NEWSLETTER

INDICE:

BIBLIOGRAFIA ADHD FEBBRAIO 2015

Acad Pediatr. 2015.

ENERGY DRINKS AND YOUTH SELF-REPORTED HYPERACTIVITY/INATTENTION SYMPTOMS.

Schwartz DL, Gilstad-Hayden K, Carroll-Scott A, et al.

Objective: To describe patterns in sweetened beverage consumption by race/ethnicity and sex, documenting both the amount and types of sweetened beverages consumed; and to examine the association of sweetened beverage consumption with hyperactivity/inattention symptoms among middle school students in a single urban school district.

Methods: Middle school students (n=1649; 47% Hispanic and 38% black, non-Hispanic) from 12 schools, randomly selected out of 27 district schools, completed health behavior surveys in fall 2011. Students reported quantity and types of sweetened beverages consumed in the past 24hours and completed the 5-item Hyperactivity/Inattention subscale of the Strengths and Difficulties Questionnaire to measure symptoms.

Results: Amount and variety of reported sweetened beverage consumption (including energy drinks) were greater among boys versus girls and among black and Hispanic versus white students. Risk of hyperactivity/inattention increased by 14% for each additional sweetened beverage consumed, adjusting for age, race/ethnicity, sex, school lunch eligibility, family structure, and sugary food consumption. Students reporting consumption of energy drinks were 66% more likely to be at risk for hyperactivity/inattention after adjusting for number of drinks, other types of drinks consumed, and other potential confounders.

Conclusions: Results support recommendations to limit consumption of sweetened beverages and to avoid consumption of energy drinks among children. Interventions to reduce sweetened beverage consumption should explicitly focus on energy drinks and other emerging sweetened beverages such as sports and sweetened coffee drinks. More research is needed to understand the direction of effects and the mechanisms behind the association between sweetened beverages and hyperactivity/inattention symptoms.

……..

……..

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

Acta Clin Croat. 2014;53:28.

ADHD IN CHILDREN AND EXPOSURE TO ABUSE.

Kralj D, Buljan FG, Coric SR, et al.

A child with ADHD is demanding both to parent and to educate. S/he can have difficulties in social and family relationships, which are often loaded with tension. It is possible that parents do not recognise and understand their child's needs and difficulties, have high expectations the child cannot possibly fulfill and react inadequately due to their own frustration. Therefore, children with ADHD are at risk of inadequate parenting, parental neglect and abuse. Data from the clinical practice of the Child Protection Center of Zagreb are presented in this paper and include exposure of children with ADHD syndrome (N=530) to inadequate parenting, parental neglect and abuse. They also include an analysis attempting to determine the existence of some specific factors both in the parents and in the children, which may be risk factors for the exposure of children with ADHD to the aforementioned parental behaviours. Descriptive statistics was used for data processing and nonparametric procedures were used for the analysis. Results show that among the children with ADHD, the level of parents' education, divorce, child's gender and the loss of a close person, are the variables which may help differentiate between the children exposed to a certain type of inadequate parenting, as compared to children who are not exposed to such parenting. With regard to the obtained data, we reviewed general guidelines for work with parents of children with ADHD syndrome.

……..

Acta Clin Croat. 2014;53:27.

GROUP TREATMENT OF CHILDREN WITH ADHD.

Koren D, Gajski M.

ADHD is a neurodevelopmental disorder of inadequately controlled behavior that affects about 3-6% of the population and it is more common between male children. Due to it's relatively high prevalence, it is a major obstacle for children with ADHD, their families and the entire educational system. Through child's development different symptoms of ADHD become more or less visible. The most important is to prevent and reduce all the extra null nonspecific null symptoms that are comorbid to ADHD, such as bad self image, low self-esteem, aggression, poor school performance, social withdrawal, inadequate strategies to cope with stress, etc. Children with ADHD have problems in social skills and because of this problem they are often rejected from other children and negatively labeled in classroom environment. Looking from this point of view, the ideal intervention for them is to participate in group workshops with many different topics helping them to understand social situations and also to know that there are other children with similar problems and feelings. Considering that ADHD children are often confused with their own aggressive energy and that they have behavioral problems and problems in relationships with others, it is important to give them an opportunity to express their energy and experience, project, accept and express their emotions in a safe way. This helps ADHD children to develop social skills and feelings of being accepted, this helps them to learn adequate mechanisms how to solve a problem and how to cope with stressful situations, how to recognize and resolve conflicts in a socially acceptable way, how to change their behaviour, establish a better self-control, etc. Children with ADHD have difficulties to generalize learned, they rapidly lose their motivation for harder, uninteresting, long-lasting tasks, which is also a big challenge for parents, school staff, therapists and other professionals. That is why professionals should put an effort to find a way how to set realistic and achievable goals in the treatment children with ADHD.

……..

Acta Clin Croat. 2014;53:25.

ADHD-TRUTHS AND FABLES.

Kocijan HD.

Since 1884. to today we can find the diagnosis ADHD in literature and in much research under different name: Sturwelpeter, restless Philip, defect of moral control, minimal cerebral dysfunction and since 1960. ADHD. The evaluation of diagnosis changes though classification from the appearance of the first symptoms, how many criteria must be present. Today we have more and more children with the ADHD. Many authors connect this with a better understanding and recognizing symptomatology. Others think that the professionals give the diagnosis

without equall criteria and under that diagnosis we can find many different disorders and illnesses. There isn't the same attitude in relation of prevalence either. In the most cases in school children we can find the presence of ADHD between 2-12%, sometimes up to 20%. In relation to etiology we can find numerous factors that depend on their basic education and professions, like social, psychological, biological and genetic. This is very important because on this depends the therapeutic approach. Because of different etiology and similar symptoms the obligation of professionals is to do an algorithm for diagnosis and therapy.

……..

Acta Clin Croat. 2014;53:26.

CONCLUSIONS FROM NULLROUND TABLENULLA MULTIDISCIPLINARY APPROACH IN THE DETECTION, DIAGNOSIS AND TREATMENT OF CHILDREN WITH ADHD.

Hercigonja N, V, Kocijan HD.

The authors present the conclusions from the nullRound tablenull which was held with the aim of findind the equall methods and diagnostic criteria for ADHD disorder. Previous experiences indicate unsteadiness of the diagnostic of ADHD disorder which offten results with inadequate therapeutic approaches such as stigmatization of these children which leads to numerous emotional problems for them, from leaving school to development of behavior disorders. Mental health professionals presented their vision of problem children and adolescents with ADHD disorder, and found same attitude to acceptance equall algorith for diagnosis and therapy which exists in many countries across Europe and in the whole world. The next step as the result of the nullRound tablenull are seminar for professionals and teachers to teach them how to better identify the problem and through their optimal approach enable the children with ADHD to use all their capaticy and not to develop numerous behavioral disorders.

……..

Acta Neuropsychol. 2014;12:445-58.

PREDICTORS OF CHANGE IN SHORT-TERM MEMORY SPAN FOLLOWING WORKING MEMORY TRAINING.

Hunt AD, Kronenberger WG, Dunn DW, et al.

Background: Computer-based working memory training exercises produce improvements in performance on ability measures that are similar to the trained tasks (near-transfer), but results have been inconsistent regarding generalization of training outcomes to other abilities and behaviors, particularly those reflecting symptoms of attention deficit/ hyperactivity disorder (ADHD). In contrast to the growing body of efficacy research in this area, almost no studies have systematically investigated characteristics of subjects that predict response to working memory training. This study is an investigation of subject characteristics that predicted change in near-transfer immediate memory span performance following working memory training.

Methods: Children and adolescents aged 9-16 years (N=62) with a broad range of reported symptoms of attention-deficit/hyperactivity disorder (ADHD) completed working memory training for a 25-day period. Assessments of verbal and visual working memory span and ADHD symptoms were completed at the beginning and end of working memory training.

Results: Greater improvement in working memory span from baseline to post-training was predicted by poorer memory span, more hyperactivity- impulsivity symptoms, and fewer inattention symptoms at the baseline.

Conclusions: For baseline memory span and hyperactivity-impulsivity symptoms, study results are consistent with a remediation or rehabilitation model in which working memory training produces more near-transfer improvement for individuals who have more baseline delay or impairment. However, the opposite relationship was found for inattention, perhaps because poor attention skills interfere with the ability to actively engage in working memory training. Clinically, this information may be useful for identifying individuals who are more likely to benefit from working memory training.

……..

ADHD Atten Deficit Hyperact Disord. 2015.

CHILD IMPACT ON FAMILY FUNCTIONING: A MULTIVARIATE ANALYSIS IN MULTIPLEX FAMILIES WITH CHILDREN AND MOTHERS BOTH AFFECTED BY ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Fleck K, Jacob C, Philipsen A, et al.

ADHD seriously impacts family functioning, even the more in families with simultaneous parental and child ADHD. The aim of the study was to examine associations between family impact of child ADHD and child, mother and family characteristics in multiplex families with children and mothers both affected by ADHD. One hundred and forty-four mothernullchild pairs were assessed (children: mean age 9.4 (plus or minus) 1.7 years, 73.6 % male). Family impact of child ADHD was rated by mothers using the Family Impact Questionnaire (FIQ). Multiple linear regression analyses were performed with child and maternal psychopathology and basic family characteristics such as employment, partnership status and number of children as predictors and FIQ subscores as criteria. Rates of variance explained by family variables were 49 % for negative feelings towards the child, 37 % for impact on partnership, 31 % for impact on social life and 27 % for impact on finances ($p < .001$, respectively). Pearson correlations with family impact were especially strong for child externalizing symptoms, maternal ADHD and co-morbid symptoms of the mother. The strongest independent predictor was oppositional defiant child behaviour. In ADHD multiplex families, mothersnull perception of the impact of an ADHD child on its family can be explained to a substantial degree by child psychopathology, maternal psychopathology and basic family characteristics. Although a cross-sectional design does not allow for causal interpretations, the findings of this study offer important targets for the treatment of ADHD in a family context pointing to the need for assessing and treating parental mental health and co-morbid symptoms besides ADHD core symptoms.

……..

Am J Med Genet Part B Neuropsychiatr Genet. 2015;168:89-96.

AN ASSOCIATION BETWEEN A DOPAMINE TRANSPORTER GENE (SLC6A3) HAPLOTYPE AND ADHD SYMPTOM MEASURES IN NONCLINICAL ADULTS.

Tong JHS, Cummins TDR, Johnson BP, et al.

Previous genetic studies have postulated that attention deficit hyperactivity disorder (ADHD) should be regarded as the extreme end of a set of behavioural traits that can be continuously measured in the general population. The current study adopted a quantitative trait approach to examine the relationship between dopamine gene variants and self-reported ADHD symptoms in 517 nonclinical adults. Although genetic associations with variants of both the dopamine transporter (DAT1; SLC6A3) and D4 receptor (DRD4) genes have been reliably reported in children, results in adults are less consistent. We probed two potentially functional variable number of tandem repeat (VNTR) polymorphisms in the 3'UTR and intron 8 of DAT1, the 10-repeat and 6-repeat alleles of which respectively form a haplotype (10/6 DAT1 haplotype) that is associated with childhood ADHD. We also genotyped the exon 3 VNTR of DRD4, the 7-repeat allele of which is also an established risk factor for childhood ADHD. Permutation analysis showed an influence of the 10/6 DAT1 haplotype on both CAARS-G and CAARS-H (DSM-IV ADHD Symptoms Total and ADHD Index respectively), such that ADHD symptom scores increased with each additional copy of the 10/6 DAT1 haplotype. This result survived corrections for multiple comparisons both at the level of genotype and phenotype. A nominal association with CAARS-G was also found for the 7-repeat allele of the DRD4 VNTR however this did not survive multiple comparison correction. Our results provide further support for the influence of variation in the 10/6 DAT1 haplotype and individual differences in ADHD symptoms in adults.

……..

Am J Med Genet Part B Neuropsychiatr Genet. 2015.

THE ROLE OF AGE IN ASSOCIATION ANALYSES OF ADHD AND RELATED NEUROCOGNITIVE FUNCTIONING: A PROOF OF CONCEPT FOR DOPAMINERGIC AND SEROTONERGIC GENES.

Thissen AJ, Bralten J, Rommelse NN, et al.

Elucidating genetic mechanisms involved in Attention-Deficit/Hyperactivity Disorder (ADHD) has been challenging. Relatively unexplored is the fact that genetic mechanisms can differ with age. The current study explored the association between dopaminergic and serotonergic genes, ADHD symptoms, and neurocognitive functioning in relation to age. Associations of three genetic ADHD risk factors, DAT1, DRD4, and 5-HTT with

symptoms and six neurocognitive measures were explored in two samples of the NeuroIMAGE study: 756 children, adolescents, and young adults with ADHD, their siblings, and controls (M age 17 years, SD 3.2), and 393 parents with and without ADHD (M age 48 years, SD 4.8). Association analyses were performed in both samples, and effects were compared to address dichotomous age effects. Gene*age interactions were examined to address continuous age effects. Moderating effects of age were found for DRD4-7R carriership and ADHD symptoms in the adult group only; in the adolescents the 5-HTT LL genotype was differentially associated with inhibition and with motor timing at different ages, and to inhibition in adults; DAT1 10-6 haplotype carriership showed differential working memory performance depending on age. None of our effects survived correction for multiple comparisons. Our results are preliminary, but may point to differential genotype-phenotype associations at different ages. This can be seen as a proof of concept for the importance of age in dopaminergic and serotonergic genetic association analyses. Our findings are consistent with the idea that genetic and neurocognitive mechanisms underlying ADHD may change throughout life.

……..

American Journal on Intellectual and Developmental Disabilities. 2015 Jan;120:1-14.

SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN DOWN SYNDROME: EFFECTS OF THE DOPAMINE RECEPTOR D4 GENE.

Mason GM, Spanó G, Edgin J.

This study examined individual differences in ADHD symptoms and executive function (EF) in children with Down syndrome (DS) in relation to the dopamine receptor D4 (DRD4) gene, a gene often linked to ADHD in people without DS. Participants included 68 individuals with DS (7-21 years), assessed through laboratory tasks, caregiver reports, and experimenter ratings. Saliva samples were collected from the DS group and 66 children without DS to compare DRD4 allele distribution, showing no difference between the groups. When the sample with DS was stratified for ethnicity (n = 32), the DRD4 7-repeat allele significantly related to parent and experimenter ratings, but not to laboratory assessments. These results suggest that nontrisomy genetic factors may contribute to individual differences in ADHD symptoms in persons with DS.

……..

Behav Genet. 2014;44:646.

PERSISTENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS THROUGH ADOLESCENCE.

Anderson A, Elkins I, Iacono W, et al.

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders: according to the CDC, 5 % of American children are affected. Once diagnosed exclusively in children, ADHD is now increasingly thought of as a potentially life-long disorder. The DSM-V altered the diagnostic criteria for ADHD to be more adult-friendly, and new medications are being marketed specifically to sufferers of nulladult ADHD.null But ADHD in adults is not a separate disorder-the DSM-V still requires onset of symptoms before age 12 for diagnosis. The extent to which genetic factors contribute to persistent (adult) ADHD is not yet well established: some clinical studies have reported that persistent ADHD may be more heritable than ADHD in general (Faraone 2004), while many studies of adult twins show decreasing heritability of ADHD with age (Kan et al. 2013), and others show consistent heritability over time (Chang, Lichtenstein, Asherson, & Larsson 2013). The goal of this ongoing study is to observe the trajectory of ADHD symptom persistence (and remittance) through adolescence: 1. Does genetic contribution to ADHD increase (or diminish) as individuals approach adulthood? 2. Are the same genetic factors that contribute to ADHD symptoms in children still contributing to those symptoms in late adolescence? 3. Can ADHD patients be neatly divided into nullpersistentnull and nullremittentnull groups, or is there no clear dividing line between the two? Participants were 486 same-sex twin pairs from the Minnesota Center for Twin & Family Research nullEnrichment Sample.null Initial results suggest high, stable heritability of ADHD symptoms through adolescence.

……..

Behavior Modification. 2015 Jan;39:191-214.

BRIEF EXPERIMENTAL ANALYSIS OF READING DEFICITS FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Fienup DM, Reyes-Giordano K, Wolosik K, et al.

Reading difficulties are especially high among children with attention-deficit/hyperactivity disorder (ADHD). Although there are a number of empirically supported reading interventions for children with ADHD, there is little data to guide the selection of the most efficacious reading intervention for a specific child. Brief experimental analysis (BEA) is a procedure that directly compares the efficacy of various academic interventions with the goal of guiding the selection of the intervention that results in optimal efficacy. The current proof of concept study examined the efficacy of the BEA methodology for determining the relative effectiveness of seven reading interventions for children with ADHD. The seven interventions included empirically supported ADHD interventions as well as traditional interventions found in the BEA literature. Six children diagnosed with ADHD completed the proof of concept study. Results indicated that the BEA successfully determined an efficacious intervention for each participant. The efficacy of the interventions and the optimal intervention based on BEA procedures varied for each child, suggesting the importance of a BEA approach when comparing various interventions for reading in children with ADHD. Implications and future directions for selecting effective reading interventions for children with ADHD are discussed.

……..

Biol Psychiatry. 2014;76:664-71.

GENETIC RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER CONTRIBUTES TO NEURODEVELOPMENTAL TRAITS IN THE GENERAL POPULATION.

Martin J, Hamshere ML, Stergiakouli E, et al.

Background Attention-deficit/hyperactivity disorder (ADHD) can be viewed as the extreme end of traits in the general population. Epidemiological and twin studies suggest that ADHD frequently co-occurs with and shares genetic susceptibility with autism spectrum disorder (ASD) and ASD-related traits.

The aims of this study were to determine whether a composite of common molecular genetic variants, previously found to be associated with clinically diagnosed ADHD, predicts ADHD and ASD-related traits in the general population.

Methods Polygenic risk scores were calculated in the Avon Longitudinal Study of Parents and Children (ALSPAC) population sample (N = 8229) based on a discovery case-control genome-wide association study of childhood ADHD. Regression analyses were used to assess whether polygenic scores predicted ADHD traits and ASD-related measures (pragmatic language abilities and social cognition) in the ALSPAC sample. Polygenic scores were also compared in boys and girls endorsing any (rating (greater-than or equal to)1) ADHD item (n = 3623).

Results Polygenic risk for ADHD showed a positive association with ADHD traits (hyperactive-impulsive, p =.0039; inattentive, p =.037). Polygenic risk for ADHD was also negatively associated with pragmatic language abilities (p =.037) but not with social cognition (p =.43). In children with a rating (greater-than or equal to)1 for ADHD traits, girls had a higher polygenic score than boys (p =.003).

Conclusions These findings provide molecular genetic evidence that risk alleles for the categorical disorder of ADHD influence hyperactive-impulsive and attentional traits in the general population. The results further suggest that common genetic variation that contributes to ADHD diagnosis may also influence ASD-related traits, which at their extreme are a characteristic feature of ASD.

……..

Biol Psychiatry. 2014;76:629-38.

WIDESPREAD REDUCTIONS IN CORTICAL THICKNESS FOLLOWING SEVERE EARLY-LIFE DEPRIVATION: A NEURODEVELOPMENTAL PATHWAY TO ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

McLaughlin KA, Sheridan MA, Winter W, et al.

Background Children exposed to early-life psychosocial deprivation associated with institutional rearing are at markedly elevated risk of developing attention-deficit/hyperactivity disorder (ADHD). Neurodevelopmental

mechanisms that explain the high prevalence of ADHD in children exposed to institutionalization are unknown. We examined whether abnormalities in cortical thickness and subcortical volume were mechanisms explaining elevations in ADHD among children raised in institutional settings.
Methods Data were drawn from the Bucharest Early Intervention Project, a cohort of children raised from early infancy in institutions in Romania (n = 58) and age-matched community control subjects (n = 22). Magnetic resonance imaging data were acquired when children were aged 8 to 10 years, and ADHD symptoms were assessed using the Health and Behavior Questionnaire.
Results Children reared in institutions exhibited widespread reductions in cortical thickness across prefrontal, parietal, and temporal regions relative to community control subjects. No group differences were found in the volume of subcortical structures. Reduced thickness across numerous cortical areas was associated with higher levels of ADHD symptoms. Cortical thickness in lateral orbitofrontal cortex, insula, inferior parietal cortex, precuneus, superior temporal cortex, and lingual gyrus mediated the association of institutionalization with inattention and impulsivity; additionally, supramarginal gyrus thickness mediated the association with inattention and fusiform gyrus thickness mediated the association with impulsivity.
Conclusions Severe early-life deprivation disrupts cortical development resulting in reduced thickness in regions with atypical function during attention tasks in children with ADHD, including the inferior parietal cortex, precuneus, and superior temporal cortex. These reductions in thickness are a neurodevelopmental mechanism explaining elevated ADHD symptoms in children exposed to institutional rearing.

……..

BMJ (Online). 2015;350.

IMPACT OF A BEHAVIOURAL SLEEP INTERVENTION ON SYMPTOMS AND SLEEP IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER, AND PARENTAL MENTAL HEALTH: RANDOMISED CONTROLLED TRIAL.

Hiscock H, Sciberras E, Mensah F, et al.

Objective: To examine whether behavioural strategies designed to improve children's sleep problems could also improve the symptoms, behaviour, daily functioning, and working memory of children with attention deficit hyperactivity disorder (ADHD) and the mental health of their parents.
Design: Randomised controlled trial.
Setting: 21 general paediatric practices in Victoria, Australia.
Participants: 244 children aged 5-12 years with ADHD attending the practices between 2010 and 2012.
Intervention: Sleep hygiene practices and standardised behavioural strategies delivered by trained psychologists or trainee paediatricians during two fortnightly consultations and a follow-up telephone call. Children in the control group received usual clinical care.
Main outcome measures: At three and six months after randomisation: severity of ADHD symptoms (parent and teacher ADHD rating scale IV - primary outcome), sleep problems (parent reported severity, children's sleep habits questionnaire, actigraphy), behaviour (strengths and difficulties questionnaire), quality of life (pediatric quality of life inventory 4.0), daily functioning (daily parent rating of evening and morning behavior), working memory (working memory test battery for children, six months only), and parent mental health (depression anxiety stress scales).
Results: Intervention compared with control families reported a greater decrease in ADHD symptoms at three and six months (adjusted mean difference for change in symptom severity -2.9, 95% confidence interval -5.5 to -0.3, P=0.03, effect size -0.3, and -3.7, -6.1 to -1.2, P=0.004, effect size -0.4, respectively). Compared with control children, intervention children had fewer moderate-severe sleep problems at three months (56% v 30%; adjusted odds ratio 0.30, 95% confidence interval 0.16 to 0.59; P<0.001) and six months (46% v 34%; 0.58, 0.32 to 1.0; P=0.07). At three months this equated to a reduction in absolute risk of 25.7% (95% confidence interval 14.1% to 37.3%) and an estimated number needed to treat of 3.9. At six months the number needed to treat was 7.8. Approximately a half to one third of the beneficial effect of the intervention on ADHD symptoms was mediated through improved sleep, at three and six months, respectively. Intervention families reported greater improvements in all other child and family outcomes except parental mental health. Teachers reported improved behaviour of the children at three and six months. Working memory (backwards digit recall) was higher in the intervention children compared with control children at six months. Daily sleep duration measured by actigraphy tended to be higher in the intervention children at three months (mean difference 10.9 minutes, 95% confidence interval -19.0 to 40.8 minutes, effect size 0.2) and six months (9.9 minutes, -16.3 to 36.1 minutes, effect size

0.3); however, this measure was only completed by a subset of children (n=54 at three months and n=37 at six months).
Conclusions: A brief behavioural sleep intervention modestly improves the severity of ADHD symptoms in a community sample of children with ADHD, most of whom were taking stimulant medications. The intervention also improved the children's sleep, behaviour, quality of life, and functioning, with most benefits sustained to six months post-intervention. The intervention may be suitable for use in primary and secondary care. Trial registration Current Controlled Trials ISRCTN68819261.

……..

BMJ Open. 2015;5.

ELECTROENCEPHALOGRAPHY AS A CLINICAL TOOL FOR DIAGNOSING AND MONITORING ATTENTION DEFICIT HYPERACTIVITY DISORDER: A CROSS-SECTIONAL STUDY.

Helgadottir H, Gudmundsson OO, Baldursson G, et al.

Objectives: The aim of this study was to develop and test, for the first time, a multivariate diagnostic classifier of attention deficit hyperactivity disorder (ADHD) based on EEG coherence measures and chronological age.
Setting: The participants were recruited in two specialised centres and three schools in Reykjavik.
Participants: The data are from a large cross-sectional cohort of 310 patients with ADHD and 351 controls, covering an age range from 5.8 to 14 years. ADHD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria using the K-SADS-PL semistructured interview. Participants in the control group were reported to be free of any mental or developmental disorders by their parents and had a score of less than 1.5 SDs above the age-appropriate norm on the ADHD Rating Scale-IV. Other than moderate or severe intellectual disability, no additional exclusion criteria were applied in order that the cohort reflected the typical cross section of patients with ADHD.
Results: Diagnostic classifiers were developed using statistical pattern recognition for the entire age range and for specific age ranges and were tested using cross-validation and by application to a separate cohort of recordings not used in the development process. The age-specific classification approach was more accurate (76% accuracy in the independent test cohort; 81% cross-validation accuracy) than the age-independent version (76%; 73%). Chronological age was found to be an important classification feature.
Conclusions: The novel application of EEG-based classification methods presented here can offer significant benefit to the clinician by improving both the accuracy of initial diagnosis and ongoing monitoring of children and adolescents with ADHD. The most accurate possible diagnosis at a single point in time can be obtained by the age-specific classifiers, but the age-independent classifiers are also useful as they enable longitudinal monitoring of brain function.

……..

Brain Stimul. 2015;8:299-304.

AN EIGHT-WEEK, OPEN-TRIAL, PILOT FEASIBILITY STUDY OF TRIGEMINAL NERVE STIMULATION IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

McGough JJ, Loo SK, Sturm A, et al.

Background: This study examined the potential feasibility and utility of trigeminal nerve stimulation (TNS) for attention-deficit/hyperactivity disorder (ADHD) in youth.
Methods: Twenty-four participants ages 7-14 with ADHD enrolled in an 8-week open trial of TNS administered nightly during sleep, and were assessed weekly with parent- and physician-completed measures of ADHD symptoms and executive functioning as well as measures of treatment compliance, adverse events, and side effects. Computerized tests of cognitive functioning were administered at baseline and weeks 4 and 8.
Results: Significant improvements were seen on the ADHD-IV Rating Scale (P <.0001) and parent-completed Conners Global Index (P <.0001), as well as the majority of scales on the parent-completed Behavior Rating Inventory of Executive Functioning (BRIEF). Improvements were also noted on the computerized Attention Network Task (ANT) Incongruent Reaction Time (P =.006), suggesting that TNS has positive effects on response inhibition.

Conclusions: TNS therapy for youth with ADHD appears to be both feasible and without significant risk. Subjective improvements on rating scales and laboratory measures of cognition suggest a potential role for TNS in treating ADHD that merits further investigation. Future research in anticipation of designing definitive controlled efficacy trials should evaluate time to onset of TNS response and durability of treatment effects following TNS discontinuation, as well as validate an effective active sham comparator suitable for blinded studies.

……..

Bratisl Lek Listy. 2014;115:635-42.

CORRELATIONS OF ADHD SYMPTOMS WITH NEUROMETABOLITES MEASURED BY 1H MAGNETIC RESONANCE SPECTROSCOPY.

Husarova V, Bittsansky M, Ondrejka I, et al.

OBJECTIVES: Despite the number of studies on neurometabolite changes in ADHD (Attention deficit/hyperactivity disorder), there is lack of evidence on neurometabolite associations with ADHD symptoms.
BACKGROUND: We aimed to find the correlations of neurometabolites with ADHD symptoms.
METHODS: Twenty ADHD children were examined by means of 1H-MRS. The spectra were taken from dorsolateral prefrontal cortex (DLPFC) and white matter behind DLPFC, bilaterally. Neurometabolites were correlated with ADHD-RS-IV (ADHD-Rating Scales IV), CPRS (Conners Parent rating Scale) and DPREMB (Daily Parent Rating of Evening and Morning Behavior) scores.
RESULTS: NAA/Cr (N-acetylaspartate/creatine) in the right DLPFC positively correlated with CPRS subscale IV learning problems and negatively correlated in the left white matter with DPREMB morning behavior subscale and ADHD-RS-IV score. Glx/Cr (glutamate + glutamine/creatine) positively correlated in the right white matter with ADHD-RS-IV and negatively correlated in the left white matter with DPREMB morning behavior subscale score. Cho/Cr (choline/creatine) in the left white matter negatively correlated with DPREMB morning behavior subscale and ADHD-RS-IV score.
CONCLUSION: ADHD symptoms could result from different activities of the left- and right-hemisphere prefrontal circuits. In consequence to impulses to novel task searching the increased right prefrontal circuit activity could be mediated by different motivational control (Fig. 9, Ref. 73).

……..

Can J Psychiatry. 2015;60:42-51.

THE PHARMACOLOGICAL MANAGEMENT OF OPPOSITIONAL BEHAVIOUR, CONDUCT PROBLEMS, AND AGGRESSION IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER, OPPOSITIONAL DEFIANT DISORDER, AND CONDUCT DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS. PART 1: PSYCHOSTIMULANTS, ALPHA-2 AGONISTS, AND ATOMOXETINE.

Pringsheim T, Hirsch L, Gardner D, et al.

Objective: Children with attention-deficit hyperactivity disorder (ADHD) may have oppositional behaviour, conduct problems, and aggression. These symptoms vary in severity, and may be related to a comorbid diagnosis of oppositional defiant disorder (ODD) or conduct disorder (CD). Critical evaluation of the efficacy of ADHD medications may guide the clinician regarding the usefulness of medications for these symptoms.
Method: We performed a systematic review and meta-analysis of psychostimulants, alpha-2 agonists, and atomoxetine for oppositional behaviour, conduct problems, and aggression in youth with ADHD, ODD, and CD. The quality of evidence for medications was rated using the Grading of Recommendations Assessment, Development and Evaluation approach.
Results: Two systematic reviews and 20 randomized controlled trials were included. There is high-quality evidence that psychostimulants have a moderate-to-large effect on oppositional behaviour, conduct problems, and aggression in youth with ADHD, with and without ODD or CD. There is very-low-quality evidence that clonidine has a small effect on oppositional behaviour and conduct problems in youth with ADHD, with and without ODD or CD. There is moderate-quality evidence that guanfacine has a small-to-moderate effect on oppositional behaviour in youth with ADHD, with and without ODD. There is high-quality evidence that atomoxetine has a small effect on oppositional behaviour in youth with ADHD, with and without ODD or CD.

Conclusions: Evidence indicates that psychostimulants, alpha-2 agonists, and atomoxetine can be beneficial for disruptive and aggressive behaviours in addition to core ADHD symptoms; however, psychostimulants generally provide the most benefit.

……..

Can J Psychiatry. 2015;60:62-76.

CANADIAN GUIDELINES ON PHARMACOTHERAPY FOR DISRUPTIVE AND AGGRESSIVE BEHAVIOUR IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER, OPPOSITIONAL DEFIANT DISORDER, OR CONDUCT DISORDER.

Gorman DA, Gardner DM, Murphy AL, et al.

Objective: To develop evidence-based guidelines on pharmacotherapy for severe disruptive and aggressive behaviour in children and adolescents with attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), or conduct disorder (CD). The guidelines assume that psychosocial interventions have been pursued but did not achieve sufficient improvement.

Method: A multidisciplinary consensus group used the Grading of Recommendations Assessment, Development and Evaluation approach for rating evidence quality and for grading recommendations. We conducted a systematic review of medications studied in placebo-controlled trials for treating disruptive and aggressive behaviour in children and adolescents with ADHD, ODD, or CD. We followed consensus procedures to make 1 of 4 recommendations for each medication: strong, in favour ((up arrow)(up arrow)); conditional, in favour ((up arrow)?); conditional, against ((down arrow)?); and strong, against ((down arrow)(down arrow)).

Results: For children and adolescents with disruptive or aggressive behaviour associated with ADHD, psychostimulants received a strong recommendation in favour of use, while atomoxetine and alpha-2 agonists received a conditional recommendation in favour of use. If these patients do poorly with ADHD medications, the medication with the most evidence is risperidone. Risperidone also has the most evidence for treating disruptive or aggressive behaviour in the absence of ADHD. However, given risperidone's major adverse effects, it received only a conditional recommendation in favour of use. We recommended against using quetiapine, haloperidol, lithium, or carbamazepine because of the poor quality of evidence and their major adverse effects.

Conclusion: When severe disruptive or aggressive behaviour occurs with ADHD, medications for ADHD should be used first. Other medications have major adverse effects and, with the exception of risperidone, very limited evidence to support their use.

……..

Child Adolesc Psychiatr Clin North Am. 2014;23:699-715.

MIDDLE SCHOOL-BASED AND HIGH SCHOOL-BASED INTERVENTIONS FOR ADOLESCENTS WITH ADHD.

Evans SW, Langberg JM, Egan T, et al.

……..

Child Adolesc Psychiatry Ment Health. 2014 Dec;8.

EFFECTS OF METHYLPHENIDATE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: A NEAR-INFRARED SPECTROSCOPY STUDY WITH CANTAB®.

Matsuura N, Ishitobi M, Arai S, et al.

Background: A wide range of evidence supports the methylphenidate (MPH)-induced enhancement of prefrontal cortex (PFC) functioning and improvements in behavioral symptoms in patients with attention deficit hyperactivity disorder (ADHD). Although working memory (WM) has been hypothesized to be impaired in patients with ADHD, no pharmacological studies have examined visuospatial WM (VSWM) with near-infrared spectroscopy (NIRS).

Study aim: The present study was designed to investigate the acute effects of MPH on neuropsychological performance and hemodynamic activation in children with ADHD during VSWM tasks.

Methods: The subject group included 10 boys and 1 girl previously diagnosed with ADHD. Two VSWM tasks of differing degrees of difficulty were conducted. This is the first study on the pharmacological effects of MPH in children with ADHD to evaluate hemodynamic responses in the PFC with simultaneous NIRS.
Results: No significant differences were found in the scores for both spatial working memory (SWM) and score of spatial span (SSP) tasks between the MPH-off and MPH–on conditions. However, a significant MPH-effect on changes in oxy-hemoglobin levels in the PFC was found only in the SWM task.
Conclusion: These findings suggest that PFC activation might be affected by MPH, depending on the degree of difficulty of the particular task. Although the MPH-induced change on behavior may or may not be obvious, NIRS measurements might be useful for assessing the psychological effects of MPH even when performance changes were not observed in the cognitive tasks.

……..

Child Adolesc Psychiatry Ment Health. 2015 Jan;9.

CROSS-SECTIONAL SURVEY ON PREVALENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS AT A TERTIARY CARE HEALTH FACILITY IN NAIROBI.

Wamithi S, Ochieng R, Njenga F, et al.

Background: Attention deficit hyperactivity disorder is the most common childhood neurobehavioral disorder with well documented adverse consequences in adolescence and adulthood, yet 60-80% of cases go undiagnosed. Routine screening is not practiced in most pediatric outpatient services and little information exists on factors associated with the condition in developing countries.
Methods: This was a questionnaire based cross-sectional survey whose primary objective was to determine prevalence of attention deficit hyperactivity disorder (ADHD) symptoms in children aged 6-12 years attending a tertiary care hospital Accidents and Emergency unit. Secondary objectives were to: (i) ascertain if physical injury and poor academic performance were associated with ADHD, (ii) compare diagnostic utility of parent-filled Vanderbilt Assessment Scale (VAS) against Statistical Manual of Mental Disorders-IV (DSM-IV) as the gold reference and (iii) establish if there exists an association between ADHD symptoms cluster and co-morbid conditions.
Results: Prevalence of cluster of symptoms consistent with ADHD was 6.3% (95% CI; 3.72-10.33) in 240 children studied. Those affected were more likely to repeat classes than the asymptomatic (OR 20.2; 95% CI 4.02-100.43). Additionally, 67% of the symptomatic had previously experienced burns and 37% post-traumatic open wounds. The odds of having an injury in the symptomatic was 2.9 (95% CI; 1.01-8.42) compared to the asymptomatic. Using DSM-IV as reference, VAS had a sensitivity of 66.7% (95%; CI 39.03-87.12) and specificity of 99.0% (95% CI; 96.1-99.2). Positive predictive value was 83.0% (95% CI; 50.4-97.3) and negative predictive value 98.0% (CI 95.1-99.1). Oppositional defiant disorder symptoms, anxiety, depression and conduct problems were not significantly associated with ADHD cluster of symptoms.
Conclusion: The study found a relatively high prevalence of symptoms associated with ADHD. Symptomatic children experienced poor school performance. These findings support introduction of a policy on routine screening for ADHD in pediatric outpatient service. Positive history of injury and poor academic performance should trigger further evaluation for ADHD. Vanderbilt assessment scale is easier to administer than DSM-IV but has low sensitivity and high specificity that make it inappropriate for screening. It however provides a suitable alternative confirmatory test to determine who among clinically symptomatic patients requires referral to a psychiatrist.

