerase chain reaction-restriction fragment length polymorphism in a group of 54 children with ADHD and 67 healthy controls. The distribution of AA genotype and A allele frequencies of rs5320 in the dopamine beta-hydroxylase gene in ADHD children differed significantly from that in healthy controls; however, no associations were found between four other polymorphisms in dopaminergic/GABAergic genes and ADHD. We also identified the best model consisting of four loci. We conclude that the rs5320 polymorphism may be considered as a genetic risk factor of ADHD, but the other four polymorphisms were not confirmed to be related directly to ADHD. The multilocus of dopaminergic/GABAergic genes acted in combination to affect susceptibility to ADHD in the children studied.

……..

Neurol Psychiatry Brain Res. 2012.

LINK OF PARENTING AND TRANSGENERATIONAL PARENTING WITH ADHD SYMPTOM SEVERITY IN CHILDREN: A GERMAN SELF-HELP GROUP STUDY.

Cicerali LK, Ziyalar N, Neber H.

Objective: This survey study aimed to explore the impacts of parental and grandparental child-rearing attitudes on the differential symptom severity of children with ADHD. Based on literature, additional queries on the general nature of ADHD were also posed.

Methods: It was a survey study. Respondents were 43 mothers, attending a self-help group in Germany, Bayern area, for parents whose children received a clinical diagnosis of ADHD. Mothers gave information about their children and themselves. Children's age range was 6-16 (M =11.19).

Results: With regards to the primary hypotheses, the influence of parenting on the course of the disorder was generally negligible. Nevertheless, the attention deficit levels of children significantly predicted their grandparents' rejection towards their parents. Parents' education level did not differentiate children concerning ADHD symptom severity. Analyses of data regarding secondary hypotheses confirmed that boys were more frequently diagnosed with ADHD, and demonstrated more hyperactivity symptoms, which reduced while they grew into adolescence. However, no significant changes in attention deficit symptoms were observed.

Conclusion: Factors cited in literature besides parenting (e.g. genetic factors, child-related factors, environmental factors, pre-natal developmental factors) may be more important in shaping ADHD. The hypothesis concerning the likely effect of transgenerational-parenting on ADHD was verified only for rejection. Re-test of hypotheses from literature concerning age and gender related symptom-level changes verified the literature.

……..

Neurosci Lett. 2012;530:47-52.

AFFECTIVE INHIBITORY CONTROL IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: ABNORMALITIES IN ELECTROCORTICAL LATE POSITIVITY.

Kochel A, Leutgeb V, Schienle A.

Boys afflicted with ADHD (Attention-deficit/hyperactivity disorder) are characterized by deficient response inhibition and reduced electrocortical late positivity when presented with facial expressions of anger. This deficit might contribute to their problems in social interactions. We conducted the present event-related potential study with 15 men suffering from ADHD and 15 healthy controls in order to investigate whether similar dysfunctions are present in adult ADHD. The participants underwent an emotional version of a Go/NoGo task while event-related potentials (ERPs) were recorded. They were instructed to inhibit a motor response to one of four facial emotional expressions: anger, fear, sadness, or happiness. There were no behavioral differences in inhibitory control between the ADHD and the control group. However, the patients showed a reduced right parietal late positivity when instructed to inhibit a response to negative emotions. Obviously, the patients have learned to compensate for their deficit on a behavioral level, while it is still visible on the electrocortical level in this relatively simple task. Interestingly, the reduced positivity correlated with lowered self-reported emotional intelligence in the ADHD group.

……..

Neurotherapeutics. 2012;9:639-48.

WILL WORKING MEMORY TRAINING GENERALIZE TO IMPROVE OFF-TASK BEHAVIOR IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Green CT, Long DL, Green D, et al.

Computerized working memory and executive function training programs designed to target specific impairments in executive functioning are becoming increasingly available, yet how well these programs generalize to improve functional deficits in disorders, such as attention-deficit/hyperactivity disorder (ADHD), beyond the training context is not well-established. The aim of this study was to examine the extent to which working memory (WM) training in children with ADHD would diminish a core dysfunctional behavior associated with the disorder, "off-task" behavior during academic task performance. The effect of

computerized WM training (adaptive) was compared to a placebo condition (nonadaptive) in a randomized, double-blind, placebo-controlled design in 26 children (18 males; age, 7 to 14 years old) diagnosed with ADHD. Participants completed the training in approximately 25 sessions. The Restricted Academic Situations Task (RAST) observational system was used to assess aspects of off-task behavior during the completion of an academic task. Traditional measures of ADHD symptoms (Conners' Parent Rating Scale) and WM ability (standardized WM tests) were also collected. WM training led to significant reductions in off-task ADHD-associated behavior on the RAST system and improvement on WM tests. There were no significant differences between groups in improvement on parent rating scales. Findings lend insight into the generalizability of the effects of WM training and the relation between deficits in WM and off-task behavioral components of ADHD. These preliminary data suggest WM training may provide a mechanism for indirectly altering academic performance in children with ADHD.

……..

No To Hattatsu. 2012;44:378-86.

A STUDY OF READING DISORDER COMORBID WITH PERVASIVE DEVELOPMENTAL DISORDER OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Oka M, Takeuchi A, Morooka T, et al.

Objective: We investigated the frequency and characteristics of reading disorder comorbid with pervasive developmental disorder (PDD) or attention-deficitlhyperactivity disorder (AD/HD).

Methods: Articulation times and reading errors were evaluated using four Japanese reading tasks (a monomoraic syllable reading task, a word reading task, a non-word reading task, and a short Sentence reading task) in 31 children with PDD (22 boys and 9 girls) aged 6-14 years (average 9.5 years) and 39 children with AD/HD (33 boys and 6 girls) aged 6-12 years (average 9.6 years). Poor readers (PRs) were identified when articulation times were significantly longer than those of typically-developing children ((greater-than or equal to)2.0 SD) for two or more reading tasks, and non-PRs were identified when articulation times were within normal range (<2.0 SD) for all reading tasks.

Results: Eight children with PDD (25.8%) and 17 children with AD/HD (43.6%) were identified as PRs. For 13 of the 70 subjects, the chief complaints were difficulties in reading and writing words at their first Visit to our hospital. All 13 of these subjects had AD/HD, and twelve of these were additionally identified as PRs. Among the remaining 26 children with AD/HD, five (19.2%) were identified as PRs. In AD/HD children, PRs made significantly more reading errors and had lower lQ scores than did non-PRs, but in PDD children, there were no significant differences between these two groups regarding IQ or reading errors. An analysis using the Clinical-Symptoms-Checklist for Reading and Writing Words revealed that PRs in our study showed difficulties in reading words in daily life.

Conclusions: PRs in our study had reading disorders, which would, in turn, mean that reading disorder was often comorbid with PDD or AD/HD. These results strongly indicate the necessity of testing for the presence of reading disorder in children with PDD or AD/HD.

……..

Nord J Psychiatry. 2012;66:320-28.

SUICIDAL AND SELF-HARM BEHAVIOUR ASSOCIATED WITH ADOLESCENT ATTENTION DEFICIT HYPERACTIVITY DISORDERA STUDY IN THE NORTHERN FINLAND BIRTH COHORT 1986.

Hurtig T, Taanila A, Moilanen I, et al.

Background: Suicidal behaviour, i.e. suicidal ideation and suicidal acts, as well as self-harm behaviour, are relatively common among adolescents. Depression and/or female gender seem to be risk factors for suicidal behaviour. However, the role of attention deficit hyperactivity disorder (ADHD) in these behaviours is still unclear.

Aim: To study the effect of ADHD on suicidal or self-harm behaviour in adolescents from a general population sample. Methods: The sample was derived from a population-based Northern Finland Birth Cohort 1986 (n 9432). Based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (Kiddie-SADS-PL) interview performed in a subpopulation (n 457),

the associations between suicidal behaviour and deliberate self-harm (DSH) and the diagnosis of ADHD were studied.
Results: Compared with adolescents without ADHD (n 169), those with ADHD (n 104) had more suicidal ideation (57% vs. 28%, P<0.001) and DSH (69% vs. 32%, P<0.001). In binary logistic models, the effect of ADHD on suicidal ideation remained strong (OR 6.1) after controlling for several other predictors. Other contributing factors in suicidal behaviour included female gender, childhood emotional and behavioural problems, concurrent depression and anxiety, and, specifically in DSH, behavioural disorder, substance abuse and strains in family relations.
Discussion and clinical implications: ADHD is a risk factor for suicidal ideation and DSH. These findings in a general population sample speak for a need to target mental health interventions at children and adolescents with relevant symptoms of ADHD.

……..

Pediatr Blood Cancer. 2012;59:1290-95.
THE IMPACT OF ATTENTION ON SOCIAL FUNCTIONING IN SURVIVORS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA AND BRAIN TUMORS.
Moyer KH, Willard VW, Gross AM, et al.
Background: The cognitive late effects experienced by many survivors of pediatric acute lymphoblastic leukemia (ALL) and brain tumors are well-established. The most commonly reported deficit is difficulty with attention. Problems with social functioning have also been identified, but their relationship with cognitive functioning is not well understood. This multi-site, cross-sectional study aimed to examine the impact of attention on social functioning.
Procedure: Four hundred sixty nine survivors of ALL and brain tumors (55% ALL; 57% male) completed study procedures, including parent- and teacher-report measures of attention (Conners' Rating Scales, Revised) and parent-report of social functioning [Social Skills Rating System (SSRS)] as part of their screening evaluation for a large clinical trial. Survivors were 12.1 years of age and 4.9 years from the end of treatment at the time of study.
Results: Results revealed that survivors' parent-reported attention problems were uniquely associated with their social functioning, relative to known demographic- and treatment-related risk factors. Teacher-reported attention problems, in contrast, were not, despite a significant correlation between the two. Deficits in intelligence and female gender were also significantly associated with poor social functioning.
Conclusions: Attention problems uniquely impact difficulties with social functioning in survivors of pediatric cancer. Future studies will need to further examine the relationship between attention and social functioning in survivors, particularly when assessed by teacher report.

……..

Pediatr Cardiol. 2012;1-7.
SUDDEN UNEXPLAINED CARDIAC ARREST IN APPARENTLY HEALTHY CHILDREN: A SINGLE-CENTER EXPERIENCE.
Alapati S, Strobel N, Hashmi S, et al.
This study aimed to determine the causes of sudden cardiac arrest (SCA) in apparently healthy children at a single center in the era of primary prevention (screening questionnaire [SQ]) and secondary prevention (automated external defibrillator [AED] and the automated implantable cardioverter defibrillator [AICD]). Any child 0 to 18 years of age without prior known disease, except for attention deficit disorder, who underwent out-of-the hospital cardiopulmonary resuscitation was included in the study as a SCA subject. A retrospective chart review was used to evaluate the efficacy of the SQ, electrocardiogram (ECG), chest roentgenogram (CXR), and echocardiogram. The findings showed that for 44 of 6,656 children admitted to intensive care with SCA, an AED was used for 39 %, an AICD was placed in 18 %,and survival to hospital discharge was 50 %. The etiology for SCA was identified in 57 % of the cases, mostly in those older than 1 year, and the majority of these had a cardiac etiology (50 %), whereas 7 % had rupture of an arteriovenous malformation. Stimulant medication use was seen in 11 % of the SCA subjects. In the best-case scenario of hypothesized primary prevention, a prior SQ, CXR, ECG, or echocardiogram may have detected respectively 18, 9, 23 and 16 % of the at-risk cases, and 32 % of the cases may have been detected with

ECG and SQ together. Based on a historical control cohort, a positive ECG was significantly higher in the children with SCA (p=0.014). An ECG together with a screening SQ may be more effective in identifying children potentially at risk for SCA than an SQ alone.

……..

Pediatr Emerg Care. 2012;28:1060-61.

TREATMENT OF GUANFACINE TOXICITY WITH NALOXONE.

Tsze DS, Dayan PS.

ABSTRACT: We describe a 4-year-old boy who presents to the emergency department with lethargy, bradycardia, and initial hypertension followed by hypotension due to guanfacine toxicity after ingestion of standard doses of the extended release formulation. This is the first case report to describe the use of naloxone to treat these symptoms and document improvements in level of consciousness, blood pressure, and heart rate associated with this therapy.

……..

Pediatr Int. 2012;54:688-92.

FERRITIN AND HYPERACTIVITY RATINGS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Oner P, Oner O, Azik FM, et al.