……..

Child Development. 2015 Jan;86:224-40.

PARENTAL INVOLVEMENT MODERATES ETIOLOGICAL INFLUENCES ON ATTENTION DEFICIT HYPERACTIVITY DISORDER BEHAVIORS IN CHILD TWINS.

Nikolas MA, Klump KL, Burt SA.

Although few would now contest the presence of Gene × Environment (G × E) effects in the development of child psychopathology, it remains unclear how these effects manifest themselves. Alternative G × E models have been proposed (i.e., diathesis–stress, differential susceptibility, bioecological), each of which has notably

different implications for etiology. Child twin studies present a powerful tool for discriminating between these models. The current study examined whether and how parental involvement moderated etiological influences on attention deficit hyperactivity disorder (ADHD) within 500 twin pairs aged 6–11 years. Results indicated moderation of genetic and nonshared environmental contributions to ADHD by parental involvement, and moreover, suggested both differential susceptibility and bioecological models of G × E. Results highlight the utility of child twin samples in testing different manifestations of G × E effects.

……..

Child Psychiatry Hum Dev. 2015 Feb;46:118-29.

THE ASSOCIATION BETWEEN PARENTING STRESS, PARENTING SELF-EFFICACY, AND THE CLINICAL SIGNIFICANCE OF CHILD ADHD SYMPTOM CHANGE FOLLOWING BEHAVIOR THERAPY.

Heath CL, Curtis DF, Fan W, et al.

We examined parenting stress (PST) and self-efficacy (PSE) following participation in behavioral parent training (BPT) with regard to child treatment response. Forty-three families of children diagnosed with ADHD participated in a modified BPT program. Change in PST and PSE was evaluated using a single group, within-subjects design. Parenting outcomes based on child treatment response were evaluated based upon (1) magnitude and (2) clinical significance of change in child symptom impairment. Parents reported significant improvements in stress and self-efficacy. Parents of children who demonstrated clinically significant reduction in ADHD symptoms reported lower stress and higher self-efficacy than those of children with continued impairments. Magnitude of child impairment was not associated with parent outcomes. Clinical implications for these results include

extending treatment duration to provide more time for symptom amelioration and parent-focused objectives to improve coping and stress management.

……..

Child Psychiatry Hum Dev. 2015 Feb;46:67-74.

ASSOCIATION BETWEEN INTERNALIZING DISORDERS AND DAY-TO-DAY ACTIVITIES OF LOW ENERGETIC EXPENDITURE.

Gosmann NP, Salum GA, Schuch F, et al.

The objective of this study is to compare energetic expenditure in day-to-day activities among subjects with internalizing disorders (depression and anxiety), externalizing disorders (attention deficit/hyperactivity disorder and oppositional defiant disorder) and healthy children and adolescents without any psychiatric diagnosis. One hundred and five (n = 105) students from a community sample were evaluated throughout a structured psychiatric interview and categorized into three groups: internalizing (n = 54), externalizing (n = 12) and typically developing controls (TDC, n = 39). Energetic expenditure was evaluated using 3-day physical activity record. Subjects with internalizing disorders performed activities with lower energetic expenditure as compared to those with externalizing disorders and TDC. Participants with externalizing disorders had more energetic expenditure variability. Our study suggests that internalizing disorders are associated with activities of low energetic expenditure in day-to-day activities, extending previous findings with physical exercise. These findings may further contribute to the understanding of the associated morbidity previously described in patients with internalizing disorders.

……..

Clin Transl Sci. 2014;7:245.

CONSTRUCT VALIDITY OF THE ADHD RATING SCALE-IV IN HIV-EXPOSED UGANDAN CHILDREN.

Burkey MD, McIvor MS, Opoka R, et al.

Objectives/Specific Aims Few studies have examined ADHD-the paradigmatic clinical neurocognitive disorder of childhood-in sub-Saharan Africa (SSA) where risk factors for neurocognitive delay are prevalent. This study aimed to evaluate the construct validity of the ADHD Rating Scale-IV (ADHD-RS-IV) in a group of Ugandan children.

Methods/Study Population Neuropsychological and demographic data were collected in a nonclinical sample of children born to HIV-infected mothers. Internal consistency of the ADHD-RS-IV was assessed with Cronbach's alpha. Construct validity was assessed via exploratory factor analysis (EFA); tests of convergent validity (correlation with executive function (BRIEF) and TOVA ADHD score); and divergent validity (correlation with KABC-II Mental Processing Index (MPI)).
Results/Anticipated Results 179 children (54% female; mean age 7.8 yrs (SD 2.0)) were assessed for ADHD in 2013. The mean score on the ADHD-RS-IV was 12.7 (SD 8.6). Using DSM-IV symptom criteria cutoffs, the point prevalence of ADHD was 6.7%. The ADHD-RS-IV showed good internal consistency (alpha = 0.80.) EFA suggested a one-factor solution (Eigenvalues: F-1 = 4.44, F-2 = 0.63) explaining 81% of the variance. ADHD symptom scores were strongly correlated with the BRIEF ($p < 0.001$) and poorly correlated with the KABC-II MPI ($p = 0.11$) and TOVA ADHD Score ($p = 0.43$).
Discussion/Significace of Impact The ADHD-RS-IV demonstrated good internal consistency, a unitary factor structure, and good convergent validity with measures of executive function, but not with visual performance tasks among Ugandan HIV-exposed children. The one-factor solution differs from international reference samples and raises questions about the validity and transferability of the ADHD construct in SSA.

……..

Clin Neuropharmacol. 2015;38:30-35.

THE RELATIONSHIP BETWEEN SYMPTOMATIC AND FUNCTIONAL CHANGES OF KOREAN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATED WITH OSMOTIC-CONTROLLED RELEASE ORAL DELIVERY SYSTEM-METHYLPHENIDATE.

Kim E, Cheon K-A, Joung YS, et al.

Objectives: This study examined the effect of osmotic-controlled release oral delivery system-methylphenidate (OROS-MPH) on the adaptive functioning of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and investigated the relationship between reduced ADHD symptoms and improvements in functioning and factors that are predictive of functional improvement.
Methods This study was a prospective, multicenter, open-label study of 116 children with ADHD treated with OROS-MPH for 12 weeks. Attention-deficit/hyperactivity disorder symptoms, functional impairment, and other comorbid disorders were evaluated using various clinical scales. Correlational and multiple regression analyses were conducted to examine the relationship between symptomatic versus functional changes after OROS-MPH treatment.
RESULTS: Correlation analysis showed a moderately strong association between changes in the ADHD core symptoms versus functional measure scores ($r = -0.65$). The self-control subscale of the Life Participation Scale showed higher correlations with symptomatic measures than did the happy/social subscale. Functional outcomes were impacted by several factors including the baseline severity of ADHD symptoms, changes in ADHD, and oppositional defiant symptoms after treatment. Attention was more associated with functional outcomes than hyperactivity/impulsivity.
CONCLUSIONS: Treatment with OROS-MPH was associated with symptomatic functional changes that were moderately correlated; therefore, symptomatic functional outcomes appear to be partially overlapped but distinct domains. Consequently, functional measures should be incorporated as important outcome measures in future treatment studies; the importance of treatments targeting functional improvement should be emphasized in the treatment of children with ADHD.

……..

Clin Neurophysiol. 2015;126:532-40.

THE UTILITY OF QUANTITATIVE ELECTROENCEPHALOGRAPHY AND INTEGRATED VISUAL AND AUDITORY CONTINUOUS PERFORMANCE TEST AS AUXILIARY TOOLS FOR THE ATTENTION DEFICIT HYPERACTIVITY DISORDER DIAGNOSIS.

Kim J, Lee Y, Han D, et al.

Objective: This study investigated the clinical utility of quantitative electroencephalography (QEEG) and the Integrated Visual and Auditory Continuous Performance Test (IVA. +. CPT) as auxiliary tools for assessing Attention Deficit Hyperactivity Disorder (ADHD).

Methods: All of 157 subjects were assessed using the Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV). We measured EGG absolute power in 21 channels and conducted IVA. +. CPT. We analyzed QEEG according to the Hz range: delta (1-4. Hz), theta (4-8. Hz), slow alpha (8-10. Hz), fast alpha (10-13.5. Hz), and beta (13.5-30. Hz). To remove artifacts, independent component analysis was conducted (ICA), and the tester confirmed the results again.
Results: All of the IVA. +. CPT quotients showed significant differences between the ADHD and control groups. The ADHD group showed significantly increased delta and theta activity compared with the control group. The z-scores of theta were negatively correlated with the scores of IVA. +. CPT in ADHD combined type, and those of beta were positively correlated.
Conclusions: IVA. +. CPT and QEEG significantly discriminated between ADHD and control groups. The commission error of IVA. +. CPT showed an accuracy of 82.1%, and the omission error of IVA. +. CPT showed an accuracy of 78.6%.
Significance: The IVA. +. CPT and QEEG are expected to be valuable tools for aiding ADHD diagnosis accurately.

……..

Clin Pharmacol Ther. 2015;97:S97.

SINGLE DOSE PHARMACOKINETICS OF ATOMOXETINE IN CHILDRENWITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) STRATIFIED BY THEIR CYP2D6 ACTIVITY SCORE (AS).

Brown JT, Abdel-Rahman SM, Van HL, et al.

BACKGROUND: The objective of this study was to determine the magnitude of effect of CYP2D6 genotype on atomoxetine (ATX) systemic exposure in children with ADHD.
METHODS: A single 0.4360.07 mg/kg dose of ATX was administered to 23 children aged 6-17 years of age with CYP2D6 activity scores of 0 (n=4; PM), 0.5 (n=3; IM), 1 (n=8; EM1) and 2 (n=8; EM2) after an overnight fast. Plasma was obtained at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours after dosing; two additional samples at 48 and 72 hr were obtained in PMs. ATX was measured by LC/MS/MS. Area under the curve (AUC) was calculated using the mixed log linear method and extrapolated to infinity AUC. ANOVA and Tukey's HSD were used for statistical comparisons.
RESULTS: CYP2D6 alleles found in the study patients were null1, null2, null2x2, null3, null4, null5, null9, null10, null17, and null29. Dose (mg/kg)-corrected AUC varied 25.8-fold across the study cohort, and was 2.5-fold higher in PMs (60.0610.9 (mu)Mnullh) compared to IMs (24.068.8 (mu)Mnullh; p<0.0001), and 8.5- to 10.8-fold greater than the EM1 (7.1617 (mu)Mnullh; p<0.001) and EM2 groups (5.662.3 (mu)Mnullh; p<0.0001), respectively (Figure).
CONCLUSION: Weight-based dosing of ATX is associated with a 25-fold range of systemic exposure in a treated population. CYP2D6 genotype-based dosing strategies should reduce variability in the dose-exposure relationship between individual patients. (Figure Presented).

……..

Cognition, Brain, Behavior: An Interdisciplinary Journal. 2014 Dec;18:315-33.

THE INDEPENDENT CONTRIBUTIONS OF NEGATIVE PEER FUNCTIONING AND SOCIAL/FAMILIAL RISK FACTORS TO SYMPTOMS OF ADHD AMONG ITALIAN PRIMARY SCHOOL CHILDREN.

Piumatti G, Sacconi B, Zucchetti G, et al.

This study investigated the association between negative peer functioning and social/familial risk factors with the occurrence of symptoms of attention deficit/ hyperactivity disorder (ADHD) among Italian primary school children. We hypothesized that negative peer functioning and the cumulative number of indexes of adversity would be independently associated to ADHD. We also tested for gender moderated effects. 103 primary school children (48 girls, 46.6%; Mage = 8.25, SD = .61, Range = 6-10), their parents and their teachers took part into this study. The assessment included a measurement of: symptoms of attention deficit (ADD) and hyperactivity (HYP), conflictual and affective friendship quality, prosocial and aggression behaviors and emotional and behavioral instability. In addition, an index of social risk was assessed by considering multiple social and familial risk factors. Results showed that conflictual friendship quality and aggressive behaviors were positively

associated with symptoms of ADD and HYP respectively, while higher social risk was associated to higher HYP especially among girls.

……..

Cogn Behav Pract. 2015.

COGNITIVE-BEHAVIORAL THERAPY FOR ADHD IN ADOLESCENTS: CLINICAL CONSIDERATIONS AND A CASE SERIES.

Sprich SE, Burbridge J, Lerner JA, et al.

Although ADHD in adolescents is an impairing and prevalent condition, with community prevalence estimates between 2% and 6%, psychosocial treatments for adolescents compared to younger children are relatively understudied. Our group has successfully developed an evidence base for cognitive-behavioral therapy (CBT) for ADHD in medication-treated adults with ADHD with clinically significant symptoms. In the current paper, we describe an adaptation of this treatment to adolescents, and provide case reports on 3 adolescents who participated in an open pilot trial. The results suggest that the treatment approach was well tolerated by the adolescents and that they experienced clinical benefit. This early report of the approach in adolescents is promising and requires further efficacy testing.

……..

Compr Psychiatry. 2015.

TEMPERAMENTAL AND CHARACTER PROFILES OF PRESCHOOL CHILDREN WITH ODD, ADHD, AND ANXIETY DISORDERS.

Melegari MG, Nanni V, Lucidi F, et al.

Background: The aim of the present research was to identify profiles of Cloninger's temperament and character dimensions associated with anxiety disorders, oppositional defiant disorder (ODD) and attention-deficit/hyperactive disorder (ADHD) in preschoolers.

Method: The parents of 120 children (mean age = 4.65. years; S.D.= .88) completed the Preschool Temperament and Character Inventory (PsTCI). The sample consisted of 4 groups (n = 30 per group): ADHD, anxious, ODD and control children. To diagnose the different disorders, the Preschool Age Psychiatric Assessment and Child Behavior Checklist 1.5-5 was administered to the parents.

Results: The discriminant analysis showed that three temperamental dimensions (Harm Avoidance, Novelty Seeking and Persistence) enabled the correct classification of 75% of cases within their own group, which demonstrated an adequate accuracy rate. The ADHD children showed a temperamental profile that was characterized by high Novelty Seeking, low Reward Dependence and low Persistence, while the anxious children obtained high scores in Harm Avoidance. The profiles of the ODD children shared some common features (high Novelty Seeking) with the ADHD children, but the ODD children were characterized by higher Persistence and Harm Avoidance compared with ADHD children.

Conclusions: The present results indicate that Cloninger's temperamental dimensions allow to differentiate the three most frequent psychiatric disorders in preschoolers.

……..

Cortex. 2015.

POSTNATAL ARSENIC EXPOSURE AND ATTENTION IMPAIRMENT IN SCHOOL CHILDREN.

Rodriguez-Barranco M, Gil F, Hernandez AF, et al.

Over the last few decades there has been an increased concern about the health risks from exposure to metallic trace elements, including arsenic, because of their potential neurotoxic effects on the developing brain. This study assessed whether urinary arsenic (UA) levels are associated with attention performance and Attention-Deficit/Hyperactivity Disorder (ADHD) in children living in an area with high industrial and mining activities in Southwestern Spain. A cross-sectional study was conducted on 261 children aged 6-9 years. Arsenic levels were determined in urine samples. Attention was measured by using 4 independent tools: a) tests from the Behavioral Assessment and Research System (BARS) designed to measure attention function: Simple Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT); b) AULA Test, a virtual reality (VR)-based test that evaluates children's response to several stimuli in an environment simulating a

classroom; c) Child Behavior Checklist (CBCL), administered to parents; and d) Teacher's Report Form (TRF), administered to teachers. Multivariate linear and logistic regression models, adjusted for potential confounders, were used to estimate the magnitude of the association between UA levels and attention performance scores. Higher UA levels were associated with an increased latency of response in RTT ((beta)=12.3; 95% confidence interval (CI): 3.5-21.1) and SAT ((beta)=3.6; 95% CI: .4-6.8) as well as with worse performance on selective and focalized attention in the AULA test ((beta) for impulsivity=.6; 95% CI: .1-1.1; (beta) for inattention=.5; 95% CI: .03-1.0). A dose-response relationship was observed between UA levels and inattention and impulsivity scores. In contrast, results from the CBCL and TRF tests failed to show a significant association with UA levels. In conclusion, UA levels were associated with impaired attention/cognitive function, even at levels considered safe. These results provide additional evidence that postnatal arsenic exposure impairs neurological function in children.

……..

Dev Cognitive Neurosci. 2015;12:114-22.

SPONTANEOUS ACTIVITY IN THE WAITING BRAIN: A MARKER OF IMPULSIVE CHOICE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER?

Hsu C-F, Benikos N, Sonuga-Barke EJS.

Background Spontaneous very low frequency oscillations (VLFO), seen in the resting brain, are attenuated when individuals are working on attention demanding tasks or waiting for rewards (Hsu et al., 2013). Individuals with attention-deficit/hyperactivity disorder (ADHD) display excess VLFO when working on attention tasks. They also have difficulty waiting for rewards. Here we examined the waiting brain signature in ADHD and its association with impulsive choice.

Methods DC-EEG from 21 children with ADHD and 21 controls (9-15 years) were collected under four conditions: (i) resting; (ii) choosing to wait; (iii) being "forced" to wait; and (iv) working on a reaction time task. A questionnaire measured two components of impulsive choice.

Results Significant VLFO reductions were observed in controls within anterior brain regions in both working and waiting conditions. Individuals with ADHD showed VLFO attenuation while working but to a reduced level and none at all when waiting. A closer inspection revealed an increase of VLFO activity in temporal regions during waiting. Excess VLFO activity during waiting was associated with parents' ratings of temporal discounting and delay aversion.

Conclusions The results highlight the potential role for waiting-related spontaneous neural activity in the pathophysiology of impulsive decision-making of ADHD.

……..

Dev Cognitive Neurosci. 2015;11:155-74.

CHARACTERIZING HETEROGENEITY IN CHILDREN WITH AND WITHOUT ADHD BASED ON REWARD SYSTEM CONNECTIVITY.

Costa Dias TG, Iyer SP, Carpenter SD, et al.

One potential obstacle limiting our ability to clarify ADHD etiology is the heterogeneity within the disorder, as well as in typical samples. In this study, we utilized a community detection approach on 106 children with and without ADHD (aged 7-12 years), in order to identify potential subgroups of participants based on the connectivity of the reward system. Children with ADHD were compared to typically developing children within each identified community, aiming to find the community-specific ADHD characteristics. Furthermore, to assess how the organization in subgroups relates to behavior, we evaluated delay-discounting gradient and impulsivity-related temperament traits within each community. We found that discrete subgroups were identified that characterized distinct connectivity profiles in the reward system. Importantly, which connections were atypical in ADHD relative to the control children were specific to the community membership. Our findings showed that children with ADHD and typically developing children could be classified into distinct subgroups according to brain functional connectivity. Results also suggested that the differentiation in "functional" subgroups is related to specific

behavioral characteristics, in this case impulsivity. Thus, combining neuroimaging data and community detection might be a valuable approach to elucidate heterogeneity in ADHD etiology and examine ADHD neurobiology.

……..

Dev Med Child Neurol. 2014;56:24-25.

SPATIAL ATTENTION DEFICITS AS POSSIBLE EXPLANATION FOR DEVELOPMENTAL DISREGARD IN UNILATERAL CEREBRAL PALSY.

Zielinski I, Baas M, Aarts P, et al.

Introduction: Some children with unilateral cerebral palsy (CP) disregard the preserved capacity of the affected upper limb, known as developmental disregard (DD). This phenomenon has frequently been explained due to delayed or deficient developmental milestones and related cognitive aspects of information processing. Using eventrelated potentials (ERPs) cognitive processes preceding hand movement have already been studied. It has been shown that in a dual-hand situation, children with DD require a disproportional amount of attention when preparing a response with their affected hand. An interesting question is whether children with DD also lag behind concerning higher order cognitive processes that are directly related to goal directed behaviour, such as response inhibition. The goal of this study is to investigate the cognitive processes preceding goaldirected behaviour related to movement initiation as well as inhibition in a Go/NoGo task.

Participants and methods: Twenty-four children with unilateral CP participated in the study. Twelve were diagnosed with DD. All participants performed a dual-hand Go/NoGo task. The ERP components elicited by lateralized cue, target and stop stimuli were analysed.

Results: No differences in ERP components related to response inhibition were found between groups. However, in children with DD the N1 component following cue and target stimuli was significantly diminished. This component is known to reflect aspects of spatial attention.

Conclusion: In line, it has already been stated that DD conceivably is a neurological based phenomenon similar to post stroke neglect syndrome. The current results therefore strongly suggest that DD can be linked to deficits in spatial attention, as it is the case in neglect.

……..

Dev Med Child Neurol. 2014;56:1040-41.

DEFICITS IN ATTENTION, MOTOR CONTROL, AND PERCEPTION AND INCREASED RISK OF INJURY IN CHILDREN.

Cairney J.

This commentary is on the original article by Chou et al. on pages 1111-1116 of this issue.

……..

Dev Med Child Neurol. 2014;56:44.

MICROSTATES IN ADHD CHILDREN DURING A VISUAL CUED GO/NOGO TASK.

Cevallos C, Baijot S, Hoellinger T, et al.

Introduction: Children with attention deficit/hyperactivity disorder (ADHD) have been found to show theta-beta correlation in rhythmic brain oscillations. We aimed to further analyse scalp activity in order to study global amplitude of activation and topographical stability during a visual-cued task in children with ADHD.

Participants and methods: Fourteen ADHD and 14 aged-matched control children underwent EEG while performing a visual-cued GO/ NOGO task. We performed theta-beta corroboration, topographical activation study, including global field potential (GFP) and transiently stable brain states (microstates). We performed a topographical ANOVA to establish differences between conditions and other statistical analysis (comprising unpaired t-tests) to fit maps within subject.

Results: ADHD children had significantly smaller amplitude at first and third peak and larger second peak in the W-shaped GFP after CUE, GO and NOGO visual onsets than control children, who showed the reverse image to this. W-shaped GFP peak topography remained almost the same for the three peaks. Children with ADHD also had more intermediary topographies than controls.

Conclusion: There were significant differences in microstates between children with ADHD and controls. Excess intermediary topographies in ADHD group may index and give insights into abnormal executive function in ADHD.

……..

Dev Med Child Neurol. 2015;57:257-64.

DISTINCT PATTERNS OF CORTICAL THINNING IN CONCURRENT MOTOR AND ATTENTION DISORDERS.

Langevin LM, MacMaster FP, Dewey D.

Aim: Many neurodevelopmental disorders co-occur yet are rarely studied in terms of brain development. Developmental coordination disorder (DCD) and attention-deficit-hyperactivity disorder (ADHD) co-occur at a high frequency and are associated with functional and structural brain alterations.

The objective of this study was to examine whether the effects of comorbid motor and attention problems influence cortical thickness in children and whether the pattern of changes for concurrent disorders is distinct from the alterations seen in single disorders.

Method: A total of 34 children (19 males, 15 females, mean age 9y 9mo, range 8-17y) who met the criteria for DCD (n=14), ADHD (n=10), or DCD+ADHD (n=10) were recruited into the study. Fourteen participants with typical development (eight males, six females, mean age 11y 9mo, range 8-17y) were also recruited for comparison. Participants underwent neuropsychological assessment and magnetic resonance imaging. Cortical thickness analysis was performed to determine the patterns of cortical thinning in each disorder, which was then compared across groups.

Results: Children with comorbid DCD+ADHD demonstrated more widespread decreases in cortical thickness than participants with a diagnosis of DCD or ADHD alone. Cortical thinning was found to be concentrated in the frontal, parietal, and temporal lobes, and was correlated with measures of motor and attentional functioning.

Interpretation: The co-occurrence of DCD+ADHD was associated with a distinct global pattern of regional cortical thickness decrease, highlighting the unique neurobiology of comorbid neurodevelopmental disorders. This novel feature of concurrent DCD and ADHD may help inform diagnostic definitions and provide clues to both the shared and the isolated genetic and environmental origins of motor and attention disorders. What this paper adds: We examined children with single and comorbid motor and attention issues for cortical thickness differences. In participants with ADHD alone, thickness reductions were found in the left superior temporal gyrus and parahippocampal gyrus. In participants with DCD alone, cortical thickness reductions were found in the medial orbitofrontal cortex. In comorbid DCD+ADHD, global cortical thinning deficits were found in the frontotemporal, parietal, and occipital regions Concurrent DCD+ADHD correlated with poorer motor and attentional performance. This article is commented on by Brossard-Racine on pages 211-212 of this issue.

……..

Early Intervent Psychiatry. 2014;8:110.

VISUAL PERCEPTION, PROCESSING SPEED AND SHORT-TERM MEMORY BASED ON THE THEORY OF VISUAL ATTENTION: DEFICITS IN 7-YEAR-OLD CHILDREN AT HIGH RISK OF DEVELOPING SCHIZOPHRENIA OR BIPOLAR DISORDER IN THE DANISH HIGH RISK AND RESILIENCE STUDY - VIA 7.

Hemager N, Jepsen JR, Vangkilde S, et al.

Background: Offspring at genetic high risk for developing schizophrenia spectrum psychosis (SZ) show attention deficits and increased prevalence of ADHD compared to children of parents without this disorder. However, the evidence for attention deficits in offspring of parents with bipolar disorder (BD) has been mixed.

Objectives: The aim of this sub study is to measure attentional functioning - specifically visual processing speed and capacity of visual short-term memory - in children at genetic high risk for developing SZ or BD. We expect that children at genetic high risk for SZ will show more severe impairments compared with children at genetic high risk for BD. Whereas the latter group may show more deficits in visual attention than children of parents without BD and SZ.

Methods: We are establishing a stratified cohort of 500 children aged 7 with either 0, 1 or 2 parents with SZ or BD. In this sub study of 30 children from each of the three subgroups we assessed visual attention using the instrument TVA-based Whole Report based on Bundesen's Theory of Visual Attention.

Results: Data collection in this sub study has been completed by April 2014 and data analyses will commence in May 2014.

……..

Emot Behav Difficulties. 2015.

MISMATCHED: ADHD SYMPTOMATOLOGY AND THE TEACHERNULLSTUDENT RELATIONSHIP.

Rogers M, Belanger-Lejars V, Toste JR, et al.

The goal of this study was to investigate the relationship between children with attention-deficit/hyperactivity disorder (ADHD) symptoms and their teachers, and to examine whether this relationship was associated with childrennulls academic motivation. The sample comprised 35 children with clinically elevated levels of ADHD symptoms and 36 children with no ADHD symptoms between the ages of 6 and 10. Children with symptoms of ADHD and their teachers reported impairments in both the emotional and collaborative aspects of their relationships, particularly for girls in the ADHD group. For children in the ADHD group, a self-reported close bond in the teachernullstudent relationship was associated with increased academic motivation. These findings were significant after controlling for co-occurring behaviour problems and academic impairments. These findings suggest that the symptoms of ADHD may interfere with teachernullstudent relationship and may serve as a barrier in studentnulls academic achievement.

……..

European Child & Adolescent Psychiatry. 2015 Jan;24:1-4.

CONTEXTUAL VARIABILITY OF ADHD SYMPTOMS: EMBRACEMENT NOT ERASEMENT OF A KEY MODERATING FACTOR.

Rommelse N, Bunte T, Matthys W, et al.

The authors argue that the vaguely defined criterion in the DSM-5 for a diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD) (i.e., a diagnosis of ADHD is warranted— when all other criteria are met— if only two out of the minimal six symptoms occur at school, even though this is clearly below the clinical cut-off) reflects a broader neglected issue of variability in number and contextual (in)stability of symptoms that is so typical in ADHD affected populations. The authors suggest that It is remarkable that the DSM-5 stresses symptoms rather than impairment in relation to different contexts in the diagnostic criteria for ADHD. One would expect that pervasiveness (criterion C) means the presence of impairment of functioning, due to ADHD symptoms, in two or more settings. They conclude that ADHD is not at all context insensitive. Viewing ADHD as a strongly genetically determined disorder may have falsely generated the belief that the disorder must be context independent and rater differences are best viewed as measurement error. Rather, it may be the case that high contextual variability itself has strong genetic underpinnings and may differ according to sex. Instead of ignoring or erasing variation in number and contextual expression of symptoms, we believe there is a persuasive case for accounting for this variation in diagnostic practice.

……..

Eur Child Adolesc Psychiatry. 2015.

CLASSIFYING ADOLESCENT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) BASED ON FUNCTIONAL AND STRUCTURAL IMAGING.

Iannaccone R, Hauser TU, Ball J, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common disabling psychiatric disorder associated with consistent deficits in error processing, inhibition and regionally decreased grey matter volumes. The diagnosis is based on clinical presentation, interviews and questionnaires, which are to some degree subjective and would benefit from verification through biomarkers. Here, pattern recognition of multiple discriminative functional and structural brain patterns was applied to classify adolescents with ADHD and controls. Functional activation features in a Flanker/NoGo task probing error processing and inhibition along with structural magnetic resonance imaging data served to predict group membership using support vector machines (SVMs). The SVM pattern recognition algorithm correctly classified 77.78 % of the subjects with a sensitivity and specificity of 77.78 % based on error processing. Predictive regions for controls were mainly detected in core areas for error

processing and attention such as the medial and dorsolateral frontal areas reflecting deficient processing in ADHD (Hart et al., in Hum Brain Mapp 35:3083null3094, 2014), and overlapped with decreased activations in patients in conventional group comparisons. Regions more predictive for ADHD patients were identified in the posterior cingulate, temporal and occipital cortex. Interestingly despite pronounced univariate group differences in inhibition-related activation and grey matter volumes the corresponding classifiers failed or only yielded a poor discrimination. The present study corroborates the potential of task-related brain activation for classification shown in previous studies. It remains to be clarified whether error processing, which performed best here, also contributes to the discrimination of useful dimensions and subtypes, different psychiatric disorders, and prediction of treatment success across studies and sites.

……..

Eur J Paediatr Neurol. 2015;19:122-33.

CURRENT ROLE OF MELATONIN IN PEDIATRIC NEUROLOGY: CLINICAL RECOMMENDATIONS .

Bruni O, Alonso-Alconada D, Besag F, et al.

Background/purpose Melatonin, an indoleamine secreted by the pineal gland, plays a key role in regulating circadian rhythm. It has chronobiotic, antioxidant, anti-inflammatory and free radical scavenging properties. Methods A conference in Rome in 2014 aimed to establish consensus on the roles of melatonin in children and on treatment guidelines.

Results and Conclusion The best evidence for efficacy is in sleep onset insomnia and delayed sleep phase syndrome. It is most effective when administered 3-5 h before physiological dim light melatonin onset. There is no evidence that extended-release melatonin confers advantage over immediate release. Many children with developmental disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability have sleep disturbance and can benefit from melatonin treatment. Melatonin decreases sleep onset latency and increases total sleep time but does not decrease night awakenings. Decreased CYP 1A2 activity, genetically determined or from concomitant medication, can slow metabolism, with loss of variation in melatonin level and loss of effect. Decreasing the dose can remedy this. Animal work and limited human data suggest that melatonin does not exacerbate seizures and might decrease them. Melatonin has been used successfully in treating headache. Animal work has confirmed a neuroprotective effect of melatonin, suggesting a role in minimising neuronal damage from birth asphyxia; results from human studies are awaited. Melatonin can also be of value in the performance of sleep EEGs and as sedation for brainstem auditory evoked potential assessments. No serious adverse effects of melatonin in humans have been identified

……..

Exp Brain Res. 2015.

IMPAIRED VISUOMOTOR ADAPTATION IN ADULTS WITH ADHD.

Kurdziel LBF, Dempsey K, Zahara M, et al.

Attention-deficit hyperactivity disorder (ADHD) is a prevalent psychiatric disorder in children that often continues into adulthood. It has been suggested that motor impairments in ADHD are associated with underlying cerebellar pathology. If such is the case, individuals with ADHD should be impaired on motor tasks requiring healthy cerebellar function. To test this, we compared performance of individuals with ADHD and ADHD-like symptoms with non-ADHD controls on a visuomotor adaptation task known to be impaired following cerebellar lesions. Participants adapted reaching movements to a visual representation that was rotated by 30(degrees). Individuals with ADHD and those with ADHD-like symptoms took longer to correct the angle of movement once the rotation was applied relative to controls. However, post-adaptation residual effect did not differ for individuals with ADHD and ADHD-like symptoms compared to the control group. These results are consistent with the hypothesis that mild cerebellar deficits are evident in the motor performance of adults with ADHD.

……..

Explor J Sci Heal. 2014;10:398-403.

IMPROVEMENTS IN SLEEP AND HANDWRITING AFTER COMPLEMENTARY MEDICAL INTERVENTION USING ACUPUNCTURE, APPLIED KINESIOLOGY, AND RESPIRATORY EXERCISES IN A NINE-YEAR-OLD ADHD PATIENT ON METHYLPHENIDATE.

Molsberger F, Raak C, Witthinrich C.

The case study reports on the effect of pharmacological, complementary, and alternative medicine including acupuncture, Applied Kinesiology, and respiratory exercises in a boy with attention-deficit hyperactivity disorder (ADHD) on methylphenidate. A nine-year-old male patient was referred to treatment with a three-year diagnosis of ADHD, sleeping troubles, and dissatisfaction with methylphenidate. Examination included Applied Kinesiology, the coachman's test, assessment of breathing pattern disorders, and traditional chinese medicine (TCM) diagnosis. Muscle weakness related to thoracic breathing was found in the coachman's test. Respiratory exercises, acupuncture with permanent needles, and Applied Kinesiology treatments were given. Within the first treatment, muscle function as assessed by the coachman's test normalized. After two treatments, sleep behavior improved rapidly, and with further treatments, handwriting was improving. Methylphenidate continues to be given. The results were stable after 15 months. A multimodal approach to ADHD integrating pharmacological treatment and complementary and alternative medicine (CAM) including Applied Kinesiology, breathing exercises, and acupuncture.

……..

Hum Brain Mapp. 2014 Dec;35:6032-48.

STRUCTURAL AND FUNCTIONAL CONNECTIVITY OF THE HUMAN BRAIN IN AUTISM SPECTRUM DISORDERS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A RICH CLUB-ORGANIZATION STUDY.

Ray S, Miller M, Karalunas S, et al.

Attention-deficit/hyperactive disorder (ADHD) and autism spectrum disorders (ASD) are two of the most common and vexing neurodevelopmental disorders among children. Although the two disorders share many behavioral and neuropsychological characteristics, most MRI studies examine only one of the disorders at a time. Using graph theory combined with structural and functional connectivity, we examined the large-scale network organization among three groups of children: a group with ADHD (8–12 years, n = 20), a group with ASD (7–13 years, n = 16), and typically developing controls (TD) (8–12 years, n = 20). We apply the concept of the rich-club organization, whereby central, highly connected hub regions are also highly connected to themselves. We examine the brain into two different network domains: (1) inside a rich-club network phenomena and (2) outside a rich-club network phenomena. The ASD and ADHD groups had markedly different patterns of rich club and non rich-club connections in both functional and structural data. The ASD group exhibited higher connectivity in structural and functional networks but only inside the rich-club networks. These findings were replicated using the autism brain imaging data exchange dataset with ASD (n = 85) and TD (n = 101). The ADHD group exhibited a lower generalized fractional anisotropy and functional connectivity inside the rich-club networks, but a higher number of axonal fibers and correlation coefficient values outside the rich club. Despite some shared biological features and frequent comorbity, these data suggest ADHD and ASD exhibit distinct large-scale connectivity patterns in middle childhood.

……..

Hum Brain Mapp. 2015;36:1180-89.

SMOKING AND THE DEVELOPING BRAIN: ALTERED WHITE MATTER MICROSTRUCTURE IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND HEALTHY CONTROLS.

van EH, Groenman AP, Zwiers MP, et al.

Brain white matter (WM) tracts, playing a vital role in the communication between brain regions, undergo important maturational changes during adolescence and young adulthood, a critical period for the development of nicotine dependence. Attention-deficit/hyperactivity disorder (ADHD) is associated with increased smoking and widespread WM abnormalities, suggesting that the developing ADHD brain might be especially vulnerable to effects of smoking. This study aims to investigate the effect of smoking on (WM) microstructure in adolescents and young adults with and without ADHD. Diffusion tensor imaging was performed in an extensively phenotyped sample of nonsmokers (n=95, 50.5% ADHD), irregular smokers (n=41, 58.5% ADHD), and regular smokers

(n=50, 82.5% ADHD), aged 14-24 years. A whole-brain voxelwise approach investigated associations of smoking, ADHD and their interaction, with WM microstructure as measured by fractional anisotropy (FA) and mean diffusivity (MD). Widespread alterations in FA and MD were found for regular smokers compared to irregular and nonsmokers, mainly located in the corpus callosum and WM tracts surrounding the basal ganglia. Several regions overlapped with regions of altered FA for ADHD versus controls, albeit in different directions. Irregular and nonsmokers did not differ, and ADHD and smoking did not interact. Results implicate that smoking and ADHD have independent effects on WM microstructure, and possibly do not share underlying mechanisms. Two mechanisms may play a role in the current results. First, smoking may cause alterations in WM microstructure in the maturing brain. Second, pre-existing WM microstructure differences possibly reflect a risk factor for development of a smoking addiction.

……..

Hum Brain Mapp. 2015.

ALTERED SALIENCE PROCESSING IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Tegelbeckers J, Bunzeck N, Duzel E, et al.

Attentional problems in patients with attention deficit hyperactivity disorder (ADHD) have often been linked with deficits in cognitive control. Whether these deficits are associated with increased sensitivity to external salient stimuli remains unclear. To address this issue, we acquired functional brain images (fMRI) in 38 boys with and without ADHD (age: 11-16 years). To differentiate the effects of item novelty, contextual rareness and task relevance, participants performed a visual oddball task including four stimulus categories: a frequent standard picture (62.5%), unique novel pictures (12.5%), one repeated rare picture (12.5%), and a target picture (12.5%) that required a specific motor response. As a main finding, we can show considerable overlap in novelty-related BOLD responses between both groups, but only healthy participants showed neural deactivation in temporal as well as frontal regions in response to novel pictures. Furthermore, only ADHD patients, but not healthy controls, engaged wide parts of the novelty network when processing the rare but familiar picture. Our results provide first evidence that ADHD patients show enhanced neural activity in response to novel but behaviorally irrelevant stimuli as well as reduced habituation to familiar items. These findings suggest an inefficient use of neuronal resources in children with ADHD that could be closely linked to increased distractibility.

……..

Indian J Psychiatry. 2015;57:S137-S138.

STUDY ON QUALITY OF LIFE AND PSYCHOPATHOLOGY IN PARENTS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Islam SKM, Sarkhel S, Saha PK.

Aims and Objectives: The study was conducted to assess the Quality Of Life and Psychopathology in parents of children with Attention Deficit Hyperactivity Disorder.

Methods and Tools Used: Parents of children diagnosed with ADHD (According to DSM-lV-TR) were evaluated at one point for their Quality Of Life (using WHO-QOL-BREF) & for any psychopathology (using The MINI International Neuropsychiatric interview), and were compared with age - sex matched control group whose children were free from any chronic medical or psychiatric illness.

Result: Child ADHD was associated with increased rate of mood disorder in parents, specially Major Depressive Disorder and Dysthymia as compared to parents of healthy children. Child ADHD also adversely affected the Quality Of Life of their parents than parents of healthy children.

Conclusion: To conclude, it is not only child with ADHD who needs health care but also parents in order to prevent the adverse effect of parental ill health on the out come of ADHD child.

……..

Indian J Psychiatry. 2015;57:S109.

BEHAVIOURAL PROFILES OF CHILDREN OF ALCOHOLICS IN TWO VILLAGES IN SOUTH INDIA.

Pansari P, Shetty P, Sharma R, et al.

Introduction: Prevalence rate of childhood behavioral disorders is significantly high in children of alcoholics (CoAs) compared to offspring of non-alcoholic subjects. Studies have indicated that children of alcoholics need increased mental health inputs and may also be at risk for adult psychiatric morbidity. Literature on CoAs from the Indian context is scanty. An earlier study looking at social correlates of childhood behavioral problems in Mugalur village had suggested that certain behavior profiles may be more related to parental alcoholism. We wish to explore this further with a cross sectional study in the same population, through independent ascertainment of the two variables - namely parental alcoholism and childhood behavioral problems.
Objectives: To study childhood behavioural disorders among COA's
Methodology: Presence or absence of FIGS determined parental alcoholism was established in households with a total of 250 children in the age group of 4-16 years in Mugalur and Bovipalya. Child behavior Checklist and Strength and Difficulties questionnaire based childhood behavioral problems were determined in these 250 children by investigators blind to parental alcoholism status.
Results: The results suggest an excess of behavioral and emotional problems in CoAs, compared to those without parental alcoholism. The need for both primary and secondary preventive interventions for this group and other potential implications are discussed and the need to follow up in these children is emphasized.

……..

Indian J Psychiatry. 2015;57:S149-S150.

KNOWLEDGE AND MISPERCEPTIONS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AMONG PRIMARY SCHOOL TEACHERS OF VADODARA DISTRICT.

Chhasatia AH, Kataria LR.

Objective/Introduction: Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed psychiatric disorders of childhood. Teachers can play a key role in identifying and supporting students with ADHD. In order to fulfill this important role, it is imperative for teachers to have explicit knowledge about ADHD. Teachers are seen as one of the most valuable sources of information with regard to referral and diagnosis of ADHD. They also have the responsibility for creating an environment conducive to academic, social and emotional success for children with ADHD. However, since there is some doubt as to whether teachers have the appropriate knowledge of ADHD to fulfill this important role.
Aim: This study aimed at assessing the knowledge and misperceptions of ADHD of primary school teachers in Vadodara district.
Material & Methods: Total 491 schoolteachers participated in the study. The Knowledge of Attention Deficit Disorder Scale (KADDS) along with a demographic questionnaire was used as the survey instruments to collect data. Descriptive statistics and correlation test were used to analyze the data.
Results: Results indicated that teachers' knowledge of ADHD was insufficient. Significant difference about knowledge was found between Urban & Rural (0. 00429); Gujarati & English medium school teachers (P = 0. 0013). Misperception was significantly higher (P = 0.05) in teachers teaching in primary standard compared to upper primary standard.
Conclusion: As the lack of knowledge was apparent from the study teacher's training in the field of ADHD is required as they are the first person to come in direct contact with the children; for early intervention & better future of the children.

……..

Indian J Psychiatry. 2015;57:S102-S103.

TO STUDY THE OBJECTIVE BURDEN IN MOTHERS OF CHILDREN DIAGNOSED AS ATTENTION DEFICIT HYPERACTIVE DISORDER(ADHD).

Parkar SR, Raikar SU, Kate N, et al.

Background: Attention-deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder of childhood onset characterized by severe, developmentally inappropriate motor hyperactivity, inattention and impulsiveness that

result in impairment in more than one setting. ADHD decreases parents' productivity and places a psychological and emotional burden on the family especially on the mother.
Objectives: To study the burden experienced by the mothers of children diagnosed as ADHD.
Method: Study participants are the mothers of children diagnosed as ADHD.Those who satisfy the inclusion and exclusion criteria have been enrolled for the study after taking informed consent . A semistructured proforma has been designed to collect information on the socio-demographics. Family burden scale has been administered to assess the burden in a sample of 40 subjects. Appropriate statistics will be applied. The mean measurement structures will be generated and the findings will be analyzed using SPSS.
Results And Discussion: Results will be discussed in paper.
Conclusion: The conclusion will be discussed in the paper.

……..

Indian J Psychiatry. 2015;57:S141-S142.

EXPLORATION OF VARIOUS DOMAINS OF SELF ESTEEM IN CHILDREN WITH ADHD: A CROSS-SECTIONAL STUDY.

Palaniappan P, Seshadri S, Girimaji S, et al.

Background: Self-esteem is based on the ratio between perceived competence and the person's aspirations in any one specific area of life. Though Low Self esteem(50%) was found in ADHD subjects, very few studies evaluating various domains of low self esteem exist.
Objectives: To study various domains of self esteem and factors associated with self esteem in children with ADHD.
Methods: 60 subjects aged 6 to 16 years who were diagnosed as ADHD based on DSM IV TR were recruited with informed consent, from NIMHANS Child and Adolescent Psychiatry clinic. Detailed interview of subjects and their respective parents were carried out using the Semi structured assessment schedule K- SADS - PL (for comorbidities), Conner's ADHD severity index, Children Global assessment scale (CGAS) and Culture free self-esteem inventory.
Results: Recruited subjects were predominantly boys (86%), between 6- 9 years of age (66%), middle socio economic status (45%), and living in Nuclear family (77%). Score of Conner's ADHD severity index was 14. 02 (plus or minus) 4. 66 and CGAS was 44. 32 (plus or minus) 10. 04. Parental conflicts were seen in 58% of the children with ADHD. 55 % of subjects had at least one comorbidity. Significant percentile of subjects had low self esteem in various domains, i. e; General (49%), Social (72%), Academic (80%), Parent (32%) and Global(68%). Presence of parental conflicts significantly affected academic (P = 0. 016), parental (P < 0. 001) and Global (P = 0. 03) domains, but not the others. Presence of comorbidity affected parental domain alone (P = 0. 005).
Conclusion: Factors that determine self esteem differentially influences various domains of self esteem in children with ADHD.

……..

Indian J Psychiatry. 2015;57:S174.

ADHD & COMORBIDITY: DIAGNOSTIC ISSUES AND ITS MANAGEMENT.

Jayanthini V, Nambi S, Vaithiyam A.

Background: Attention - deficit hyperactivity disorder (ADHD) is an early - onset, highly prevalent neurobehavioral disorder, with genetic, environmental, and biologic etiologies, that persists into adolescence and adulthood in a sizable majority of afflicted children of both sexes. ADHD is characterized by behavioral symptoms of inattention, hyperactivity, and impulsivity across the life cycle and is associated with considerable morbidity and disability. The new DSM 5 criterion makes narrower definition of childhood ADHD. Comorbidity is a distinct clinical feature of ADHD in children. Although its etiology remains unclear, emerging evidence documents its strong neurobiologic and genetic underpinnings. Approximately 54% to 67% of children and adolescents diagnosed with ADHD meet the criteria for ODD; 20% to 56% of children and adolescents diagnosed with ADHD meet the diagnostic criteria for CD; 25% to 33% of children and adolescents diagnosed with ADHD meet the diagnostic criteria for somatization disorders, and 40% of children and adolescents with ADHD have some form of a learning disability. Children with inattentive ADHD type are more likely to display internalizing Symptomatology, learning disorders and speech & language problems compared with those with

hyperactive/ impulsive or combined subtypes. Children who display comorbid features often show more serious levels of impairment, often challenging treatment which includes multimodal form of treatment with medications, parents or family focused strategies, child interventions at home and school. Treating ADHD and comorbidity with pharmacological drugs is a challenging task due to the fluctuating symptoms. Drug intervention from western studies differs from Indian continent and ramification of medicines is needed.

……..

Indian J Psychiatry. 2015;57:S106-S107.

PANDAS PRESENTING IN A YOUNG BOY: A CASE REPORT.

Singh A, Kumar TS, Padhy SK.

Background: PANDAS (Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) is characterised by presence of multiple neuropsychiatric disorders like OCD, ADHD, tic disorders, learning difficulty and hoarding. The aetiology is autoimmune mediated following infections with group - A beta-haemolytic streptococci. This condition is rarely reported in the literature.

Objective: To present the case of 8 years old boy with PANDAS presenting with multiple neuropsychiatric symptoms and discuss its management.

Methodology (Case description): A 9 year-old boy studying in 3rd standard, belonging to a Sikh family of upper socio economic status and urban background presented with symptoms of acute onset from last one year. The symptoms comprised of hyperactivity, deterioration of handwriting, learning disability, hoarding and compulsive behaviour. He also had fluctuating motor tics including eye blinking and shoulder shrugging and vocal tics included throat clearing. Exploration of history revealed that he had multiple upper respiratory tract infections one year back and these were temporally related with onset of symptoms. Throat swab was positive for beta haemolytic streptococci. Serum antibodies were positive for CaM Kinase II activity, Dopamine receptor D1 and beta tubulin. Based on these findings he was diagnosed with PANDAS. Management involved treatment with Fluoxetine, Risperidone and Methylphenidate in required doses and behaviour therapy for learning disability. There was improvement in tics and hoarding but insignificant improvement in other domains. Response to I.V. Immunoglobulin administration is awaited.

Conclusion: The PANDAS subgroup has a distinct clinical presentation and an identifiable course of symptoms with a clear relationship between streptococcal infections and neuropsychiatric symptom onset and exacerbations. Some cases may need IV Ig or plasmapharesis for improvement. Additional studies are required to determine the role of immunomodulatory therapies and antibiotics prophylaxis for this group of patients.

……..

Indian J Psychiatry. 2015;57:S185.

MANAGEMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) ACROSS THE LIFE SPAN.

Manohari S, Galgali RB, Raman V, et al.

ADHD is a neurodevelopmental disorder where the core symptoms present in different ways through the lifespan. Identification of the disorder needs a high level of suspicion. Discerning ADHD from co-morbid illness is also a challenge. Though the core symptoms are the same through the life/different ages, management of the same problem has to be tailored to the developmental stages/age. This symposium will focus on identifying nuances in how ADHD presents in children, adolescents, young adults and older adults with special emphasis on distinguising differential diagnosis. We will highlight the intricacies of pharmacological and psychosocial management in children and adults. The management of the disability and impairment in various spheres of functioning across the lifespan will be addressed.

……..

Indian J Psychiatry. 2015;57:S190.

CRITICAL EVALUATION AND MANAGEMENT OF A HYPERACTIVE CHILD IN A CLINICAL SETUP.

Mishra KK, Gujar K, Prakash J, et al.

Background: Every hyperactive child brought to a Child guidance clinic or a referred for the Psychiatric evaluation and management may not be ADHD per se. Selecting a medication, when to start and for how long is the difficult discussion for clinician. What behavioral therapy work well at what setup needs to be discussed. In spite of best of management certain percentage of children (20-25%) continue to have ADHD in the Adulthood. We intend to throw light in this dark area with recent development in this field through symposium cum workshop module.

……..

Indian J Psychiatry. 2015;57:S179.

MANAGING ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PRESCHOOL AGE.

Moyal D, Garg B, Gupta SK, et al.

Introduction: Deepak Moyal Presentation of ADHD in preschool children: Bhavuk Garg Update for pharmacological management: Sumit Kumar Gupta Non-pharmacological management: Uday Kumar Sinha IHBAS experience: Deepak Kumar Background: With increasing awareness, more and more number of children are being diagnosed with ADHD at an earlier age. In absence of any approved medication and nuances of clinical presentation, ADHD in preschool children becomes challenging. However, there are leads from emerging evidences with regard to clinical management of ADHD in preschool children. The evidence coupled with insights from clinical experience of one of the busiest Child and Adolescent Psychiatry Clinic in India may help expert audience to generate practical strategies to deal with this challenge.

……..

Indian J Psychiatry. 2015;57:S157-S158.

DIFFICULT TO TREAT: ENURESIS WITH ADHD AND TIC DISORDER.

Deepika V, Aneek S, Saurabh K, et al.

Background: Enuresis is an elimination disorder which is difficult to manage in the young children. When it is associated with ADHD and Tic disorder it becomes all the more difficult to treat effectively. The following case illustrates the problem. null7 years old male child was brought by parents with complaints of difficulty in paying attention to routine tasks, fighting with siblings and children in school, losing things, destroying /damaging things at home, cannot sit at one place since 4 years. The child has facial grimacing & blinking of eyes repeatedly since 2 years. He also passes urine at night in bed almost 3 to 4 times in a week. All routine including urine analysis were WNL. EEG showed no abnormality. USG Abdomen and pelvis were normal. MRI was normal. Patient was treated with Tab Atomoxetine 10 mg HS & then increased to 15 mg. Tab Imipramine 25 mg HS. Opinion of Neurologist was taken for tic disorder and was advised Tab Revocon 25mg (Tetrabenazine) 1/2 tab in the morning & 1/2 tab at night. Emotional support, bladder training techniques was explained to the parents. Patient showed good results on follow upnull

Discussion: Very little empirical information regarding the course and outcome of Tic disorders in ADHD exists as on date. However the onset of Tic disorders are generally seen in children and most studies on Tic disorder in ADHD have been reported in adult ADHD. Presence of Enuresis in ADHD complicates the treatment profile. It is necessary to rule out organic causes for the presence of Enuresis and Tic disorder and also basal ganglia dysfunction.

Conclusion: The case highlights the rarity of its association with three major problems in the childhood.

……..

Indian J Psychiatry. 2015;57:S34.

PROFILE OF CHILDREN DIAGNOSED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) ATTENDING A STATE MEDICAL COLLEGE HOSPITAL.

Arun N, Palayat AM.

Background: ADHD is a chronic neuropsychiatric disorder with onset in early childhood. In fact it is the most common childhood psychiatric disorder precipitating the consultation with a child mental health professional. **Objectives**: Assess the demographic and clinical profile of children diagnosed with ADHD attending child psychiatric services of a state medical college hospital in Kerala To describe the interventions and medication prescription patterns offered to these children

Methods: This was a descriptive cross sectional hospital based study. Children were assessed using Socio-demographic data sheet, Vanderbilt ADHD diagnostic parent rating scale,Conner's rating scales-parent's evaluation.

Results: Among 52 children diagnosed with ADHD during the study period, 47 gave informed consent to participate in the study. Male to female ratio was 4.2:1. Mean age of the sample was 9.57 (plus or minus)2.8 years 55.3% were Hindu, 21.3% Muslim and 23.4% were Christians. 61.7% of the sample was first in birth order. Antenatal period was uneventful in 80.9% of cases. Delivery was normal in 63.8% of cases. 53.2% sought consultation for behavioural problems and rest due to academic difficulties. 2.1% cases were referred due to speech delay. In 48.9% of children, problems noticed before 5years of age. 59.6% had behavioural problems in school. 68.1% had history of psychiatric illness in the family. 11.5% had history of developmental mental disorder. Medications were prescribed for majority of patients but 38.3%preferred only non pharmacological interventions Combined type of ADHD was the predominant (61.7%) followed by inattention (31.9%) subtype.

Conclusion: ADHD is a common cause for help seeking among Indian children and the profile and pattern of the illness is similar to reports in western studies.

……..

Indian J Psychiatry. 2015;57:S46.

TRENDS OF PSYCHIATRIC FOLLOW-UP OF PATIENTS WITH ADHDA RETROSPECTIVE ANALYSIS.

Gholap TJ, Ahmed S, Mazumdar K, et al.

Background: ADHD is one of the most common behaviour disorder encountered in children. It makes up for nearly 50% of the attendance in Child Psychiatry Clinics. ADHD has been described as a developmental disorder characterised by varying degrees of inattention, hyperactivity and impulsivity arising in childhood. If not treated in chldhood then such children are at risk of academic failure and peer rejection. While the adolescent with ADHD who remain untreated face other risks such as increased proneness to automobile accidents, substance use and abuse and trouble with the law. Though effective drug therapy is available for treatment of ADHD the parents are resistant to medicate their children because of their concerns regarding side effects, stigma, other social factors, etc. Resultantly there is high dropout rate from treatment as has been seen in clinical trials of methylphenidate versus placebo. This study will help us understand the follow up trends of patients with ADHD especially in a setting where the treatment is provided free of cost (to all CHSS beneficiaries) and hence the effect of factors like availability and cost of health care is neutralized

Aim & Objectives: 1) To study the duration of follow up of patients with ADHD. 2) To correlate duration of follow up with age at onset, gender, birth order. 3) To correlate duration of follow up with educational and occupational status of parents. 4) To correlate duration of follow up with co-morbidities (especially with specific learning disability), and level of intelligence.

Material and Methods: Data will be retrieved from all the available case records of patients diagnosed with ADHD during the period of 2007 to 2013. Data will include socio-demographic details, illness profile, associated co-morbidity, Intelligence Quotient and details about follow up.

Results and Discussion: Data will be analyzed and discussed in accordance with available literature.

……..

Int J Psychophysiol. 2014;94:209-10.

NEUROPSYCHOLOGICAL AND PSYCHOPHYSIOLOGICAL MECHANISMS OF ATTENTION DEFICIT.

Glozman J, Shevchenko I, Kiselev S, et al.

Problem: Attention deficit and hyperactivity disorder (ADHD) is one of the most common behavioral and learning problems among children and a frequent reason for asking psychological help in childhood. This disorder is due to different causes, the most important of themare difficulties of activity programming andmonitoring and low neurodynamic capabilities. Eye tracking method permits to reveal psychophysiological mechanisms of cognitive and executive disturbances in children of different age.

Methods: Schulte Table from A.R. Luria battery (Luria, 1973) and test of figures matching. Both of these tests measure the sustaining of activity and attention. Hayling Sentence Completion Test (Shallice et al., 2002) and similar test from Luria battery measure selectivity in decision making. Dynamic praxis, test of conventional reactions (from Luria battery) and Numeric Stroop (Marzocchi, Re, Cornoldi, 2010) test measure shifting. Problem solving test and Everyday Planning Test (Ibid) measure planning of steps and coherence between planning and execution. Jowa Junior Gambling test (Bechara, Damasio, Damasio, Anderson, 1994) measure prognostic abilities, ability to compare gains and losses and to recall the performance. Eye tracking during some of these tests execution shows an objective setting in accordance to motivation and purpose of actual activity. Conners Scale determines the level of ADHD (Passolt, 2004).

Subjects: 37 learning disabled primary school pupils diagnosed with ADHD and 30 learning disabled primary school pupils without ADHD.

Results: The difference between children with and without ADHD was both in worse scores for all tests in the first group and in qualitative differences as follows: lack of steps planning and comparing own actions with previous results, impulsivity, and difficult recall of performance. The most discriminative for groups with and without ADHD were Numeric Stroop test and the Test of conventional reactions. Significant differences were revealed also in the specific eye tracking measures.

Conclusion: Our experimental study reveals the complex structure of executive function disturbances in ADHD, including: neurodynamic deficit, providing difficulty in sustaining of activity and attention; bad selectivity in decision making, defects of shifting from one executed activity to another; of planning, prognostics, recalling of performance and errors correction.

……..

Int J Psychophysiol. 2014;94:180-81.

TEMPERAMENT, CHARACTER AND QEEG IN CHILDREN WITH ADHD-C AND ADHD-C + ODD.

Chiarenza GA, Bosch-Bayard J, Villa S, et al.

Low levels of harm avoidance, reward dependence, self-directedness (SD), cooperativeness (C) and high novelty seeking (NS) are the distinctive temperament and character traits of ADHD-C children when assessed with Junior Temperament Character Inventory (JTCI). Typical patterns of resting EEGs in ADHD children show abnormal values of absolute power in theta, alpha and beta bands while frontal hypercoherence in the theta and beta bands. ADHD is frequently associated with oppositional defiant disorder (ODD) but no clear neurophysiological evidence exists that distinguishes the two groups. Aim of this study is to combine personality inventory and qEEG to identify biomarkers that could be used to discriminate between the two groups. 29 ADHD-C and 22 ADHD-C+ODD children participated in the study. All the subjects met the DSMV criteria for these disorders. JTCI and 2-5min of artefactfree EEG were collected and analysed. Stability based Biomarkers identification, amodification of the technique proposed byWehrens et al., 2011 was applied to the JTCI and to the EEG separately and combined. This technique is aimed to diminish the negative effects produced by the high number of variables, compared to the small number of subjects. The biomarkers are extracted in a multivariate analysis, which preserves the correlation between the variables, eliciting a group of biomarkers with a reasonable predictive performance. To measure the classification power of the selected set of biomarkers the stable ROC technique was used. The ROC area was calculated for the 10, 20 and 100% of False Positive (FP). The ADHD-C+ODD children had significant higher values of NS (Z score=2.35), and significant lower values of SD (Z score=-2.39) and C (Z score=-2.88) than ADHD-C children. TCI measurements showed a high regression between the two groups: SD ($m=-1.3$ $p < 0.001$) and C ($m=-2.4$ $p < 0.001$) showed the highest scores during the biomarkers selection procedure (90%). NS ($m=0.86$, $p < 001$) was selected about 70% of the times. t-Tests of qEEG (FDR corrected for multiple comparisons) for all sources and frequencies revealed group differences at

1.95 Hz and at 9.75 Hz (ADHD-C < ADHD-C+ODD). The classification method showed that TCI and qEEG when analyzed together, had the best discriminant power, especially at the low FP range (AUC=0.9 at FP=0.10, AUC=0.96 at FP=0.20). The most significant classifiers (channels and frequencies) were F4 at 1.17 Hz and at 5.47 Hz and F8 at 17.58. The right prefrontal and frontal areas that regulate attention and behaviour are impaired in the two groups.

……..

Int Psychogeriatr. 2015.

NO LOWER COGNITIVE FUNCTIONING IN OLDER ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Semeijn EJ, Korten NCM, Comijs HC, et al.

Background: Research illustrates cognitive deficits in children and younger adults with attention-deficit/hyperactivity disorder (ADHD). Few studies have focused on the cognitive functioning in older adults. This study investigates the association between ADHD and cognitive functioning in older adults

Methods: Data were collected in a cross-sectional side study of the Longitudinal Aging Study Amsterdam (LASA). A diagnostic interview to diagnose ADHD was administered among a subsample (N = 231, age 60null94). ADHD symptoms and diagnosis were assessed with the Diagnostic Interview for ADHD in Adults (DIVA) 2.0. Cognitive functioning was assessed with tests in the domains of executive functioning, information processing speed, memory, and attention/working memory

Results: Regression analyses indicate that ADHD diagnosis and ADHD severity were only negatively associated with cognitive functioning in the attention/working memory domain. When adjusting for depression, these associations were no longer significant

Conclusion: The study shows that ADHD in older adults is associated with lower cognitive functioning in the attention/working memory domain. However, this was partly explained by depressive symptoms.

……..

Iran J Child Neurol. 2015;9:64-70.

A COMPARATIVE STUDY OF SUSTAINED ATTENTIONAL BIAS ON EMOTIONAL PROCESSING IN ADHD CHILDREN TO PICTURES WITH EYE-TRACKING.

Pishyareh E, Tehrani-Doost M, Mahmoodi-Gharaie J, et al.

Objective: ADHD children have anomalous and negative behavior especially in emotionally related fields when compared to other. Evidence indicates that attention has an impact on emotional processing. The present study evaluates the effect of emotional processing on the sustained attention of children with ADHD type C

Materials&Methods: Sixty participants form two equal groups (each with 30 children) of normal and ADHD children) and each subject met the required selected criterion as either a normal or an ADHD child. Both groups were aged from 6null11-years-old. All pictures were chosen from the International Affective Picture System (IAPS) and presented paired emotional and neutral scenes in the following categories: pleasant-neutral; pleasant-unpleasant; unpleasant-neutral; and neutralnullneutral. Sustained attention was evaluated based on the number and duration of total fixation and was compared between the groups with MANOVA analysis

Results: The duration of sustained attention on pleasant in the pleasant-unpleasant pair was significant. Bias in duration of sustained attention on pleasant scenes in pleasant-neutral pairs is significantly different between the groups

Conclusion: Such significant differences might be indicative of ADHD children deficiencies in emotional processing. It seems that the highly deep effect of emotionally unpleasant scenes to gain the focus of ADHD childrennulls attention is responsible for impulsiveness and abnormal processing of emotional stimuli.

……..

Ir J Med Sci. 2015.

ADHD IN CHILDREN: A PATH TO FREE MEDICINES.

Hayden J, Flood M, McNicholas F.

Background: Recent media coverage has highlighted discrepancies in the entitlements of children to free ADHD medication across the country. The Department of Health has since ruled that children with ADHD under 16 are entitled to receive free medications

Aims: This study examines the cost to the State of ADHD medication and implications for universal coverage under the long-term illness (LTI) scheme for under 16s. We estimate a potential cost for universal coverage for under 16s

Methods: Drug reimbursement entitlements were explored for children with ADHD. Data were retrieved from the Primary Care Reimbursement Services for the Community Drug Schemes for 2011. The cumulative and percentage-spent on the LTI scheme was calculated

Results: (euro)107,894 (4.4 %) of the (euro)2.4 million State spent on ADHD medicines was under the LTI scheme in 2011. We estimate a potential cost of (euro)8.4 million for costs of ADHD medicines for the state based on current prescribing patterns

Conclusions: There appears to be a significant underutilisation of the LTI scheme affording children free ADHD medication. Public and professional awareness campaigns are required to ensure families get the benefits to which they are entitled, and cost does not become a barrier to treatment adherence and improved outcomes. Leading from this, we propose suggestions for cost-effective prescribing to minimise potential cost implications.

……..

J Abnorm Child Psychol. 2015 Feb;43:259-70.

INFERENCE GENERATION AND STORY COMPREHENSION AMONG CHILDREN WITH ADHD .

Van Neste J, Hayden A, Lorch EP, et al.

Academic difficulties are well-documented among children with ADHD. Exploring these difficulties through story comprehension research has revealed deficits among children with ADHD in making causal connections between events and in using causal structure and thematic importance to guide recall of stories. Important to theories of story comprehension and implied in these deficits is the ability to make inferences. Often, characters' goals are implicit and explanations of events must be inferred. The purpose of the present study was to compare the inferences generated during story comprehension by 23 7– to 11-year-old children with ADHD (16 males) and 35 comparison peers (19 males). Children watched two televised stories, each paused at five points. In the experimental condition, at each pause children told what they were thinking about the story, whereas in the control condition no responses were made during pauses. After viewing, children recalled the story. Several types of inferences and inference plausibility were coded. Children with ADHD generated fewer of the most essential inferences, plausible explanatory inferences, than did comparison children, both during story processing and during story recall. The groups did not differ on production of other types of inferences. Group differences in generating inferences during the think-aloud task significantly mediated group differences in patterns of recall. Both groups recalled more of the most important story information after completing the think-aloud task. Generating fewer explanatory inferences has important implications for story comprehension deficits in children with ADHD.

……..

J Abnorm Child Psychol. 2015 Jan;43:121-31.

MATERNAL EMOTION REGULATION MEDIATES THE ASSOCIATION BETWEEN ADULT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS AND PARENTING.

Mazursky-Horowitz H, Felton JW, MacPherson L, et al.

Mothers with elevated Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms demonstrate parenting deficits, as well as difficulties in emotion regulation (ER), which may further impact their ability to effectively parent. However, no empirical research has examined potential mediators that explain the relations between maternal ADHD symptoms and parenting. This prospective longitudinal study examined difficulties with ER as a mediator of the relation between adult ADHD symptoms and parenting among 234 mothers of adolescents recruited from

the community when they were between the ages of nine to twelve. Maternal ratings of adult ADHD symptoms, difficulties with ER, and parenting responses to their adolescents' expressions of negative emotions were collected over the course of three years. We found that maternal ADHD symptoms were negatively associated with positive parenting responses to adolescents' negative emotions, and positively associated with harsh parenting and maternal distress reactions. Moreover, maternal ER mediated the relation between adult ADHD symptoms and harsh parenting responses, while controlling for adolescent ADHD and disruptive behavior symptoms. However, maternal ER did not mediate the relation between ADHD symptoms and positive or distressed parental responses. Thus, it appears that ER is one mechanism by which maternal ADHD symptoms are associated with harsh responses to their adolescents' expressions of negative emotion. These findings may have downstream implications for adolescent adjustment.

……..

J Abnorm Child Psychol. 2015 Feb;43:283-96.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SOCIAL SKILLS IN YOUTH: A MODERATED MEDIATION MODEL OF EMOTION DYSREGULATION AND DEPRESSION.

Bunford N, Evans SW, Becker SP, et al.

Although studies document an association between Attention-Deficit/Hyperactivity Disorder (ADHD) and social problems, little is known about mediating or moderating mechanisms underlying this association. We examined whether, among youth, emotion dysregulation (ED) mediates the negative association between ADHD and social skills, and whether this mediational process is moderated by symptoms of depression. A total of 171 youth with ADHD (76 % male; Mage = 12.15, SD = 0.95) and their parents completed measures of ED, depression, and social skills. Results indicated that, after controlling for oppositional defiant disorder, the negative association between ADHD and social skills was mediated by ED. Further, this indirect effect was relevant for youth with non-clinical and subclinical levels of depression but not for those with clinical levels of depression. These findings underscore the importance of ED in the association between ADHD and social functioning among youth and suggest a need for additional research to understand how and when ED impacts such functioning.

……..

J Abnorm Child Psychol. 2015 Jan;43:133-47.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS MEDIATE THE ASSOCIATION BETWEEN DEFICITS IN EXECUTIVE FUNCTIONING AND SOCIAL IMPAIRMENT IN CHILDREN .

Bunford N, Brandt NE, Golden C, et al.

We investigated whether symptoms of attention-deficit/hyperactivity disorder (ADHD) are pathways through which deficits in inhibition and working memory are associated with teacher- and parent-rated social impairment in children. Participants were 64 children (55 % males; 53 % with ADHD) in grades 3–6. Consistent with our hypotheses, the association between inhibition and social impairment was mediated by hyperactivity/impulsivity and the association between working memory and social impairment was mediated by inattention. Support was not obtained for alternative models wherein the association between inhibition and social impairment was mediated by inattention, and the association between working memory and social impairment was mediated by hyperactivity/impulsivity. Further, tests of hierarchical models suggest that neither inhibition nor working memory is primary but, rather, that these cognitive processes are related to one another and that they collectively (but not uniquely) contribute to hyperactivity/impulsivity and inattention. These findings have implications for conceptual models of ADHD, for understanding factors that influence and sustain social impairment among youth with symptoms of the disorder, and for interventions aimed to addressing such impairment.

……..

J Abnorm Child Psychol. 2015 Jan;43:107-19.

CHILD ADHD AND ODD BEHAVIOR INTERACTS WITH PARENT ADHD SYMPTOMS TO WORSEN PARENTING AND INTERPARENTAL COMMUNICATION.

Wymbs BT, Wymbs FA, Dawson AE.

Attention-deficit hyperactivity disorder (ADHD) in children and adults increases risk of parenting difficulties and interparental discord. However, little is known about whether disruptive child behavior and adult ADHD operate additively or synergistically to predict parenting and interparental relationship quality. As part of a larger study, 90 parent couples were randomly assigned to interact with a 9–12 year-old confederate child exhibiting either ADHD/ODD-like behavior or typical behavior. Before these interactions, parents reported their own ADHD symptoms. Afterwards, parents reported on their partner's parenting and interparental communication behavior. Observers coded the parenting and communication behavior of both partners during the tasks. Child ADHD/ODD-like behavior was found to predict less positive and more negative parenting and communication reported by partners and observers beyond adult ADHD symptoms and other covariates. Elevated adult ADHD symptoms only uniquely increased risk of observer-coded negative parenting. Child and adult ADHD behavior interacted synergistically to predict partner-reported negative parenting and interparental communication, such that parents reporting greater ADHD symptoms—especially inattentiveness—were rated by their partners as parenting and communicating more negatively when managing child ADHD/ODD-like behavior than parents with fewer ADHD symptoms or those managing typical child behavior. Child and adult ADHD behavior did not interact to predict observer-coded parenting or interparental communication, and patterns did not differ for mothers or fathers. Our results underscore the potential risk of parents with elevated ADHD symptoms parenting and communicating negatively, at least as perceived by their partners, during interactions with children exhibiting ADHD/ODD behavior.

……..

J Abnorm Child Psychol. 2015 Feb;43:271-81.

MODERATORS OF NEUROPSYCHOLOGICAL MECHANISM IN ATTENTION-DEFICIT HYPERACTIVITY DISORDER.

Nikolas MA, Nigg JT.