Background: Iron is a co-factor of tyrosine hydroxylase which is a critical enzyme in dopamine synthesis. Dopamine has been implicated in the pathophysiology of attention deficit hyperactivity disorder (ADHD). Our objective was to investigate the association of ferritin level with parent and teacher ratings and cognitive measures after controlling for age, sex, ADHD subtype, comorbid conditions, hemoglobin, mean corpuscular volume and reticulocyte distribution width in a large sample.
Methods: The study included 713 children and adolescents with ADHD (613 boys; age 7-15 years). Conners' Parent Rating Scale (CPRS) and Conners' Teacher Rating Scale (CTRS) were obtained. In a subgroup of patients we conducted Digit Span, Digit Symbol, Trail-making Tests as measures of attention and executive functioning.
Results: Multiple regression analysis indicated that CPRS Hyperactivity score was significantly associated with ferritin level (B =-0.12; t =-3.1; P <0.01). Other CPRS and CTRS scores as well as cognitive measures were not associated with ferritin level.
Conclusions: Although it is not possible to make an inference on causality in cross-sectional studies, the results of this largest-scale cross-sectional field study to date suggest that lower ferritin level might be associated with parent-reported hyperactivity after controlling for important confounding factors.

……..

Phys Ther Sport. 2012.

TIMING PERCEPTION AND MOTOR COORDINATION ON ROPE JUMPING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Chen YY, Liaw LJ, Liang JM, et al.

Objectives: To evaluate timing perception ability and motor coordination in children with ADHD (Attention Deficit Hyperactivity Disorder) while rope jumping at different rates.
Design and setting: Rope jumping at (1) a constant tempo of 100 for 15 s (RJ-C) and (2) two randomly permutated tempos (80, 100, or 120) for 15 s (RJ-V).
Main Outcome Measures: The "timing variation while jumping", "timing variation while whirling", and "hand-foot deviation time" in each rope jumping cycle were recorded, to assess the time estimation ability.
Participants: 10 children with ADHD (9.65 (plus or minus) 1.27 years) and 10 children without ADHD (9.93 (plus or minus) 1.54 years) were recruited.
Results: The ADHD group showed greater variation in time between the foot jumping and the rope whirling tasks. Also, the median value of hand-foot deviation time was greater in the ADHD group (3.34 ms) than in

the control group (1.75 ms). In RJ-V, the control group was able to modify their pace and respond to the target speed in the post-phase, while the ADHD group could not.
Conclusion: Impaired timing perception leads to less accurate performance during rope jumping for ADHD children. The findings also reveal that poor hand-foot coordination results in poor control of simultaneous movements of the upper and lower limbs during rope jumping.

……..

PLoS ONE. 2012;7.
TIME COURSE ANALYSIS OF MOTOR EXCITABILITY IN A RESPONSE INHIBITION TASK ACCORDING TO THE LEVEL OF HYPERACTIVITY AND IMPULSIVITY IN CHILDREN WITH ADHD.
Hoegl T, Heinrich H, Barth W, et al.
Short interval intracortical inhibition (SICI) of motor cortex, measured by transcranial magnetic stimulation (TMS) in a passive (resting) condition, has been suggested as a neurophysiological marker of hyperactivity in attention-deficit/hyperactivity disorder (ADHD). The aim of this study was to determine motor excitability in a go/nogo task at stages of response preparation, activation and suppression in children with ADHD, depending on the level of hyperactivity and impulsivity. Motor evoked potentials were recorded in 29 typically developing children and 43 children with ADHD (subdivided in two groups with higher and lower levels of hyperactivity/impulsivity; H/I-high and H/I-low). In the H/I-high group, SICI was markedly reduced in the resting condition and during response preparation. Though these children were able to increase SICI when inhibiting a response, SICI was still reduced compared to typically developing children. Interestingly, SICI at rest and during response activation were comparable, which may be associated with their hypermotoric behaviour. In the H/I-low group, response activation was accompanied by a pronounced decrease of SICI, indicating reduced motor control in the context of a fast motor response. In summary, different excitability patterns were obtained for the three groups allowing a better understanding of dysfunctional response activation and inhibition processes within the motor cortex in children with ADHD.

……..

PLoS ONE. 2012;7.
RESPONSE INHIBITION IMPAIRMENT IN HIGH FUNCTIONING AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: EVIDENCE FROM NEAR-INFRARED SPECTROSCOPY DATA.
Xiao T, Xiao Z, Ke X, et al.
Background: Response inhibition, an important domain of executive function (EF), involves the ability to suppress irrelevant or interfering information and impulses. Previous studies have shown impairment of response inhibition in high functioning autism (HFA) and attention deficit hyperactivity disorder (ADHD), but more recent findings have been inconsistent. To date, almost no studies have been conducted using functional imaging techniques to directly compare inhibitory control between children with HFA and those with ADHD.
Method: Nineteen children with HFA, 16 age- and intelligence quotient (IQ)-matched children with ADHD, and 16 typically developing (TD) children were imaged using functional near-infrared spectroscopy (NIRS) while performing Go/No-go and Stroop tasks.
Results: Compared with the TD group, children in both the HFA and ADHD groups took more time to respond during the No-go blocks, with reaction time longest for HFA and shortest for TD. Children in the HFA and ADHD groups also made a greater number of reaction errors in the No-go blocks than those in the TD group. During the Stroop task, there were no significant differences between these three groups in reaction time and omission errors. Both the HFA and ADHD groups showed a higher level of inactivation in the right prefrontal cortex (PFC) during the No-go blocks, relative to the TD group. However, no significant differences were found between groups in the levels of oxyhemoglobin concentration in the PFC during the Stroop task.

Conclusion: Functional brain imaging using NIRS showed reduced activation in the right PFC in children with HFA or ADHD during an inhibition task, indicating that inhibitory dysfunction is a shared feature of both HFA and ADHD.

……..

Psychiatr Serv. 2012;63:1011-18.

OVERLAPPING PRESCRIPTIONS OF STIMULANTS FOR CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Chen CY, Yeh HH, Fang SY, et al.

Objectives: The study aimed to assess the occurrence of overlapping prescriptions for methylphenidate among children and adolescents with newly diagnosed attention-deficit hyperactivity disorder (ADHD) and to evaluate the extent to which physician-level and patient-level characteristics affected the risk of prescription overlap during a one-year treatment period.

Methods: The analytic sample comprised 3,081 incident cases of ADHD in 2002 involving children aged 17 years or younger from a retrospective cohort study in Taiwan. Medical and pharmacy claims data from 1999 to 2002 were retrieved from the National Health Insurance Program. All records of methylphenidate prescriptions within a year of treatment initiation were retrieved for each patient, and the number of overlapping days for any two successive prescriptions (new, renewal, or refill) was measured. Multilevel analyses were performed to identify predictors of methylphenidate prescription overlap.

Results: Within a year of treatment initiation, approximately 3% to 4% individuals with a new diagnosis of ADHD had experienced methylphenidate prescription overlap. Youngsters who resided in a rural region (adjusted odds ratio [AOR]=2.68) or who had ever changed prescribing doctors (AOR=3.04) were more likely to have visits with a methylphenidate prescription overlap. Receiving methylphenidate from physicians aged 46 or older was associated with 3.6-fold increased odds of prescription overlap.

Conclusions: In an effort to improve the quality and safety of prescription of controlled substances in younger populations, interventions or policies should be devised to target both the service providers and the patients.

……..

Res Dev Disabil. 2012;34:505-15.

CORRELATES FOR ACADEMIC PERFORMANCE AND SCHOOL FUNCTIONING AMONG YOUTHS WITH AND WITHOUT PERSISTENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Wu SY, Gau SSF.

Childhood attention-deficit hyperactivity disorder (ADHD) is associated with academic underachievement and school dysfunction. Little is known whether such association varies with the persistence of ADHD symptoms. The authors investigated school functioning among youths with and without persistent ADHD and identified the clinical correlates for school functioning in a large sample of 333 youths with persistent ADHD, 166 with non-persistent ADHD, and 266 without ADHD. The participants and their mothers received structured interviews for diagnosis of ADHD and other psychiatric conditions according to the DSM-IV diagnostic criteria by using the Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia, and for school functioning by using the Chinese Social Adjustment Inventory for Children and Adolescents. The results showed that both ADHD groups had more impairment in all domains of school functioning than youths without ADHD with a gradient relationship in the order of persistent ADHD, non-persistent ADHD, and non-ADHD. The most consistent correlates for all domains of impaired school functioning were youth- and mother-reported inattention symptoms and increased age. Childhood hyperactivity-impulsivity symptoms also predicted more severe problems in social interactions and school behaviors. Psychiatric comorbid conditions also predicted poorer attitudes toward school works and interactions at school. Our findings indicate that lifetime diagnosis of ADHD, regardless of persistence of ADHD, associate with the impairment of overall school functioning sustaining from childhood into adolescence, and imply that early intervention of childhood inattention may offset school dysfunction at late childhood and adolescence.

……..

Inverse association of intellectual function with very low blood lead but not with manganese exposure in Italian adolescents

Roberto G. Lucchini [a,b,*], Silvia Zoni [b], Stefano Guazzetti [c], Elza Bontempi [d], Serena Micheletti [e], Karin Broberg [f], Giovanni Parrinello [g], Donald R. Smith [h]

[a] Department of Preventive Medicine, Mount Sinai School of Medicine, NY, USA
[b] Section of Occupational Medicine, University of Brescia, P.le Spedali Civili 1, 25123 Brescia, Italy
[c] Public Health Service, Reggio Emilia, Italy
[d] INSTM and Chemistry for Technologies Laboratory, University of Brescia, Italy
[e] Cognition Psychology Neuroscience lab., University of Pavia and Unit of Child Neurology and Psychiatry, Civil Hospital of Brescia, Italy
[f] Division of Occupational and Environmental Medicine, Lund University, Sweden
[g] Statistics and Biometry, University of Brescia, Italy
[h] Microbiology and Environmental Toxicology, University of California at Santa Cruz, USA

ARTICLE INFO

Article history:
Received 28 April 2012
Received in revised form
21 July 2012
Accepted 2 August 2012
Available online 24 August 2012

Keywords:
Cognitive functions
Lead
Manganese
Children

ABSTRACT

Background: Pediatric lead (Pb) exposure impacts cognitive function and behavior and co-exposure to manganese (Mn) may enhance neurotoxicity.
Objectives: To assess cognitive and behavioral function in adolescents with environmental exposure to Pb and Mn.
Methods: In this cross sectional study, cognitive function and behavior were examined in healthy adolescents with environmental exposure to metals. The Wechsler Intelligence Scale for Children (WISC) and the Conners-Wells' Adolescent Self-Report Scale Long Form (CASS:L) were used to assess cognitive and behavioral function, respectively. *ALAD* polymorphisms rs1800435 and rs1139488 were measured as potential modifiers.
Results: We examined 299 adolescents (49.2% females) aged 11–14 years. Blood lead (BPb) averaged 1.71 μg/dL (median 1.5, range 0.44–10.2), mean Blood Manganese (BMn) was 11.1 μg/dL (median 10.9, range 4.00–24.1). Average total IQ was 106.3 (verbal IQ=102, performance IQ=109.3). According to a multiple regression model considering the effect of other covariates, a reduction of about 2.4 IQ points resulted from a two-fold increase of BPb. The Benchmark Level of BPb associated with a loss of 1 IQ-point (BML01) was 0.19 μg/dL, with a lower 95% confidence limit (BMLL01) of 0.11 μg/dL. A very weak correlation resulted between BPb and the ADHD-like behavior (Kendall's tau rank correlation=0.074, $p=0.07$). No influence of ALAD genotype was observed on any outcome. Manganese was not associated with cognitive and behavioral outcomes, nor was there any interaction with lead.
Conclusions: These findings demonstrate that very low level of lead exposure has a significant negative impact on cognitive function in adolescent children. Being an essential micro-nutrient, manganese may not cause cognitive effects at these low exposure levels.

1. Introduction

Lead effects on the central nervous system (CNS) are prominent in the developing brain, and cognitive dysfunction may persist into adulthood (Mazumdar et al., 2012; Needleman et al., 1990). Lead-induced deficits in children have been reported in most functional domains, including total Intelligence Quotient (IQ) and academic skills such as reading and mathematics (Bellinger, 2008). Lead exposure has been also associated with hyperactivity (Nigg et al., 2008) with a large effect-size (Nicolescu et al., 2010). Attentional deficits may affect the performance on the Intelligence Scales (Jepsen et al., 2009); therefore the cognitive effects of lead may be mediated by a basic impairment of attention level.