Neuropsychological measures have been proposed as both a way to tap mechanisms and as endophenotypes for child ADHD. However, substantial evidence supporting heterogeneity in neuropsychological performance among youth with ADHD as well as apparent effect differences by sex, age, and comorbidity have slowed progress. To address this, it is important to understand sibling effects in relation to these moderators. 461 youth ages 6–17 years (54.8 % male, including 251 youth with ADHD, 107 of their unaffected biological siblings, and 103 non-ADHD controls) completed diagnostic interviews and a theoretically informed battery of neuropsychological functioning. A structural equation model was used to consolidate neuropsychological domains. Group differences between unaffected siblings of youth with ADHD and controls across each domain were first examined as the primary endophenotype test for ADHD. Moderation of these effects was evaluated via investigation of interactions between diagnostic group and both proband and individual level characteristics, including sex, age, and comorbidity status. Unaffected siblings performed worse than control youth in the domains of inhibition, response time variability, and temporal information processing. Individual age moderated these effects, such that differences between controls and unaffected siblings were pronounced among younger children (ages 6–10 years) but absent among older youth (ages 11–17 years). Evidence for moderation of effects by proband sex and comorbidity status produced more variable and smaller effects. Results support the utility of inhibition, response time variability, and temporal processing as useful endophenotypes for ADHD in future genetic associations studies of the disorder, but suggest this value will vary by age among unaffected family members.

……..

J Abnorm Child Psychol. 2015 Jan;43:149-61.

REINFORCEMENT ENHANCES VIGILANCE AMONG CHILDREN WITH ADHD: COMPARISONS TO TYPICALLY DEVELOPING CHILDREN AND TO THE EFFECTS OF METHYLPHENIDATE.

Bubnik MG, Hawk LWJ, Pelham WEJr, et al.

Sustained attention and reinforcement are posited as causal mechanisms in Attention-Deficit/Hyperactivity Disorder (ADHD), but their interaction has received little empirical study. In two studies, we examined the impact of performance-based reinforcement on sustained attention over time, or vigilance, among 9- to 12-year-old children. Study 1 demonstrated the expected vigilance deficit among children with ADHD (n = 25; 12 % female) compared to typically developing (TD) controls (n = 33; 22 % female) on a standard continuous performance task (CPT). During a subsequent visit, reinforcement improved attention more among children with ADHD than controls. Study 2 examined the separate and combined effects of reinforcement and acute methylphenidate (MPH) on CPT performance in children with ADHD (n = 19; 21 % female). Both reinforcement and MPH enhanced overall target detection and attenuated the vigilance decrement that occurred in no-reinforcement, placebo condition. Cross-study comparisons suggested that the combination of MPH and reinforcement eliminated the vigilance deficit in children with ADHD, normalizing sustained attention. This work highlights the clinically and theoretically interesting intersection of reinforcement and sustained attention.

……..

J Autism Dev Disord. 2015 Feb;45:481-94.

CARDIAC REACTIVITY AND STIMULANT USE IN ADOLESCENTS WITH AUTISM SPECTRUM DISORDERS WITH COMORBID ADHD VERSUS ADHD.

Bink M, Popma A, Bongers IL, et al.

A large number of youngsters with autism spectrum disorders (ASD) display comorbid attention deficit/hyperactivity disorder (ADHD) symptoms. However, previous studies are not conclusive whether psychophysiological correlates, like cardiac reactivity, are different for ASD with comorbid ADHD (ASD+) compared to ADHD. Therefore, the current study investigated (dis)similarities in cardiac reactivity and attention task performance. In a clinical sample, adolescents diagnosed with ASD+ (n = 20) versus ADHD (n = 36) and stimulant medication use (56 %) were compared during a baseline with eyes closed and task performance. Results for cardiac reactivity were similar for both diagnostic groups. Stimulant-medicated adolescents showed decreased adaptation of LF/HF ratio and faster reaction times than stimulant-free adolescents. The current study underlines the psychophysiological overlap of ADHD symptoms in adolescents with ASD+ and adolescents with ADHD.

……..

J Autism Dev Disord. 2015.

BRIEF REPORT: ADAPTIVE FUNCTIONING IN CHILDREN WITH ASD, ADHD AND ASD + ADHD.

Ashwood KL, Tye C, Azadi B, et al.

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) often co-occur. Children with ASD and ADHD demonstrate deficits in adaptive functioning, yet pure and comorbid groups have not been directly compared. Vineland Adaptive Behaviour Scales (VABS-II) data were examined in boys with ASD (n = 17), ADHD (n = 31) and ASD + ADHD (n = 38). Results demonstrated lower socialisation and composite scores and greater discrepancy between cognitive and adaptive abilities in the ASD + ADHD group compared to the ADHD-only group. Significant associations were shown between reduced adaptive functioning and autism symptoms, but not ADHD symptoms. Children with ASD + ADHD present with exacerbated impairments in adaptive functioning relative to children with ADHD, associated with ASD symptoms. Disentangling variation in adaptive skills may aid the assessment of complex cases.

……..

Journal of Behavioral Education. 2014 Dec;23:421-34.

IMPLEMENTATION OF A SELF-MONITORING APPLICATION TO IMPROVE ON-TASK BEHAVIOR: A HIGH-SCHOOL PILOT STUDY.

Wills HP, Mason BA.

Technological innovations offer promise for improving intervention implementation in secondary, inclusive classrooms. A withdrawal design was employed with two high-school students in order to assess the effectiveness of a technologically delivered, self-monitoring intervention in improving on-task behavior in a science classroom. Two students ages 14 and 15 with diagnoses of specific learning disability (Student 1) and attention deficit hyperactivity disorder (ADHD; Student 2) were selected by case manager referral due to difficulties with on-task behavior despite long-term administration of psychostimulant medication. After baseline data were collected, both students were trained in the use of a self-monitoring application (I-Connect) delivered via a handheld tablet. On-task prompts were delivered at 5-min intervals in an ABAB withdrawal design. The intervention resulted in positive, stable improvements in the primary dependent variable of on-task behavior for both students and less clear improvement in the generalization variable of disruptive behavior.

……..

Journal of Career Development. 2015 Feb;42:19-32.

ENHANCING ADHD AND LD DIAGNOSTIC ACCURACY USING CAREER INSTRUMENTS.

Dipeolu A, Hargrave S, Storlie CA.

Individuals diagnosed with mental health disorders may have work-related difficulties that impact functioning in all life domains. With limited research on the integration of career and mental health counseling, authors used a discriminant function analysis to assess the predictability of accurately identifying diagnostic categories among 258 adolescents with attention-deficit hyperactivity disorder (ADHD) and learning disabilities (LDs) through the use of constructs derived from three career development inventories. Results showed that using an appropriate interpretive T-score from individuals with the same diagnosis enhanced the ability to discriminate between diagnoses of LD and ADHD in young adults. Implications for the practice of career counseling and development are provided.

……..

Journal of Child and Family Studies. 2015 Jan;24:76-94.

EVALUATION OF MBCT FOR ADOLESCENTS WITH ADHD AND THEIR PARENTS: IMPACT ON INDIVIDUAL AND FAMILY FUNCTIONING.

Haydicky J, Shecter C, Wiener J, et al.

Adolescents with Attention Deficit/Hyperactivity Disorder (ADHD) often experience emotional and behavioural difficulties which contribute to stress and conflict in their family relationships. Mindfulness-based cognitive therapy (MBCT) is a promising intervention for these families. We evaluated the efficacy of an adaptation of a MBCT intervention for 13–18 year olds with ADHD and their parents. Adolescents (n = 18) and parents (n = 17) attended 8 weekly parallel group sessions. Participants completed questionnaires at four time points: 4 weeks before the intervention to control for general time effects, on the first and last days of the intervention, and 6 weeks after the intervention. Participants reported on adolescent ADHD symptoms, internalizing and externalizing problems, functional impairment, family functioning, parenting stress, and mindfulness. There were no significant changes on parent rated variables during the baseline period. Results of repeated measures ANOVA revealed reductions in the adolescents' inattention, conduct problems, and peer relations problems after the intervention, according to parental report. Parents also reported reductions in parenting stress and increases in mindful parenting. Adolescents did not report improvements on any variables during the intervention period. Paired t-tests indicated that improvements in adolescent symptomatology and mindful parenting were maintained 6 weeks after the intervention ended. Parents reported additional reductions in parenting stress at follow-up. Adolescents reported reductions in internalizing problems at follow-up. Overall, our results support and extend the preliminary findings of previous investigations of MBCT showing it to be a promising treatment for adolescents with ADHD and their parents.

……..

Journal of Child Psychology and Psychiatry. 2014 Dec;55:1345-53.

ADHD AND RISKY SEXUAL BEHAVIOR IN ADOLESCENTS: CONDUCT PROBLEMS AND SUBSTANCE USE AS MEDIATORS OF RISK.

Sarver DE, McCart MR, Sheidow AJ, et al.

Background: Recent studies have linked attention-deficit/hyperactivity disorder (ADHD) to elevated rates of risky sexual behavior (RSB) in adult samples. The current study tested whether ADHD symptoms were associated with RSB among adolescents, and examined comorbid conduct problems and problematic substance use as joint mediators of this association.

Methods: ADHD symptoms, conduct problems (oppositional defiant disorder/conduct disorder symptoms), problematic alcohol use (alcohol use disorder symptoms, alcohol use frequency), problematic marijuana use (marijuana use disorder symptoms, marijuana use frequency), and RSB were assessed among an ethnically diverse cross-sectional sample of adolescents (N = 115; mean age = 14.9 years) involved in the juvenile justice system.

Results: Bootstrapped mediation models revealed an initial association between ADHD symptoms and RSB that was accounted for fully by the influence of problematic alcohol and marijuana use, but not conduct problems. A follow-up multiple groups mediation analysis demonstrated that the relationship between ADHD symptoms and RSB emerged only among youth with clinically elevated conduct problems, and that problematic marijuana use fully accounted for this relationship. Hyperactive/impulsive, but not inattentive, symptoms were related to RSB, although the pattern of indirect effects was consistent with the multiple groups analysis.

Conclusions: The association between ADHD and adolescent RSB is restricted to youth with elevated comorbid conduct problems and reflects the contributions of comorbid marijuana use problems, and to a lesser extent alcohol use problems. Early identification and treatment of these comorbid conditions may be important for the prevention of negative sexual health outcomes among youth with ADHD.

……..

Journal of Child Psychology and Psychiatry. 2015 Feb;56:122-29.

PARENTAL PSYCHOPATHOLOGY IN FAMILIES OF CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EXPOSED TO MATERNAL SMOKING DURING PREGNANCY.

Sengupta SM, Fortier MÈ, Thakur GA, et al.

Background: Both genetic and environmental factors have been implicated in the etiology of attention-deficit/ hyperactivity disorder (ADHD). We had previously suggested that exposure to maternal smoking during pregnancy (MSDP) may be a valid basis for delineating a distinct subtype of ADHD, where children exposed to MSDP present with a more severe clinical picture. Here, we examine the psychopathology of parents in this group, to better understand the etiology of ADHD.

Methods: Using the Family Interview for Genetic Studies in a sample of 514 families of children with ADHD, we collected data pertaining to lifetime parental psychopathology. Families were stratified based on maternal smoking during the complete gestational period. The frequency of different disorders was compared using the x^2 statistic.

Results: In the group where mothers smoked during pregnancy, both parents were significantly more likely to have antisocial personality disorder, and problems with alcohol and drug abuse. Mothers had a significantly higher frequency of major depressive disorder (MDD), while fathers showed a trend for both MDD and bipolar disorder.

Conclusions: Based on the pattern of psychopathology in parents of children exposed to MSDP, as well as earlier reports of the severe clinical, behavioral, and cognitive phenotype in these children, combined with the large body of epidemiological evidence, we propose that these children present a distinct subtype of ADHD with comorbid conduct disorder. Furthermore, we propose that MSDP may be a proxy measure to help delineate this subtype. Keywords: Attention-deficit/hyperactivity disorder, behavior problems, comorbidity, family history, smoking.

……..

Journal of Child Psychology and Psychiatry. 2015 Jan;56:40-48.

DIFFERENTIAL IMPACT OF METHYLPHENIDATE AND ATOMOXETINE ON SUSTAINED ATTENTION IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Bédard AC, Stein MA, Halperin JM, et al .

Background This study examined the effects of atomoxetine (ATX) and OROS methylphenidate (MPH) on laboratory measures of inhibitory control and attention in youth with attention-deficit/hyperactivity disorder (ADHD). It was hypothesized that performance would be improved by both treatments, but response profiles would differ because the medications work via different mechanisms.

Methods One hundred and two youth (77 male; mean age = 10.5 ± 2.7 years) with ADHD received ATX (1.4 ± 0.5 mg/kg) and MPH (52.4 ± 16.6 mg) in a randomized, double-blind, crossover design. Medication was titrated in 4–6-week blocks separated by a 2-week placebo washout. Inhibitory control and attention measures were obtained at baseline, following washout, and at the end of each treatment using Conners' Continuous Performance Test II (CPT-II), which provided age-adjusted T-scores for reaction time (RT), reaction time variability (RT variability), and errors. Repeated-measures analyses of variance were performed, with Time (premedication, postmedication) and Treatment type (ATX, MPH) entered as within-subject factors. Data from the two treatment blocks were checked for order effects and combined if order effects were not present.

Clinical trial registration: Clinicaltrials.gov: NCT00183391.

Results Main effects for Time on RT ($p = .03$), RTSD ($p = .001$), and omission errors ($p = .01$) were significant. A significant Drug × Time interaction indicated that MPH improved RT, RTSD, and omission errors more than ATX ($p < .05$). Changes in performance with treatment did not correlate with changes in ADHD symptoms.

Conclusions MPH has greater effects than ATX on CPT measures of sustained attention in youth with ADHD. However, the dissociation of cognitive and behavioral change with treatment indicates that CPT measures cannot be considered proxies for symptomatic improvement. Further research on the dissociation of cognitive and behavioral endpoints for ADHD is indicated.

……..

Journal of Clinical Child and Adolescent Psychology. 2015 Jan;44:68-79.

REPLICATION AND EXTERNAL VALIDATION OF A BI-FACTOR PARAMETERIZATION OF ATTENTION DEFICIT/HYPERACTIVITY SYMPTOMATOLOGY.

Willoughby MT, Blanton ZE.

This study evaluated the fit and criterion validity of a recently proposed bi-factor structure for attention deficit/hyperactivity disorder (ADHD) symptoms. Participants were 1,093 children, drawn from an ongoing prospective longitudinal study, whose ADHD symptoms were rated by parents and teachers when children were in 1st grade. The criterion validity of the bi-factor model was established using a range of school-based outcomes that included treatment utilization, teacher perceptions of the need for treatment, academic functioning, and peer and teacher relationship quality. Results indicated that a bi-factor model parameterization provided an equally good fit to parent, teacher, and combined reports of ADHD symptoms as did traditional 1-, 2-, and 3-factor models. However, in contrast to traditional models, the bi-factor parameterization acknowledged both the unity and diversity of ADHD symptoms. The general ADHD latent factor explained the vast majority of the observed variation in every symptom. Whereas the general ADHD latent factor was significantly associated with all 15 outcomes, the specific Inattentive factor explained unique variation in 9 (primarily the academically oriented) outcomes and the specific Hyperactive-Impulsive factor explained unique variation in 2 outcomes. The general ADHD factor was more strongly correlated with each of the observed ADHD symptom scores (total, inattentive, hyperactive-impulsive) than was either specific factor. Results are discussed with respect to how changes in the conceptualization of the factor structure correspond to recent changes to the diagnostic criteria for ADHD, as well as whether/how individual differences in inattention and hyperactivity-impulsivity might be used to differentiate children who are diagnosed with ADHD.

……..

J Dev Behav Pediatr. 2015 Feb;36:124-26.

APRAXIA, AUTISM, ATTENTION-DEFICIT HYPERACTIVITY DISORDER: DO WE HAVE A NEW SPECTRUM?

Schumacher J, Strand KE, Augustyn M .

CASE: Gio is a bilingual 6-year 10-month-old boy new to your practice who presents for an unscheduled visit with concerns for speech and language delay. He was born in Portugal, and his native language is Portuguese. When he was 21 months old, his family moved to Italy and then moved to the United States 3 years later. He had very little contact with other children while living in Italy, but his parents report that he has made friends quickly in the United States. His family speaks Portuguese at home, although his father is fluent in English. He started school 3 months after moving to the United States and is currently repeating kindergarten. He is in a sheltered English classroom with several other students who speak Portuguese. He is able to understand and follow directions in English. A recent school evaluation revealed solidly average nonverbal reasoning skills and relative weaknesses in verbal reasoning and working memory. His speech is described as unintelligible in conversation, both in English and Portuguese.

Results of a special education evaluation qualified him for services with a bilingual therapist. His teachers are very concerned that he may have autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). They describe him as having limited interest in other children, poor eye contact, and hypersensitivities. He wanders at recess. He is very skilled at art and seems to prefer to draw rather than interact with others. He needs constant support and redirection throughout the school day. He has difficulty putting on his coat, using playground equipment, and following daily classroom routines. On the Vanderbilt Rating Scale, his teacher endorses 17 of 18 ADHD symptoms as present often or very often and significant impairment in his performance. Gio presents to your clinic as a relatable young boy with childhood apraxia of speech. Only his productions of single words and short routine phrases are intelligible. He attempts to engage in conversation but averts his gaze and becomes frustrated when asked to repeat things. Scores on the Parent Conners Rating Scale and Social Responsiveness Scale are not elevated. When you bring up school's concerns, his father describes feeling somewhat badgered by his teachers about possibility of ASD. School is considering placement in an inclusion classroom for children with ASD. What do you recommend? How would you advise his parents?

……..

J Headache Pain. 2014;15.

EHMTI-0013. THE RELATIONS BETWEEN ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND DIFFERENT TYPES OF HEADACHES IN A NON-CLINICAL SAMPLE OF ADOLESCENTS.

Genizi J, Marom D, Srugo I, et al.

Introduction: Stress is considered to be a major trigger for aggravation of headaches. In a previous study we demonstrated a high prevalence of ADHD among patients who were referred to a pediatric clinic due to headaches. In the present study we examined whether this is true for the general population of adolescents.

Aims: To assess the prevalence of primary headaches among school students and the relation to learning disorders and ADHD.

Methods: A Computerized questionnaire that was filled out anonymously by tenth grade students attending a high school in Haifa, after receiving informed consent from parents and informed ascent from the students participating in the study.

Results: Out of 310 valid questionnaires, 230 students (81%) complained about headaches (88% of the girls and 76% of the boys, p=0.08), 98 of them (43%) elaborated on the characteristics of their headaches: 50% matched migraine, 28% Tension Type Headache, and in 22% there was not enough data to make a definitive diagnosis. Out of the students who had headaches, 27% were diagnosed with ADHD and 32% with learning disabilities. Students who felt as if they had ADHD and or learning disabilities but were not diagnosed formally with these diagnoses had significantly more headaches than their diagnosed peers (p=0.002).

Conclusions: Our work indicates that students who feel that they have learning disabilities and or ADHD but were not diagnosed, complain more about headaches compared to their peers who were either diagnosed or did not feel they had one of the two diagnoses.

……..

J Intellect Disabil Res. 2015.

INTELLECTUAL FUNCTIONING IN RELATION TO AUTISM AND ADHD SYMPTOMATOLOGY IN CHILDREN AND ADOLESCENTS WITH 22Q11.2 DELETION SYNDROME.

Hidding E, Swaab H, Vorstman JAS, et al.

The 22q11.2 deletion syndrome (22q11DS; velo-cardio-facial syndrome) is associated with an increased risk of various disorders, including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). With this study, we aimed to investigate the relation between intellectual functioning and severity of ASD and ADHD symptomatology in 22q11DS.

Method: A sample of 102 individuals (62 females) with 22q11DS aged 9 to 18.5 years were assessed using age appropriate Wechsler scales of intelligence as well as psychological and psychiatric assessment to evaluate the presence of ASD and ADHD symptomatology. Results: Intelligence profiles were characterised by lower scores on the factor perceptual organisation and higher scores on the factor processing speed, with on subtest level higher scores on digit span and lower scores on arithmetic and vocabulary as compared with the mean factor or subtest score respectively. No differences in intelligence profiles were found between subgroups with and without ASD and/or ADHD. Low scores on coding were associated with higher severity of ASD symptomatology, while lower scores on block design were associated with more severe ADHD symptomatology. Conclusions: On several sub-domains of intelligence, poorer performance was associated with higher severity of ASD and ADHD symptomatology. The impact of developmental disorders in 22q11DS can be traced in specific domains of intellectual functioning as well as in severity of symptomatology.

……..

J Invest Med. 2015;63:334-35.

IMPACT OF RACE AND GENDER IN THE DIAGNOSIS OF ATTENTION DEFICIT HYPERACTVITY DISORDER.

Holmes J, Preudhomme D, Connelly R, et al.

Purpose of Study: Attention deficit hyperactivity disorder(ADHD) is the most commonly diagnosed behavioral disorder in children. Recent assessments suggest a prevalence from 4%-10% in the U.S. The prevalence of ADHD in females or African Americans (AAs) is reported at a lower rate. There is a paucity of research of ADHD symptoms, diagnosis, and treatment in females and AAs. We hypothesize that AA children and females may be under diagnosed compared with other cohorts.

Methods Used: Between July 1st, 2011 and February 28th, 2014, we performed a cross sectional analysis of patients aged 5 to 18 years old in a pediatric outpatient department using ICD9 diagnosis code of 314.01. Patient characteristics such as race, gender, co-morbidities, treatment types, and number of visits were collected. Descriptive statistics and odds ratio were calculated as appropriate.

Summary of Results: Out of a total of 9,423 patients, 1,046 (11%) were diagnosed with ADHD. Amongst patients with ADHD, 580 (55%) were AA. Of the ADHD population, 293 (28%) were females. The average age was 10(+/- 3.3) years old. The number of visits was on average 4(+/- 3.1) times over 31 months. Long-acting medications were used in 883 patients, 79% were prescribed Vyvanse. Patients receiving behavioral therapy and medication totaled 275(26%). Secondary analysis shows that the prevalence of ADHD diagnosis in AA population is 8% compared to 17% in our Caucasian population. The prevalence of ADHD in females was 6%compared to 13% in males. The likelihood of being diagnosed with ADHD as Caucasian was twice that of the AA population (OR 2.2, 95% CI 1.9-2.6). The possibility of males to be diagnosed with ADHD was more than twice that of females (OR 2.4, 95% CI 2.1-2.8).

Conclusions: In the past decade, the research evaluating ADHD across gender and race is limited. Our review indicates that AA and female children are significantly less likely to be diagnosed with ADHD. These disparities may be the consequence of rating scale bias, difference in symptom presentation, or a cultural difference in the approach to mental illness. An understanding of which etiological and cultural mechanisms account for the observed racial and gender differences would allow for more appropriate diagnosis and care for these children.

……..

J Neuropsychiatry Clin Neurosci. 2013;25:18.

INTEGRATING NEUROPSYCHOLOGY, NEUROBIOLOGY, AND PHENOMENOLOGY: A CRITIQUE ON ADHD-OCD COMORBIDITY ACROSS THE LIFESPAN.

Abramovitch A, Mittelman A, Dar R.

Background: The concept of comorbidity between ADHD and OCD has been discussed for two decades. However, stark contrast in the phenomenology, neurobiology, and pharmacotherapy of these disorders, taken alongside the high variability in reported co-occurrence rates, demands a comprehensive examination.
Objective: We reviewed studies reporting ADHD-OCD co-occurrence rates in children and adults, critically examining methodological, phenomenological, and etiological issues.
Methods: Medline and ISI databases were searched for relevant keywords. We recorded prevalence rates, age, gender, recruitment characteristics, and exclusion criteria. This review includes 45 samples, spanning 22 years, and 4,042 subjects.
Results: Unusually high variability of co-occurrence rates was identified (range: 0-55%). Studies suffered from a variety of methodological problems, including very few community samples and inconsistent exclusionary criteria. Etiological (i.e., genetic) backing has been provided only for a pediatric comorbidity. Also, inflated rates of ADHD-OCD cooccurrence may be mediated by the presence of tic disorders. Moreover, some evidence of impaired neuronal maturational processes in pediatric OCD may lead to transient phenotypical expressions that resemble ADHD symptomatology.
Conclusion: Unusually high variability in co-occurrence rates was identified. Average sample age was negatively correlated with co-occurrence rates. Methodological concerns and lack of an etiological account for adult ADHD-OCD comorbidity might weaken the validity of this comorbidity. Neurobiological and clinical differences may be masked by similar neuropsychological impairments. Clinicians should consider the possibility that ADHD-like symptoms associated with OCD-specific symptomatology may be misdiagnosed as ADHD. Recommendations for practitioners and for future research are discussed.

……..

J Pediatr. 2015;166:20-25.

ANTENATAL AND EARLY POSTNATAL ANTECEDENTS OF PARENT-REPORTED ATTENTION PROBLEMS AT 2 YEARS OF AGE.

Downey LC, O'Shea TM, Allred EN, et al.

Objectives: To assess antenatal and early postnatal antecedents of attention problems identified by the Child Behavior Checklist in extremely preterm children.
Study design: In a cohort of 826 children born between 23 and 27 weeks' gestation, we collected demographic, birth, and postnatal information. We then identified behavior problems by using parent ratings from the Child Behavior Checklist at 2 years' adjusted age. We created time-oriented logistic regression risk models to identify significant risk factors for attention problems and Diagnostic and Statistical Manual of Mental Disorders-compatible attention deficit/hyperactivity problems (ADHPDSM).
Results: Children were at increased risk of both attention problems if they were born to a woman who had no formal education beyond high school and/or a woman who was exposed to secondhand smoke. Recovery of a single organism from the placenta was associated with increased risk of an attention problem, and fetal stem vessel thrombosis and recovery of Mycoplasma species were associated with increased risk of ADHPDSM. Infants of multifetal gestations were at reduced risk of both attention problems. The only postnatal risk factor for an attention problem was recovery of bacteria from a tracheal aspirate.
Conclusion: Among extremely preterm infants, several potentially modifiable antenatal and perinatal antecedents are associated with increased risk for attention problems and ADHPDSM at 2 years adjusted age.

……..

J Psychophysiol. 2015;29:26-32.

PHYSICAL FITNESS AND RESTING EEG IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: AN EXPLORATORY STUDY.

Huang C-W, Huang C-J, Hung C-L, et al.

Children with attention deficit hyperactivity disorder (ADHD) are characterized by a deviant pattern of brain oscillations during resting state, particularly elevated theta power and increased theta/alpha and theta/beta ratios that are related to cognitive functioning. Physical fitness has been found beneficial to cognitive performance in a wide age population. The purpose of the present study was to investigate the relationship between physical fitness and resting-state electroencephalographic (EEG) oscillations in children with ADHD. EEG was recorded during eyes-open resting for 28 children (23 boys and 5 girls, 8.66 (euro) 1.10 years) with ADHD, and a battery of physical fitness assessments including flexibility, muscular endurance, power, and agility tests were administered. The results indicated that ADHD children with higher power fitness exhibited a smaller theta/alpha ratio than those with lower power fitness. These findings suggest that power fitness may be associated with improved attentional self-control in children with ADHD.

……..

J Sport Health Sci. 2015.

EFFECTS OF ACUTE AEROBIC EXERCISE ON RESPONSE PREPARATION IN A GO/NO GO TASK IN CHILDREN WITH ADHD: AN ERP STUDY.

Chuang L-Y, Tsai Y-J, Chang Y-K, et al.

Purpose: The purpose of this study was to investigate the impact of acute exercise on reaction time and response preparation during a Go/No Go Task in children with attention deficit hyperactivity disorder (ADHD).

Methods: Nineteen children with ADHD (aged between 8 and 12 years old) undertook a 30-min intervention that consisted of treadmill running or video-watching presented in a counterbalanced order on different days. A Go/No Go Task was administrated after exercise or video-watching.

Results: The results indicated a shorter reaction time and smaller contingent negative variation (CNV) 2 amplitude following exercise relative to the video-watching. For event related potential (ERP) analyses, greater CNV 1 and CNV 2 amplitudes in response to No Go stimuli in comparison to Go stimuli was observed in the video-watching session only.

Conclusion: These findings suggest that acute exercise may benefit children with ADHD by developing appropriate response preparation, particularly in maintaining a stable motor preparatory set prior to performing the given task.

……..

Lakartidningen. 2014 Sep;111:1638-41.

DIAGNOSIS AND THERAPY ARE STILL CHALLENGING, DESPITE THE RAPID GROWTH OF KNOWLEDGE.

Bejerot S, Gardener A, Humble MB.

Psychiatric diagnoses are not reflections of the aetiology of the disorder, but rather lists of symptoms with considerable overlaps, which hamper research and may cause confusion. The diagnoses of autism spectrum disorder, attention deficit hyperactivity disorder and tic disorder are often comorbid along with a number of other symptomatic syndromes. Individual immune responsivity is possibly involved in pathophysiological mechanisms. Multiple environmental factors may contribute to the clinical phenotypes. Recent research supports to some extent the involvement of dietary and nutritional factors in ADHD. In spite of impressive progress in the molecular biological understanding of the pathophysiology of these disorders, treatment options are still limited and more research is warranted.

……..

Mol Psychiatry. 2015.

THE MOLECULAR GENETIC ARCHITECTURE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Hawi Z, Cummins TDR, Tong J, et al.

Attention deficit hyperactivity disorder (ADHD) is a common childhood behavioral condition which affects 2null10% of school age children worldwide. Although the underlying molecular mechanism for the disorder is poorly understood, familial, twin and adoption studies suggest a strong genetic component. Here we provide a state-of-the-art review of the molecular genetics of ADHD incorporating evidence from candidate gene and linkage designs, as well as genome-wide association (GWA) studies of common single-nucleotide polymorphisms (SNPs) and rare copy number variations (CNVs). Bioinformatic methods such as functional enrichment analysis and proteinnullprotein network analysis are used to highlight biological processes of likely relevance to the aetiology of ADHD. Candidate gene associations of minor effect size have been replicated across a number of genes including SLC6A3, DRD5, DRD4, SLC6A4, LPHN3, SNAP-25, HTR1B, NOS1 and GIT1. Although case-control SNP-GWAS have had limited success in identifying common genetic variants for ADHD that surpass critical significance thresholds, quantitative trait designs suggest promising associations with Cadherin13 and glucosenullfructose oxidoreductase domain 1 genes. Further, CNVs mapped to glutamate receptor genes (GRM1, GRM5, GRM7 and GRM8) have been implicated in the aetiology of the disorder and overlap with bioinformatic predictions based on ADHD GWAS SNP data regarding enriched pathways. Although increases in sample size across multi-center cohorts will likely yield important new results, we advocate that this must occur in parallel with a shift away from categorical case-control approaches that view ADHD as a unitary construct, towards dimensional approaches that incorporate endophenotypes and statistical classification methods. Molecular Psychiatry advance online publication, 20 January 2015; doi:10.1038/mp.2014.183.

……..

Neuropsychiatr Dis Treat. 2015;11:343-52.

PSYCHOPATHOLOGY, SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, AND RISK FACTORS IN JUVENILE OFFENDERS.

Margari F, Craig F, Margari L, et al.

Background: The aim of this study was to assess the prevalence of potential environmental and psychopathological risk factors, with special focus on symptoms of attention-deficit/hyperactivity disorder (ADHD), in a sample of adolescent offenders in relation to the type of crime committed.

Methods: The assessment included data collection and administration of clinical standardized scales such as the Youth Self-Report and Connersnull Adolescent Self-Report Scale. A total of 135 juvenile offenders participated in the study. In relation to the type of crime committed, we identified three groups matched for age and sex (crimes against people, property crimes, and alcohol-drug-related crimes).

Results: Fifty-two percent of juvenile offenders reported educational achievement problems and 34% reported a family history of psychiatric disorders. We detected a statistically significant difference between the three groups with regard to ADHD (P=0.01) and conduct problems (P=0.034). Juvenile offenders who had committed crimes against people showed more ADHD symptoms (18%) and conduct problems (20%) than adolescents who had committed property crimes and alcohol-drug-related crimes. Sixty percent of the juvenile offenders who had committed property crimes and 54% of those who had committed alcohol-drug-related crimes showed problems in academic achievement.

Conclusion: These findings suggest the need to implement specific interventions for prevention and treatment of specific criminal behavior.

……..

Neurosci Lett. 2015;590:12-17.

RELATIONSHIP BETWEEN THETA-PHASE GAMMA-AMPLITUDE COUPLING AND ATTENTION-DEFICIT/HYPERACTIVITY BEHAVIOR IN CHILDREN.

Kim JW, Lee J, Kim H-J, et al.

The Continuous Performance Test (CPT) is a valuable tool for assessing behavior in attention-deficit/hyperactivity disorder (ADHD). Quantitative electroencephalography (QEEG) is a promising tool for the

diagnosis of ADHD. Recently, theta-phase gamma-amplitude coupling (TGC) measurement has received attention because it is a feasible method of assessing brain function. We investigated the relationship between CPT performance and EEG measures such as TGC and theta and gamma activity. EEGs were recorded from 68 volunteers from a camp for hyperactive children using a 19-electrode system. Their TGC, theta and 40. Hz gamma activity were estimated and compared with results obtained on the Korean ADHD Rating Scale (KARS) and the Intermediate Visual and Auditory (IVA) CPT. The results demonstrated significant negative partial correlations between TGC and the IVA CPT, such as the Response Control Quotient (RCQ) and Attention Quotient (AQ). TGC successfully identified the level of dysfunctional interaction of the attention/arousal system at a multi-scale large network level. It is thought that as the TGC increases, the efficacy of the system is very low or dysfunctional. Compensatory hyper-arousal patterns of the dysfunctional attention/arousal system may account for this effect. TGC is a promising neurophysiological marker for ADHD behavior in children.

……..

Patient. 2015.

SYSTEMATIC REVIEW OF PATIENTSNULL AND PARENTSNULL PREFERENCES FOR ADHD TREATMENT OPTIONS AND PROCESSES OF CARE.

Schatz NK, Fabiano GA, Cunningham CE, et al.

Results: Methods and designs varied considerably across studies. Relatively few studies focused on preferences among children, adolescents, and adults compared with those that focused on the preferences of parents of children with ADHD. The majority of studies focused primarily on medication treatments, with many fewer focused on psychosocial treatments. Some studies indicated that parents of children with ADHD prefer to avoid stimulant medications in favor of behavioral or psychosocial interventions. Others report that parents see medication as a preferred treatment. Treatment outcome is a particularly salient attribute for treatment decisions for many informants

Conclusions: Potential outcomes of various treatments play a proximal role in patientsnull and familiesnull decisions for ADHD treatment. Because the majority of studies focus on medication treatments for children with ADHD, more research is necessary to understand preferences related to behavioral and other psychosocial treatments both as stand-alone interventions and used in combination with medication. Additional research is also needed to assess the treatment preferences of adults with ADHD. In general, DCE, BWS, and SGI methods allow measurement of patient preferences in a manner that approximates the uncertainty and trade-offs inherent in real-world treatment decision making and provides valuable information to inform patient-centered and family-centered treatment

Objective: The purpose of this review was to synthesize reports across existing DCE, BWS, TTO, and SGI studies to assess which aspects of ADHD treatment are most studied as well as most preferred and influential in treatment decisions

Background: Patient preferences are an important topic of study with respect to attention-deficit hyperactivity disorder (ADHD) interventions, as there are multiple treatment choices available, multiple developmental levels to consider, and multiple potential individuals involved in treatment (children, parents, and adults with ADHD). Stated preference methods such as discrete choice experiment (DCE), best-worst scaling (BWS), and other utility value methods such as standard gamble interview (SGI) and time trade-off (TTO) are becoming more common in research addressing preferences for ADHD treatments. A synthesis of this research may facilitate improved patient-centered and family-centered treatment for ADHD

Data Sources: MEDLINE, PsycINFO

Study Selection: A total of 41 studies referring to preferences for ADHD treatment were identified through the initial search and contact with researchers. Of these, 13 reported ADHD treatment preference data from a study using DCE, BWS, or SGI methods. No TTO studies were identified that met inclusion criteria.

……..

Pediatr Integr. 2014;18:655-67.

LEARNING DISORDERS AND ADHD. DIAGNOSIS AND TREATMENT.

Aguilera AS, Mosquera GA, Blanco BM.

Learning difficulties in children with ADHD are frequent during school age. Social and school changes can act as a trigger, but also attention deficit and comorbid learning disorders. Of these, specific learning disorders include reading, writing and math that represent 39[%], 60[%] and 26[%] respectively. Global cognitive deficit or borderline intelligence can also be underlying learning difficulties in a child with an initial ADHD diagnosis. The presence of clumsiness in a child with ADHD is also remarkable, and pediatrician must be aware of procedural learning disorders that associate low academic achievement, social communication difficulties leading to low self-esteem, high risk of bullying and psychiatric disorders.

……..

Pediatr Integr. 2014;18:678-88.

ADHD: ETHICAL AND LEGAL ASPECTS.

Ruiz Lazaro PJ.