Manganese can affect cognitive function in children (Bouchard et al., 2011; Menezes-Filho et al., 2011; Riojas-Rodriguez et al., 2010; Wasserman et al., 2006; Wright et al., 2006), and co-exposure of lead and manganese may further affect neurodevelopment beyond exposure to either one alone (Henn et al.,

* Corresponding author at: Section of Occupational Medicine, University of Brescia, P.le Spedali Civili 1, 25123 Brescia, Italy.
Fax: + 39 030 744 31150.
E-mail address: lucchini@med.unibs.it (R.G. Lucchini).

0013-9351/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.envres.2012.08.003

2012). There is large variation in the individual susceptibility to the effects of lead exposure that may be explained, at least in part, by genetic factors. Polymorphisms in the δ-aminolevulinic acid dehydratase (*ALAD*) gene modify the effects of lead on heme synthesis, kidney function, central and peripheral nervous system (Pawlas et al., 2012; Scinicariello et al., 2010; Zheng et al., 2011). Lead inhibits the ALAD enzyme, which catalyzes a step in the heme biosynthetic pathway. Heterozygote and homozygote carriers of the variant allele (often called *ALAD2*) of *ALAD* rs1800435 appear protected against lead toxicity compared to the *ALAD1* homozygote carriers. Pawlas et al. recently reported that *ALAD* rs1139488 TT and CT carriers were more susceptible to lead impairment of IQ compared to CC carriers (Pawlas et al., 2012).

Intense scientific discussion has focused on the identification of adverse neurocognitive effects at very low BPb levels. Blood lead levels above 10 μg/dL are clearly associated with adverse outcomes on the IQ (Pocock et al., 1994). Moreover, a notable body of evidence has emerged showing cognitive declines in children at BPb levels below 10 μg/dL (Canfield et al., 2003; Lanphear et al., 2005). Several cohort and cross sectional studies and meta-analysis support that there is no identified BPb without deleterious effects (Wigle and Lanphear, 2005), consistent with estimates that BPb levels in contemporary humans are >50-fold higher than natural levels (Flegal and Smith, 1992; Smith and Flegal, 1992). Recently, U.S. CDC accepted the recommendation by the Advisory Committee on Childhood Lead Poisoning Prevention that a blood lead level reference value of 5 μg/dL, based on the 97.5th percentile of the NHANES blood lead level distribution in children 1–5 years old, be used to identify children with elevated blood lead levels (ACCLPP, 2012). The European Food and Safety Authority (EFSA) did not establish a guidance level for lead, in absence of a clear threshold below which adverse effects would not occur for fetuses, infants and children (EFSA, 2010).

Here, we examined cognitive and behavioral functions in 299 adolescents aged 11–14 years with environmental exposure to various metals including lead and manganese in the Valcamonica and Garda Lake regions of Northern Italy. Our prior epidemiological studies in this region had shown high prevalence of Parkinsonism in aged adults in the vicinities of ferroalloy emission points, with significant associations between regional prevalence of Parkinsonism and manganese levels in deposited dust (Lucchini et al., 2007). Increased tremor, impaired motor coordination and odor identification have been also observed in adolescents (Lucchini et al., 2012) and elderly (Rentschler et al., 2012) from the same area as associated to manganese exposure.

2. Methods

2.1. Study area and subjects

In this cross sectional study, cognitive function and behavior were examined in healthy adolescents with environmental exposure to metals, including lead and manganese, from anthropogenic emissions in the Province of Brescia, Italy.

The study sites were Valcamonica, a valley in the pre-Alps where ferroalloy plants had been operating for about a century until 2001, and the Garda Lake, a tourist area with limited industrial activity. Analysis of metals in deposited dust (Zacco et al., 2009), airborne particles (Borgese et al., 2011) and surface soil (Lucchini et al., 2012) showed higher levels of manganese, lead, iron, zinc, in the area of Valcamonica compared to Garda Lake.

Subjects were recruited from junior high schools (total 20 schools) of the local public school district. Children, parents and teachers were invited to group discussions with the research team at the schools, where the study aims and methodology were explained in details and informed consent was obtained from the primary caregiver of each child. Inclusion criteria were: (i) to be born in the respective areas within a family residing in the area for at least two generations, (ii) have been a resident in the study areas since birth, and (iii) being between 11 and 14 years old. Exclusion criteria included: (i)presence of a diagnosed neurological, hepatic, metabolic, endocrine or psychiatric clinical condition, (ii) previous total parental nutrition as it may contain high manganese levels (Chalela et al., 2011), (iii) family history of neurodegenerative disease, (iv) consumption of medications with known neuro-psychological side-effects, (v) deficits in hand and/or finger function, and (vi) visual deficits not adequately corrected.

2.2. Exposure assessment

Venous whole blood (4 mL) was collected from the cubital vein using a 19 gauge butterfly catheter into a lead-free Li-heparin Sarstedt Monovette Vacutainer. A spot urine sample (50–200 mL) was collected into a clean, sterile polyethylene container. All samples were stored at 4 °C until analyzed at the laboratory facility of the University of Brescia. Lead and manganese were measured in blood and urine with Zeeman graphite furnace atomic absorption spectrometry (GFAAS, Varian SpectrAA) in the Industrial Hygiene laboratory at the University of Brescia, Italy, using methods previously reported (Apostoli et al., 2000). Quality control was assured within the Inter-comparison Program 44, 2009, by the Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg, Germany. The detection limit for BPb measurements by GFAAS was 0.40 μg/dL. Blood lead values that fell near or below the detection limit by GFAAS (i.e., ≤0.6 μg/dL, $n=32$ samples) were reanalyzed by high resolution inductively coupled plasma mass spectrometry (Finnigan XR ICP-MS) at the trace metal clean laboratory of the University of California, Santa Cruz. The detection limit for these analyses was 0.010 μg/dL blood, with an accuracy of 95% or better based on repeated analyses of U.S. National Institutes of Standards and Technology Standard Reference Material 955c, and analytical reproducibility of 5% relative standard deviation based on triplicate processing and analyses of blood samples.

Because of the lack of predicitvity of manganese biomarkers (Apostoli et al., 2000; Smith et al., 2007), manganese was measured also in environmental media including PM10 airborne particles and soil, in addition to blood, urine, hair. Further details on exposure assessment methodology are available in a separate publication (Lucchini et al., 2012).

2.3. Genetic analysis

DNA was extracted from peripheral whole blood using the QIAamp DNA Blood Mini kit (QIAGEN, Hilden). *ALAD* rs1139488 (also referred to as *RsaI*, T/C exchange) and rs1800435 (also referred to as *MspI* with *ALAD*1 and 2 as alleles, C/G exchange) were analyzed. The genotyping was determined by Taqman assay on an ABI7900 instrument (Applied Biosystems, CA, USA) according to the manufacturer's protocol. Five percent of the samples were re-assayed for each SNP and there was a perfect concordance between the runs. The distribution of genotypes for *ALAD* showed no deviation from the Hardy–Weinberg equilibrium calculated by Fisher's exact test.

2.4. Assessment of cognitive behavioral functions

The adolescents were examined in the morning, according to standardized conditions in well illuminated and quiet rooms within the local schools. The Wechsler Intelligence Scale for Children-Third Edition was administered. This scale is a test of general intelligence, developed for the use with children aged 6–16 years. In addition to providing a rating of children's overall intelligence, the test is composed by a verbal IQ, which provides a rating for verbal comprehension and output, and a performance IQ, which provides a rating for perceptual organization. Two trained neuro-psychologists administered the 10 subtests for the determination of the total IQ. The mean standard score is 100±15. All IQ scores are normalized by age.

The Conners-Wells' Adolescent Self-Report Scale-Long Form (CASS.L) (Conners et al., 1997) was administered to all children. It contains 87 items which yield scores for eight subscales concerning adolescent's behavior and is recommended for adolescents aged from 12 to 17 years. We included the 11 years old children for this test, as the percentage of this age class was lower and equally distributed in the study areas.Adolescents rate their feelings and behaviors over the past month on a 4 point Likert scale. The following 10 subscales are assessed: family problems, emotional problems, conduct problems, cognitive problems/inattention, anger control problems, hyperactivity, attention deficit hyperactivity disorder (ADHD) index, DSM-IV (disattention), DSM IV (hyperactivity/impulsivity), and DSM IV (Total).

Subjects' examination took place at school, which did not allow for blind assessment from the target area. Therefore we adopted a repeated blinded test scoring procedure that was performed by different examiners from the one who administered the test on site. Repeated scoring did not show significant differences between blind and not blind examiners.

2.5. Potential confounders

The demographic factors included: adolescent's gender and age at testing, the educational level of both parents and a measure of socioeconomic status (SES), family size, parity order and the body mass index (BMI). The SES was assessed according to a methodology developed in Italy that combines parental education and occupations (Cesana et al., 1995). Education was divided into three levels: low (elementary and junior high school), medium (senior high school) and high (university degree and post-degree). Occupations were grouped in three categories according to an ordinal scale according to WHO criteria (WHO, 1988) and based on information provided by the Italian National Institute for Statistics. The low SES category included housewives, low-unskilled workers, hospital ancillaries, social workers; the middle SES employees, teachers, educators, nurses, craftsmen, carpenters; the high SES lawyers, engineers, entrepreneurs, physicians. We considered also the effect of the area of residence (Lower, Median, Upper Valcamonica and Garda Lake), to account for possible unmeasured socio-cultural, genetic differences. Alcohol consumption was ascertained by questionnaire as both a dichotomic variable (yes/no) and a quantitative estimate of the weekly intake in grams, based on the number of declared alcoholic beverages. Smoking habits was also assessed as a dichotomic variable (yes/no) and number of cigarettes per week.

Hematological parameters were hemoglobin and ferritin levels, based on the observation of negative effect on cognition in anemic conditions (Lanphear et al., 2005). However, as hemoglobin and ferritin were collinear, only hemoglobin was retained in the statistical analysis.

2.6. Statistical analysis

Study participants were enrolled from various classes within different sections from twenty different schools, therefore we used a hierarchical mixed-effects regression (ME) model (Pinheiro, 2000), to account for the possible non independence of the observations within the same classes, sections and schools. The analysis of the variance component showed that the structure of hierarchical error (i.e., class within section within school) accounted for only 2% of the residual variance and therefore it was considered as negligible. Consequently, we reduced the ME regression model to a simpler Ordinary Least Squares regression model (OLS). To obtain a parsimonious model and test the conjoint effects of all variables on the IQ scores, a full regression model was used and the unrelated variables were eliminated in a backward fashion, using an AIC-based (Akaike's Information Criterion) stopping rule (Venables, 2002). The BPb variable was log transformed in its natural logarithm in order to meet the following regression requirements: (i) approximate normality of residuals, and (ii) homogeneity of residual variance. Log-transformation of BPb is a common procedure to obtain a linear relationship between BPb and IQ (Budtz-Jørgensen, 2001), and in fact the transformation yielded a better fit of the data. Deviations from linearity was evaluated by comparing the OLS model with a semi-parametric model (GAM), where the degree of smoothness of the non-parametric part (that represents here the effect of Pb and/or Mn) was determined by generalized cross validation (Wood, 2006). The possible interaction between blood Pb and the Mn-related exposure variables (Blood Mn, hair Mn, soil Mn and air Mn) was tested in the final model. Main genetic effects of *ALAD* polymorphisms as well as the effect of an interaction between ALAD (considered here as a categorical variable with 3 levels) and Pb (by including an interaction term $ALAD \times \ln(BPb)$) considering the genotypes as categorical variables in the OLS model).

The methodology described by Budtz-Jørgensen (2001) was used to derive the Benchmark Dose (BMD) of BPb for a loss of 1 IQ-point (BMD_{01}) and its 95%-confidence lower bound (BMDL) from the regression model. The BMD is defined as the dose which induces a pre-specified loss in the outcome. This loss is known as the Benchmark response (BMR). We used a BMR of 1 IQpoint (BMR01). Analyses and graphics were made with Core Team, (2011).

Table 1
Socio-demographic and genetic variables (total *n.*: 299 subjects).

Variable	Levels	*n*	%
Geographic area	GL	148	49.5
	LVC	46	15.4
	MVC	83	27.8
	UVC	22	7.4
Gender	F	147	49.2
	M	152	50.8
Age (years)	11	53	17.7
	12	102	34.1
	13	122	40.8
	14	22	7.4
Socioeconomic Status	low	73	24.5
	medium	124	41.6
	high	109	40.0
Mother's education	low	112	37.5
	medium	157	52.5
	high	30	10.0
Siblings	none	47	15.7
	one	183	61.2
	two	58	19.4
	≥ three	11	3.7
Birth order	first	155	51.8
	second	114	38.1
	third-fourth	30	10.0
ALAD rs1800435	2–2 (CC)	3	1.0
	1–2 (CG)	43	14.5
	1–1 (GG)	251	84.5
ALAD rs1139488	CC	32	10.8
	CT	140	47.1
	TT	125	42.1

VC—Lower ValCamonica, MVC—Mid ValCamonica, UVC—Upper ValCamonica.

3. Results

3.1. Descriptive statistics

We successfully tested 299 subjects, or 72% of the 414 consented adolescents. A total of 115 subjects were excluded for the following reasons: not meeting the residency requirement (14.7%); presence of neurological or psychiatric disease (2.9%); refusal to participate after initial consent (5.3%); not signing the informed consent (1.2%); endocrine disease (0.25%), metabolic disease (0.25%), history of total parental nutrition (0.25%). Enrolled subjects (49.2% female) were from different families and households, 151 residing in Valcamonica and 148 in the Garda Lake area. Categorical socio-demographic variables and *ALAD* allele frequencies are reported in Table 1. Participant subjects had mostly one sibling (61%) and they were mostly the first born (52%). No siblings were included in the cohort. Participants' age was on average 154 months (median 155), and the average BMI was 21.3 (median 20.0, range 13–40). Nine subjects declared a history of alcohol consumption (mean: 1.3 g/week), and three subjects declared a history of smoking cigarettes (mean: 0.1/week). The frequency for the variant allele of rs1800435 (*ALAD*2) was 8.2% and for the variant allele of rs1139488 (C) 34.3%.

Table 2 shows the descriptive statistics of the exposure biomarkers to lead and manganese. The average BPb was 1.71 μg/dL (median 1.5). Only one case exceeded the BPb level of 10 μg/dL. Manganese in blood (BMn) averaged 11.1 μg/L (median 10.9) whereas hair manganese averaged 0.166 μg/g (median 0.096). The analysis of PM10 particles and surface soil

Table 2
Exposure indicators and biomarkers to lead and manganese (IQR: InterQuartile Range).

Variable	*n*	Min	1st q.le	Mean	Median	3rd q.le	Max	IQR
Blood lead (BPb) (μg/dL)	299	0.44	1.10	1.71	1.50	2.10	10.2	1.00
Blood manganese (μg/L)	299	4.00	8.80	11.1	10.9	12.9	24.1	4.10
Hair manganese (μg/g)	186	0.024	0.062	0.166	0.096	0.182	3.45	0.120
Air manganese (ng/m^3)	189	1.24	15.38	41.99	29.37	47.20	516.70	31.82
Soil manganese (ppm)	299	159.76	424.92	722.07	529.12	1001.10	1729.10	483.14

substrates showed air manganese averaging 42.0 μg/m^3 (median 29.4), air Pb 17.8 μg/m^3 (median 14.1), soil manganese 711 μg/g (median 579), and soil Pb 43.1 μg/g (median 40.4). The scores of WISC and CASS-L subscales are reported in Table 3. The total IQ averaged 106.3 points (median 106), while the verbal IQ averaged 102.0 points (median 103) and the performance IQ averaged 109.2 (median 109).

3.2. Regression analysis and BMD calculation

The OLS regression analysis considered firstly the IQ scores as the dependent variable. All biological and environmental exposure parameters were included, as well as area of residency, *ALAD* polymorphisms, and the potential confounders. Unrelated variables were eliminated according to the AIC-based stopping rule. They included all internal and external parameters of manganese exposure, *ALAD* genetic variants and most potential confounders like age, gender, BMI, family size, SES, self-reported alcohol consumption, area of residence, hemoglobin, ferritin,and parity order. The regression on the IQ total score yielded a negative association with ln (BPb) (beta coefficient: −3.5; Fig. 2), alcohol consumption (beta coefficient: −12.7 as dichotomous variable yes Vs no), and a positive association with SES-medium Vs low (beta coefficient: 4.8), SES-high Vs low (beta coefficient: 8.8), hemoglobin (beta coefficient: 1.5 for a 1 g/dl increase) (see Table 4). The overall effect of the area of residence was significant (p=0.027 - the comparisons in Table 4 are done with the reference area, i.e., tah Garda Lake Area), Table 5 shows also the results for verbal and performance IQ, with the 95% C.I. of the estimates. The relation with alcohol consumption and SES was stronger for the verbal compared to the performance IQ score. The estimated BMD_{01} value from the regression model was 0.19 μg/dL, and the BMDL value 0.11 μg/dL.

The regression analysis was also conducted using the 10 subscales of CASS:L as dependent variable and showed a weak border-line association only between BPb and the ADHD subscale (Kendall's rank correlation z=1.82, tau=0.0742, p-value=0.069) (Fig. 3). To ascertain a possible role of manganese exposure on both cognitive and behavioral scores, all biological and environmental indicators of manganese exposure were considered in the final regression model as interaction variables between the ln(BpB) and the log-transformed Mn levels and both the main effect of Mn and its interaction with lead was found to be not significant from a statistical or biological point of view. Also, no interaction between ln(BPb) and either of the two *ALAD* polymorphisms was detected.

Table 3
WISC and CASS:L scores (IQR: InterQuartile Range, total *n*. 299 subjects).

Variable	Min	1st Q.le	Mean	Median	3rd Q.le	Max	IQR
WISC							
Verbal IQ	69	93	102.0	103	111	135	18
Performance IQ	66	100	109.2	109	118	136	18
Total_IQ	71	98	106.3	106	115	138	17
CASS.L							
Family problems	35	38	45.0	42	50	92	12
Emotional problems	35	40	47.6	45	54	88	14
Conduct problems	37	42	45.9	45	49	79	7
Cognitive problems/ Inattention	35	41	47.5	46	52	95	11
Anger control problems	35	41	47.3	45	51	76	10
Hyperactivity	35	41	50.5	48	58	88	17
ADHD Index	36	40	46.7	45	51	89	11
DSM-IV (disattention)	35	44	49.7	48	55	77	11
DSM IV (hyperactivity/ impulsivity)	35	41	47.0	45	52	87	11
DSM IV (total)	35	42	48.3	47	53	83	11

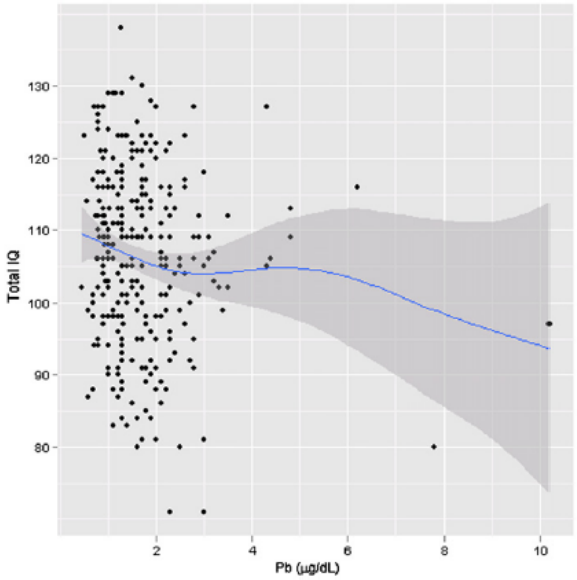


Fig. 1. Relationship between blood lead and IQ: natural scale (Restricted Cubic Spline fit).

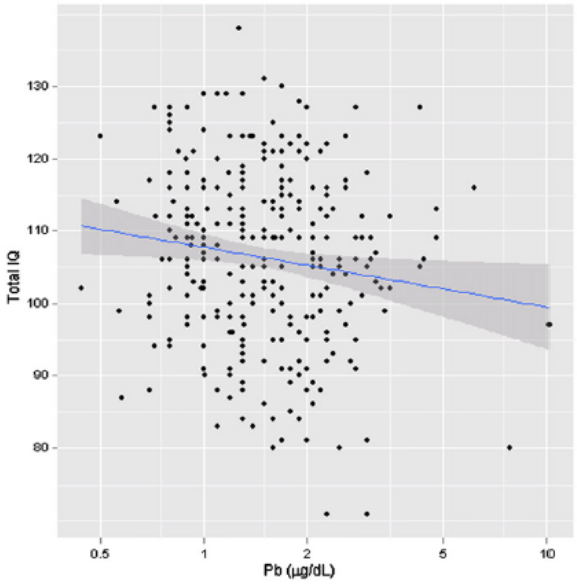


Fig. 2. BPb-IQ relationship: logarithmic transformation of the BPb axis (Tick marks are labeled in the original (untransformed) scale (Ordinary Least Square fit).

4. Discussion

Our results are the first, which we are aware of, to demonstrate significant adverse cognitive effects of lead at such very low BPb levels. This finding further supports the growing awareness of adverse effects of lead at increasing lower levels of exposure over

the past 15 years and our BPb is the lowest showing cognitive effects (Table 6). Lead exposure levels reported here actually overlap those currently observed among children in most European Countries (Hruba et al., 2012).

In our study, the regression coefficient associated with the ln (BPb) indicates that after controlling for the other variables considered we expected a reduction of about 2.4 ($-3.483 \times \ln(2)$) IQ points in the IQ score for a two-fold increase of the BPb (Figs. 1 and 2). The log-transformation of the BPb values not only linearized the BPb-IQ relationship but conceptually implies that the effect is not constant over this relatively narrow range of BPb levels (i.e., 0.44–10.2 μg/dL), and depends on the ratio (not on the difference) between two BPb levels. Therefore, the expected absolute IQ reduction depends on the BPb level itself and is greater at the lower BPb levels (where a minor increase causes a greater percent variation). This is consistent with observations showing that the relative partitioning of Pb in plasma, expressed as the percentage of whole blood Pb in plasma, increases with decreasing BPb levels of 10 μg/dL or lower, suggesting that the relative proportion of whole blood Pb in the more readily exchangeable, and likely more toxicologically active plasma fraction is actually higher at blood lead levels <10 than at moderately elevated blood lead levels (Smith et al., 2002).

A Benchmark for effective prevention of lead neurotoxicity was suggested at BPb level of 2 μg/dL (Gilbert and Weiss, 2006). In 2007 the "Declaration of Brescia on Prevention of the Neurotoxicity of Metals" proposed a reduction of the BPb action level to 5 μg/dL worldwide *"as a temporary level that may need to be revised further downward in future years as new evidence accumulates on toxicity at still lower blood lead levels"* (Landrigan et al., 2007). The same concentration of 5 μg/dL resulted as a BMDL estimated by Murata et al. (2009). The Benchmark Dose modeling performed by Budtz-Jørgensen (2010) for the European Food and Safety Authority (EFSA) on the cohorts summarized by Lanphear et al. (2005) yielded a BMDL value of 0.21 μg/dL. The BMDL calculated from our dose-response curve (BMDL=0.11 μg/dL) is slightly lower than the BMDL calculated by Budtz-Jørgensen (2010) (BMDL=0.21 μg/dL). It is important to note that since the blood lead—IQ relationship is non-linear, the BMDL would be specific to the range of blood lead level, being higher at the lower range of blood lead. Our estimate further supports the lack of a safe threshold for pediatric lead exposure, supporting the EFSA's indication on this matter.

The BPb association was stronger with the performance IQ compared to verbal IQ score, differently from other studies that found a stronger association between BPb and verbal IQ (Surkan et al., 2007; Kim et al., 2009). Some studies observed a consistent performance decrements associated with higher lead exposure throughout the preschool/elementary school ages (Bellinger et al., 1991; Wasserman et al., 1997) while verbal decrements were not apparent until 10–11 years of age. Min et al. (2009) observed a significant relation, at 4 years, between blood lead level and Performance IQ, but not Verbal IQ; while verbal decrements became apparent only at age 11. Mazumdar et al. (2011) found that Performance IQ was significantly related to blood-lead concentration but in the earlier childhood: at age of 6 months

Table 4
Multiple regression model with total IQ as dependent variable.