Working with children and adolescents with ADHD should be based on universal ethical principles that can be accepted by all (non-maleficence, autonomy, beneficence and distributive justice). The spanish legal system tackles the difficult reconciliation of the rights of minors to the exercise of parental rights and recognizes that the growth and development of children from infancy through adolescence passes the progressive maturation of participatory power of the child in making decisions about their health care so that as children get older and their skills increase, they should include more fully in decisions about your treatment. Every action of a pediatrician in children and adolescents with ADHD should respond, to fit a correct ethical standard, three parameters: suitability, necessity and proportionality.

……..

Pediatr Neurol. 2015.

PRIMARY COMPLEX MOTOR STEREOTYPIES IN OLDER CHILDREN AND ADOLESCENTS: CLINICAL FEATURES AND LONGITUDINAL FOLLOW-UP.

Oakley C, Mahone EM, Morris-Berry C, et al.

Background: Complex motor stereotypies are rhythmic, repetitive, fixed, and purposeless movements that stop with distraction. Once believed to occur only in children with autism spectrum or other developmental disorders, their presence in otherwise typically developing children (primary) has been well-established. In primary complex motor stereotypies, little information is available about the long-term outcome of these movements or existing comorbidities.

Methods: Forty-nine healthy participants (31 boys), ages 9 to 20years with primary complex motor stereotypies who were previously diagnosed at a pediatric movements disorder clinic, were identified from medical records. Parents or the young adult (if older than age 18), completed a telephone interview evaluating family history, outcome, and comorbidities including attention-deficit hyperactivity disorder, obsessive compulsive disorder, anxiety, and tics/Tourette syndrome. Standardized questionnaires assessing attention-deficit hyperactivity, obsessive compulsive disorder, and anxiety were used to validate parent report of comorbidities.

Results: Stereotypy onset occurred before age 3years in 98%. In all but one individual, stereotypies persisted at thetime of phone follow-up (follow-up range: 6.8-20.3years). Positive family history of complex motor stereotypies was identified in 39%. Most participants (92%) had concern for at least one comorbid disorder, including parent-/patient-reported clinically elevated levels of anxiety (73%), attention-deficit hyperactivity (63%), obsessive compulsive disorder (35%), and tics/Tourette syndrome (22%).

Conclusion: Primary motor stereotypies typically begin in early childhood and, although reduced in frequency and duration, persist at least through the teenage years. Repetitive movements are associated with a variety of comorbidities that often have a greater functional impact than the stereotypic behavior.

……..

Preventive Med Reports. 2015;2:1-3.

A TELEVISION IN THE BEDROOM IS ASSOCIATED WITH HIGHER WEEKDAY SCREEN TIME AMONG YOUTH WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADD/ADHD).

Lo CB, Waring ME, Pagoto SL, et al.

Objective: A TV in the bedroom has been associated with screen time in youth. Youth with attention deficit hyperactivity disorder (ADD/ADHD) have higher rates of screen time, but associations with bedroom TVs are unknown in this population. We examined the association of having a bedroom TV with screen time among youth with ADD/ADHD.

Methods: Data were from the 2007 National Survey of Children's Health. Youth 6-17. years whose parent/guardian reported a physician's diagnosis of ADD/ADHD (n. =. 7024) were included in the analysis. Parents/guardians reported the presence of a bedroom TV and average weekday TV screen time. Multivariate linear and logistic regression models assessed the effects of a bedroom on screen time.

Results: Youth with ADD/ADHD engaged in screen time with an average of 149.1. min/weekday and 59% had a TV in their bedroom. Adjusting for child and family characteristics, having a TV in the bedroom was associated with 25. minute higher daily screen time (95% CI: 12.8-37.4. min/day). A bedroom TV was associated with 32% higher odds of engaging in screen time for over 2. h/day (OR. =. 1.3; 95% CI: 1.0-1.7).

Conclusion: Future research should explore whether removing TVs from bedrooms reduces screen time among youth with ADD/ADHD.

……..

Prim Care Clin Off Pract. 2015;42:99-112.

MANAGING ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN AND ADOLESCENTS.

McClain EK, Burks EJ.

Attention-deficit/hyperactivity disorder (ADHD) is the most frequently diagnosed neurodevelopmental disorder; 6.4 million children and adolescents have been diagnosed with ADHD as of 2011. However, only 3.5 million children and adolescents are taking medication for ADHD. Adolescents with ADHD are much less willing to pursue or adhere to medication or psychosocial therapy, often because of their perceptions of side effects or perceived value of treatment, which places them at greater risk for difficulties at school, work, and home environments. Providing adolescents with increased autonomy through patient-centered approaches can increase their involvement and ability to manage their ADHD symptoms and treatment.

……..

Psychiatr Serv. 2015;66:208-11.

A BEST-WORST SCALING EXPERIMENT TO PRIORITIZE CAREGIVER CONCERNS ABOUT ADHD MEDICATION FOR CHILDREN.

Ross M, Bridges JFP, Ng X, et al.

Objective: The objective of this feasibility study was to develop and pilot an instrument to elicit caregivers' priorities when initiating attention-deficit hyperactivity disorder (ADHD) medication for their child.

Methods: A best-worst scaling experiment was used to rank competing priorities when initiating ADHD medicine. Forty-six participants were recruited for a two-phase study involving survey development (phase 1, N=21) and the survey pilot (phase 2, N=25). Best-worst scores and 95% confidence intervals indicating the relative importance of 16 concerns were determined, and t tests were used to determine the scores' significance.

Results: The significance of best-worst scores for most concerns indicated that the choices were purposeful. Concerns about helping the child become a successful adult, having a doctor who addresses caregivers' concerns, and improving school behavior were ranked highest.

Conclusions: The best-worst scaling method can elicit priorities for children's mental health treatment. Future work using this method will guide family-centered care.

……..

Psychiatr Serv. 2015;66:177-85.

FACTORS ASSOCIATED WITH TREATMENT MODE AND TERMINATION AMONG PRESCHOOLERS WITH ADHD IN TAIWAN.

Lien Y-T, Yeh H-H, Soong W-T, et al .

Objectives: This study examined the extent to which characteristics of family and health care providers predict treatment initiation, treatment mode, and treatment termination among preschool children with newly diagnosed ADHD.

Methods: A cohort of 3,583 preschoolers with ADHD was identified from the National Health Insurance Research Database of Taiwan. Individual characteristics and health care records, including medication and nonmedication treatment, were documented. Logistic regression and time-dependent survival analyses were used to evaluate association estimates.

Results: Over 80% of the children with newly diagnosed ADHD received initial treatment within a month of diagnosis, with 41% starting with combined treatment. Only one-quarter remained in treatment by the end of 12 months. In the first year, the termination rate was lowest for those who received rehabilitation treatment only (log-rank test, p<.001). Predictors of termination varied by treatment mode. For combined treatment, factors that marginally increased the likelihood of treatment termination were coming from a family in poverty (adjusted hazard ratio [AHR]=1.72) or from a rural region (AHR=1.40). Receiving initial treatment from a psychiatrist was associated with an increased likelihood of treatment termination for children receiving psychosocial treatment (AHR=1.80, 95% confidence interval [CI]=1.46-2.22) and combined treatment (AHR=1.38, CI=1.20-1.60).

Conclusions: Family and service provider characteristics appeared to have differential effects on initial receipt and mode of treatment and on one-year treatment termination among preschoolers with ADHD in Taiwan's universal health insurance program. Future efforts should aim at reducing access barriers to comprehensive and continuous health care for very young children with mental or developmental disorders.

……..

Psychiatr Invest. 2015;12:66-72.

ASSOCIATION OF HAIR MANGANESE LEVEL WITH SYMPTOMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Shin D-W, Kim E-J, Lim S-W, et al.

Objective The study examined the association between hair manganese level and symptoms of attention-deficit/hyperactivity disorder (ADHD) in Korean children

Methods Forty clinic-referred children with ADHD and 43 normal control children participated in this study. The participants were 6-15 years old and were mainly from the urban area of Seoul, Korea. ADHD was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition and Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version-Korean Version. The severity and symptoms of ADHD was evaluated according to the ADHD Diagnostic System, and parentnulls Korean ADHD Rating Scale (K-ARS). All participants completed intelligence test and hair mineral analysis. We divided the data of hair Mn into two groups to determine whether a deficit or excess of Mn are associated with ADHD. Multiple logistic regression analyses were performed to identify hair manganese levels associated with ADHD, controlling for age, sex, and full scale intelligence quotient (IQ)

Results The proportion of abnormal range Mn group was significantly high in ADHD compared to controls. However, after statistical control for covariates including age and sex, abnormal range Mn group was significantly associated with ADHD (OR=6.40, 95% CI=1.39-29.41, p=0.017)

Conclusion The result of this study suggests that excess exposure or deficiency of Mn were associated with ADHD among children in Korea. Further investigation is needed to evaluate the effects of hair manganese levels on symptoms in ADHD.

……..

Psychiatr Invest. 2015;12:150-51.

THE EFFECTIVENESS OF METHYLPHENIDATE IN THE TREATMENT OF ENCOPRESIS INDEPENDENT FROM ATTENTION-DEFICIT HYPERACTIVITY DISORDER SYMPTOMS.

Akca OF, Yilmaz S.

Several medications are reported to be effective in treatment of encopresis. However, mechanisms of action related to these drugs are not known. We report a patient with ADHD and encopresis whose encopretic signs have disappeared with long acting methylphenidate while they have not changed with atomoxetine.

……..

Psychiatry Res. 2015.

SIBLING DIFFERENCES IN LOW BIRTH WEIGHT, DOPAMINERGIC POLYMORPHISMS, AND ADHD SYMPTOMATOLOGY: EVIDENCE OF GXE.

Jackson DB, Beaver KM.

Low birth weight has been found to increase the risk of attention-deficit hyperactivity disorder (ADHD) in children. However, few studies adequately control for shared environmental influences (e.g., concentrated disadvantage, family structure) or examine whether interactions between birth weight and genetic factors predict ADHD. The present study addresses these limitations in prior research by examining a) whether sibling differences in low birth weight status are significantly predictive of sibling differences in behaviors symptomatic of ADHD and b) whether sibling differences in dopaminergic genes interact with sibling differences in low birth weight status to predict sibling differences in ADHD symptomatology. The results suggest that low birth weight siblings are at significantly greater risk of exhibiting symptoms of ADHD during childhood relative to their normal birth weight siblings. Moreover, possessing greater genetic risk on three dopaminergic genes (DAT1, DRD2, and DRD4) relative to a sibling appears to exacerbate the link between sibling differences in birth weight and sibling differences in ADHD symptomatology. Limitations and directions for future research are discussed.

……..

Psychol Assess. 2015.

THE CHILD CONCENTRATION INVENTORY (CCI): INITIAL VALIDATION OF A CHILD SELF-REPORT MEASURE OF SLUGGISH COGNITIVE TEMPO.

Becker SP, Luebbe AM, Joyce AM.

Sluggish cognitive tempo (SCT) is characterized by excessive daydreaming, mental confusion, slowness, and low motivation. Several teacher- and parent-report measures of SCT have recently been developed but a child self-report measure of SCT does not yet exist despite clear links between SCT and internalizing psychopathology (for which self-report is often desired). This study examined the initial reliability and validity of the Child Concentration Inventory (CCI), a child self-report measure of SCT symptoms, in a school-based sample of 124 children (ages 8-13; 55% female). Children completed the CCI and measures of academic/social functioning, emotion regulation, and self-esteem. Teachers completed measures of psychopathology symptoms (including SCT) and academic/social functioning. Although exploratory structural equation modeling (ESEM) supported a 3-factor model of the CCI (consisting of slow, sleepy, and daydreamer scales closely resembling the factor structure of the parent-report version of this measure), bifactor modeling and omega reliability indices indicated that the CCI is best conceptualized as unidimensional. CCI scores were significantly correlated with teacher-rated SCT and were statistically distinct from teacher-rated ADHD and child-rated anxiety/depression. After controlling for sex, grade, and other psychopathology symptoms, the CCI total score was significantly associated with poorer child-reported academic/social functioning and self-worth in addition to increased loneliness and emotion dysregulation. Child ratings on the CCI were moderately to strongly correlated with poorer teacher-rated academic/social functioning but these associations were reduced to nonsignificance after controlling for demographics and other psychopathology symptoms. Findings provide preliminary support for the CCI, and future directions include replication with adolescents and clinical samples in order to further examine the CCI's factor structure, reliability, validity, and clinical utility.

……..

Res Dev Disabil. 2015;40:1-10.

MOTOR ABILITIES OF ADOLESCENTS WITH A DISRUPTIVE BEHAVIOR DISORDER: THE ROLE OF COMORBIDITY WITH ADHD.

Van DT, Sabbe B, van WD, et al.

The aim of this study was to explore the incidence, type and severity of motor impairment in male adolescents with a disruptive behavior disorder (DBD) and evaluate the role of comorbid ADHD. The Bruininks-Oseretsky test of motor proficiency, Second Edition was administered to examine a detailed motor profile and to compare the motor abilities of individuals with DBD (n = 99) to those of controls (n = 87). Additional subgroup analyses were conducted within the clinical population and encompassed (1) analyzing differences in motor profiles between individuals diagnosed with oppositional defiant disorder (ODD) or conduct disorder (CD) and (2) comparing the motor profiles of individuals with or without comorbid ADHD.

The results indicated that individuals with a DBD showed a mixed motor impairment profile. Even after controlling for IQ, the DBD group obtained significantly lower scores in comparison to controls. The ODD and CD subgroups showed a similar motor profile. Presence of comorbid ADHD did not produce major differences in the motor profile. As approximately 79% of the adolescents with a DBD suffered from motor impairment, motor ability needs to be adequately addressed in research as well as in clinical practice.

……..

Rev Colomb Psiquiatr. 2014;43:186-93.

SUICIDAL BEHAVIOR AND ATTENTION DECIFIT HYPERACTIVITY DISORDER IN ADOLESCENTS OF MEDELLIN (COLOMBIA), 2011-2012.

Restrepo-Bernal D, Bonfante-Olivares L, Torres de GY, et al.

Background: Suicide is a public health problem. In Colombia, teenagers are considered a group at high risk for suicidal behavior.

Objective: To explore the possible association between suicidal behavior and attention deficit hyperactivity disorder in adolescents of Medellin.

Methodology: Observational, cross-sectional, analytical study. The Composite International Diagnostic Interview was applied to a total of 447 adolescents and the sociodemographic, clinical, familiar, and life event variables of interest were analyzed. The descriptive analysis of qualitative variables are presented as absolute values and frequencies, and the age was described with median [interquartile range]. A logistic regression model was constructed with explanatory variables that showed statistical association. Data were analyzed with SPSS(registered trademark) software version 21.0.

Results: Of the total, 59.1% were female, and the median age was 16 [14-18] years. Suicidal behavior was presented in 31% of females and 23% of males. Attention deficit was present in 6.3% of adolescents. The logistic regression analysis showed that the variables that best explained the suicidal behavior of adolescents were: female sex, post-traumatic stress disorder, panic disorder, and cocaine use.

Conclusions: The diagnosis and early intervention of attention deficit hyperactivity disorder in children may be a useful strategy in the prevention of suicidal behavior in adolescents.

……..

Schizophr Res. 2012;136:S209.

PSYCHOPHYSIOLOGICAL AND NEUROCOGNITIVE PROFILING OF ATTENTIONAL DEFICITS IN CHILDREN AND ADOLESCENTS WITH PSYCHOSIS OR ADHD.

Rydkjaer J, Jepsen JR, Pagsberg AK, et al.

Background: Information processing deficits are thought to be of core significance in schizophrenia and in the development of psychotic symptoms. A large number of psychophysiological and neurocognitive deficits are usually found in adult schizophrenia while deficits in information processing have been far less studied in children and adolescents with early onset psychosis. Deficits in information processing are also found in children and adolescents with ADHD; however, it is unknown whether these impairments are comparable to those of psychosis. The aim of this study is to characterize psychophysiological and neurocognitive deficits in children and adolescents with psychosis or ADHD and compare the severity and profiles of these impairments between the two groups.

Methods: A cohort of children and adolescents with either first episode psychosis (ICD-10: F20-29, F30.2, F31.2, F31.5, F32.3, F33.3) or ADHD (ICD- 10: F90, F98.8) and age and gender matched healthy controls are currently being recruited (N=35 in each of the three groups, age 12-17 year). The assessments include a diagnostic interview (Kiddie-SADS-PL), psychopathological ratings, neurocognitive tests, parental and teacher questionnaires and a blood or saliva sample for genetic testing. Core aspects of daily functioning daily areassessed with the Vineland Adaptive Behaviour Scales. Psychophysiological parameters are investigated by means of the Copenhagen Psychophysiological Test Battery (CPTB) which includes paradigms on prepulse inhibition of the startle reflex, P50 suppression, P300 amplitude, processing negativity and mismatch negativity.
Results: The study is currently in the recruitment phase, wherefore no data has been analyzed yet.
Discussion: It is expected that patients with early onset psychosis will show more severe and more widespread deficits in psychophysiological and neurocognitive functions compared to patients with ADHD, who are expected to show more specific attention related deficits.

……..

Stroke. 2014;45:e263-e264.

ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN PERINATAL STROKE.

Jadavji ZA, Brooks B, Mineyko A, et al.

Background: Perinatal stroke is leading cause of early brain injury. Most survivors suffer lifelong disability including cerebral palsy, epilepsy, and cognitive dysfunction. Attention disorders are likely common but have not been well characterized. Attention deficits negatively impact academic success and other comorbidities and treatments are readily available. We hypothesized that attention problems are increased in perinatal stroke and associated with arterial lesions and basal ganglia injury.
Methods: Children (5-19 years) from the Alberta Perinatal Stroke Project (APSP) with MRI-confirmed perinatal stroke and protocol-driven neuropsychological assessments were included. Basal ganglia damage was confirmed by MRI analysis. Percentile scores from the parent ADHD rating scale (ADHD-RS) were collected as the primary outcome, including the hyperactivity-impulsivity (ADHD-RS-HI), inattention (ADHD-RS-IA), and total (ADHD-RS-T) scales. Associations between stroke type, basal ganglia injury, and ADHD scores were assessed (student t-test).
Results: From 99 age-eligible APSP children, 30 had neuropsychological data (mean=11.9 years, SD=3.9, 43% female). Of these, 24 (80%) had arterial lesions, 11 (46%) involving basal ganglia. Mean ADHD-RS percentile scores were ADHD-RS-T 65 (SD=26), ADHD-RS-IA 70 (SD=24), and ADHD-RS-HI 55 (SD=30). ADHD-RS-T and ADHD-RS-IA scores were significantly elevated ($p=0.004$, $p<0.001$). No statistical differences in scores were found between arterial and venous strokes. ADHD-HI scores were higher in patients with (mean=68.82, SD=27.16) versus without (mean=44.54, SD=28.92) basal ganglia involvement ($p=0.03$). ADHD-RS-IA and ADHD-RS-T were not significantly different in those with or with basal ganglia damage. ADHD-RS-HI scores were higher in patients with pathological EEGs (mean=81.25, SD=17.35) versus those without (mean=45.67, SD=17.35; $p=0.02$), but differences were not found in those with or without clinical epilepsy.
Conclusions: Attention problems are increased in children with perinatal stroke. Worse problems with hyperactivity-impulsivity are found in those youth with basal ganglia injury and abnormal EEGs. Larger studies with inclusion of parental measures are required to inform screening and treatment strategies.

……..

Swiss Med Wkly. 2014;144:6S.

TRANSLATING NEUROPHYSIOLOGY AND IMAGING IN ADHD.

Brandeis D.

Introduction: Attention-Deficit/ Hyperactivity Disorder (ADHD) is a highly prevalent persistent disorder with childhood onset. Despite heterogeneity and developmental changes, neurophysiology and imaging reveal systematic alterations in ADHD patient's brain systems for state regulation, attention, inhibition and motivation. Translating these findings into diagnostic or subtyping aids into clinical routine has been encouraged by the reliability of brain markers for development and attention. However, the most current diagnostic scheme (DSM-5)

explicitly states that neurophysiological or imaging based biomarkers which may be altered in ADHD are not diagnostic.
Methods and Results: Despite much research and commercial efforts and some opposing claims, most promising markers have not proven sufficiently diagnostic or prognostic for clinically defined ADHD in typical settings [1, 2]. This holds for simple and multimodal imaging, tests, and pattern classification approaches. Similarly, ADHD treatments based on consistent deviance such classical neurofeedback may not sufficiently tap into disorder-specific mechanisms.
Conclusions: One road to progress is to focus on homogenous neuroscience-based subtypes and clarify their predictive power for individualized treatment [3], while ensuring that the current expertise with ADHD as a heterogeneous disorder is not nulllost in translationnull.

……..

Cognition, Brain, Behavior. An Interdisciplinary Journal

ISSN: 1224-8398
Volume XVIII, No. 4 (December), 315-333

THE INDEPENDENT CONTRIBUTIONS OF NEGATIVE PEER FUNCTIONING AND SOCIAL/FAMILIAL RISK FACTORS TO SYMPTOMS OF ADHD AMONG ITALIAN PRIMARY SCHOOL CHILDREN

Giovanni PIUMATTI, Beatrice SACCONI [*], *Giulia ZUCCHETTI, Emanuela RABAGLIETTI*

University of Turin, Department of Psychology

ABSTRACT

This study investigated the association between negative peer functioning and social/familial risk factors with the occurrence of symptoms of attention-deficit/hyperactivity disorder (ADHD) among Italian primary school children. We hypothesized that negative peer functioning and the cumulative number of indexes of adversity would be independently associated to ADHD. We also tested for gender moderated effects. 103 primary school children (48 girls, 46.6%; M_{age} = 8.25, SD = .61, Range = 6-10), their parents and their teachers took part into this study. The assessment included a measurement of: symptoms of attention deficit (ADD) and hyperactivity (HYP), conflictual and affective friendship quality, prosocial and aggression behaviors and emotional and behavioral instability. In addition, an index of social risk was assessed by considering multiple social and familial risk factors. Results showed that conflictual friendship quality and aggressive behaviors were positively associated with symptoms of ADD and HYP respectively, while higher social risk was associated to higher HYP especially among girls.

KEYWORDS: *ADHD, peer functioning, social and familial risk, gender differences*

Attention-deficit/hyperactivity disorder (ADHD) is currently one of the most prevalent disorders seen in childhood (Merikangas et al., 2010) affecting 6 to 7 percent of school-aged children (Willcutt, 2012). The *Diagnostic and Statistical Manual (DSM-V)* classifies it as age inappropriate behavioral symptoms of inattention and/or hyperactivity/ impulsivity (American Psychiatry Association,

[*] Corresponding author:
E-mail: beatrice.sacconi@unito.it

2013). Among the main challenges for this syndrome is the fact that it appears to occur in presence of various social and behavioral comorbidity factors (Jensen et al., 2001; Newcorn et al., 2001), including negative peer functioning and aversive behaviors to peers (Biederman, Faraone & Monuteaux, 2002) and low levels of social competence (Biederman et al., 2004; Maedgen & Carlson, 2000). In addition, several studies have shown that ADHD is associated with low socio-economic status, family disturbance and various social risk factors (Counts, Nigg, Stawicki, Rappley, & Von Eye, 2005; DuPaul, McGoey, Eckert, & VanBrakle, 2001). These facts, together with the absence of an adequate diagnosis, favor the probability of both under-diagnosing and over-diagnosing children with ADHD (Cuffe, Moore, & Mc Keown, 2005).

Indeed, previous research has demonstrated that children who suffer from ADHD symptoms but haven't been formally diagnosed with ADHD report equally academic, social, emotional difficulties and other impairments as diagnosed children (Barry, Lyman, & Klinger, 2002; Polderman, Boomsma, Bartels, Verhulst, & Huizink 2010). Overall, this raises several questions concerning possible independent contributions of behavioral and relational factors and how environmental risk factors contribute to the expression of ADHD symptoms. Specifically, despite the established link between ADHD symptoms and impaired peer functioning, a number of limitations remain in the literature. First, very few studies have showed that peer relationship problems may exacerbate ADHD symptoms (Tseng, Kawabata, Shur-Fen Gau, & Crick, 2014) moreover, relatively little is known regarding the unique relationship of children's peer functioning and inattention versus hyperactivity/impulsivity. The two groups of symptoms may each be linked to specific peer problems (Hoza, 2007). Last, since maladaptation is a result of reciprocal transactions between individuals and their socio-ecological contexts (Cicchetti & Rogosch, 2002) considering social/familial risk factors and peer functioning together will contribute to our knowledge regarding specific pathways trough which symptoms of ADHD occur. Indeed, a better understanding of these issues would facilitate our understanding and treatment of ADHD. Accordingly, in the current study, we examined the association of negative and positive peer functioning and the presence or absence of social risk factors with the onset of ADHD symptoms among a group of Italian primary school children.

Peer functioning, social risk factors and ADHD symptoms

It has been documented that early childhood manifestations of negative peer functioning and aversive behaviors to peers are usually associated with ADHD's symptomatologies (Loeber, Burke, Lahey, Winters, & Zera, 2000), while several studies found that aggression or conduct problems in childhood contributed to the persistence of ADHD well beyond childhood (Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Loney, Kramer, & Milich, 1981; Taylor, Sandberg, Thorley, & Giles, 1991). In fact, negative peer experiences, such as dislikes, friendlessness,

and peer rejection may deprive a child of important developmental opportunities to interact with peers and friends and to learn social knowledge or practice social skills (Murray-Close et al. 2010), which may lead him or her to continue behaving in maladaptive ways (e.g., being inattentive, hyperactive, or impulsive) during peer interactions (Parker, Rubin, Erath, Wojslawowicz, & Buskirk, 2006). However, past research has demonstrated an association between ADHD symptoms and children's peer relationship problems through a "symptom-driven" perspective. What remains unknown is the reciprocal influences that impaired peer functioning can have on children's development or maintenance of ADHD symptoms. If we agree that inattention and hyperactivity/impulsivity may invite rejection or low acceptance from peers, then it seems reasonable to argue that peer problems may give rise to more inattentive or hyperactive/impulsive behaviors or may exacerbate symptoms of ADHD. We know that the quality of the relationship among peers during childhood are better predictors of later psychological functioning than teacher ratings, grades, IQ, or absenteeism (Hamre & Pianta, 2001; Woodward, 2000). Accordingly, here we focused on both positive and negative peer functioning among primary school children by looking at conflictual and affective friendship quality (Weimer, Kerns, & Oldenburg, 2004), aggressive and prosocial behaviors (Caprara & Pastorelli 1993; Pastorelli, Mazzotti, & Prezza, 1988), and emotional and behavioral instability (Pastorelli, Caprara, Barbaranelli, Cermak, & Rozsa, 1997).

In relation to social risk factors, despite the fact that studies have shown that ADHD is associated with low socio-economic status, family disturbance and parents' marital conflict (Counts, Nigg, Stawicki, Rappley, & Von Eye, 2005; Biederman, Faraone & Monuteaux, 2002; DuPaul, McGoey, Eckert, & VanBrakle, 2001) their role in the onset of ADHD has been less studied than other aspects of the disorder (Johnston & Mash, 2001). Nevertheless, research findings have shown that social risk factors contribute to the difficulties in children and adolescents who already experience behavioral problems (Mathijssen Koot & Verhulst, 1999) or lead to an earlier occurrence of the problems (Nigg, 2006). Therefore, it is plausible to assume that environmental risk factors also play an important role in the expression of ADHD symptoms as problems in the social environment are a universal risk factor for the development and onset of mental disorder (Biederman, 2005; Johnston & Mash, 2001; Sandberg, Rutter, Pickles, McGuinnes, & Angold, 2001). Specifically, research has shown that it is the aggregate of risk factors rather than the presence of a single factor alone that impairs cognitive development (Institute of Medicine, 1988; Rutter, 1988). Accordingly, as adverse risk factors accumulate the degree of impaired outcome may increase proportionally (Cohen, 1968). Previous studies that found an association between psychosocial adversity and the occurrence of ADHD have adopted measures of social risk such as Rutter's indicators of adversity (e.g., Biederman, Faraone & Monuteaux, 2002; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002). This set of indicators includes family conflict,

socio-economic status, family size, maternal psychopathology, and paternal criminality (Rutter, Cox, Tupling, Berger, and Yule, 1975). In the current study, we partially draw from such previous set of indicators for social risk by taking into account individual cultural differences. In fact, research findings point out possible differences by race and ethnicity in the prevalence of psychiatric disorders in general and ADHD in particular (Cuffe, Moore, & Mc Keown, 2005). Moreover, the lack of resources in schools and of bilingual mental health services can result in obstacles to diagnosis and management of ADHD (Boshert, 2007). Now, reading from research literature on risk factors that are, in various degrees, related to child development, the following were accounted as indicators of adversity: family composition (Rydell, 2009; Vollebergh et al., 2005), maternal age at birth (Roberts et al., 2008; Treyvaud et al., 2009), parents' nationality (Cuffe, Moore, & Mc Keown, 2005), child's years of residence in Italy (Vollebergh et al., 2005) and teachers' reports regarding the presence of discomfort in children lacking family support (Boshert, 2007).

Gender differences

Research findings on the moderator role of gender on the relations between peer functioning and ADHD and between social risk factors and ADHD remain controversial. One reason for this current state of affairs may be the lack of previous studies that include large numbers of diagnosed female participants (see Hoza, 2007). The limited available evidence based on peers' perspectives, suggests that both boys and girls with ADHD are impaired in their peer relationships relative to non-ADHD children. However, results on specific gender differences regarding peer-perceived impairment are not univocal (Mikami, 2010; Hoza, et al. 2005; Pelham, & Bender, 1982). For instance, in a recent study by Zucchetti, Ortega, Scholte, and Rabaglietti (2014) emerged that boys and girls differed in the relationship between ADHD symptoms and best friend conflict. In boys, best friend conflicts were related to the presence of HYP symptoms but not ADD symptoms, whereas in girls best friend conflicts were associated only with ADD symptoms. Anyhow, although this recent study confirms other research on ADHD children friendship (e.g., Blachman & Hinshaw 2002) the gender manifestation of friendship among ADHD children is not completely established.

Low SES/parental education has been associated with ADHD symptoms particularly for boys (Cuffe, Moore, & McKeown, 2005; Rydell, 2009; Sauver, et al. 2004). Furthermore, a broad measure of social disadvantage showed similar patterns for boys and girls regarding ADHD (Rowe, Maughan, Pickles, Costello, & Angold, 2002). Moreover, there have been no investigations, to our knowledge, of gender effects in relations of ethnicity/immigrant background to ADHD problems. Thus, whether peer functioning and social risk factors are similarly related to ADHD symptoms for boys and girls is a relatively open question. In order to shed

light on this phenomenon, our study will explore the association among these factors considering the moderating role of gender.

Aims and hypotheses

Therefore, the purpose of this study was to examine the association of negative and positive peer functioning and social/familial adversity on the occurrence of ADHD symptoms among primary school children. Based on previous research literature, we expected to observe a positive association between the presence of problematic and conflictual peer relationship (Loeber, Burke, Lahey, Winters, & Zera, 2000; Taylor, Sandberg, Thorley, & Giles, 1991) and social/familial adversity (Biederman, Faraone & Monuteaux, 2002; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002) with ADHD symptoms. Specifically, we hypothesized that maladjusted peer functioning and the cumulative number of indexes of adversity would be independently associated to ADHD. Last, reading from research findings pointing out to possible gender differences regarding peer-perceived impairment and its relationship with the occurrence of ADHD symptoms (Hoza, et al. 2005; Pelham, & Bender, 1982), we also tested for gender moderate effects of both peer functioning and social/familial risk factors.

METHODS

Samples and procedures

103 children were sampled for the present study (48 girls, 46.6%; M_{age} = 8.25; *SD* = .62). Parents' countries of origin included various geographical areas, from European, Asian, African, and South-American locations. Table 1 reports descriptive statistics regarding sample's characteristics and measures. The only criterion for inclusion was the informed consent from parents. In addition, we also involved primary school teachers in the study who filled out questionnaires regarding each child.

Questionnaires were submitted in class during school hours in the presence of the teachers and of professional researchers. The latter read each item of the questionnaires to the children, who responded verbally, and indicated their answers. Teachers' questionnaires were submitted individually on a separate occasion. As reported by the teachers, no child was diagnosed with ADHD or any other serious psychopathological disorders at the time the questionnaires were submitted.

Table 1.
Descriptive statistics – sample's characteristics and measures.

	(N = 103)	
	%	*M (SD)*
Child gender (% female)	46.6	
Age in years		8.25 (.62)
Family composition		
Two caregivers	72.8	
Separated parents or other intact family	13.6	
Single parent	13.6	
Parents' nationality		
Both Italian	58.3	
One parent originally not from Italy	2.9	
Both parents originally not from Italy	38.8	
Child's years of residence in Italy		
Born in Italy	94.2	
More than three years	2.9	
Less than three years	2.9	
Maternal age at birth		
More than 21 years	94.2	
Between 18 and 21 years	3.9	
Less than 18 years	1.9	
Degree of discomfort		
Absence of discomfort	82.5	
Presence of discomfort	13.6	
Discomfort and lack of family support	3.9	
Peer functioning		
Friendship conflict		1.96 (.77)
Friendship affection		3.21 (.53)
Prosocial behavior		2.20 (.44)
Aggressive behavior		1.67 (.58)
Emotional and behavioral instability		1.86 (.49)
ADHD		
ADD		7.39 (6.78)
HYP		5.17 (7.08)

Measures

Peer functioning

Friendship Quality Scale (FQS; Bukowski, Hoza, & Boivin, 1994). The FQS is a 22-item questionnaire based on a 5-point Likert scale, ranging from 0 = "not true" to 5 = "really true". Children were asked to rate how true each item was for their friendship. The authors originally identified 5 dimensions: Companionship (e.g., "We spend our time together"); Conflict (e.g., "We can argue a lot/my friend and I disagree"); Help (e.g., "My friend helps me if I need it"); Closeness (e.g., "I feel happy when I am with my friend"); and Security measured with two sets of items, one regarding transcending problems (e.g., "If my friend and I have a fight or argument, we can say 'I am sorry' and everything will be all right"), and the other regarding the reliability of the alliance (e.g., "If I have a problem at school or at home I can talk to my friend about it"). However, a review of the recent literature provides clear evidence for a 2 factorial solution: *affection* and *conflict* (Lecce, Primi, Pagnin, & Menzione, 2006; Weimer, Kerns, & Oldenburg, 2004). Internal consistency of these two factors was found to be acceptable in the present study (Cronbach's alpha Conflict = .68; Cronbach's alpha Affection = .81).

Prosocial behavior (Caprara & Pastorelli, 1993). To measure prosocial types of behaviors, children completed a 10-item scale (e.g., "I try to help the others") with answers ranging from 1 (*almost never*) to 3 (*many times*). This type of scale has been used elsewhere in populations of primary school children (Pastorelli, Mazzotti, & Prezza, 1988). The scale yielded good internal consistency (Cronbach's alpha =.79).

Aggressive behavior (Caprara, Pastorelli, Barbaranelli, Incatasciato, & Rabasca, 1997). To measure aggressive behavior, children completed a 15-item Likert scale ranging from 1 (*almost never*) to 3 (*many times*) to rate how often they engaged in each of the listed behaviors – e.g. non-play fighting, kicking, punching, teasing others and hurting. The scale yielded good internal consistency (Cronbach's alpha =.94).

Emotional and behavioral instability (Caprara & Pastorelli, 1993). To measure emotional and behavioral instability, children completed a 15-item scale (e.g., "I interrupt someone when he/she is talking", "I play noisy games") with answers ranging from 1 (*almost never*) to 3 (*many times*). This type of measure has been adopted in previous studies (Caprara, Pastorelli, Barbaranelli, Incatasciato, & Rabasca, 1997) as one overall indicator of these proposed behaviors. The scale yielded good internal consistency (Cronbach's alpha =.90).

Social risk

An overall familial social risk score was calculated based on a composite measure assessing five social risk factors in various degrees related to child development. Each domain was scored on a 3-point scale where 0 represented lowest risk, and

2 represented highest risk to give a total scores 0 – 10: family composition (0 – two caregivers; 1 – separated parents with shared custody, or cared for by other family members; 2 – single caregiver), parents' nationality (0 – both parents from Italy; 1 – one parent with a different original nationality than Italian; 2 – both parents not originally from Italy), child's years of residence in Italy (0 – born in Italy; 1 – more than three years; 2 – less than three years), maternal age at birth (0 – more than 21 years old; 1 – 18–21 years old; 2 – less than 18 years old), and teachers' reports regarding the presence of discomfort in children that lacking family support (0 – absence of discomfort; 1 – presence of discomfort; 2 – presence of discomfort and lack of family support). Regarding this latter factor, it was specified to the teachers to indicate those children that they considered in need of specific individual support in class without already receiving it and to further specify whether their families were acknowledging such situation, for example attending parents/teachers meetings at school. Finally, based on these factors, children were categorized as at a lower social risk (total score < 2) or at a higher social risk (total score ≥ 2). This cut-point was based on other composite social risk scales that have been used in previous studies focusing on samples of primary school children and adopting similar categories of social risk (see Roberts et al., 2008; Treyvaud et al., 2009).