	Estimate	Std. Error	*T* value	Pr (>|*t*|)
Intercept	82.362	10.538	7.816	<0.0001
ln(B-Pb)	−3.483	1.481	−2.351	0.0194
SES (medium Vs low)	4.790	1.698	2.821	0.0051
SES (high Vs low)	8.826	1.781	4.955	<0.0001
Area* (lower VC Vs Garda)	−2.735	1.938	−1.411	0.1592
Area (mid VC Vs Garda)	2.512	1.602	1.568	0.1180
Area (upper VC Vs Garda)	−4.328	2.663	−1.625	0.1053
Hemoglobin	1.501	0.760	1.975	0.0493
Alcohol (yes Vs no)	−12.698	3.905	−3.252	0.0013

VC—Lower ValCamonica, MVC—Mid ValCamonica, UVC—Upper ValCamonica, n.s.—not significant.

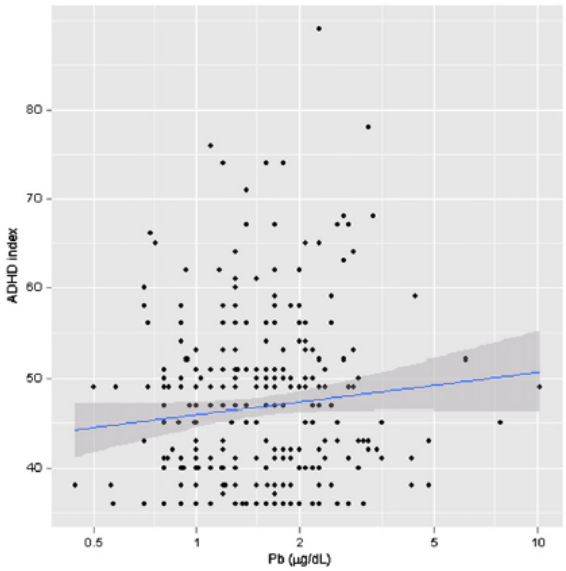


Fig. 3. BPb-ADHD relationship: logarithmic transformation of the BPb axis (Tick marks are labeled in the original (untransformed) scale (OLS fit).

Table 5
Regression models with total, verbal and performance IQ as dependent variables.

	Total IQ		Verbal IQ		Performance IQ	
	Estimate	95% C.I.	Estimate	95% C.I.	Estimate	95% C.I.
Intercept	82.4	(61.7, 103.0)	86.5	(64.7, 108.2)	82.7	(61.4, 104.0)
Ln(BPb)	−3.5	(−6.4, −0.6)	−2.9	(−5.9, 0.1)	−3.1	(−6.1, −0.1)
SES (medium Vs low)	4.8	(1.5, 8.1)	5.1	(1.6, 8.6)	3.2	(−0.2, 6.7)
SES (high Vs low)	8.8	(5.3, 12.3)	8.7	(5.1, 12.4)	6.5	(2.9, 10.1)
Area (LVC Vs GL)	−2.7	(−6.5, 1.1)	−2.7	(−6.7, 1.3)	−2.6	(−6.5, 1.3)
Area (MVC Vs GL)	2.5	(−0.6, 5.7)	1.9	(−1.4, 5.2)	2.7	(−0.6, 5.9)
Area (UVC Vs GL)	−4.3	(−9.5, 0.9)	−4.3	(−9.8, 1.2)	−3.5	(−8.8, 1.9)
Alcohol	−12.7	(−20.4, −5.0)	−12.6	(−20.7, −4.6)	−9.3	(−17.2, −1.4)
Hemoglobin	1.5	(0.0, 3.0)	0.9	(−0.7, 2.5)	1.8	(0.2, 3.3)

VC—Lower ValCamonica, MVC—Mid ValCamonica, UVC—Upper ValCamonica (the overall effect of the residence area was considered significant (p=0.027).

Table 6
B-Pb levels (in μg/dL) in studies on cognitive effects of lead in children.

Reference	Subjects #	Study site	Study design	Age (years)	BPb Mean (SD)
Chen et al. (2005)	780	Baltimore, MD, USA	longitudinal	2	26.2 (5.1)
	731	Cincinnati, OH, USA	longitudinal	5	12.0 (5.2)
	622	Newark, NJ, USA, Philadelphia, PA, USA	longitudinal longitudinal	7	8.0 (4.0)
Canfield et al. (2003)	154	Rochester, NY, USA	longitudinal	0.5	3.4
				2	9.7
				5	6.0
Roy et al. (2011)	651	Chennai, India	cross-sectional	3–7	11.42 (5.43)
Bellinger et al. (2005)	74	Chennai, India	cross-sectional	4–14	11.10 (5.6)
Schnaas et al. (2006)	150	Mexico City, Mexico	longitudinal	1–5	9.8
				6–10	6.2
Ahamed et al. (2005)	62	Lucknow, India	cross-sectional	4–12	7.47 (3.06)
Després et al. (2005)	110	Nunavik, Canada	cross-sectional	4–6	5.0 (3.7)
Chiodo et al. (2007)	506	Detroit, MI, USA	cross-sectional	7	5.0 (3.0)
Pawlas et al. (2012)	175	Upper Silesia, Poland	cross-sectional	6–10	4.66 (1.23)
Nicolescu et al. (2010)	83	Bucharest and Pantelimon, Romania	cross-sectional	8–12	4.15
This study	299	Brescia, Italy	cross-sectional	11–14	1.71 (0.99)

and 4 years and average blood-lead concentration, while Verbal IQ was significantly related to blood-lead concentration at 10 years. The model also confirmed the positive influence on IQ of socio-economic status (SES) and parental education levels. No influence on the IQ was noted by family size, nor by birth order, confirming a previous observation (Kristensen and Bjerkedal, 2007). A limitation of our study is that we collected some information about the environment (caregivers' level of study and type of job, number of siblings, birth order) and parents' education through questionnaires; there was no direct evaluation of the home environment and a measurement of parents' IQ.

Genetic modifications by *ALAD* on the lead toxicity was not observed, which may due to limited statistical power for *ALAD* rs1800435, for which the variant genotype was quite rare in our population. That may explain why we could not prove or disregard our main hypothesis, i.e., that carriers of *ALAD*2 are more protected against neurotoxic effects of lead. For *ALAD* rs1139488, the gene frequencies were more favorable from a statistical power point of view, but no significant effects were observed. Pawlas et al. (2012) reported an influence of *ALAD* rs1139488 T on lead. However, the average BPb (4.66 μg/dL) was about three times higher compared to our study.

Alcohol can influence the child's IQ, as shown for mother's prenatal alcohol consumption (Mazumdar et al., 2011) or caregivers' home alcohol consumption (Chiodo et al., 2007). We observed a strong and negative association of alcohol consumption by the adolescents with their total, verbal and performance IQ. However it should be noted that very few subjects reported alcohol consumption and that our data are self-reported. It is possible those children with lower IQ have a greater tendency towards drinking, and that our self-reporting questionnaire did not capture this.

A weak association was also observed between BPb and ADHD index of the Conners Scales. Nigg (Nigg, et al., 2008) found that lead was related to weakened cognitive control, a mechanism often associated with risk for ADHD via breakdowns in frontal-striatal neural circuits.

In our study the association of lead exposure and the ADHD score was weak and this may be due to several factors: (i) the very low BPb levels observed in our cohort; (ii) the exclusion of clinical ADHD cases from enrollment; and/or (iii) the cut-off minimum value of the ADHD score, which precludes our assessment of this relationship at lower scores.

No association was found between manganese exposure and cognitive/behavioral functions. The co-exposure between lead and manganese in previous pediatric studies (Menezes-Filho et al., 2011; Riojas-Rodriguez et al., 2010) has been approached using BPb as a covariate to which manganese exposure was adjusted for. In those studies, there was an effect of blood manganese on IQ, but not BPb as reported by the authors. The studies on lead-manganese co-exposure in maternal-infant pairs by Kim et al. (2009) and Henn et al. (2012) considered instead both manganese and lead in blood as independent variables in the regression models. These studies found evidence of a positive interaction between lead and manganese on IQ and Mental Development, respectively. The lack of a manganese influence on the IQ in our study should be interpreted in light of the fact that manganese is a micronutrient and the effect on neurodevelopmental functions are based on an inverse *U*-shaped curve. Manganese exposure in this study is historical and currently quite low, therefore it may not be sufficient to cause cognitive impairment. The ferroalloy emission ceased in 2001, therefore exposure intensity was likely greatest when our subjects were 0–2 yr of age. This implies that cognitive effects from manganese may have occurred at a younger age but became reversible after exposure cessation. Reversibility did not occur with the effects of manganese on tremor, motor and odor function, that are still persistent today, as shown in a different publication (Lucchini et al., 2012). Exposure to lead is, instead, more ubiquitous and depending from different sources other than ferroalloy emission. These hypotheses may explain the current effect of lead, and not of manganese, on the IQ.

In conclusion, the present study shows a significant negative association between BPb level on IQ and a borderline positive correlation between BPb and hyperactivity in adolescents. The fact that these effects were observed over a range of BPbs considered near 'background' in many countries underscores the importance of primary prevention and of further reducing the levels of lead in the environment.

Acknowledgments

This study was supported by funding from the European Union through its Sixth Framework Programme for RTD (contract no FOOD-CT-2006- 016253). It reflects only the authors' views, and the European Commission is not liable for any use that may be made of the information contained therein. The project was supported also by Award Number R01ES019222 from the National Institute Of Environmental Health Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Of Environmental Health Sciences or the National Institutes of Health. We

thank Karin Paulsson for help with the genetic analyses and Phil Landrigan for reviewing the manuscript.

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The research protocol was approved by the Ethical Committees of the local Public Health agencies of Valcamonica and Brescia, Italy.

References

ACCLPP, 2012. Low level lead exposure harms children: a renewed call for primary prevention. USA Center for Disease Control and Prevention. 〈http://www.cdc.gov/nceh/lead/acclpp/acclpp_main.htm〉 (accessed 16.05.2012).

Ahamed, M., et al., 2005. Environmental exposure to lead and its correlation with biochemical indices in children. Sci. Total Environ. 346 (1–3), 48–55.

Apostoli, P., et al., 2000. Are current biomarkers suitable for the assessment of manganese exposure in individual workers? Am. J. Ind. Med. 37, 283–290.

Bellinger, et al., 1991. Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics 87 (2), 219–227.

Bellinger, D.C., et al., 2005. A pilot study of blood lead levels and neurobehavioral function in children living in Chennai, India. Int. J. Occup. Environ. Health 11 (2), 138–143.

Bellinger, D.C., 2008. Very low lead exposures and children's neurodevelopment. Curr. Opin. Pediatr. 20, 172–177.

Borgese, L., et al., 2011. A new non-destructive method for chemical analysis of particulate matter filters: the case of manganese air pollution in Vallecamonica (Italy). Talanta 84, 192–198.

Bouchard, M.F., et al., 2011. Intellectual impairment in school-age children exposed to manganese from drinking water. Environ. Health Perspect. 119, 138–143.

Budtz-Jørgensen, E., An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children. In: REPORT, E. S. T., (Ed.), Vol. CT/EFSA/CONTAM/2009/03, 2010.

Budtz-Jørgensen, E.K.N.G.P., 2001. Benchmark dose calculation from epidemiological data. Biometrics 57, 698–706.

Canfield, R.L., et al., 2003. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N. Engl. J. Med. 348, 1517–1526.

Cesana, G.C., et al., 1995. [Evaluation of the socioeconomic status in epidemiological surveys: hypotheses of research in the Brianza area MONICA project]. Med. Lav. 86, 16–26.

Chalela, J.A., et al., 2011. Manganese encephalopathy: an under-recognized condition in the intensive care unit. Neurocrit Care 14, 456–458.

Chen, A., et al., 2005. IC and blood lead from 2 to 7 years of age: are the effect in older children the residual of high blood lead concentrations in 2-years-olds? Environ. Health Perspect. 113 (5), 597–601.

Chiodo, L.M., et al., 2007. Blood lead levels and specific attention effects in young children. Neurotoxicol. Teratol. 29, 538–546.

Conners, C.K., et al., 1997. A new self-report scale for assessment of adolescent psychopathology: factor structure, reliability, validity, and diagnostic sensitivity. J. Abnorm. Child Psych. 25, 487–497.

Després, C., et al., 2005. Neuromotor functions in Inuit preschool children exposed to Pb, PCBs, and Hg. Neurotoxicol. Teratol. 27 (2), 245–257.

EFSA, E.F.S.A., 2010. Scientific Opinion on Lead in food. EFSA J. 8, 1570.

Flegal, A.R., Smith, D.R., 1992. Lead levels in preindustrial humans. N. Eng. J. Med. 326, 1293–1294.

Gilbert, S.G., Weiss, B., 2006. A rationale for lowering the blood lead action level from 10 to 2 microg/dL. Neurotoxicology 27, 693–701.

Henn, B.C., et al., 2012. Associations of early childhood manganese and lead coexposure with neurodevelopment. Environ. Health Perspect. 120, 126–131.

Hruba, F., et al., 2012. Blood cadmium, mercury, and lead in children: an international comparison of cities in six European countries, and China, Ecuador, and Morocco. Environ. Int. 41C, 29–34.

Jepsen, J.R., et al., 2009. Do attention deficits influence IQ assessment in children and adolescents with ADHD? J. Atten. Disord. 12, 551–562.

Kim, Y., et al., 2009. Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. Neurotoxicology 30, 564–571.

Kristensen, P., Bjerkedal, T., 2007. Explaining the relation between birth order and intelligence. Science 316, 1717.

Landrigan, P., et al., 2007. The Declaration of Brescia on prevention of the neurotoxicity of metals June 18, 2006. Am. J. Ind. Med. 50, 709–711.

Lanphear, B.P., et al., 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect. 113, 894–899.

Lucchini, R.G., et al., 2007. High prevalence of Parkinsonian disorders associated to manganese exposure in the vicinities of ferroalloy industries. Am. J. Ind. Med. 50, 788–800.

Lucchini, R.G., et al., 2012. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. Neurotoxicology.

Mazumdar, M., et al., 2011. Low-level environmental lead exposure in childhood and adult intellectual function: a follow-up study. Environ. Health 10, 24.

Mazumdar, M., et al., 2012. Prenatal Lead Levels, Plasma Amyloid beta Levels and Gene Expression in Young Adulthood. Environ Health Perspect.

Menezes-Filho, J.A., et al., 2011. Elevated manganese and cognitive performance in school-aged children and their mothers. Environ. Res. 111, 156–163.

Min, M.O., et al., 2009. Cognitive development and low-level lead exposure in poly-drug exposed children. Neurotoxicol. Teratol. 31, 225–231.

Murata, K., et al., 2009. Lead toxicity: does the critical level of lead resulting in adverse effects differ between adults and children? J. Occup. Health 51, 1–12.

Needleman, H.L., et al., 1990. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. N. Eng. J. Med. 322, 83–88.

Nicolescu, R., et al., 2010. Environmental exposure to lead, but not other neurotoxic metals, relates to core elements of ADHD in Romanian children: performance and questionnaire data. Environ. Res. 110, 476–483.

Nigg, J.T., et al., 2008. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. Biol. Psychiatry 63, 325–331.

Pawlas, N., et al., 2012. Modification by the genes ALAD and VDR of lead-induced cognitive effects in children. Neurotoxicology 33, 37–43.

Pinheiro, J.C.B.D.M., 2000. Mixed-Effects Models in S and S-PLUS. Springer, New York.

Pocock, S.J., et al., 1994. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ 309, 1189–1197.

Rentschler, G., et al., 2012. ATP13A2 (PARK9) polymorphisms influence the neurotoxic effects of manganese. Neurotoxicology.

Riojas-Rodriguez, H., et al., 2010. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. Environ. Health Perspect. 118, 1465–1470.

R Core Team, R., 2011. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

Roy, A., et al., 2011. Hemoglobin, lead exposure, and intelligence quotient: effect modification by the DRD2Taq IA polymorphism. Environ. Health Perspect. 119 (1), 144–149.

Schnaas, L., et al., 2006. Reduced intellectual development in children with prenatal lead exposure. Environ. Health Perspect 114 (5), 791–797.

Scinicariello, F., et al., 2010. Modification by ALAD of the association between blood lead and blood pressure in the U.S. population: results from the Third National Health and Nutrition Examination Survey. Environ. Health Perspect. 118, 259–264.

Smith, D., et al., 2007. Biomarkers of Mn exposure in humans. Am. J. Ind. Med. 50, 801–811.

Smith, D., et al., 2002. The relationship between lead in plasma and whole blood in women. Environ. Health Perspect. 110, 263–268.

Smith, D.R., Flegal, A.R., 1992. The public health implications of humans' natural levels of lead. Am. J. Public Health 82, 1565–1566.

Surkan, P., et al., 2007. Neuropsychological function in children with blood lead levels < 10 microg/dL. Neurotoxicology 28 (6), 1170–1177 2007 Nov.

Venables, W.N.R.B.D., 2002. Modern Applied Statistics with S. Springer, New York.

Wasserman, et al., 1997. Lead exposure and intelligence in 7-year-old children: the Yugoslavia Prospective Study. Environ. Health Perspect. 105, 956–962.

Wasserman, G.A., et al., 2006. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ. Health Perspect. 114, 124–129.

WHO, 1988. MONICA Psychosocial Optional Study: MOPSY Suggested Measurement Instruments. WHO Regional Office for Europe, Copenhagen.

Wigle, D.T., Lanphear, B.P., 2005. Human health risks from low-level environmental exposures: no apparent safety thresholds. PLoS Med. 2, e350.

Wood, S.N., 2006. Generalized Additive Models: An introduction with R. CRC/Chapman &Hall, Boca Raton, Florida.

Wright, R.O., et al., 2006. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. Neurotoxicology 27, 210–216.

Zacco, A., et al., 2009. Analysis of settled dust with X-ray Fluorescence for exposure assessment of metals in the province of Brescia, Italy. J. Environ. Monit. 11, 1579–1585.

Zheng, G., et al., 2011. delta-Aminolevulinic acid dehydratase genotype predicts toxic effects of lead on workers' peripheral nervous system. Neurotoxicology 32, 374–382.

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Attention Deficit Hyperactivity Disorder and Cognitive Function in Duchenne Muscular Dystrophy: Phenotype-Genotype Correlation

Marika Pane, MD[1,*], Maria Elena Lombardo, MD[1,2,*], Paolo Alfieri, MD[3], Adele D'Amico, MD[4], Flaviana Bianco, MD[1], Gessica Vasco, MD[1], Giorgia Piccini, Dpsych[3], Maria Mallardi, Dpsych[1], Domenico M. Romeo, MD[1], Valeria Ricotti, MD[5], Alessandra Ferlini, MD[6], Francesca Gualandi, MD[6], Stefano Vicari, MD[3], Enrico Bertini, MD[4], Angela Berardinelli, MD[7], and Eugenio Mercuri, MD[1]

Objectives To assess attention deficit hyperactivity disorder (ADHD) in boys affected by Duchenne muscular dystrophy (DMD) and to explore the relationship with cognitive abilities and genetic findings.

Study design Boys with DMD (n = 103; 4-17 years of age, mean: 12.6) were assessed using a cognitive test (Wechsler scales). Assessment of ADHD was based on the *Diagnostic Statistical Manual, Fourth Edition, Text Revision* criteria and on the long version of the Conners Parents and Teachers Rating Scales.

Results ADHD was found in 33 of the 103 boys with DMD. Attention problems together with hyperactivity (17/33) or in isolation (15/33) were more frequent than hyperactivity alone, which was found in 1 patient. Intellectual disability (ID) was found in 27/103 (24.6%). Sixty-two of the 103 boys had no ID and no ADHD, 9 had ID but no ADHD, 14 had ADHD but no ID, and 18 had both. ADHD occurred more frequently in association with mutations predicted to affect Dp140 expression (exon 45-55) and in those with mutations predicted to affect all dystrophin product, including Dp71 (ie, those that have promoter region and specific first exon between exons 62 and 63 but were also relatively frequent).

Conclusions Our results suggest that ADHD is a frequent feature in DMD. The risk of ADHD appears to be higher in patients carrying mutations predicted to affect dystrophin isoforms expressed in the brain and are known to be associated with higher risk of cognitive impairment. *(J Pediatr 2012;161:705-9).*

The mean IQ reported in children with Duchenne muscular dystrophy (DMD) is approximately 1.0-1.5 SDs below the mean. One-third of boys with DMD exhibit nonprogressive cognitive impairment compared with age- and sex-matched controls and with those with other neuromuscular disorders. There is a higher degree of impairment in verbal vs nonverbal performance both in older[1-3] and younger patients.[4]

The gene encoding dystrophin includes 79 exons interspersed with large introns. Several studies have reported the association between severe learning difficulties and mutations in the 3′ end of the gene.[5-8] Mutations occurring downstream of exon 44 affect the short isoform of dystrophin Dp140, largely expressed in the central nervous system, and mutations downstream of exon 63 disrupt all short isoforms, including Dp71, which is abundant in the brain.[9,10]

Other studies have also assessed autistic features,[11-13] obsessive-compulsive disorder, and more recently, attention deficit hyperactivity disorder (ADHD).[14-17] The frequency of ADHD in DMD reported varies in the literature, possibly reflecting the different methods used to test for ADHD. In a survey, 12% of parents reported that their boy had been diagnosed with ADHD[14]; in another study, the Child Behavior Checklist scales identified approximately 1 in 4 boys with significant attention problems.[15] In a small study, 10 boys with DMD were tested with the Conners Parent Rating Scale-Revised, and 5 were reported to have ADHD.[16] Other anecdotal reports by clinicians also suggest that ADHD is one of the most commonly observed psychiatric comorbidities in DMD, although a correlation with cognitive abilities has not been explored. Cognitive assessments in DMD showed that deficits in executive function, attention, and verbal memory are a frequent feature,[18-20] but it remains unclear whether this is a result of a specific cognitive deficit or a primary attention problem. Although the genotype/phenotype correlation for cognitive impairment in DMD has become increasingly clearer, the relationship between ADHD and genotype has not yet been systematically explored.

ADHD	Attention deficit hyperactivity disorder
CGI	Conners Global Index
CPRS-R:L	Conners Parents Rating Scales-Revised
CTRS-R:L	Conners Teachers Rating Scales-Revised
DMD	Duchenne muscular dystrophy
DSM IV	*Diagnostic Statistical Manual, Fourth Edition, Text Revision*
ID	Intellectual disability

From the [1]Department of Pediatrics, Child Neurology and Psychiatry, Catholic University, Rome, Italy; [2]Department of Physiological Sciences, University of Catania, Catania, Italy; [3]Child Neuropsychiatry Unit, Department of Neuroscience, [4]Department of Laboratory Medicine, Unit of Molecular Medicine, Bambino Gesù Hospital, Rome, Italy; [5]Dubowitz Neuromuscular Centre, University College London Institute of Child Health and Great Ormond Street Hospital for Children, London, United Kingdom; [6]Section of Medical Genetics, Department of Experimental and Diagnostic Medicine, University of Ferrara, Ferrara, Italy; and [7]Child Neurology and Psychiatry Unit, IRCCS C. Mondino Foundation, Pavia, Italy

*Contributed equally.

The authors declare no conflicts of interest.

 10.1016/j.jpeds.2012.03.020

THE JOURNAL OF PEDIATRICS • www.jpeds.com Vol. 161, No. 4

We assessed a cohort of boys with DMD using a battery of tests for cognitive functions and ADHD. We explored the prevalence of ADHD in DMD, and explored a possible relation with cognitive impairment and genotype.

Methods

This is prospective multicentric study involving 3 tertiary neuromuscular centers (Catholic University and Hospital Bambino Gesù, in Rome; Istituto Mondino, in Pavia). The study was approved by the Ethical Committee of each center. All patients with DMD between the age of 4 and 16 years regularly followed at the 3 centers were asked to participate. Inclusion criterion was genetically proven DMD. In all patients, diagnosis was confirmed by multiplex ligation-dependent probe amplification (ie, exons deletions and duplications) or by polymerase chain reaction amplification and direct sequencing of all 79 exons and adjacent introns (ie, intronic deletions, rearrangements). Mutations were classified according to the Leiden Muscular Dystrophy database (http://www.dmd.nl/) using the nomenclature system published in 2000 in Human Mutation.

Patients were broadly subdivided into 3 groups according to their steroid treatment: (1) no steroids: this included steroid-naïve boys or boys who had been on steroids for less than a year and had stopped treatment at least 1 year before the study; (2) intermittent steroid regime: boys on pulsed administration of steroids for over a year (alternate days, alternate weeks, 10 days on/10 days off); or (3) daily regime: boy on daily prednisolone 0.75 mg or deflazacort 0.9 mg/kg/day for over a year. Duration of steroids treatment was recorded.

Diagnosis of ADHD was first based on the *Diagnostic Statistical Manual, Fourth Edition, Text Revision* (DSM IV-TR)[21] criteria, administered to all 103 boys with DMD. The boys who met the criteria for ADHD were further assessed using the long version of the Conners Parents Rating Scales-Revised (CPRS-R:L) and of the Conners Teachers Rating Scales-Revised (CTRS-R:L).[22] Both the parents and school teachers were invited complete forms.