ADHD

To measure ADHD symptoms we used the ADHD Rating Scale for Teachers (SDAI) (Marzocchi & Cornoldi, 2000). The SDAI Scale was designed for use in screening but not for clinical diagnosis. It includes 18 items based on the 18-item ADHD symptoms list from the fourth edition of the Diagnostic and Statistic Manual of Mental Disorder (American Psychiatry Association, 1994). Nine of these items are about inattention (ADD) (e.g., "Has difficulty sustaining attention in tasks or play activities") while the rest are about hyperactivity (HYP) (e.g., "Is on the go or acts as if driven by a motor"). The questionnaire was administered to teachers who were then asked to assesses the frequency of the appearance of the proposed behavior, scoring these answers using Likert scale values from 0 to 3, considering "0" to signify if the child never has a certain behavior, "1" if the child sometimes has a certain behavior, "2" if the child often has this behavior, and "3" if it appears very often. The 18 items were summed up to calculate the total score of the ADHD symptoms. A higher score indicates that the given behavior occurs more frequently therefore no cut-offs were adopted to distinguish among children with higher or lower symptomatology expressions (see Zucchetti, Ortega, Scholte, & Rabaglietti, 2014). Cronbach's alpha for the ADD and HYP subscales were .93 and .94 respectively.

Analysis

All the scores of the items for each scale were examined for accuracy of data entry, detecting and replacing missing values, identifying univariate and multivariate outliers and dealing with the question. We also examined the data for detecting non normal distribution among dependent variables. Subsequently, correlations were calculated to assess the relations between input variables (age, gender, friendship conflict, friendship affection, pro-social behavior, aggressive behavior, emotional and behavioral instability and social risk) and symptoms of ADHD. The main analyses consisted of multiple hierarchical regressions. The two symptom subscales (ADD and HYP) were used as output variables in separate analyses. Age and gender were covariates in all models and were entered in the first step, friendship conflict, friendship affection, pro-social behavior, aggressive behavior and emotional and behavioral instability, were entered in the second step, and social risk, categorized as at a lower social risk (total score < 2) or at a higher social risk (total score ≥ 2), was entered in step three. In a fourth step we entered the interaction terms between gender and social risk and between gender and each measure of peer functioning. As covariates, age and gender where entered in the first step to control for the portion of explained variance they accounted for ADHD scores since we were specifically interested in the effects of the sets of variables at the second (i.e., peer functioning) and third (i.e., social risk) step. This analytical strategy allowed us to determine whether peer functioning and social risk contributed with unique variance to the two ADHD symptom measures by examining the ΔR^2 statistic. A significant effect of the block of measures in the second step (after the covariates) indicates that the block of measures contributes to the outcome. A significant effect in the third step indicates that the block of measures contributes independently, provided that the block in the second step is also significant. This strategy also gave us the opportunity to examine whether social risk explained additional variance after the measures on peer functioning had been entered, also by examining the ΔR^2 statistic.

RESULTS

Preliminary analysis

No transformation of the distributions was found that could accommodate the model well. Given the significant low rates of missing values on each item of the scales (less than 5%), we performed total mean substitution for each missing value. This decision was also made as no systematic correlation between these missing values and the scores of other variables among these subjects was detected ($r < |.20|$) (see Raaijmakers, 1999). Prior to the analysis, data was carefully examined for univariate outliers (classified as scores more than three standard deviations above or below the mean; see Hoaglin & Iglewicz, 1987). As a result, no case was excluded from further analysis.

As can be seen in Table 2, correlations among studied variables ranged from .03 to .69. Specifically, the highest negative correlation was found between aggressive behavior and pro-social behaviour (r = -.63, $p < .01$), whereas the highest positive correction was found between emotional and behavioral instability and aggressive behaviour (r = .69, $p < .01$). Accordingly, children with high scores on aggressive behavior were more likely to have low scores on pro-social behavior, and children with high scores on emotional and behavioral instability were more likely to have also high scores on aggressive behavior.

Table 2.
Bivariate correlations among studied variables.

	Age	Gender	Conflict	Affection	Prosocial behavior	Aggressive behavior	Emotional and behavioral instability	ADD	HYP
Gender	-.06	–							
Friendship conflict	-.11	.06	–						
Friendship affection	.03	-.22*	-.03	–					
Prosocial behavior	.23*	-.12	.01	.23*	–				
Aggressive behavior	-.30**	.15	.03	-.15	-.63**	–			
Emotional and behavioral instability	-.08	.14	.08	-.12	-.47**	.69**	–		
ADD	.06	.31**	.29**	-.01	-.23*	.25*	.16	–	
HYP	.16	.23*	.16	.04	-.04	.16	.10	.62**	–
Social risk	.15	.14	.05	-.09	-.01	.04	.06	.27**	.18

Note. Gender was categorized with "0" for female and "1" for male. Social risk was categorized with "0" for lower social risk and "1" for higher social risk.
* p < .05, ** p < .01.

Descriptive statistics

The mean of the aggregated score of social risk – based on the sum of the 0 to 2 scores for each of the five risk factors – was equal to 1.59 (SD = 1.47). According to its categorization (i.e., total score < 2 = lower social risk; total score ≥ 2 = higher social risk), 46 children (44.7%) were categorized as being at a lower social risk while 57 children (55.3%) were categorized as being at a higher social risk. Chi-square test and t-test for independent samples did not show significant differences between the two sub-groups of risk as related to gender composition, X^2 (1, 103) = 2.00, $p > .05$, and age, $t(103) = -1.48$, $p > .05$.

Results of hierarchical regression models

Multiple hierarchical regression analyses were performed for each ADHD symptom – inattention (ADD) and hyperactivity/impulsivity (HYP) – to evaluate

the contributions of peer functioning and social risk factors, controlling for age and gender. The results when peer functioning variables were entered in the second step, social risk (categorized "0" for lower social risk and "1" for higher social risk) in the third step and their interaction terms with gender in the fourth step are presented in Table 3. No interaction term between gender and any of the variables describing peer functioning were found to be significant in explaining scores on ADD and HYP, therefore we decided to not include them in our models of multiple hierarchical regressions.

Together, age and gender at Step 1 contributed significantly to explain variance of both symptoms of ADD (ΔR^2 = .10; $F(1, 102) = 1.91$, $p > .05$ for age effect, and $F(1, 102) = 1.92$, $p < .05$ for gender effect respectively), and HYP (ΔR^2 = .08; $F(1, 102) = 2.89$, $p < .01$, and $F(1, 102) = 3.05$, $p < .01$). Older participants had lower HYP scores, while boys had more chances to have higher scores on both ADHD's symptoms than girls.

Overall, peer functioning variables contributed with significant variance to symptoms of ADD when they were entered in the second step (ΔR^2 = .18, $p < .001$; βs ranging between -.18 and .30). In particular, conflict was found to be the main source of explained variance in ADD's scores among peer functioning variables, $F(1, 102) = 3.43$, $p < .001$. Accordingly, higher scores on friendship conflict increased the probability of having higher scores on ADD. Regarding HYP, only aggressive behavior significantly explained variance in symptoms' scores, $F(1, 102) = 2.07$, $p < .05$, at Step 2 (ΔR^2 = .08, $p > .05$; βs ranging between .01and .31). Accordingly, higher scores on aggressive behavior increased the probability of having higher scores on HYP.

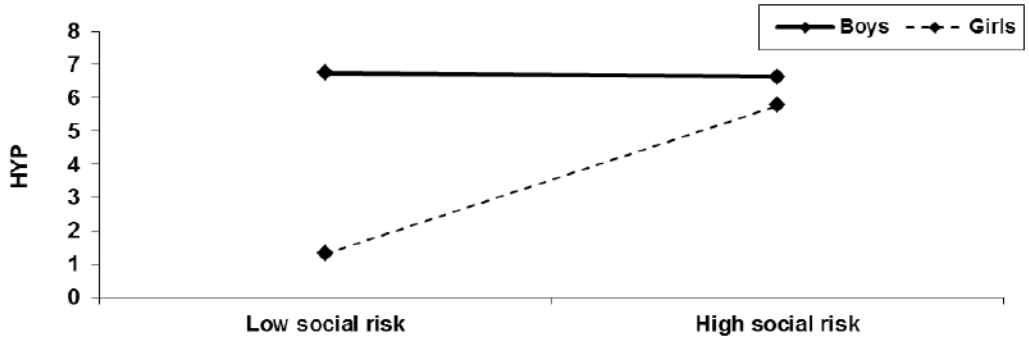
Regarding social risk, it demonstrated independent contributions to scores on HYP's symptoms, (ΔR^2 = .01, $p > .05$; $F(1, 102) = 2.27$, $p < .05$), indicating that higher social risk increased the probability of having higher scores on HYP's symptoms. Lastly, the interaction term between gender and social risk significantly explained variance in HYP's scores, (ΔR^2 = .01, $p < .05$; $F(1, 102) = -2.27$, $p < .05$). As suggested by (Aiken & West, 1991) the significant interaction was plotted in order to facilitate interpretation (Figure 1). Reading from this last result, we can say that the positive relationship between social risk and HYP scores was especially evident for girls in comparison to boys.

Table 3.
Results of hierarchical regressions for variables predicting symptoms of inattention (ADD) and hyperactivity/impulsivity (HYP).

	ADD		HYP	
Variables	ΔR^2	β	ΔR^2	β
Step1:	.10**		.08*	
Age		.18		.30**
Gender		.25*		.43**
Step 2:	.28***		.17	
Friendship conflict		.30***		.18
Friendship affection		.14		.08
Prosocial behavior		-.18		.03
Aggressive behavior		.25		.31*
Emotional and behavioral instability		.14		.12
Step 3:	.31		.18	
Social risk		.19		.11*
Step4:	.31		.21*	
Gender X Social risk		.02		-.38*

Note. Gender was categorized with "0" for female and "1" for male. Social risk was categorized with "0" for lower social risk and "1" for higher social risk.
* p < .05, ** p < .01, *** p < .001.

Figure 1.
Interaction between gender and social risk with respect to HYP scores.



DISCUSSION

Results from the current study confirmed the presence of a positive association between negative peer functioning and social/familial adversity with the occurrence of ADHD symptoms during primary school years (Biederman, Faraone & Monuteaux, 2002; Loeber, Burke, Lahey, Winters, & Zera, 2000). Specifically, the main contribution of our study was to evidence the independent contributions of relational and environmental risk factors for the occurrence of ADHD symptoms and to point out to gender differences of such relationship.

Our hypotheses about the independent contributions of maladjusted peer functioning and the cumulative number of indexes of adversity, were supported by the findings from this study that showed how both negative peer functioning and social risk factors were associated with ADHD symptoms. Specifically, in the present sample the result of the hierarchical regression models pointed out to the independent contributions of conflictual friendship quality for ADD symptoms and aggressive conduct behaviors for what concerning HYP symptoms. These results are aligned with prior work (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011; Sandberg, Thorley, & Giles, 1991) that showed conduct/aggressive symptoms were associated with the persistence of ADHD well beyond childhood. Children showing symptoms of ADD might also exhibit difficulties regarding their peer relationships due to a degree of inattention towards the needs and feelings of others (Pelham & Bender, 1982). In turn, this may become an obstacle to build positive relationships and a cause of conflict between friends. Indeed, children who take part in daily conflicts and disputes with peers may be more exposed to the risk of inattention and lack of concentration. Moreover, ADD symptoms are linked to social withdrawal and disinterest that are responsible behaviors for less positive friendship engagement and more peer disagreements, especially among girls (Blachman, & Hinshaw 2002). Finally, the association between aggressive behavior and HYP symptoms found in this study confirms the existence of a link between aggression, anti-social behaviors and ADHD (Biederman, Petty, Clarke, Lomedico, & Faraone, 2011; Gillberg et al. 2004).

In addition, our findings add support to previous studies that have found a relationship between the social/familial environment and ADHD (Counts et al., 2005; Biederman, Faraone, & Monuteaux, 2002; DuPaul, McGoey, Eckert, & VanBrakle, 2001; Pressman et al., 2006). In particular, social risk was found to be independent contributors of HYP symptoms especially among females. In general, previous research findings showed that the association between environmental adversity and the risk for ADHD does not differ by gender (e.g., Biederman, Faraone, & Monuteaux, 2002; Faraone et al., 2000). However, despite the fact that ADHD is much more common in males than in females according to all clinical studies published to date, recent studies suggest that ADHD may often be missed in girls (Gillberg et al., 2004). For example, the marked overrepresentation is less pronounced in population studies (Gillberg et al., 2004). Indeed, in our sample we

found boys to be significantly more affected than girls for both symptoms of ADD and HYP. However, we did not include children with an existing history of diagnosis regarding any form of psychopathology, therefore our results are limited to non-clinical groups. Also, these results could be related to the specificity of our sample and adopted measures of social risk. Specifically, our findings could be better interpreted by the "gender stereotype" response to different situations and difficulties (Fisher, & Dubé, 2005). For example, Keenan and Shaw (1997) showed that socialization efforts influence the development of girls' psychopathology by channeling early problems into predominantly internalizing and externalizing problems. Moreover, it is possible that girls, especially with an immigrant background, due to their high level of "fragility and sensibility" could experience more stressful feelings connected to their family environments than boys. In turn, such a source of stress may favour the occurrence of higher levels of hyperactivity and instability. Indeed, Short and Johnston (1997) showed that in a population of children from immigrant families living in England lower levels of maternal support were associated to higher adjustment problems only among girls. Thus, our results regarding these specific gender differences should be read in light of the specific risk indexes that were taken into account in order to build an overall assessment of social risk and regarding which specific prior research might lack.

In conclusion, it necessary to remind that this study had several limitations. First, the strict correlational nature of our data does not allow us to report on any specific effects between the variables but it rather represents a descriptive attempt to draw on the relationship between peer functioning and environmental variables from a side and ADHD symptoms from another side. Second, being that only teachers provided ratings we do not know to what extent the behavior problems penetrated out-of-school contexts. This is a specific problem with regard to ADHD, for which the manifestation of symptoms in multiple contexts is important (American Psychiatric Association, 2013). Third, the cross-sectional design precluded proper mediation analyses, which could have shed light on pathways in the associations. Finally, there are numerous important family factors we did not include, such as parental psychopathology, parents' educational level and domestic violence.

Nevertheless, our results not only confirm once again the existence of a relationship between peer problem behaviours and environmental risk factors with the occurrence of ADHD symptoms during childhood, but evidence how relational and environmental factors may both play an independent role for the onset of such psychopathology.

Implications for future research

Overall, the results of the current study highlight the importance of working on the behavioral correlates of ADHD syndrome already in childhood. Indeed, for prevention and early intervention strategies in potentially affected children, possible negative social and familial influences should be taken into account. However, further research is needed to assess the association between peer functioning, social risk and ADHD among children with a formal diagnosis. For example, our results need to be confirmed by future research that will examine possible mediation effects (e.g., psychological feelings) between social risk and ADHD symptoms, according to the gender and other socio-demographic characteristics of the children.

REFERENCES

Aiken, L. S., & West, S. G. (1991). *Multiple regression: Testing and interpreting interactions.* Newbury Park, CA: Sage.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Publishing.

Barry, T. D., Lyman, R. D., & Klinger, L. G. (2002). Academic underachievement and Attention-Deficit /Hyperactivity Disorder: The negative impact of symptom severity on school performance. *Journal of School Psychology 40*, 259–283.

Biederman, J. (2005). Attention-deficit/hyperactivity disorder: A selective overview. *Biological Psychiatry, 57,* 1215–1220.

Biederman, J., Faraone, S. V., & Monuteaux, M. C. (2002). Differential effect of environmental adversity of gender: Rutter's index of adversity in a group of boys and girls with and without ADHD. *American Journal of Psychiatry, 159,* 1556–1562.

Biederman, J., Petty, C. R., Clarke, A., Lomedico, A. & Faraone, S. V. (2011). Predictors of Persistent ADHD: An 11-year Follow-up Study. *Journal of Psychiatric Research, 45*(2), 150–155.

Biederman, J., Monuteaux, M. C., Doyle, A. E., Seidman, L. J., Wilens, T. E., Ferrero, F., Morgan, C., & Faraone, S. V. (2004). Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. *Journal of Consulting and Clinical Psychology* 72, 757–766.

Blachman, D. R., & Hinshaw, S.P. (2002). Patterns of friendship in girls with and without attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology, 30,* 625–640.

Boshert, S. (2007). ADHD Underdiagnosed in N.Y. Chinese Immigrants. *Pediatric News, 4*(12), 20.

Bukowski,W. M., Hoza, B., & Boivin, M. (1994). Measuring friendship quality during pre- and early adolescence: The development and psychometric properties of the Friendship Qualities Scale. *Journal of Social & Personal Relationships, 11*, 477–484.

Caprara, G. V., Pastorelli, C. (1993). Early emotional instability, prosocial behavior, and aggression. Some methodological aspects. *European Journal of Personality, 7*, 19–36.

Cicchetti, D., & Rogosch, F. A. (2002). A Developmental Psychopathology Perspective on Adolescence. *Journal of Consulting and Clinical Psychology, 70*, 6–20.

Cohen, J. (1968). Nominal scale agreement with provision for scaled disagreement or partial credit. *Psychological Bulletin, 70*, 213–220.

Counts, C. A., Nigg, J. T., Stawicki, J. A., Rappley, M. D., & Von Eye, A. (2005). Family adversity in DSM-IV ADHD combined and inattentive subtypes and associated disruptive behavioral problems. *Journal of the American Academy of Adolescent Psychiatry, 44,* 690–698.

Cuffe S., Moore C. H., & Mc Keown R. (2005). Prevalence and correlates of ADHD symptoms in the National Health Interview Survey. *Journal of Attention Disorders, 9*, 392–401.

DuPaul, G. J., McGoey, K. E., Eckert, T. L.,& VanBrakle, J. (2001). Preschool children with attention-deficit/hyperactivity disorder: Impairments in behavioral, social, and school functioning. *Journal of the American Academy of Child and Adolescent Psychiatry, 40,* 508–515.

Faraone, S. V., Biederman, J., Mick, E., Williamson, S., Wilens, T., Spencer, T., Weber, W., Jetton, J., Kraus, I., Pert, J., & Zallen B. (2000). Family study of girls with attention deficit hyperactivity disorder. *The* American Journal of Psychiatry*, 157*, 1077–1083

Fischer, M., Barkley, R. A., Fletcher, K. E., & Smallish, L. (1993). The stability of dimensions of behavior in ADHD and normal children over an 8-year followup. *J Abnorm Child Psychol 3*, 315–337.

Fisher, R. J., & Dubé, L. (2005). Gender differences in responses to emotional advertising: A social desirability perspective. *Journal of Consumer Research*, *31*(4), 850–858.

Gillberg, C., Gillberg, I. C., Rasmussen, P., Kadesjö, B., Söderstöm, H., Rastam, M., Johnson, M., Rothenberger, A., & Niklasson, L. (2004). Co-existing disorders in ADHD – Implications for diagnosis and intervention. *European Child and Adolescent Psychiatry 13*(1), 80–92

Gittelman, R., Mannuzza, S., Shenker, R., & Bonagura, N. (1985). Hyperactive boys almost grown up: I. Psychiatric status. *Archives of General Psychiatry, 42*, 937–947.

Hamre, B. K., & Pianta, R. C. (2001). Early Teacher-Child Relationships and the Trajectory of Children's School Outcomes Through Eighth Grade. Child Development, *72*(2), 625–638.

Hinshaw, S. P., &Melnick, S. M. (1995). Peer relationships in boys with attention-deficit hyperactivity disorder with and without comorbid aggression. *Development and Psychopathology, 7,* 627–647.

Hoaglin, D. C., & Iglewicz, B. (1987). Fine tuning some resistant rules for outlier labeling, *Journal of American Statistical Assiciation, 82*, 1147–1149.

Hoza, B. (2007). Peer Functioning in Children With ADHD, *Journal of Pediatric Psychology 32*(6), 655–663

Hoza, B., Gerdes, A. C., Mrug, S., Hinshaw, S. P., Bukowski, W. M., Gold, J. A., et al. (2005). Peer-assessed outcomes in the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder. *Journal of Clinical Child and Adolescent Psychology, 34,* 74–86.

Institute of Medicine (1989). Research on Children and Adolescents With Mental, Behavioral, and Developmental Disorders. Washington, DC, National Academy Press.

Keenan, K., & Shaw, D. (1997). Developmental and social influences on young girls' early problem behavior. *Psychological bulletin*, *121*(1), 95.

Lecce, S., Primi, C., Pagnin, A., & Menzione, M. (2006). Analisi della struttura della Friendship Quality Scale: un confronto tra modelli [Analysis of the structure of the Friendship Quality Scale: A comparison between factor models]. *Testing Psicometria Metodologia, 13*, 1–16.

Loeber, R., Burke, J. D., Lahey, B. B., Winters, A., & Zera, M. (2000). Oppositional defiant disorder and conduct disorder: A review of the past 10 years, part I. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 1468–1484.

Loney, J., Kramer, J., Milich, R. S. (1981). The hyperactive child grows up: predictors of symptoms, delinquency and achievement at follow-up. In: Gadow, KD.; Loney, J., editors. *Psychosocial Aspects of Drug Treatment for Hyperactivity*. Boulder, CO: Westview Press; p. 381–416.

Jensen, P. S., Hinshaw, S. P., Kraemer, H. C., Lenora, N., Newcorn, J. H., Abikoff, H. B., et al. (2001). ADHD comorbidity findings from the MTA study: Comparing comorbid subgroups. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40,* 147–158.

Johnston, C., & Mash, E. J. (2001). Families of children with attention-deficit/hyperactivity disorder: Review and recommendations for future research. *Clinical Child and Family Psychology Review, 4,* 183–207.

Maedgen, J. W., & Carlson, C. L. (2000). Social Functioning and emotional regulation in the attention deficit hyperactivity disorder subtypes. *Journal of Clinical Child Psychology, 29*, 30–42.

Marzocchi, G. M., & Cornoldi, C. (2000). Una scala di facile uso per l'individuazione di comportamenti problematici dei bambini con deficit di attenzione e iperattività. *Psicologia Clinica dello Sviluppo, 4*, 43–61.

Mathijssen, J. J., Koot, H. M.,&Verhulst, F. C. (1999). Predicting change in problem behavior from child and family characteristics and stress in referred children and adolescents. *Development and Psychopathology, 11,* 305–320.

Merikangas, K. R., He, J., Burstein, M., Swanson, S. A., Aveneoli, S., Cui, L., et al. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry, 49*, 980-989.

Mick, E., Biederman, J., Faraone, S.V., Sayer, J., & Kleinman, S. (2002). Case control study of attention deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*, 378–385.

Murray-Close, D., Hoza, B., Hinshaw, S. P., Arnold, L. E., Swanson, J. Jensen, P. S., & Wells, K. (2010). Developmental Processes in Peer Problems of Children with Attention-Deficit/Hyperactivity Disorder in the Multimodal Treatment Study of Children With ADHD: Developmental Cascades and Vicious Cycles. *Development and Psychopathology, 22*, 785–802.

Newcorn, J. H., Halperin, J. M., Arnold, L. E., Abikoff, H. B., Arnold, E. L., Cantwell, D. P., et al. (2001). Symptom profiles in children with ADHD: Effects of comorbidity and gender. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40,* 137–146.

Nigg, J. (2006). *What causes ADHD? Understanding what goes wrong and why.* New York: The Guilford Press.

Parker, J. G., Rubin, K. H., Erath, S. A.,Wojslawowicz, J. C., & Buskirk, A. A. (2006). Peer relationships, child development, and adjustment: A developmental psychopathology perspective. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology*, Vol. 1: Theory and method (2nd ed., pp. 419–493). Hoboken: Wiley.

Pastorelli, C., Caprara, G. V., Barbaranelli, C., Cermak, I., & Rozsa, S. (1997). Measuring emotional instability, prosocial behavior and aggression in pre-adolescents: a cross-national study. *Personality and Individual Differences, 23*, 691–703.

Pastorelli, C., Mazzotti, E., & Prezza, M. (1988). Validazione delle tre scale per la misura dell'aggressivita' fisica e verbale, del comportamento prosociale e dell'instabilita' emotiva, con i metodi della valutazione e della nomina dei pari. In G.V. Caprara & M. Laeng (Eds.), *Indicatori e precursori della condotta aggressiva* (pp.121–143). Rome: Bulzoni.

Pelham, W. E., & Bender, M. E. (1982). Peer relationships in hyperactive children: description and treatment. In: K. D. Gadow, & I. Bialer (Eds.). *Advances in Learning and Behavioral Disabilities*. vol 1 (pp. 365–436). Greenwich, Conn: JAI Press.

Polderman, T. J. C., Boomsma, D. I., Bartels, M., Verhulst, F. C., & Huizink, A. C. (2010). A systematic review of prospective studies on attention problems and academic achievement. *Acta Psychiatrica Scandinavica*, 271–284.

Pressman, L. J., Loo, S. K., Carpenter, E., Asarnow, J. R., Lynn, D., McCracken, J. T., et al. (2006). Relationship of family environment and parental psychiatric diagnosis to impairment in ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry, 45,* 346–354.

Raaijmakers, Q. (1999) Effectiveness of different missing data treatments in survey with Likert-type data: introducing the relative mean substitution approach. *Educational and Psychological Measurement, 59*, 725–748.

Roberts, G., Howard, K., Spittle, A.J., Brown, N.C., Anderson, P.J., & Doyle, L.W. (2008). Rates of early intervention services in very preterm children with developmental disabilities at age 2 years. *Journal of Paediatrics & Child Health, 44*(5), 276–280.

Rowe, R., Maughan, B., Pickles, A., Costello, E. J., & Angold, A. (2002). The relationship between DSM-IV oppositional defiant disorder and conduct disorder: findings from the Great Smoky Mountain Study. *Journal of Child Psychology and Psychiatry, 43*, 365–373

Rutter, M. (1988). Studies of Psychosocial Risk: The Power of Longitudinal Data. Cambridge, UK, Cambridge University Press.

Rutter, M., Cox, A., Tupling, C., Berger, M., & Yule, W. (1975). Attainment and adjustment in two geographical areas, I: the prevalence of psychiatric disorder. *British Journal of Psychiatry, 126*, 493–509.

Rutter, M., & Quinton, D. (1977). Psychiatric disorder: ecological factors and concepts of causation, in Ecological Factors in Human Development. In McGurk H. (Ed.) Amsterdam, North Holland, 173–187.

Rydell, A. M. (2009). Family factors and children's disruptive behavior: an investigation of links between demographic characteristics, negative life events and symptoms of ODD and ADHD. *Social* Psychiatry *and* Psychiatric Epidemiology, *45*, 233–244.

Sandberg, S., Rutter, M., Pickles, A., McGuinnes, D., & Angold, A. (2001). Do high-threat life events really provoke the onset of psychiatric disorder in children? *Journal of Child Psychology and Psychiatry, 42,* 523–532.

Sauver, J. L. S., Barbaresi, W. J., Katusic, S. K., Colligan, R. C., Weaver, A. L., & Jacobsen, S. J. (2004). Early risk factors for attention-deficit/ hyperactivity disorder: a population-based cohort study. *Mayo Clinic Proceedings, 79,* 1124–1131

Short, K. H., & Johnston, C. (1997). Stress, maternal distress, and children's adjustment following immigration: The buffering role of social support. *Journal of Consulting and Clinical Psychology*, *65*(3), 494.

Taylor, E., Sandberg, S., Thorley, G., & Giles, S. (1991). *The epidemiology of childhood hyperactivity*. New York: Oxford University Press.

Treyvaud, K., Anderson, V.A., Howard, K., Bear, M., Hunt, R.W., Doyle, L.W., et al. (2009). Parenting is associated with the early neurobehavioral development of very preterm children. *Pediatrics, 123*(2), 555–561.

Tseng, W., Kawabata, Y., Gau, S., Shur, F., & Crick, N. (2014). Symptoms of Attention-Deficit/Hyperactivity Disorder and Peer Functioning: a Transactional Model of Development, *Journal of Abnormal Child Psychology, 42*, 1–13.

Vollebergh, V. A. M., ten Have, M., Dekovic, M., Oosterwegel, A., Pels, T., Veenstra, R., de Winter, A., Ormel, H., & Verhulst, F. (2005). Mental health in immigrant children in the Netherlands. *Social Psychiatry* and *Psychiatric Epidemiology, 40*, 489–496

Weimer, B. L., Kerns, K. A., & Oldenburg, C. (2004). Adolescents' interactions with a best friend: Associations with attachment style. *Journal of Experimental Child Psychology, 88*,102–120.

Willcutt, E. G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics, 9*(3),490–499.

Woodward, L. J. F. D. (2000) Childhood peer relationship problems and later risk of educational underachievement and unemployment. Journal of Child Psychology and Psychiatry, 41, 191–201.

Zucchetti, G., Ortega, E., Scholte, R. H. J., & Rabaglietti, E. (2014). The mediating role of aggressive behaviour, emotional and behavioural instability on the association between ADHD symptoms and best friend conflicts. *Current Psychology*. Available online at http://link.springer.com/article/10.1007/s12144-014-9243-4.

ARTICLE IN PRESS

Available online at www.sciencedirect.com

ScienceDirect

Comprehensive Psychiatry xx (2015) xxx–xxx

COMPREHENSIVE PSYCHIATRY

www.elsevier.com/locate/comppsych

Temperamental and character profiles of preschool children with ODD, ADHD, and anxiety disorders

Maria Grazia Melegari[a], Valentina Nanni[a], Fabio Lucidi[b], Paolo M. Russo[c,*], Renato Donfrancesco[d], C. Robert Cloninger[e]

[a]Child and Adolescent Mental Health Center "La Scarpetta", ASL RM/A, Rome, Italy
[b]Department of Developmental and Social Psychology–Sapienza University of Rome, Rome, Italy
[c]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
[d]Child and Adolescent Mental Health Pertini Hospital, ASL RM/B, Rome, Italy
[e]Center for Well Being, Washington University School of Medicine, St Louis, MO, USA

Abstract

Background: The aim of the present research was to identify profiles of Cloninger's temperament and character dimensions associated with anxiety disorders, oppositional defiant disorder (ODD) and attention- deficit/hyperactive disorder (ADHD) in preschoolers.
Method: The parents of 120 children (mean age = 4.65 years; S.D. = .88) completed the Preschool Temperament and Character Inventory (PsTCI). The sample consisted of 4 groups (n = 30 per group): ADHD, anxious, ODD and control children. To diagnose the different disorders, the Preschool Age Psychiatric Assessment and Child Behavior Checklist 1.5-5 was administered to the parents.
Results: The discriminant analysis showed that three temperamental dimensions (Harm Avoidance, Novelty Seeking and Persistence) enabled the correct classification of 75% of cases within their own group, which demonstrated an adequate accuracy rate. The ADHD children showed a temperamental profile that was characterized by high Novelty Seeking, low Reward Dependence and low Persistence, while the anxious children obtained high scores in Harm Avoidance. The profiles of the ODD children shared some common features (high Novelty Seeking) with the ADHD children, but the ODD children were characterized by higher Persistence and Harm Avoidance compared with ADHD children.
Conclusions: The present results indicate that Cloninger's temperamental dimensions allow to differentiate the three most frequent psychiatric disorders in preschoolers.

1. Introduction

Temperamental dimensions have a dual role that consists of predictive factors for the onset of psychopathology and as the basis for a better understanding of future developmental trajectories [1–3]. The temperamental predisposition to emotional–behavioral regulation problems has long been considered a risk factor by many authors [4,5]. Empirical evidence suggests that several disorders, including ADHD (attention deficit hyperactive disorder), ODD (oppositional defiant disorder) and anxiety disorders, are often characterized by affective temperamental traits, such as negative emotionality, that moderate the relationship between emotional self-regulation and both positive and negative outcomes [6,7]. Regarding ADHD, studies of adults suggest a genetic, neuropsychological and neuroanatomical parallel between ADHD and specific temperamental and personality traits, such as low Conscientiousness, low Agreeableness, and high Neuroticism [8–12].

Recently, the integration of dimensional models with a categorical approach in developmental research and early onset psychopathology has become more frequent and important than in the past, as demonstrated in the relevant scientific literature [2,13]. In particular, Korean studies on school-age children with ADHD, based on Cloninger's psycho-social model, highlight a personality profile that is characterized by high Novelty Seeking [14,15] and low Self-Directedness in both the parents' and children's

* Corresponding author at: Department of Experimental, Diagnostic and Specialty Medicine-DIMES University of Bologna, Viale Berti Pichat 5, 40127 Bologna, Italy. Tel.: +39 3403657002; fax: +39 051243086.
E-mail address: p.russo@unibo.it (P.M. Russo).

http://dx.doi.org/10.1016/j.comppsych.2015.01.001
0010-440X/

self-ratings. Moreover, using a wide sample of school-age children and adolescents with ADHD, it has been established that the dimensional model can explain the heterogeneity of the disorder better than categorical criteria [16]. There are also important contributions in the literature regarding anxiety disorders and temperamental profiles. In adults with social anxiety, high Harm Avoidance, low Novelty Seeking and low Self-Directedness have been reported [17]. Research on children and adolescents (6–17 years old) with social phobia has reached similar conclusions, including high Harm Avoidance and low Self-Directedness [18].

Most developmental research concerns school-age children and adolescents, but less is known about the temperamental characteristics of pre-school children that show early onset psychiatric disorders; these early clinical conditions can be considered real disorders, whether they are only beginning to emerge or previously existing [19–22]. It is noteworthy that research on the temperament of preschool age with early onset psychopathology remains controversial and requires further analyses [22].

Some studies on preschoolers have demonstrated a relationship between externalizing behaviors and disorders (mainly ADHD) significantly associated with difficult temperament [23,24], extraversion [25] and disinhibition [3]. Research highlights the frequent association between preschoolers with anxiety disorders and behavioral inhibition [26–28], low adaptability/approachability [23], and difficult temperament [24,29]. Interesting contributions have also originated from studies on ODD, which strongly represents a disorder associated with temperamental risk factors [30,31]. ODD is an early onset disorder associated to an increased risk of secondary internalizing and externalizing disorders in older children and adolescents [32–34]. Single ODD dimensions (i.e. irritability, oppositional behavior) predicts psychiatric disorders at follow-up [35,36], but in this latter field findings are not coherent [37]. ODD core traits, such as oppositional behavior and negative emotionality, are considered measures of temperamental domains [38,39]. Negative emotionality in ODD predicts both externalizing and internalizing disorders, unlike impulsivity and activity, which are only associated with externalizing disorders [40]. Similar findings have been demonstrated in community based studies: the temperamental trait of negative emotionality is a strong predictor of the association between ODD and internalizing disorders, whereas the temperamental trait of activity is a strong predictor of the association between ODD and ADHD [2]. These results suggest that individual temperamental differences that are evident in the preschool years may provide even earlier distinguishing markers for diverging internalizing or externalizing disorder pathways [41].

This brief review of the existing literature highlights the importance of studying temperamental traits; however, the overall picture of the temperamental differences in preschool children with early onset psychopathology remains unclear. Thus, it should be noted that most clinical studies are difficult to compare because temperament is measured in several ways. In addition, diagnoses are often not comparable due to the fact that different rating scales are used rather than basing all diagnoses on structured interviews and *DSM* criteria.

The aim of our research was to identify the dimensional temperament and character profiles that can significantly discriminate the three most frequent psychiatric disorders in preschoolers: anxiety disorders, ODD, and ADHD. Differently from most previous work on temperament and psychopathology that examines multiple bivariate associations, in the present study we adopted a multivariate approach that simultaneously utilizes multiple personality traits to discriminate different psychiatric disorders in preschoolers. In particular, we tested the ability of the temperamental and character dimensions measured by Cloninger's bio-psycho-social model [42–44] to distinguish preschoolers diagnosed as anxious, ODD, or ADHD. In the theoretical framework developed by Cloninger and co-workers, normal and maladaptive personality development is the result of a self-organizing multidimensional dynamic system created by complex genetic and environmental interactions [45].