The CPRS-R:L and CTRS-R:L questionnaires use a categorical approach to rating symptoms of ADHD. The parents (and/or teachers) rate 80 items on a 4-point Likert-type scale. The result includes 7 subscales: (1) oppositional; (2) cognitive problems; (3) hyperactivity; (4) anxious–shy; (5) perfectionism; (6) social problems; and (7) psychosomatic. The questionnaires encompass 3 additional scales: the ADHD Index, the Conners Global Index (CGI), and the DSM-IV Symptoms Subscale. The ADHD Index, which consists of 12 items, is an effective screener for identifying children and adolescents meeting ADHD diagnostic criteria. The CGI is the index with the 10 items found to be most sensitive to treatment effects. The DSM-IV Symptoms Subscale consists of 18 items that directly parallel the DSM-IV criteria for diagnosing ADHD. In our study, we focused on to the 3 additional scales: the ADHD Index, the CGI, and the DSM-IV-TR Symptoms Subscale that provides a score for attention, hyperactivity/impulsivity, and a total score. For each of these subscales a score above 70 was considered abnormal.

All patients underwent a cognitive assessment using the Wechsler Scale.

To compare the presence of ADHD in relation to motor function, steroid treatment, and site and type of mutation, the Fisher exact test was used. The level of significance was set at $P < .05$.

Results

Consent was received for the 103 patients who were asked to participate in the study. Their ages ranged from 4-6 years (mean 12.6). Seventy-two boys were ambulatory and 31 were not. Eighty-three were on steroids (39 daily and 44 intermittent). All had been on steroids for longer than 12 months and treatment was commenced between the age of 5 and 7 years. Of the remaining 20, 2 had been on steroids but only for a short time over a year prior to enrollment into our study; 18 had never been on steroids.

Maternal carrier status was available in 84 with 73 mothers being carriers and 11 not.

Thirty-eight of the 103 patients met the criteria for ADHD on the DSM IV-TR: 3 for hyperactivity, 16 for attention, and 19 for both. The CPRS-R:L confirmed ADHD diagnosis in all but the CTRS-R:L only confirmed in 33 of the 38 boys. The other 5 showed high scores but did not reach the threshold for abnormality.

Of the 33 patients with ADHD confirmed on both CPRS-R:L and CTRS-R:L, 17 has attention problems together with hyperactivity, 15 has attention problems, and 1 has hyperactivity.

Fourteen boys were untestable because of severe intellectual disability (ID). The IQ of the 89 who could be assessed ranged from 45-128 (mean 88.4; median 90; SD 18.5).

Sixty-two of the 103 had normal IQ (85 or above), 14 borderline (70-84), and 13 had scores below 70 that including the 14 untestable boys makes a total of 27 boys with ID.

ADHD was found in 9 of the 62 boys with normal IQ (14.5%), in 5 of the 14 with borderline (35.7%), and in 18 of the 27 with ID (66%). Altogether, 62 boys had no mental retardation and no ADHD, 14 had ADHD but normal/borderline cognitive function, 9 had ID but no ADHD, and 18 had both.

ADHD was found in 7 of the 31 (22.5%) nonambulatory and in 25 of the 72 ambulatory boys (34%). No statistical difference was found between ambulant and nonambulant boys.

There was no clear relation between steroid regime and ADHD (Figure 1). In 9 of the 20 patients in the no steroids group, behavioral problems were already obvious when treatment was discussed and parents were reluctant to start treatment because of the possible behavioral problems reported in literature.

No statistical difference was observed between daily and intermittent steroids.

Maternal carrier status was available in 84 patients. ADHD was found in 29 children of 73 carriers, in none of the 11 noncarriers, and in 4 of the 19 with unknown carrier status.

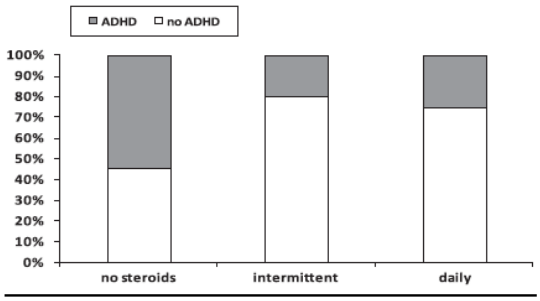


Figure 1. ADHD and steroid treatment.

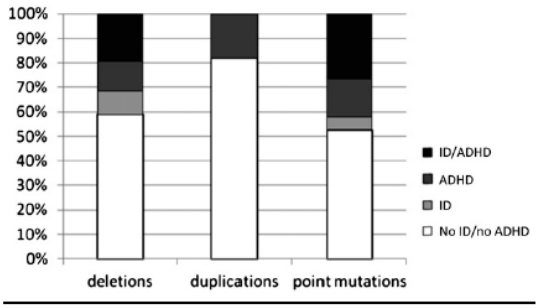


Figure 3. Type of mutations and ADHD.

Seven of the 10 patients, who had mutations affecting all the brain isoforms of dystrophin (downstream of exon 63), had ADHD (Figure 2; available at www.jpeds.com) associated with ID in 6 of the 7. ID was also found in another 2 of the 3 patients without ADHD.

Seventeen of the 58 patients with mutations in exons 45-55, predicted to affect Dp140 expression, had ADHD, associated with ID in 9 of 17. ID was also found in another 6 of the 41 patients without ADHD.

Seven of the 31 patients with mutations upstream of exon 45 had ADHD, associated with ID in 3 of 7 (Table). ID was not found in any of the 24 patients without ADHD.

Patients with identical mutation did not always have the same cognitive of behavioral outcome (eg, mutations 45-50 or 45-52; Figure 2).

A statistical difference for ADHD was observed between patients with mutations downstream of exon 63 and those with mutations in the exons 45-55 ($P < .05$). The difference was also significant between those with mutations downstream of exon 63 and upstream or in the exon 44 ($P < .05$), but not between exons 45-55 and upstream or in the exon 44 ($P > .05$).

Patients with identical mutation did not always have the same cognitive of behavioral outcome (eg, mutations 45-50 or 45-52; Figure 2).

The analysis of the type of mutation showed that 23 of the 73 (31.5%) patients with deletions had ADHD, associated with ID in 14 of the 23.

Two of the 11 (18%) patients with duplications had ADHD and none had ID.

Eight of the 19 patients (42%) with point mutations had ADHD; 5 of which were associated with ID (Figure 3).

The difference among patients with different types of mutation was not significant.

Discussion

There is a growing interest on the neurobehavioral aspects of DMD, but only a few studies have addressed ADHD.[14-17] These studies mainly used parental questionnaires or surveys. Furthermore, none of these studies explored the association between ADHD and cognitive abilities or genotype.

In our study, 103 boys with DMD were assessed for ADHD criteria. All the boys were screened by using the DSM-IV-TR criteria. In the 38 boys who met the DSM-IV-TR criteria for ADHD, we administered the CPRS-R:L and CTRS-R:L, which have been found to be highly effective for discriminating between children with ADHD and normal controls.[23] The teachers were also invited to complete the questionnaires, measuring the child's behavior outside the familiar environment. The diagnosis of ADHD was confirmed in 33 of the 38 (32% of the whole cohort) compared with 3%-7% of ADHD in the general population.[24,25] The frequency of ADHD in DMD previously reported in the literature varies between 12% and 50%,[14-16] but the results are not easily comparable because of the different tools used and of the low number of patients included in some of the previous studies.

Attention problems together with hyperactivity (17/33) or in isolation (15/33) were the most frequent findings, hyperactivity alone was found in only 1. Only one patient at the time of the assessment was treated with methylphenidate.

ADHD did not appear to be related to level of motor ability as the proportion of ADHD/non ADHD was present in both ambulatory and nonambulatory patients. In our study, only

Table. Site of genetic mutation and presence of ADHD or ID

	Patients with mutations upstream or in exon 44 (n = 31)	Patients with mutations in exons 45-55 predicted to affect Dp140 expression (n = 58)	Patients with mutations downstream exon 62 predicted to affect Dp71 expression (n = 10)
No ID/no ADHD	24/31 (75%)	35/58 (61.4%)	1/10 (10%)
ID/no ADHD	0/31 (0%)	6/58 (10.5%)	2/10 (20%)
No ID/ADHD	4/31 (12.5%)	8/58 (13.3%)	1/10 (10%)
ID/ADHD	3/31 (9%)	9/58 (14%)	6/10 (60%)
Total ID and/or ADHD	8/31 (25%)	22/58 (38.5%)	9/10 (90%)

THE JOURNAL OF PEDIATRICS • www.jpeds.com Vol. 161, No. 4

31 of the 103 patients were nonambulant and few had extremely reduced mobility, therefore, reducing the chance that some aspects of hyperactivity may have been underestimated by questionnaires investigating motor activities such as fidgety and restlessness.

It is recognized that behavioral problems can be side effects of steroid therapy. The effect of steroids on behavior is controversial; another study has reported that the long-term effect of prolonged corticosteroid exposure on behavior may be associated with initial mood swings and memory and attention problems that stabilize with time.[26] In our study, we found no significant difference in ADHD between children on daily and intermittent regimen. We did not analyze our results for the groups on steroids comparing the untreated group as there was an obvious bias. In most of the untreated boys, behavioral problems had been obvious before considering treatment with steroids, and the families were reluctant to start.

ADHD was more commonly found in patients with ID but there was no consistent association for individual cases as some children with normal IQ had ADHD, and a significant proportion of patients with ID did not have ADHD.

As expected, ADHD occurred more frequently in association with mutations predicted to affect Dp140 expression and, even more frequently, in those with mutations predicted to affect all dystrophin short isoforms including Dp71, ie, those that have promoter region and specific first exon between exons 62 and 63. Patients with mutations affecting the middle and 3′ end of the gene are known to be at higher risk of developing cognitive difficulties,[6] but we were able to demonstrate that this holds true also for ADHD. It is of interest that ADHD was also found in approximately 25% of the group of patients with mutations upstream exon 44.

Another interesting finding is that in this subgroup, 3 boys have severe ID associated with ADHD, and all 3 had a single exon mutation in exon 19 (2-point mutations and a deletion). The reason why a mutation that solely affects the long dystrophin isoforms and not the expression of the brain short isoforms may still present with ADHD, and, in the 3 cases, also with severe ID, remains unknown.

The analysis of individual results also allowed a few additional comments. Although we observed that some specific mutations, such as 45-55 deletion, were associated with higher risk of cognitive involvement, we also found that the same mutation could be associated with the whole spectrum of results, ranging from normal IQ and no ADHD to severe ID and ADHD. This may be explained by recent hypothesis that other genetic or environmental modifiers may play a role in determining the severity of the phenotype.[27]

When we analysed IQ and ADHD in relation to the type of mutation (deletions, duplications, and point mutations), the numbers in some of the subgroups were too small for a meaningful statistical analysis, but we were able to confirm recent findings that patients with DMD carrying point mutations show more severe cognitive involvement compared with deletions or duplications.[7] We found that ADHD was also more frequent in the group with point mutations.

ADHD is a frequent comorbidity of DMD and does not appear to be specifically associated with ambulation and steroid regime. ADHD is more prevalent in patients with mutations that affect the expression of dystrophin in the brain but, even if less frequently, can also be found in patients with mutations not associated with cognitive impairment. The variability of cognitive and ADHD findings associated with identical mutations suggest that other genetic or environmental modifier may also play a role in determining the phenotypical spectrum of the neurocognitive profile in DMD. It has recently been suggested that osteopontin genotype is a genetic modifier of disease severity in DMD, with effects on the progression of motor impairment, but nothing has been reported on cognitive or behavioral aspects.[28]

Furthermore, the reported association of ADHD with mutations in other genes on the X chromosome and more specifically with Xp deletions raises the hypothesis that this region may be associated with increased susceptibility for ADHD, but this needs to be further confirmed.[28,29] ■

Submitted for publication Dec 5, 2011; last revision received Jan 30, 2012; accepted Mar 8, 2012.

Reprint requests: Eugenio Mercuri, MD, Department of Child Neurology, Policlinico Gemelli, Largo Gemelli 00168, Rome, Italy. E-mail: mercuri@rm.unicatt.it

References

1. Bresolin N, Castelli E, Comi GP, Felisari G, Bardoni A, Perani D, et al. Cognitive impairment in Duchenne muscular dystrophy. Neuromuscul Disord 1994;4:359-69.
2. Cotton S, Voudouris N, Greenwood KM. Intelligence and Duchenne muscular dystrophy: full-scale, verbal and performance intelligence quotients. Dev Med Child Neurol 2001;43:497-501.
3. Cotton S, Voudouris N, Greenwood KM. Association between intellectual functioning and age in children with Duchenne muscular dystrophy: further results if meta-analysis. Dev Med Child Neurol 2005;73: 257-65.
4. Dorman C, Hurley AD, D'Avignon J. Language and learning disorders of older boys with Duchenne muscular dystrophy. Dev Med Child Neurol 1988;30:316-27.
5. Daoud F, Candelario-Martínez A, Billard JM, Avital A, Khelfaoui M, Rozenvald Y, et al. Role of mental retardation-associated dystrophin-gene product Dp71 in excitatory synapse organization, synaptic plasticity and behavioral functions. PLoS One 2008;4:e6574.
6. Taylor PJ, Betts GA, Maroulis S, Gilissen C, Pedersen RL, Mowat DR, et al. Dystrophin gene mutation location and the risk of cognitive impairment in Duchenne muscular dystrophy. PLoS One 2010;20:e8803.
7. Magri F, Govoni A, D'Angelo MG, Del Bo R, Ghezzi S, Sandra G, et al. Genotype and phenotype characterization in a large dystrophinopathic cohort with extended follow-up. J Neurol 2011;258:1610-23.
8. Hodgson SV, Abbs S, Clark S, Manzur A, Heckmatt JZ, Dubowitz V, et al. Correlation of clinical and deletion data in Duchenne and Becker muscular dystrophy, with special reference to mental ability. Neuromuscul Disord 1992;2:269-76.
9. Moizard MP, Billard C, Toutain A, Berret F, Marmin N, Moraine C. Are Dp71 and Dp140 brain dystrophin isoforms related to cognitive impairment in Duchenne muscular dystrophy? Am J Med Genet 1998;80:32-41.
10. Hugnot JP, Gilgenkrantz H, Vincent N, Chafey P, Morris GE, Monaco AP, et al. Analysis of Dp71 contribution in the severity of mental retardation through comparison of Duchenne and Becker patients

differing by mutation consequences on Dp71 expression. Hum Mol Genet 2009;18:3779-94.
11. Komoto J, Usui S, Otsuki S, Terao A. Infantile autism and Duchenne muscular dystrophy. J Autism Dev Disord 1984;14:191-5.
12. Wu JY, Kuban KC, Allred E, Shapiro F, Darras BT. Association of Duchenne muscular dystrophy with autism spectrum disorder. J Child Neurol 2005;20:790-5.
13. Hinton VJ, Fee RJ, De Vivo DC, Goldstein E. Poor facial effect recognition among boys with Duchenne muscular dystrophy. J Autism Dev Disord 2007;37:1925-33.
14. Poysky J, Behavior in DMD Study Group. Behavior patterns in Duchenne muscular dystrophy: report on the Parent Project Muscular Dystrophy behavior workshop 8-9 of December 2006. Neuromuscul Disord 2007;17:986-94.
15. Hinton VJ, Nereo NE, Fee RJ, Cyrulnik SE. Social behavior problems in boys with Duchenne muscular dystrophy. J Dev Behav Pediatr 2006;27:470-6.
16. Steele M, Taylor E, Young C, McGrath P, Lyttle BD, Davidson B. Mental health of children and adolescents with Duchenne muscular dystrophy. Dev Med Child Neurol 2008;50:638-9.
17. Hendriksen JG, Vles JS. Neuropsychiatric disorders in males with Duchenne muscular dystrophy: frequency rate of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, and obsessive-compulsive disorder. J Child Neurol 2008;23:477-81.
18. Cotton S, Crowe SF, Voudouris N. Neuropsychological profile of Duchenne muscular dystrophy. Child Neuropsychol 1998;4:110-7.
19. Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Selective deficits in verbal working memory associated with a known genetic etiology: the neuropsychological profile of Duchenne muscular dystrophy. J Int Neuropsychol Soc 2001;7:45-54.
20. Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Specific cognitive deficits are common in children with Duchenne muscular dystrophy. Dev Med Child Neurol 2004;46:154-9.
21. American Psychiatric Association. Diagnostic and statistical manual for mental disorders. 4th edition. TR. (DSM-IV). Washington, DC: APA; 2000.
22. CPRS-R: L, CTRS-R: L C Keith Conners 2000. Conners Rating Scales-Revised: Technical Manual. Toronto: Multi-Health System Inc.
23. Green M, Wong M, Atkins D, Taylor J, Feinleib M. Diagnosis of attention-deficit/hyperactivity disorder. Rockville (MD): Agency for Health Care Policy and Research (AHCPR); 1999.
24. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007;164:942-8.
25. Rappley MD. Attention deficit-hyperactivity disorder. N Engl J Med 2005;352:165-73.
26. Brown ES, Vera E, Frol AB, Woolston DJ, Johnson B. Effects of chronic prednisone therapy on mood and memory. J Affect Disord 2007;99:279-83.
27. Pegoraro E, Hoffman EP, Piva L, Gavassini BF, Cagnin S, Ermani M, et al. SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology 2011;76:219-26.
28. Brookes KJ, Hawi Z, Kirley A, Barry E, Gill M, Kent L. Association of the steroid sulfatase (STS) gene with attention deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 2008;147B:1531-5.
29. Tobias ES, Bryce G, Farmer G, Barton J, Colgan J, Morrison N, et al. Absence of learning difficulties in a hyperactive boy with a terminal Xp deletion encompassing the MRX49 locus. J Med Genet 2001;38:466-70.

SEDE DELLA FORMAZIONE

Aula "Montini"
Presidio Spedali Civili di Brescia

P.le Spedali Civili, 1
Brescia (BS)

Per raggiungere la sede dell'incontro con i mezzi pubblici:

Dalla stazione autobus 1, 10, 15
Direzione Mompiano
Fermata Spedali Civili

Regione Lombardia

Progetto Regionale ADHD

Percorso Formativo
PER OPERATORI ADHD

PROF. JOSEPH A. SERGEANT*

FUNZIONI ESECUTIVE E ADHD

** Professore Emerito di*
Clinical Neuropsychology Vrije Universiteit, Amsterdam

22 NOVEMBRE 2012
BRESCIA

PROGRAMMA DELLA GIORNATA

9.00 Inizio dei lavori
Dott. ssa A.Tiberti, Prof.ssa E.Fazzi, Dott.ssa E.Zanettti

9.30
ADHD e dislessia

10.15 discussione

10.30
Il processo attentivo e i suoi disturbi

11.00
Discussione

11.15
Continuos Performance Task
e attenzione sostenuta

11.45
Discussione

12.00
Adhd e discalculia

12.30
Discussione

13.00
pausa pranzo con Tiket
per mensa interna all'ospedale

14.00
ripresa dei lavori.
Presentazione casi clinici e discussione

16.00
Chiusura dei lavori

L'incontro è rivolto agli operatori delle NPI
della **Regione Lombardia**

Appartenenti al progetto
"Condivisione di percorsi diagnostico-terapeutici
per l'ADHD in Lombardia"

Inviare l'adesione con i nominativi
via e-mail all'indirizzo:

daffi.gianluca@gmail.com

specificando:
Nome e cognome dei partecipanti
Centro di riferimento
Funzione all'interno del centro

Non è previsto un numero massimo di partecipanti, si richiede comunque di valutare con attenzione la tematica e le figure professionali cui questo intervento potrebbe essere rivolto.

SEGRETERIA ORGANIZZATIVA:

Servizio Territoriale Npi
Spedali Civili di Brescia

Fax 0303704436

Coordinamento gestionale:

Dott. Gianluca Daffi

daffi.gianluca@gmail.com

LOMBARDIA: QUALCOSA SI MUOVE PER I BAMBINI E GLI ADOLESCENTI CON DISTURBO DA DEFICIT ATTENTIVO E IPERATTIVITÀ

A distanza di un anno dalla attivazione del Registro Regionale dell'ADHD, patologia diffusa tra i bambini e gli adolescenti e nota come disturbo da deficit attenzione con iperattività, è possibile effettuare un primo bilancio.

Nel corso di un anno, i pazienti con ADHD assistiti dai 18 Centri di riferimento sono stati 1129, con una media di 63 per Centro. con una prevalenza nella popolazione lombarda di 1 per mille). In 610 casi la diagnosi di ADHD è stata posta per la prima volta nel corso dell'anno ("nuovi casi"). Solo il 31% dei pazienti con ADHD seguiti dai Centri ha necessitato anche di una terapia farmacologica. Oltre a questi pazienti, altri 257 bambini e adolescenti hanno contattato i Centri di riferimento per sospetta ADHD, ma che non è stata in seguito confermata dalle valutazioni cliniche effettuate.

"Ai Centri arrivano solo una parte degli utenti con ADHD, verosimilmente quelli più complessi o che non riescono ad avere risposte nel territorio di residenza. Presumiamo che almeno altrettanti se non il doppio siano seguiti nelle strutture territoriali delle UONPIA. Il progetto ha permesso di condividere importanti momenti formativi tra Centri e servizi territoriali e per la prima volta di confrontare i percorsi diagnostici e terapeutici previsti dalle Linee Guida con quelli che effettivamente vengono erogati nei Centri, oltre a garantire un importante supporto alle attività cliniche - commenta Antonella Costantino, direttore di uno dei Centri ADHD partecipanti e vicepresidente della Società Italiana di Neuropsichiatria Infantile (SINPIA).
"Queste prime informazioni - afferma Maurizio Bonati, responsabile del Dipartimento di Salute Pubblica dell'Istituto "Mario Negri" e del Registro Regionale - oltre ad essere a tutt'oggi uniche, ci confermano l'importanza di monitorare attentamente l'intero percorso diagnostico e terapeutico per poter rispondere in modo appropriato ai bisogni di salute. Inoltre, sebbene il Centro di riferimento copra solo parte delle richieste di cura, ci dicono che la prevalenza dell'ADHD nella popolazione lombarda è, comunque, considerevolmente inferiore rispetto a quella stimata in altre nazioni; come è considerevolmente inferiore il ricorso alla terapia farmacologica (psicofarmaci) per i pazienti lombardi con ADHD".
Il Registro, creato e gestito dall'Istituto di Ricerche Farmacologiche "Mario Negri" di Milano, è parte di uno dei progetti di neuropsichiatria infantile attivati dalla Direzione Generale Sanità della Regione Lombardia. Il progetto è volto ad intensificare la condivisione dei percorsi diagnostici e terapeutici nelle Unità Operative di Neuropsichiatria dell'Infanzia e dell'Adolescenza (UONPIA) regionali. Partecipano al progetto i 18 Centri regionali accreditati per la cura dell'ADHD e l'Istituto "Mario Negri", capofila è la UONPIA dell'Azienda Ospedaliera "Spedali Civili di Brescia". I principi che hanno guidato la realizzazione del progetto sono così riassumibili:

- La diagnosi di ADHD, e degli altri disturbi con sintomi simili, deve essere effettuata da operatori della salute mentale dell'età evolutiva e deve coinvolgere, sempre e sin dall'inizio, oltre al bambino, i suoi genitori, gli insegnanti e il pediatra di famiglia.
- Il programma di trattamento deve includere consigli e supporto per i genitori e gli insegnanti, oltre a interventi psicologici specifici. La terapia con farmaci deve essere intrapresa solo se indicata da un neuropsichiatra infantile, in accordo con le evidenze scientifiche riconosciute dalla comunità internazionale. Il neuropsichiatra infantile deve anche coordinare e monitorare con gli altri operatori e la famiglia il percorso assistenziale del bambino.
- Una rete stabile di confronto tra i Centri di riferimento è fondamentale per garantire una diagnosi che valuti in modo accurato il disturbo e per fornire un'assistenza adeguata al bambino malato e alla sua famiglia, garantendo la formazione e l'aggiornamento del personale sanitario coinvolto.

La soddisfazione per i primi risultati del progetto sarà ovviamente completa solo con l'estensione del progetto anche alle UONPIA territoriali che sinora non hanno partecipato, così da garantire a tutti i bambini e gli adolescenti con ADHD, e alle loro famiglie, di poter beneficiare delle cure efficaci e condivise su tutto il territorio regionale - conclude Alessandra Tiberti, responsabile del progetto regionale.

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*".

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