Cloninger first developed a model of temperament based on heritable differences in the way behavior is conditioned by patterns of reward and punishment that elicit basic emotional responses like fear or anger. The temperament model was based on studies of the effects of genetics and neuropsychological data on behavioral learning [42,45], which led to the identification of four dimensions of temperament related to inhibition of behavior by signals of punishment or non-reward (i.e. Harm Avoidance), activation of approach behavior by novelty (i.e., Novelty Seeking), activation of social attachment (i.e. Reward Dependence), and maintenance of behavior despite frustration (i.e., Persistence). The temperament dimensions measure the associatively conditioned aspects of personality that are not rational or self-aware but are moderately stable throughout life [46]. Cloninger next developed a model of mental self-government of these temperament traits by higher cognitive processes he called Self-directedness (the executive aspect of self-government), Cooperativeness (the legislative aspect of self-government), and Self-transcendence (the judicial aspect of self-government) [43]. These traits integrate much earlier work in humanistic and transpersonal psychology [43,44]. These character traits can be measured in pre-schoolers [47] but mature with age in the direction of culturally sanctioned norms [46].

Cloninger's model has been shown to be a useful model for discriminating different psychiatric disorders in adults [17,48], as well as in adolescents [18,49,50] and school age children [14,15,51,52]. To diagnose the different disorders in preschool children, we administered a reliable structured interview, the Preschool Age Psychiatric Assessment (PAPA) [53], which provides a comprehensive assessment of *DSM-IV-TR* diagnoses.

We describe our initial hypothesis as follows. We expected preschoolers with ADHD and anxiety disorders

to show temperament and character configurations similar to older children. More specifically, we expected higher Novelty Seeking and lower Cooperativeness scores in the ADHD children, and higher Harm Avoidance associated with low Self-Directedness scores in the anxious children. The literature does not contain distinctions in terms of the temperamental profiles between ODD and ADHD. However, because ODD criteria combines both emotional and behavioral symptoms, in contrast to ADHD, we suggest that the ODD profile may like children with ADHD but also high in Harm Avoidance like children with anxiety disorders.

2. Methods

2.1. Subjects

The participants were recruited from Child Mental Health Centers and kindergartens in Rome. The sample ($N = 120$) consisted of 90 clinical cases, including 30 ADHD children (27 males, mean age = 52.7 ± 12 months), 30 ODD children (25 males, mean age = 56.1 ± 12.2 months) and 30 anxious children (21 males, mean age = 56.9 ± 9.7 months), with Generalized anxiety (GAD n° 13) and Social Phobia (SP n°17), and 30 children in the control group. All participants were Caucasian and all the clinical cases were treatment naive. The clinical cases were recruited among those who have spontaneously turned to the services in the last 3 years. The four groups did not differ in age [$F(3,119) = 1.20$; n.s.] or gender distributions [$\chi^2 = 4.03$; d.f. = 3; n.s.].

2.2. Child assessment

2.2.1. Child Behavior Checklist 1.5-5 (CBCL/1.5-5) [54]

The CBCL is a questionnaire used to obtain parental reports of behavioral problems and pro-social adaptive skills in 1½ to 5-year-old children. The 99 items assess emotional and behavioral problems within the previous 6 months. Each item describes a specific behavior, and the parent is asked to rate its frequency on a three point scale (0, not true; 1, somewhat or sometimes true; 2, very true or often true).

2.2.2. Preschool Age Psychiatric Assessment (PAPA) [53]

The PAPA is a parent structured interview to diagnose psychiatric disorders in preschool children aged 2 through 5 years and provides a comprehensive assessment of *DSM-IV-TR* diagnoses. It uses an interviewer-based approach and includes a detailed glossary that provides guidelines for rating the symptom severity, frequency, duration, and impairment.

2.2.3. Temperament assessment

2.2.3.1. Preschool temperament and character inventory [47,55]. The PsTCI is a tool to assess individual differences in the basic dimensions of the Cloninger biosocial model of personality [44], which includes four temperament dimensions (Novelty Seeking, NS; Harm avoidance, HA; Reward Dependence, RD; Persistence, P) and three character dimensions (Self-Directedness, SD; Cooperativeness, C; Self-Transcendence, ST). The questionnaire is composed of 74 statements, which are answered by parents on a 5-point scale (ranging from 1 = "definitely false" to 5 = "definitely true"). The contents of the questions were adapted to the age of preschool children and to make them unambiguous for parents to answer; the temperament and character scales capture the same underlying Cloninger's factors assessed in adults and older children, with the exception of the ST scale, which does not cover aspects of these traits that are well-developed later in adulthood (e.g., being spiritual), but refers to the capacity to pretend in play. Recently, the validity of the Italian version of the PsTCI used in the present study was confirmed with Cronbach's alpha ranging values (|0.60|–|.81|), which indicates that the Italian PsTCI is a valid and reliable measure of Cloninger traits for Italian pre-school children [55].

2.3. Procedure

The 30 children in the control group (24 males, mean age = 57.3 ± 7.5 months) were randomly extracted from a larger sample of 103 children from kindergartens in Rome with a stratified randomization procedure in order to balance the clinical and control groups for gender. Parents of control group's children completed at their home the PsTCI and the CBCL and returned the questionnaire in an enclosed envelop within a week. As in previous works [51], studying the prevalence of psychiatric disorders in general population, the CBCL scores were used to select the control group members: the children who scored above the cutoff point of 60 in the CBCL (anxious–depressed, attention problems and aggressive behaviors and internalizing, externalizing and total scores) were excluded from the study. Other exclusion criteria for all participants were the presence of a certificated neurological disorders, autism, senso-motory disorders or intellectual disability (IQ less than 85).

All participants in the clinical groups were selected, as first step, with the same procedure of control group. All children that showed a cut of above 60 in the over mentioned CBCL dimensions, completed the 2° step, with three visits, to confirm the diagnosis. During the initial visit, the primary caregiver was asked about the case history of the child while the child was involved in a behavioral observation. During the second visit, the paper version of the PAPA was administered to the primary caregiver while the child participated in a cognitive assessment. During the third visit, the parents completed the PsTCI questionnaires, and the clinicians observed the caregiver–child interaction. Children of clinical groups that meet all the diagnostic criteria for a comorbid diagnosis were excluded from the study. The PAPA interviewers to the parents were conducted by an expert psychiatrist with officially recognized high professional competences in psychiatric and developmental disorders with early onset in infancy and preschool age.

Informed written consent was obtained from the parents or guardians of all participants.

2.4. Data analysis

Descriptive statistics of the personality traits scores were computed, and the differences among groups on the PsTCI dimensions were evaluated by one-way analysis of variance (ANOVA). To control the influence of type 1 errors for multiple comparisons, the Bonferroni post hoc test was applied. Multiple discriminant analysis (stepwise method) was used to identify the dimensional profiles of temperament and character that can significantly discriminate the preschoolers diagnosed as anxious, ODD, or ADHD and the control group. Wilk's lambda was used as the criterion with univariate F tests for the significance of each extracted function to predict group membership from the seven PsTCI dimensions. All analyses were performed with IBM SPSS software 16.0.

3. Results

3.1. ANOVA descriptive analysis

The ANOVA results and the descriptive statistics (mean ± S.D.) for the PsTCI of the four groups are reported in Table 1.

All clinical groups showed lower scores in Reward Dependence and Persistence compared with the control group. With respect to Harm Avoidance, the ADHD children showed significantly lower scores in Harm Avoidance compared with ODD and, as can be expected, the anxious children obtained higher scores in this dimension compared with all other groups. High scores in Novelty Seeking characterized both the ADHD and ODD groups compared with the anxious and control groups, whereas the ADHD children were significantly lower in Persistence compared with the ODD and anxious children.

With regard to the character dimensions, the anxious children had lower Self-directedness scores compared with the ADHD children, as well as the combination of ADHD and ODD children compared with controls. Lower scores in Cooperativeness distinguished between disruptive disorders and the anxious and control groups. Finally, lower Self-transcendence scores differentiated between the ADHD group and the anxious and control groups.

3.2. Discriminant analysis

The results of the discriminant analyses are reported in Table 2. Three discriminant functions were extracted to distinguish the four groups. Each discriminant function represents linear combinations of predictors, creating a new latent variable maximizing the differences between groups. The canonical correlations for the three functions were high (.790 for function 1; .726 for function 2; .547 for function 3, respectively). The model explains a significant relationship between the functions and the dependent grouping variables. Overall, the discriminating power is acceptable, and the model classifies correctly 75% of subjects in their original groups. The Wilks's lambda test for the 3 functions was significant ($p < .001$) and the univariate F tests evidenced that three temperament dimensions variables, namely Harm Avoidance, Novelty Seeking and Persistence, had a statistically significant contribution ($p < .001$) to the discriminant functions. Neither Reward Dependence nor the character dimensions had a statistically significant contribution.

Table 2 shows reported standardized coefficients for these variables that indicate the relative importance of each predictor in predicting group assignment from each function. Furthermore, the group centroids are reported for each function, representing mean discriminant scores for each grouping variable. For each function, the farther apart the means are, the less error there will be in classification between the groups.

The parameters reported in Table 2 suggest that the first function allowed the discrimination of the ADHD and ODD children from the anxious and control children. The second function discriminated the ODD children from the ADHD and control children, and the third function discriminated the anxious children from the ODD and control children.

The classification matrix of the discriminant analysis is reported in Table 3. The highest rate of correct classifications (24/30, 80%) was observed for the ADHD children. It is noteworthy that approximately all of the remaining ADHD

Table 1
Descriptive statistics of PsTCI dimensions and differences among groups.

PsTCI dimensions	Groups membership				F	p
	ADHD[a]	ODD[b]	ANX[c]	Control[d]		
HA	2.07 ± .51[b,c]	2.87 ± .76[a,c]	3.44 ± .62[a,b,d]	2.45 ± .60[c]	26.19	<.001
NS	3.64 ± .56[c,d]	3.94 ± .45[c,d]	2.64 ± .77[a,b]	2.37 ± .47[a,b]	51.61	<.001
P	2.14 ± .48[b,c,d]	2.96 ± .64[a,d]	2.91 ± .68[a,d]	3.68 ± .56[a,b,c]	33.40	<.001
RD	3.98 ± .50[d]	3.77 ± .64[d]	3.71 ± .64[d]	4.37 ± .28 [b,c]	9.31	<.001
SD	3.75 ± .52[c]	3.49 ± .65[d]	3.33 ± .72[a,d]	4.15 ± .42[b,c]	11.05	<.001
C	2.89 ± .56[c,d]	2.71 ± .52[c,d]	3.75 ± .68[a,b]	4.02 ± .41[a,b]	40.43	<.001
ST	3.2 ± .62[c,d]	3.59 ± .72	3.67 ± .60[a]	4.00 ± .48[a]	8.73	<.001

[a,b,c,d] Groups that result significantly different at Bonferroni post hoc test ($p < .001$).
The PsTCI dimensions: Harm Avoidance (HA), Novelty Seeking (NS), Persistence (P), Reward Dependence (RD), Self-directedness (SD), Cooperativeness (C), and Self-transcendence (ST).

Table 2
Summary results of the discriminant analysis.

PsTCI' dimensions loadings	Function 1	Function 2	Function 3
Harm Avoidance	0.426	0.771	−0.503
Novelty Seeking	−0.702	0.677	0.366
Persistence	0.466	0.500	0.804
Groups centroids			
ADHD	−1.639	−0.862	−0.238
ODD	−0.823	1.149	0.436
ANX	1.104	0.297	−0.931
Controls	1.358	−0.585	0.734
Eigenvalue	1.662	0.645	0.427
Canonical correlation	0.790	0.626	0.547
Chi square	211.643	98.556	41.087
Wilk's lambda	0.160	0.426	0.701
Significance	0.001	0.001	0.001

children were wrongly classified as ODD (5/30, 16.7%) by the discriminant analysis. Congruently, more than three-fourths of the ODD children (24/30, 76.7%) were correctly classified, and approximately all of the remaining ODD children were misclassified as ADHD (6/30, 20%). A lower rate of correct classifications was observed for anxious children (20/30, 66.7%) who were misclassified as controls (5/30, 16.7%) or ODD (4/30, 13.3%). Overall, the classification matrix shows that a substantial proportion of the cases (75.4%) were classified correctly (hit-ratio) in their respective group.

4. Discussion

The aim of the present research was to identify the profiles of Cloninger's temperament and character dimensions associated with anxiety disorders, ODD and ADHD in preschoolers. Previous studies suggest that psychopathological disorders are predominately related to multiple temperament and character dimensions, which contribute to the wide variety of different personalities in the general and clinical populations [56-58].

The main outcome of the study is that Cloninger' temperamental dimensions allow the differentiation of the three most frequent psychiatric disorders in preschoolers.

Table 3
Classification matrix of the discriminant analysis.

		Groups	Predicted group membership				Total
			ADHD	ODD	ANX	Control	
Original group membership	Count	ADHD	24	5	1	0	30
		ODD	6	23	0	1	30
		ANX	1	4	20	5	30
		Control	0	2	5	23	30
	%	ADHD	80.0	16.7	3.3	.0	100.0
		ODD	20.0	76.7	.0	3.3	100.0
		ANX	3.3	13.3	66.7	16.7	100.0
		Control	.0	6.7	16.7	76.7	100.0

75.0% of original grouped cases correctly classified.

This main result has relevant implications from both theoretical and applicative point of views. From a theoretical point of view, the present study provides, to the best of our knowledge, a first evidence that also at this very early age temperamental factors are associated with the expression of different psychiatric disorders. It emphasizes the need that future longitudinal studies should systematically evaluate whether these early temperament profiles could be predictive of later diagnoses. In addition, present results also indicate that some psychiatric disorders (e.g. ODD and ADHD) share some common features in their temperamental profiles, providing a more comprehensive understanding of the high rates of comorbidity between disorders observed in the literature [59,60]. On the other hand, as Olvera and colleagues [49] pointed out, investigating the relationships between temperament and psychopathology is not only an important research question but may have practical implications, since considering a patient's temperament may assist in implementing a patient tailored treatment program.

The temperamental profiles that emerged from our analyses are here briefly described and discussed for each disorder.

ADHD temperamental profile: the ADHD temperament profile that emerged from the discriminant analyses is characterized by the association of high Novelty Seeking and low Persistence. Extensive data indicate that high levels of Novelty Seeking could be considered causal antecedents that can contribute to the development of later psychiatric disorders [45,61,62], especially disorders characterized by difficulties in behavioral and impulse control [63,64]. The high Novelty Seeking is associated with characteristics including being impulsive, exploratory and excitable, fickle, quick-tempered and disorderly, intolerance to frustration and rules, and an extravagance described by a tendency to exceed one's capacity. Individuals with high Novelty Seeking are readily engaged in new interests and activities, but they tend to forget details and are quickly distracted and bored. As demonstrated by substantial evidence in the literature, the associated low Persistence confirm that these disorders present difficulty in maintaining behaviors without continuous social reinforcement.

Anxiety Group temperamental profile: our sample of anxious preschoolers showed a profile characterized by high Harm Avoidance scores (which involves a higher anxiety proneness), with higher scores in this dimension as compared to both control and other clinical groups. Anxious preschoolers were also lower in Novelty Seeking than those with ADHD or ODD, and they were higher in Persistence than those with ADHD. However, anxious children were lower in Persistence than healthy controls, which is plausible from observations in adults in which Persistence promotes emotional resilience [65] even though in some configurations Persistence can augment anxiety [66]. In line with previous studies on older anxious children [18,67], this peculiar combination of high Harm Avoidance and low Novelty Seeking leads children to be slowly engaged in new interests, often worried about unfamiliar situations, have difficulty adapting to change, intolerant, not confident, in

need of spending a substantial time thinking before making a decision (fear of uncertainty) and with very narrow interests often focused on details.

ODD Group temperamental profile: The ODD children's profile shares some common features with the ADHD profile. In both groups we found higher scores in Novelty Seeking (which involves impulsivity) compared with the anxious and control groups. However, the ODD profile is characterized by the association of high Novelty seeking with higher Persistence and Harm Avoidance scores compared with the ADHD profile. This configuration fits with the behavioral patterns of the children characterized by negative mood and emotional instability, irritability and the tendency to easily experience frequent unfriendly feelings toward others. In addition, higher Persistence scores make these children significantly more resistant to the extinction of non-adaptive behaviors compared with ADHD children, as expected from their stubbornness and oppositionality. In addition, univariate analyses revealed some differences in character dimensions that, although did not contribute significantly to the groups discrimination, have interesting implications for the development of later psychopathology in adolescents and adults where character development is more important. In particular, the ADHD and ODD children obtained lower scores in Cooperativeness than the anxious children and controls, which interferes with their establishing positive relationships with others. The anxious and ODD children also showed reduced Self-directedness, compared with the controls, which indicates less confidence, less initiative, and less responsibility with a tendency to blame others for their problems.

From the above mentioned profile descriptions it can derived that the combinations between Harm Avoidance, Novelty Seeking and Persistence were different within the three groups of children, which indicates that each disorder is characterized by a particular profile of emotional drives that are not well-regulated. It is noteworthy that considering only these three temperament dimensions made it possible to correctly classify 75% of the children within their own group in our Discriminant Analysis, which demonstrated an adequate accuracy rate [68]. Previous findings suggested a general link between early difficult temperament and later disruptive psychopathology, but did not identify specific aspects of temperament as predictive of a distinct disruptive psychopathology [69]. In the present study we evidenced that each disorder in preschoolers had a unique temperamental profile. The overlap among ADHD and ODD was explained by high Novelty Seeking. In contrast, children with ODD also were high in Harm Avoidance like anxious children, but the anxious children were low in Novelty Seeking and higher in Persistence. These findings are consistent with prior clinical observations [2]. Novelty Seeking explains the high comorbidity between ODD and ADHD (40–60%) [70,71]. Thus even the misclassification of subjects in our discriminant analysis is an indicator of the fuzziness of the clinical categories, which are not really mutually exclusive disorders. Future longitudinal studies could help us to understand if this overlap between different diagnoses and how the different profiles predict future development.

In the present study, the results on Cloninger's temperamental dimensions facilitated the discrimination of the clinical groups more than the character dimensions. A potential post hoc interpretation of this finding can be advanced. On one hand, at this early age, the dimensions of character, which develop through experience-dependent processes, do not have a stable organization; in contrast, it is plausible to hypothesize that the parents' perceptions of these dimensions may be less accurate and reliable compared with the temperament perception of their children. Further studies are needed to clarify this issue.

Although our results are coherent and consistent with the existing literature and clinical observations, there are some limitations that must be considered. First, the study is based on a cross-sectional design and therefore firm conclusions about the prediction of psychopathology or the influence of Cloninger's dimensions on the development of psychopathology cannot be drawn. Second, the results are based only on the parental report, and future studies should consider collecting information from other observers (e.g., teachers) in order to increase the reliability of the measurement. Third, our results should be confirmed using a wider sample of participants. Fourth, in the present study, we evaluated the basic personality factors postulated in Cloninger's model; however, future studies should consider comparing its ability to discriminate different early onset psychopathology with the same ability of other temperamental models.

Notwithstanding these limitations, to our knowledge, this research is the first to use the validated preschooler version of the TCI in distinguishing multiple clinical groups. We compared healthy controls with children with psychiatric disorders in terms of personality characteristics and we diagnosed different disorders using the well-established PAPA. The current results contribute to the growing literature that is focused on the definition and differentiation of temperamental and character profiles in different clinical psychiatric disorders. These findings may lead to a deeper understanding of the influence of temperamental traits in the organization of disorders and to a better definition of intervention based on the specific personality profiles of the different preschool psychiatric disorders.

Acknowledgment

The authors gratefully acknowledge all the families who participated in this study.

References

[1] Côté SM, Boivin M, Liu X, Nagin DS, Zoccolillo M, Tremblay RE. Depression and anxiety symptoms: onset, developmental course and risk factors during early childhood. J Child Psychol Psychiatry 2009;50:1201-8.

[2] Stringaris A, Maughan B, Goodman R. What's in a disruptive disorder? Temperamental antecedents of oppositional defiant disorder: findings from the Avon Longitudinal Study. J Am Acad Child Adolesc Psychiatry 2010;49:474-83.

[3] Dougherty LR, Buffered SJ, Carlson GA, Dyson M, Olino TM, Durbin CE, et al. Preschoolers' observed temperament and psychiatric disorders assessed with a parent diagnostic interview. J Clin Child Adolesc Psychol 2011;40:295-306.

[4] Caspi A, Henry B, McGee RO, Moffitt TE, Silva PA. Temperamental origins of child and adolescent behaviour problems: from age three to age fifteen. Child Dev 1995;66:55-68.

[5] Sonuga-Barke EJS, Halperin JM. Developmental phenotypes and causal pathways in attention deficit/hyperactivity disorder: potential targets for early intervention? J Child Psychol Psychiatry 2010;51:368-89.

[6] Eisenberg N, Fabes RA, Karbon M, Murphy BC, Wosinski M, Polazzi L, et al. The relations of children's dispositional prosocial behavior to emotionality, regulation, and social functioning. Child Dev 1996;67:974-92.

[7] Eisenberg N, Guthrie IK, Fabes RA, Shepard S, Losoya S, Murphy BC, et al. Prediction of elementary school children's problem behaviors from attentional and behavioral regulation and negative emotionality. Child Dev 2000;71:1367-82.

[8] Nigg JT, Goldsmith HH. Developmental psychopathology, personality, and temperament: reflections on recent behavioral genetics research. Hum Biol 1998;70:387-412.

[9] Plomin R, Caspi A. Behavioral genetics and personality. In: Pervin LA, & John OP, editors. Handbook of personality theory and research. New York: Guilford; 1999. p. 251-76.

[10] Nigg JT. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychol Bull 2000;126:220-46.

[11] Nigg JT. Is ADHD an inhibitory disorder? Psychol Bull 2001;127:571-98.

[12] Nigg JT, John OP, Blaskey LG, Huang-Pollock CL, Willcut EG, Hinshaw SO, et al. Big five dimensions and ADHD symptoms: links between personality traits and clinical symptoms. J Pers Soc Psychol 2001;83:451-69.

[13] Witkiewitz K, King K, McMahon RJ, Wu J, Luk J, Bierman KL, et al. Evidence for a multi dimensional latent structural model of externalizing disorders. J Abnorm Child Psychol 2013;41:223-37.

[14] Yoo HJ, Kim M, Ha JH, Chung A, Sim ME, Kim SJ, et al. Biogenetic temperament and character and attention deficit hyperactivity disorder in Korean children. Psychopathology 2006;39:25-31.

[15] Cho SC, Hwang JW, Lyoo IK, Yoo HJ, Kin BN, Kim JW. Patterns of temperament and character in a clinical sample of Korean children with attention-deficit hyperactivity disorder. Psychiatry Clin Neurosci 2008;62:160-6.

[16] Haslam N, Williams B, Prior M, Haslam R, Graetz B, Sawyer M. The latent structure of attention-deficit/hyperactivity disorder: a taxometric analysis. Aust N Z J Psychiatry 2006;40:639-47.

[17] Lochner C, Hemmings S, Seedat S, Kinnear C, Schoeman R, Annerbrink K, et al. Genetics and personality traits in patients with social anxiety disorder: a case–control study in South Africa. Eur Neuropsychopharmacol 2006;17:321-7.

[18] Cho SC, Jung SW, Kim BN, Hwang JW, Shin MS, Kim JW, et al. Temperament and character among Korean children and adolescents with anxiety disorders. Eur Child Adolesc Psychiatry 2009;18:60-4.

[19] Gadow KD, Nolan EE. Differences between preschool children with ODD, ADHD, and ODD + ADHD symptoms. J Child Psychol Psychiatry 2002;43:191-201.

[20] Luby JL, Heffelfinger AK, Mrakotsky C, Brown KM, Hessler MJ, Wallis J, et al. The clinical picture of depression in preschool children. J Am Acad Child Adolesc Psychiatry 2003;42:340-8.

[21] Luby JL, Mrakotsky C, Heffelfinger AK, Brown KM, Hessler MJ, Spitznagel EL. Modification of *DSM-IV* criteria for depressed preschool children. Am J Psychiatry 2003;160:1169-72.

[22] Egger HL, Angold A. Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. J Child Psychol Psychiatry 2006;47:313-37.

[23] Tschann M, Kaiser P, Chesney MA, Alkon A, Boyce WT. Resilience and vulnerability among preschool children: family functioning, temperament, and behavior problems. J Am Acad Child Adolesc Psychiatry 1996;35:184-92.

[24] Derauf C, LaGasse L, Smith L, Newman E, Shah R, Arria A, et al. Infant temperament and high risk environment relate to behavior problems and language in toddlers. J Dev Behav Pediatr 2011;32:125-35.

[25] Berdan LE, Keane SP, Calkins SD. Temperament and externalizing behavior: social preference and perceived acceptance as protective factors. Dev Psychol 2008;44:957-68.

[26] Hudson JL, Dodd HF, Bovopoulos N. Temperament, family environment and anxiety in preschool children. J Abnorm Child Psychol 2011;39:939-51.

[27] Mian ND, Wainwright L, Briggs-Gowan MJ, Carter AS. An ecological risk model for early childhood anxiety: the importance of early child symptoms and temperament. J Abnorm Child Psychol 2011;39:501-12.

[28] Vreeke LJ, King K, McMahon RJ, Wu J, Luk J, Bierman KL, et al. The assessment of an inhibited, anxiety-prone temperament in a Dutch multi-ethnic population of preschool children. Eur Child Adolesc Psychiatry 2012;21:623-33.

[29] Janson H, Mathiesen KS. Temperament profiles from infancy to middle childhood: development and associations with behavior problems. Dev Psychol 2008;44:1314-28.

[30] Loeber R, Jeffrey D, Burke JD, Pardini DA. Development and etiology of disruptive and delinquent behavior. Annu Rev Clin Psychol 2009;5:291-310.

[31] Loeber R, Burke JD, Pardini DA. Perspectives on oppositional defiant disorder, conduct disorder, and psychopathic features. J Child Psychol Psychiatry 2009;50:133-42.

[32] Lavigne JV, Cicchetti C, Gibbons RD, Binns HJ, Larsen L, DeVito C. Oppositional defiant disorder with onset in preschool years: longitudinal stability and pathways to other disorders. J Am Acad Child Adolesc Psychiatry 2001;40:1393-400.

[33] Nock MK, Kazdin AE, Hiripi E, Kessler RC. Lifetime prevalence, correlates, and persistence of oppositional defiant disorder: results from the National Comorbidity Survey Replication. J Child Psychol Psychiatry 2007;48:703-13.

[34] Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. J Am Acad Child Adolesc Psychiatry 2010;49:484-92.

[35] Stringeris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. J Am Acad Child Adolesc Psychiatry 2009;48:404-12.

[36] Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. Am J Psychiatry 2009;166:1048-54.

[37] Lavigne JV, Gouze KR, Bryant FB, Hopkins J. Dimensions of oppositional defiant disorder in young children: heterotypic continuity with anxiety and depression. J Abnorm Child Psychol 2014;42:937-51.

[38] Sanson A, Prior M. Temperament and behavioral precursors to oppositional defiant disorder and conduct disorder. In: Quay HC, & Hogan AE, editors. Handbook of disruptive behavior disorders. New York: Kluwer Academic/Plenum Publishers; 1999. p. 397-417.

[39] Wakschlag LS, Briggs-Gowan MJ, Carter AS, Hill C, Danis B, Keenan K, et al. A developmental framework for distinguishing disruptive behavior from normative misbehavior in preschool children. J Child Psychol Psychiatry 2007;48:976-87.

[40] Hagekull B. Infant temperament and early childhood functioning: possible relations to the five factor model. In: Halverson CF, Kohnstamm GA, & Martin RP, editors. The developing structure of temperament and personality from infancy to adulthood. Hillsdale, NJ: Erlbaum; 1994.

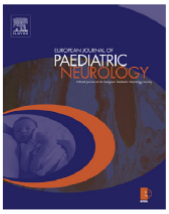
[41] Loeber R, Burke JD. Developmental pathways in juvenile externalizing and internalizing problems. J Res Adolesc 2011;21:34-46.

[42] Cloninger CR. A systematic method for clinical description and classification of personality variants. Arch Gen Psychiatry 1987;44:573-88.
[43] Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;50:975-90.
[44] Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. The Temperament and Character Inventory (TCI). A Guide to Its Development and Use. St. Louis, MO: Center for Psychobiology of Personality, Washington University; 1994.
Svrakic DM, Cloninger RC. Epigenetic perspective on behavior development, personality, and personality disorders. Psychiatr Danub 1994;22:153-66.
[45] Cloninger CR. A unified biosocial theory of personality and its role in the development of anxiety state. Psychiatr Dev 1986;4:167-226.
[46] Josefsson K, Jokela M, Cloninger CR, Hintsanen M, Salo J, Hintsa T, et al. Maturity and change in personality: developmental trends of temperament and character in adulthood. Dev Psychopathol 2013;25:713-27.
[47] Constantino N, Cloninger CR, Clarke AR, Hashemi B, Przybeck T. Application of the seven-factor model of personality to early childhood. Psychiatry Res 2002;109:229-43.
[48] Celikel FC, Koseb S, Cumurcua BE, Erkorkmazc U, Sayard K, Borckardtb JJ, et al. Cloninger's temperament and character dimensions of personality in patients with major depressive disorder. Compr Psychiatry 2009;50:556-61.
[49] Olvera RL, Fonseca M, Caetano SC, Hatch JP, Hunter K, Nicoletti M, et al. Assessment of personality dimensions in children and adolescents with bipolar disorder using the Junior Temperament and Character Inventory. J Child Adolesc Psychopharmacol 2009;19:13-21.
[50] Kim HW, Cho SC, Kim BN, Kim JW, Shin MS, Yeo JY. Does oppositional defiant disorder have temperament and psychopathological profiles independent of attention deficit/hyperactivity disorder? Compr Psychiatry 2010;51:412-8.
[51] Althoff RR, Ayer LA, Crehan ET, Rettew DC, Baer JR, Hudziak JJ. Temperamental profiles of dysregulated children. Child Psychiatry Hum Dev 2012;43:511-22.
[52] Zappitelli MC, Bordin IA, Hatch JP, Caetano SC, Zunta-Soares G, Olvera RL, et al. Temperament and character traits in children and adolescents with major depressive disorder: a case–control study. Compr Psychiatry 2013;54:346-53.
[53] Egger HL, Ascher BH, Angold A. The preschool age psychiatric assessment: version 1.1. Unpublished interview schedule. Durham, NC: Center of Developmental Epidemiology, Department of Psychiatry and Behavioural Science, Duke University Medical Centre; 1999.
[54] Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms & profiles. Burlington, VT: University of Vermont. Research Center for Children, Youth & Families; 2000.
[55] Melegari MG, Innocenzi M, Marano A, De Rosa L, Donfrancesco R, Rozsa S, et al. Application of the seven-factor-model of personality to an Italian preschool sample. Psychiatry Invest 2014;11:419-29.
[56] Petersen DJ, Bilenberg N, Hoerder K, Gillberg C. The population prevalence of child psychiatric disorders in Danish 8- to 9-year-old children. Eur Child Adolesc Psychiatry 2006;15:71-8.
[57] Pukrop R, Steinbring I, Gentil I, Schulte C, Larstone R, Livesley JW. Clinical validity of the "Dimensional Assessment of Personality Pathology (DAPP)" for psychiatric patients with and without a personality disorder diagnosis. J Pers Disord 2009;23:572-86.
[58] De la Rie SM, Duijsens IJ, Cloninger CR. Temperament, character, and personality disorders. Compr Psychiatry 2007;48:124-31 [Epub 2006 Nov 9].
[59] Wichstrøm L, Berg-Nielsen TS, Angold A, Egger HL, Solheim E, Sveen TH. Prevalence of psychiatric disorders in preschoolers. J Child Psychol Psychiatry 2012;53:695-705.
[60] Rockhill C, Violette H, Vander Stoep A, Grover S, Myers K. Caregivers' distress: youth with attention-deficit/hyperactivity disorder and comorbid disorders assessed via telemental health. J Child Adolesc Psychopharmacol 2013;23:379-85.
[61] Battaglia M, Przybeck TR, Bellodi L, Cloninger CR. Temperament dimensions explain the comorbidity of psychiatric disorders. Compr Psychiatry 1996;37:292-8.
[62] Jacob C, Gross-Lesch S, Jans T, Geissler J, Reif A, Dempfle A, et al. Internalizing and externalizing behavior in adult ADHD. Atten Deficit Hyperact Disord 2014;6:101-10.
[63] Grucza RA, Przybeck TR, Cloninger CR. Prevalence and correlates of binge eating disorder in a community sample. J Pers Disord 1998;12:362-72.
[64] Martinotti G, Andreoli S, Giametta E, Poli V, Bria P, Janiri L. The dimensional assessment of personality in pathologic and social gamblers: the role of novelty seeking and self-trascendence. Compr Psychiatry 2006;47:350-6.
[65] Eley DS, Cloninger CR, Walter L, Laurence C, Synnott R, Wilkinson D. The relationship between resilience and personality traits in doctors: implications for enhancing well-being. PeerJ 2013;1:e216.
[66] Cloninger CR, Zohar AH, Hirschmann S, Dahan D. The psychological costs and benefits of beinghighly persistent: personality profiles distinguish mood disorders from anxiety disorders. J Affect Disord 2012;136:758-66.
[67] Ettelt S, Grabe HJ, Ruhrmann S, Buhtz F, Hochrein A, Kraft S, et al. Harm avoidance in subjects with obsessive–compulsive disorder and their families. J Affect Disord 2008;107:265-9.
[68] Hair J, Black B, Babin B, Anderson R, Tatham R. Multivariate data analysis. 6th ed. Upper Saddle River, NJ: Prentice-Hall; 2006.
[69] Shaw DS, Owens EB, Giovannelli J, Winslow EB. Infant and toddler pathways leading to early externalizing disorders. J Am Acad Child Adolesc Psychiatry 2001;40:36-43.
[70] Jensen PS, Hinshaw SP, Kraemer HC, Lenora N, Newcorn JH, Abikoff HB, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry 2001;40:147-58.
[71] Kadesjö B, Gillberg C. The comorbidity of ADHD in the general population of Swedish school age children. J Child Psychol Psychiatry 2001;42:487-92.

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 19 (2015) 122–133

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Review article

Current role of melatonin in pediatric neurology: Clinical recommendations

Oliviero Bruni [a], Daniel Alonso-Alconada [b,c], Frank Besag [d], Valerie Biran [e,f], Wiebe Braam [g,h], Samuele Cortese [i,j,k], Romina Moavero [l,m], Pasquale Parisi [n], Marcel Smits [h,o], Kristiaan Van der Heijden [p], Paolo Curatolo [l,*]

[a] Department of Developmental and Social Psychology, Sapienza University, Rome, Italy
[b] Institute for Women's Health, University College London, London, UK
[c] Department of Cell Biology and Histology, University of the Basque Country, Spain
[d] South Essex Partnership University NHS Foundation Trust, Bedfordshire, & Institute of Psychiatry, London, UK
[e] Neonatal Intensive Care Unit, Hôpital Robert Debré, Assistance Publique-Hôpitaux de Paris, Univ Paris Diderot, 75019 Paris, France
[f] Univ Paris Diderot, Sorbonne Paris Cité, INSERM, U1141, 75019 Paris, France
[g] 's Heeren Loo, Department Advisium, Wekerom, The Netherlands
[h] Governor Kremers Centre, University Maastricht, The Netherlands
[i] Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[j] School of Medicine, and the Centre for ADHD and Neurodevelopmental Disorders Across the Lifespan, Institute of Mental Health, University of Nottingham, UK
[k] New York University Child Study Center, NY, USA
[l] Child Neurology and Psychiatry Unit, Systems Medicine Department, Tor Vergata University of Rome, Italy
[m] Neurology Unit, Neuroscience Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy
[n] Child Neurology-Chair of Pediatrics, c/o Sant'Andrea Hospital, NESMOS Department, Faculty of Medicine & Psychology, Sapienza University, Rome, Italy
[o] Department of Sleep-wake Disorders and Chronobiology, Hospital Gelderse Vallei Ede, The Netherlands
[p] Leiden Institute for Brain and Cognition & Institute of Education and Child Studies, Leiden University, The Netherlands

ARTICLE INFO

Article history:
Received 30 November 2014
Accepted 9 December 2014

Keywords:
Melatonin treatment
Sleep disorders
Insomnia

ABSTRACT

Background/purpose: Melatonin, an indoleamine secreted by the pineal gland, plays a key role in regulating circadian rhythm. It has chronobiotic, antioxidant, anti-inflammatory and free radical scavenging properties.
Methods: A conference in Rome in 2014 aimed to establish consensus on the roles of melatonin in children and on treatment guidelines.
Results and Conclusion: The best evidence for efficacy is in sleep onset insomnia and delayed sleep phase syndrome. It is most effective when administered 3–5 h before physiological dim light melatonin onset. There is no evidence that extended-release melatonin confers

* *Corresponding author.* Child Neurology and Psychiatry Unit, Systems Medicine Department, Tor Vergata University of Rome, Via Montpellier 1, 00133 Rome, Italy. Tel.: +39 0641400165; fax: +39 0641400343.
E-mail address: curatolo@uniroma2.it (P. Curatolo).
http://dx.doi.org/10.1016/j.ejpn.2014.12.007

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 19 (2015) 122–133

Epilepsy
ADHD
Autism

advantage over immediate release. Many children with developmental disorders, such as autism spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability have sleep disturbance and can benefit from melatonin treatment. Melatonin decreases sleep onset latency and increases total sleep time but does not decrease night awakenings. Decreased CYP 1A2 activity, genetically determined or from concomitant medication, can slow metabolism, with loss of variation in melatonin level and loss of effect. Decreasing the dose can remedy this. Animal work and limited human data suggest that melatonin does not exacerbate seizures and might decrease them. Melatonin has been used successfully in treating headache. Animal work has confirmed a neuroprotective effect of melatonin, suggesting a role in minimising neuronal damage from birth asphyxia; results from human studies are awaited. Melatonin can also be of value in the performance of sleep EEGs and as sedation for brainstem auditory evoked potential assessments. No serious adverse effects of melatonin in humans have been identified.

Contents

1. Introduction

Melatonin is an endogenously produced indoleamine secreted by the pineal gland. It is usually secreted during darkness and its secretion is suppressed by light. It plays a key role in regulating the circadian rhythm.[1,2] Melatonin has many other biological functions including chronobiotic and antioxidant properties, anti-inflammatory effects, and free radical scavenging.[3] It is critically involved in early development through its direct effects on placenta, developing neurons and glia, and its role in the ontogenetic establishment of diurnal rhythms.[4,5] Furthermore melatonin regulates the vigilance states depending on the activated melatonin receptors (MT1, MT2 or both); MT2 and MT1 receptors are mainly involved in NREM and REM sleep, respectively.[6]

Several studies have demonstrated the key chronobiotic role of melatonin as a modulator of the sleep–wake rhythm; it has both chronobiotic and hypnotic properties[7] that influence circadian rhythmicity and affect circadian rhythm sleep disorders.[8–10] Because of these strong chronobiotic and hypnotic properties, melatonin can improve sleep–wake rhythm disturbances and decrease sleep latency in children with sleep disorders, when it is administered at the right time and in the right dose.[7,9–12] As a result, it is one of the most commonly used drugs by pediatricians for infants, children and adolescents with sleep problems.[13–16] A recent study carried out in Norway showed that hypnotic drug use in young people 0–17 years old increased during the period 2004–2011, from 8.9 to 12.3 per 1000, mainly owing to doubling of melatonin use. The hypnotic drug use peaked at 15 per 1000 among those aged 1–2 years and melatonin use increased steadily from 6 to 12 years of age. Summarising the results of this study, the authors reported that melatonin was dispensed more frequently than any of the other hypnotic drugs.[16]

Melatonin is prescribed by pediatricians mainly for sleep onset insomnia (89%), delayed sleep phase syndrome (66%) and night-time awakenings (30%). It is prescribed both for typically-developing children and for children with developmental disorders, including autism, developmental delay, ADHD, and behavioral disorders.[17] Although melatonin is widely used in children and is currently recommended by many practitioners as a ''natural sleeping aid'' due to its endogenous origin,[17] there are no clinical guidelines on how to prescribe melatonin in children with different neurological disorders.

A European consensus conference was held in Rome on October 4th 2014 with the aims of assessing the current role of melatonin in childhood sleep disturbances and answering some key questions, including those relating to the correct dosage in infants, children and adolescents, timing of administration, duration of the treatment, benefits and pitfalls of immediate compared to controlled release, and predictors of response to melatonin treatment. This paper reports the main points discussed at this conference, starting with the physiology and pharmacokinetics of melatonin, followed by a review of the use of melatonin in the most relevant neuropsychiatric disorders based on meta-analyses/systematic reviews or individual studies. Finally, we provide consensus recommendations for the use of melatonin in both typically developing children and those with neuropsychiatric disorders in daily clinical practice.

2. Physiology

Night-time melatonin production during pregnancy increases after 24 weeks gestation until term. The fetus receives melatonin by rapid trans-placental transfer depending on maternal circadian secretion.[18] In 1997 Sadeh studied 20 normal, healthy infants for 1 week with actigraphy and determined the levels of 6-sulphatoxymelatonin (aMT6s), a melatonin metabolite.[19] He identified two groups of infants: 1) infants with "mature" secretion patterns (rise of aMT6s during the evening hours and suppression during the morning); and 2) infants with "immature" type, with flat distribution or rise of melatonin during the early morning hours. Those infants with the immature pattern showed a delayed peak of melatonin that was associated with more fragmented sleep during the night, suggesting that melatonin plays an important role in the development of the sleep–wake rhythm. Another recent research study attempted to relate dim light melatonin onset (DLMO) with sleep disturbances in toddlers. Toddlers with later DLMO had later bedtimes, sleep onset times, mid-sleep times, and wake times. This study highlighted the large inter-individual differences in DLMO.[20] Furthermore, morning melatonin concentrations in infants showed a negative correlation with nocturnal sleep duration and were associated with early waking time.[21]

As well as being associated with sleep disturbance, Tauman et al. suggested that 6-sulfatoxymelatonin levels at 16 weeks of age were significantly lower in infants with abnormal vs normal development at 3 and 6 months of age.[22] No other significant relation was evident between 6-sulfatoxymelatonin excretion and growth, perinatal complications or medical problems.

Several studies have shown that melatonin concentrations remain extremely low in the first 3 months and increase abruptly after 3 months of age.[23,24] This effect could be related to the fact that melatonin in human milk showed a clear circadian curve but was immeasurable in all artificial milks, and could contribute to the consolidation of sleep–wake rhythm of infants until the maturation of their own circadian system. Furthermore, endogenous nocturnal levels of melatonin show a strong age effect: they are much higher in children than in adults, they decline with age from 210 pg/ml in preschoolers (1–5 years of age) to 130 pg/ml in school-aged children (6–11 years) and to 50 pg/ml in young adults.[25] This decrease is mainly related to an increase in body size rather than to decreasing pineal secretion.[26]

3. Pharmacokinetics

As an exogenous compound, melatonin advances sleep onset in patients with circadian rhythm sleep disorders i.e. delayed sleep phase disorder, improving health status and decreasing parental stress.[7,9,27,28] Long term treatment is usually needed.[29,30]

Melatonin is a peculiar drug because timing of its administration plays a critical role in the results of treatment. According to the melatonin phase-response curve of 0.5 mg melatonin in adults, phase advances occur with from ±8 h before DLMO to ±2 h after, with maximum effect at 3–5 h before DLMO. When administered two or three hours after DLMO, no effects or reverse effect can occur. The optimal administration time is earlier for higher doses of melatonin.[31] This information was not available when the European Food and Safety Authority (EFSA) concluded incorrectly that melatonin should be administered before desired bedtime.[32,33] Furthermore, knowing DLMO helps to predict melatonin treatment success: the earlier the melatonin is administered before the DLMO the larger the phase-advance of sleep onset. Within a window of 1–6 h before DLMO, each advance of intake time of one hour resulted in an increase in effect on sleep onset of 19 min.[34] DLMO cannot be predicted by sleep diary, actigraphy or polysomnography.[31,35] It can, however, be assessed easily in home situations by measuring melatonin in saliva.[35,36] When measuring melatonin levels, children aged 6–12 yrs are invited to chew on a cotton plug for 1–2 min hourly between 7 and 11 pm, whilst it is suggested that adolescents do so between 8 and 12 pm. In cases with severe delayed or advanced sleep phase disorder, saliva should be collected at later or earlier times or hourly for 24 h[35]

Some pitfalls can be encountered when interpreting DLMO. It is advisable to measure DLMO before starting melatonin, to prevent inappropriate timing or doses of melatonin treatment.[29,36] When DLMO is measured in patients who stopped melatonin use 1–6 weeks before measuring DLMO, often strange, zig-zag, melatonin curves are seen[35] and DLMO cannot be determined reliably. It is therefore recommended that DLMO be measured before starting melatonin treatment. The main action of exogenous melatonin in patients with sleep onset insomnia and late DLMO is to "pull" at the advance of the endogenous melatonin rhythm and with it the sleep–wake rhythm. There is no evidence that prolonging the

presence of melatonin in the bloodstream is of value, implying that there no evidence to indicate that extended-release melatonin has advantages over immediate-release acting melatonin. If maintenance of sleep is the main problem, melatonin treatment usually is ineffective.

4. Delayed sleep phase syndrome and chronic sleep onset insomnia

Delayed sleep phase syndrome (DSPS) is a circadian rhythm sleep disorder characterized by a rigid delay in the timing of the major sleep period in relation to desired sleep–wake times. It is associated with a delayed 24-h melatonin rhythm, possibly linked to a PER3 polymorphism.[37–39] The etiology is likely to be heterogeneous, including delayed circadian timing, longer than normal circadian rhythm period, slower accumulation in homeostatic sleep drive, increased sensitivity to phase-delaying evening light, or an insensitivity to resetting properties of morning light.[40,41]

Recent meta-analyses have indicated that melatonin is and effective and apparently safe for treatment of primary sleep disorders or DSPS in children.[9,42,43] However, the effects probably vary from patient to patient because of inter-individual differences in etiology. Another aspect to influence variation in effect is the timing of intake in reference to endogenous circadian rhythm, as explained earlier. There are currently six published randomized controlled trials (RCTs) on melatonin treatment for primary DSPS or chronic sleep-onset insomnia in children and adolescents.[10,27,44–47] Sleep phase advanced in all but one study.[47] Sleep length increased in two studies but did not change significantly in two other studies.[27,47] Daytime sleepiness improved in one study,[45] but not in another study,[46] and health status and functional status was improved in one study.[27] Two studies showed no significant effects on various tests of cognitive performance.[27,46] The dose of melatonin varied from 1 to 5 mg/night. A dose-finding study with melatonin 0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg and a placebo group[10] showed advanced sleep onset time (SOT) and DLMO by approximately 1 h and decreased sleep onset latency (SOL) by 35 min; these effects were significantly different from placebo. No significant differences were found between the three melatonin doses. Several studies have shown that effects on SO, SOL, and DLMO increase with earlier circadian administration time. Adverse events were mild. In two studies, adverse events occurred only with melatonin treatment,[44,45] but in two other studies adverse events occurred in both the melatonin and in the placebo groups.[10,27]

When melatonin was administered at a time related to DLMO, meta-analyses showed that melatonin decreased sleep onset latency.[9,48] However, in the meta-analysis of melatonin administration without knowing DLMO, melatonin did not improve sleep.[49] This difference in results might be ascribed to the difference in melatonin administration strategy; however, other factors might also be involved, such as differences in primary diagnosis. For example, the study by Buscemi et al. showed much more pronounced effects with DSPS than with insomnia.

Melatonin treatment for primary DSPS or chronic sleep onset insomnia in children and adolescents advances sleep–wake rhythm and DLMO, possibly lengthens sleep, and appears to be safe both in the short term and in the long term. More studies are needed to evaluate the effects on daytime sleepiness and health/behavior/cognition, particularly in adolescents, given the high prevalence of DSPS in this population.

No specific studies on the use of melatonin in infants with insomnia have been reported. However, a recent survey reported that the melatonin dose administered in infants ranged from 0.5 to 3.5 mg (mean 2.1 mg), in children from 1 to 10 mg (mean 3.5 mg) and in adolescents from 2 to 12 mg (mean 5.3 mg). Maximum prescribed doses were 5 mg (infants), 10 mg (children) and 18 mg (adolescents) with a wide range. The most commonly reported starting dose was 3 mg. Duration of treatment ranged from 0 to 200 weeks, with an average of 16.5 weeks (SD 26.3 weeks).[17]

5. Melatonin in neuropsychiatric disorders

5.1. *Attention-deficit/hyperactivity disorder (ADHD)*

As many as 70% of children with ADHD have been reported as having mild to severe sleep problems. The most recent meta-analysis of sleep disturbances in ADHD, focused on children and adolescents, found significantly more sleep problems in children with ADHD than a normal comparison group, based upon subjectively-rated sleep items, including bedtime resistance, sleep onset difficulties, night awakenings, difficulties with morning awakenings, sleep disordered breathing, and daytime sleepiness.[50] The meta-analysis also indicated that children with ADHD were significantly more compromised than the comparison group with regard to several parameters assessed with objective methods (PSG or actigraphy), such as sleep onset latency (on actigraphy), the number of stage shifts/hour of sleep, the apnea–hypopnea index, sleep efficiency on polysomnography, true sleep time on actigraphy, and average times to fall asleep on the Multiple Sleep Latency Test. These results indicated that children with ADHD had higher levels of daytime sleepiness. Sleep onset insomnia is arguably the most commonly reported problem.[51] The causes of sleep onset insomnia in children with ADHD are likely to be heterogeneous and multifactorial.[52] Currently, there is no established consensus on how to treat sleep disorders in ADHD and the grade of available empirical evidence is generally low. Melatonin may be an option, at least when sleep onset insomnia is related to a delayed sleep phase disorder.[53] There is initial evidence that the use of melatonin in children with ADHD and sleep disturbance is grounded on a pathophysiological rationale, since a delay in dim-light melatonin onset (DLMO) has been reported in children with ADHD and sleep onset insomnia.[54] In addition, melatonin genetic pathways have been found to be abnormal in children with ADHD.[55]

In a systematic review of the literature, searching Pubmed, Ovid and Web of Knowledge databases (to September 29th, 2014), performed in preparation for the European Consensus meeting, we found a total of five trials of melatonin in children with ADHD, including 3 RCTs (two rated at "low risk" of bias and 1 at "uncertain risk" by means of the Cochrane tool of

bias).[56] All these trials concurred in showing that melatonin given in doses ranging from 3 to 6 mg/night) significantly reduced sleep onset delay and increased total sleep duration, but did not impact on daytime ADHD core symptoms as might have been expected, considering that better sleep quantity/quality has been related to improvement in cognitive and behavioral functioning.[57] This last finding might be accounted for by the short duration of most of the available trials that is below 3 months,[58–61] with only one long-term study (mean follow-up: 3.7 years).[29] In these studies, melatonin was generally well tolerated both in the short term and in the long term. Most of the participants who discontinued treatment did so because sleep problems were no longer a major issue rather than because of intolerable treatment effects. Adverse events included sleep maintenance insomnia, excessive morning sedation, low mood and headache, profuse perspiration and "daytime laziness".

5.2. *Autism spectrum disorders (ASD)*

Sleep disturbances such as reduced total sleep and longer sleep latency, as well as nocturnal and early morning awakenings, are commonly observed in population studies of individuals with ASD, with prevalence estimates ranging from 30 to 53%, depending on study design and definition of sleep problems.[62,63] Sleep problems can worsen the symptoms of autism and can result in challenging behaviors. Abnormalities in daytime or night-time values of melatonin compared to typically-developing controls have been often reported[64,65] suggesting that melatonin supplementation might be effective in improving sleep parameters in children with ASD. Furthermore, gene abnormalities that could contribute to decreased melatonin production have been reported in a subgroup of children with ASD and comorbid sleep onset delay.[66]

A meta-analysis of randomized double-blind placebo-controlled crossover studies showed significant improvements with large effect size in sleep duration and sleep onset latency, but not in night-time awakenings in individuals with ASD who took melatonin.[67] Children with ASD and insomnia who are responsive to low dose of melatonin, have been shown to present with relatively normal profiles of endogenous and supplemental melatonin.[65] Patients in whom the effect of melatonin disappeared have been shown to be CYP1A2 poor metabolizers due to a single nucleotide polymorphism (SNP) in the CYP1A2 gene.[68] The majority of children with ASD responded to a dose of 1–3 mg given 30 min before bedtime, with improvement in sleep latency and total sleep duration.[67,69] The overall improvement rate with melatonin was 80%. Melatonin was well tolerated with minimal adverse effects.[67]

Melatonin is of special interest in ASD, in view of the reported abnormalities in central and peripheral serotonin neurobiology[70,71]; however, the relationship between melatonin and serotonin needs to be clarified in children with ASD and comorbid sleep disorders. Further research into the sleep problems of people ASD is required both to elucidate the mechanism of action of supplemental melatonin and to identify which individuals are most likely to benefit from melatonin treatment.

5.3. *Neurodevelopmental disabilities (NDD)*

Sleep problems are reported to occur in 13–86% of individuals with NDD, depending on study design, participant characteristics, and definition of sleep problems. Such problems are often complex and usually more difficult to treat than in individuals without NDD. Melatonin is used widely in children with insomnia and NDD, because of its apparently safe profile, but there are no specific clinical guidelines on how to prescribe melatonin in this group of children.[72]

A meta-analysis of nine of randomized, placebo-controlled trials, including a total of 183 individuals with NDD, showed that melatonin decreased sleep latency by a mean of 34 min, increased total sleep time by a mean of 50 min and less significantly decreased the number of awakenings per night.[11] A recent placebo-controlled study in 146 children (age 3–15 years) with intellectual disability showed similar results.[73] In some patients with NDD and sleep problems, the initial good response to melatonin disappeared within a few weeks of starting treatment and the good response returned only after considerable dose reduction.[11] The loss of efficacy of melatonin treatment after an initial good response is a major problem possibly caused by slow metabolism because of decreased activity of the CYP1A2 enzyme.[74] This may result in increasing daily melatonin levels. Consequently melatonin levels accumulate and after some time the circadian melatonin rhythm is lost. This loss of circadian rhythm might explain why exogenous melatonin loses its effectiveness.

If the melatonin dose is high and/or the individual is a poor metabolizer, high daytime melatonin levels may result. Braam (personal communication) analyzed daytime melatonin levels in 150 patients who visited a sleep clinic between 2009 and 2014. Of the 150 patients, 74 were already taking melatonin at the first visit and 76 were not taking melatonin. In 58 (78.4%) of those who had already been taking melatonin, the daytime melatonin levels in saliva were extremely high (>50 pg/ml), whereas daytime melatonin levels in 72 of 76 those who had not already been taking melatonin users (95%) were <10 pg/ml (W. Braam, personal communication). In 40 out of 76 non-melatonin users at first visit (52.8%) a loss of effect and high daytime melatonin levels after 4–12 weeks of melatonin treatment (0.5 – 3 mg) were observed. This loss of effect may be linked to the decreased activity of the CYP1A2 enzyme that resulted in slow melatonin metabolism; slow melatonin metabolizers have been reported as being 12%–14% of the general population, but might be much higher in persons with NDD.[68]

Melatonin has been also used in clinical practice to treat severe sleep problems associated with various genetic syndromes (Table 1). In two genetic syndromes severe sleep problems are included in the diagnostic criteria and are related to melatonin disturbance. Smith Magenis syndrome is characterized by daytime somnolence, night waking and early waking caused by an inversed circadian melatonin rhythm.[75,76] Recommended treatment includes a combination of melatonin inhibition by acebutolol (10 mg/kg in one early morning dose) and evening melatonin supplementation (no dose guidelines). Children with Angelman syndrome may present with sleep onset insomnia as well as sleep maintenance problems.[77] Melatonin levels are low and melatonin

Table 1 – Summary of studies of melatonin treatment for sleep problems associated with different genetic syndromes.

Genetic syndrome	Sleep disturbances	Melatonin dosage	Results	Reference
Smith-Magenis	Multiple awakenings Decreased total sleep time Inverted circadian rhythm of melatonin	NA	Sleep amelioration (with exogenous melatonin used in combination with endogenous melatonin blockers)	De Leersnyder 2006, Chick et al., 2010, Boone et al., 2011
Angelman	Sleep onset and sleep maintenance problems	0.3–5 mg in different case series	Decreased SOL Increased total sleep time Reduction of night awakenings	Zhdanova et al., 1999, Braam et al., 2008, Takaesu et al., 2012
Rett	Multiple awakenings	2.5–7.5 mg	Decreased SOL	McArthur & Budden, 1998, De Leersnyder et al., 2011
Tuberous Sclerosis	Multiple awakenings Decreased total sleep time	5–10 mg	Decreased SOL Improved total sleep time	Bruni et al., 1995, O'Callaghan et al., 1999, Hancock et al., 2005

treatment has shown to be effective in open and in blinded studies. The melatonin dose should be low (0.3 mg) because the prevalence of slow melatonin metabolisers in Angelman syndrome is very high. Tuberous Sclerosis Complex (TSC) can be associated with different types of sleep disorders, including multiple night awakenings and reduced total sleep time.[78] Melatonin has been shown to reduce SOL and improve total sleep time[79,80] in patients with TSC. Melatonin was also reported to reduce sleep problems in children with Rett syndrome[81,82] and Sanfilippo syndrome (mucopolysaccharidosis type III).[83,84]

6. Melatonin in other neurological disorders

6.1. *Epilepsy*

Because a high proportion of children with neurodevelopmental disorders have sleep problems and either have or develop epilepsy, there is great interest in determining whether melatonin is liable to exacerbate or precipitate seizures. The increased prevalence of sleep disorders in children with NDD has been discussed earlier. The prevalence of epilepsy in NDD depends on the type of the disorder and the severity of any intellectual disability. For example, in ASD, the prevalence of epilepsy is much higher than in the general population. Woolfenden et al.[85] carried out a systematic review on outcomes of children with autism. They estimated from two studies of children with autism for whom the age at follow up was under 12, and in whom the majority did not have intellectual disability (mental retardation), that the rate of epilepsy was 6.1% (95% confidence interval 3.8%–9.0%); in nine studies in which the majority of subjects did have intellectual disability and the age at follow-up was 12 years or more, the pooled percentage estimates of those having epilepsy at follow-up was 23.7% (95% confidence interval 17.5–30.5%) In a double-blind placebo controlled crossover trial of the effect of melatonin on seizures of 12 patients with uncontrolled epilepsy, Goldberg-Stern observed a statistically significant reduction in diurnal seizures.[86] However, in subsequent reviews it was concluded that it was not possible to draw any definitive conclusion about the role of melatonin in reducing seizures frequency or improving quality of life in people with epilepsy.[87,88] There is no clear evidence that melatonin exacerbates seizures. The very limited number of randomized controlled trials and more extensive animal data not only suggest that melatonin is unlikely to exacerbate seizures but indicate that it might even protect against them, although the data are too sparse to allow firm conclusions to be drawn.

6.2. *Headache*

Melatonin can have a role in both biological regulation of sleep and headache. A strict relationship between sleep and headache has been recognized for a long time. Melatonin may play a role in headache pathophysiology via several mechanisms. The antinociceptive effects of melatonin have been demonstrated in animal models, both in inflammatory and neuropathic pain.[89,90] Melatonin interacts with a number receptor

sites, including opioid, benzodiazepine, muscarinic, nicotinic, serotonergic, α1-adrenergic, α2-adrenergic and most importantly MT1/MT2 melatonin receptors present in the dorsal horn of the spinal cord, as well at multiple central nervous system levels (hypothalamus, hippocampus, medulla oblongata, pons and retina).[90] Because of its ability to scavenge toxic free radicals, melatonin can reduce macromolecular damage in all organs. Melatonin also reduces the up-regulation of a variety of pro-inflammatory cytokines, interleukins and TNF-alfa.[90] Melatonin has been shown to reduce transendothelial cell migration and oedema; it is involved in membrane stabilization, as well as inhibiting the activity of nitric oxide synthase. It can decrease dopamine and glutamate release; it can also potentate the receptor-mediated response of GABA and the opioid immune response.[91,90]

Melatonin might regularize the sleep–wake pattern through its "chronobiological" and "sleep-hygiene effects".[92,93] Adequately timed and dosed melatonin treatment decreased headache in 78.6% of 328 patients with circadian rhythm sleep disorders and headache, while adequately timed and dosed melatonin induced (slight) headache in 13.8% of 676 patients with circadian rhythm sleep disorders without headache.[94] Individuals with migraine report a high prevalence of sleep disturbances in parents, and sleep disturbances in infancy, as well as an elevated level of familiarity of migraine, suggesting a genetic link between headache and sleep disorders.[95] An alteration of serotonergic and dopaminergic neurotransmitter pathways could predispose to both these disorders at different ages: earlier for sleep disorders and later for headache, as consequence of such a neurotransmitter imbalance.[95] In an open-label trial in children with primary headache, melatonin 3 mg twice daily reduced the number (by more than 50%), intensity and duration of headache attacks in 14 of 21 children.[96] A decrease in nocturnal melatonin secretion has also been identified in patients with cluster headaches. A study of melatonin in a single dose of 0.3 mg/kg for three months indicated that melatonin might be considered as an effective and safe drug in the prophylaxis of migraine in children.[97] However, these studies have several limitations. In particular, small samples were investigated. There is still no definitive consensus about the therapeutic use of melatonin for headache in children.

7. Neuroprotective effects of melatonin

Birth asphyxia in term newborn infants remains a significant problem throughout the world, contributing to 510,000–717,000 neonatal deaths, 1.15 million new cases of neonatal encephalopathy and 413,000 impaired survivors,[98] which may suffer from long-term neurological consequences such as cerebral palsy, mental retardation and epilepsy. To date, therapeutic hypothermia is the only clinical intervention that has shown to be effective in reducing brain damage in asphyxiated babies; however infants treated with hypothermia may have adverse outcomes, implying that there is a need for new and more effective treatments to provide safe and successful neuroprotection against neonatal encephalopathy.

Optimizing therapy for neonatal brain injury requires capitalizing on multiple pathways. Experimental evidence has demonstrated the multiple neuroprotective benefits of melatonin, such as reducing infarct volume and neuronal loss, minimizing lipid and protein peroxidation, inhibiting free radical production, blocking apoptosis and decreasing inflammation.[99] Indeed, its benign safety profile and relative ease of administration to both fetus and neonate make melatonin an attractive emerging neuroprotective agent with strong potential for clinical translation. As hypoxic-ischemic brain injury is often unpredictable, one of the key challenges for a new intervention strategy is to be able to ameliorate ongoing or secondary injury, by being administered as a post-insult therapy.

In animal studies, melatonin has been shown to be protective when given to neonatal rats 5 min after the injury and repeated 24 and 48 h later, reducing the percentage of ipsilateral damage and decreasing behavioral asymmetry and learning deficits, with long-lasting benefit.[100] Melatonin has also been shown to maintain the number of well-preserved neurons after the injury, an effect related to reduction in delayed cell death and reactive astrogliosis and also to the maintenance of myelination.[101] In addition, Robertson et al.[102] showed that melatonin augmented hypothermic neuroprotection by improving cerebral energy metabolism, as indicated by magnetic resonance spectroscopy biomarkers, and reducing cell death across the brain.

The prevention of neurological disabilities following preterm birth remains a major public health challenge. Various experimental studies have tested the neuroprotective effects of antenatal and postnatal melatonin administration in different animal models (e.g. rat, mouse, sheep, and pig) of brain lesions mimicking the lesions observed in human neonates.[103] These data strongly emphasize the neuroprotective properties of melatonin, whatever animal species has been used and in several types of brain damage across various developmental stages.[104]

The fact that melatonin easily crosses the placental barrier and can therefore be administered antenatally is a powerful argument for researching its use in minimizing, if not preventing, brain lesions in human subjects. Even though the dose and timing for optimal neuroprotection remain to be elucidated, all these data, along with the apparently benign safety profile and relative ease of melatonin administration, have favored the consideration of some small phase I and II clinical studies, the results of which should provide further relevant information about the real potential of melatonin for clinical translation.

8. Melatonin as pre-medication for neurologic diagnostic procedures

Melatonin has been used as a sleep inducing agent in neurophysiological and neuroimaging procedures in child neurology. Obtaining sleep to record EEG in childhood is of major importance because sleep can activate epileptiform abnormalities, thus helping clinicians to achieve a more accurate electroclinical assessment.[105] However, sleep deprivation, which is usually necessary to make the child fall asleep in the EEG laboratory, can be difficult and burdensome for the family,

especially in the case of challenging children. If spontaneous sleep is difficult to achieve, sedative drugs can be used. However, in the last two decades, melatonin has been used widely to induce sleep for EEG recording, initially in adults, and subsequently in children. When melatonin is administered, the yield of epileptiform abnormalities is similar to that reported for sleep-deprived EEGs, underlining that melatonin administration does not interfere with EEG interpretation nor does it hide epileptiform abnormalities.[106] Melatonin, administered at different doses ranging from 2 to 20 mg, was able to induce sleep in a high percentage of children (79–88%), reducing sleep onset latency; sleep duration was usually brief, but sufficient for an adequate EEG recording, and was rarely associated with mild somnolence after the exam.[105–108]

Melatonin has also been used to induce sleep as an alternative to sedation for performing brainstem auditory evoked potentials,[109,110] and for successfully performing brain magnetic resonance imaging (MRI) in about half of the patients.[111,112]

9. Adverse effects of melatonin

No serious safety concerns have been attributed to melatonin use in children. Systematic reviews showed that for sleep disorders such as jet lag and shift work, melatonin appears to be is safe for short-term and long-term use.[42,49] Rossignol and Frye (2011) stated that no adverse effects were reported with the use of melatonin in children with ASD in 7 of the 12 studies included in their meta-analysis.[67]

The most frequently reported side effects associated with melatonin use in children include morning drowsiness,

Table 2 – Recommendations for prescribing melatonin in children with sleep–wake rhythm disorders or sleep onset insomnia.

Consider melatonin treatment in children with sleep onset problems and/or difficulty waking up in the morning at conventional times.	
Usually melatonin is not effective for sleep maintenance problems.	
Measure DLMO (if possible).	
Minimum age for administration	No studies reported the minimum age for administering melatonin. Since it has been used in high dosage in infants to prevent neuronal injuries without side effects we can expect that melatonin administration after 6 months of age could be quite safe
Time of administration in children	If used as chronobiotic, 2–3 h before DLMO When DLMO cannot be measured: administer melatonin 3–4 h before actual sleep onset time If used as sleep inductor 30 min before bedtime
Dosage	If used as chronobiotic, start with a low dose of 0.2–0.5 mg fast release melatonin 3–4 h before bedtime; increase by 0.2–0.5 mg every week as needed (maximum 3 mg; adolescents: 5 mg) until effect If no response after 1 week: increase dose by 1 mg every week until effect appears When 1 mg is effective: try lower dose Maximum dose: <40 Kg: 3 mg; >40 Kg: 5 mg If used as a sleep inductor start with 1–3 mg 30 min before sleep of before the examination (EEG, Evoked potentials or MRI)
Treatment duration	Treatment duration should be tailored to the specific patient in relation to the peculiar neurodevelopmental disabilities but in general should be not less than 1 month Treatment can be withdrawn just before puberty (age around 12 yrs) or shortly after puberty (18–24 yrs) Stopping successful treatment too early (i.e. 4 weeks after its start) may results in reappearance of insomnia Stop melatonin treatment once a year during one week (preferably in summer) after a normal sleep cycle is established
When melatonin treatment is not effective (any more):	Check timing of administration: melatonin intake time may be shifted to too late Be aware that loss of efficacy of melatonin treatment most likely is caused by slow melatonin metabolism Reconsider diagnosis: look for neuropsychiatric comorbidity and treat that together with the insomnia For very severe delayed sleep wake rhythm: consider chronotherapy Comedication can influence melatonin metabolism: • Metabolism slower: oral contraceptives, cimetidine, fluvoxamine • Metabolism faster: carbamazepine, esomeprazole, omeprazole In some cases dose reduction is warranted instead of dose escalation
If sleep maintenance problems after start melatonin treatment:	Melatonin dose is probably too high

increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia.[73,113,114] Slight transient headache and gastrointestinal symptoms are mainly reported during the first days of the treatment.[115] In elderly the administration of 3 mg of melatonin induced hypothermia and plasma melatonin elevated into the daylight hours.[116]

Effects of the melatonin on human reproduction[117] and in auto-immune disorders[118] remain unclear. No melatonin-associated alterations of laboratory values were noted.[119]

Since melatonin is primarily metabolized by CYP1A2 and CYP2C19, inhibitors of CYP1A2 (e.g., tricyclic antidepressants, fluvoxamine, cimetidine) may increase melatonin concentrations.[120] Because melatonin may decrease blood pressure or serum glucose, particular attention should be given in patients who receive concomitant therapy with agents that affect blood pressure or serum glucose.[121]

In supporting the safety of melatonin it should be noted that melatonin has been administered in very high doses to animals (from 5 to 20 mg/kg and even >100 mg) without adverse effects but has shown neuroprotective properties. The lethal dose in animals has yet to be determined, with the implication the high doses administered so far have not been lethal. However, these data cannot be taken as assurance that melatonin can be administered in infants and children at high doses without adverse effects.

10. Clinical recommendations

As evident from the previous sections, the dose, timing and modalities of administration of melatonin vary considerably across studies. Table 2 presents the consensus of the authors regarding the use of melatonin in infants and children with sleep–wake rhythm disorders or sleep onset insomnia. It must be emphasized that these represent general recommendations that need to be tailored to each individual.

So far, the best evidence for the indication of melatonin treatment in children is for insomnia caused by circadian rhythm sleep disorders. Because insomnia due to other situations and disorders, including bad sleep hygiene, ADHD/ADD, personality disorders and depression, can mimic insomnia caused by circadian rhythm sleep disorders, the diagnosis should be only be made after careful clinical assessment and possibly measuring DLMO. There is a strong argument for determining DLMO, not only for an optimal diagnosis, but also for optimal melatonin treatment, as melatonin is most effective when it is administered 3–5 h before DLMO in children with sleep onset insomnia and late DLMO. DLMO can be measured relatively easily by collecting saliva at home. DLMO measurements contribute substantially both to optimal diagnosis and treatment of patients with chronic insomnia.

11. Conclusions and future directions

Melatonin can be effective not only for primary sleep disorders but also for sleep disorders associated with several neurological conditions. Controlled studies on melatonin for sleep disturbance in children are needed since melatonin is very commonly prescribed in infants, children and adolescents, and there is a lack of certainty about dosing regimens. The dose of melatonin should be individualized according to multiple factors, including not only the severity and type of sleep problem, but also the associated neurological pathology. Future controlled clinical studies should clarify the possible neuroprotective role of melatonin administration in infants with hypoxic-ischemic encephalopathy. Because of the lack of research and controlled trials, there is a pressing need for studies on melatonin in infants and children with sleep disorders, to identify those who will benefit from melatonin treatment and to determine the doses appropriate for the severity and type of disorder.

Conflict of interest

None.

REFERENCES

1. Gordon N. The therapeutics of melatonin: a paediatric perspective. *Brain Dev* 2000;**22**:213–7.
2. Kennaway DJ. Melatonin and development: physiology and pharmacology. *Semin Perinatol* 2000;**24**:258–66.
3. Mauriz JL, Collado PS, Veneroso C, Reiter RJ, Gonzalez-Gallego J. A review of the molecular aspects of melatonin's anti-inflammatory actions: recent insights and new perspectives. *J Pineal Res* 2013;**54**:1–14.
4. Niles LP, Armstrong KJ, Rincon Castro LM, et al. Neural stem cells express melatonin receptors and neurotrophic factors: colocalization of the MT1 receptor with neuronal and glial markers. *BMC Neurosci* 2004;**5**:41.
5. Iwasaki S, Nakazawa K, Sakai J, et al. Melatonin as a local regulator of human placental function. *J Pineal Res* 2005;**39**:261–5.
6. Comai S, Ochoa-Sanchez R, Gobbi G. Sleep–wake characterization of double MT(1)/MT(2) receptor knockout mice and comparison with MT(1) and MT(2) receptor knockout mice. *Behav Brain Res* 2013;**243**:231–8.
7. Wirz-Justice A, Armstrong SM. Melatonin: nature's soporific? *J Sleep Res* 1996;**5**:137–41.
8. Nagtegaal JE, Kerkhof GA, Smits MG, Swart AC, Van Der Meer YG. Delayed sleep phase syndrome: a placebo-controlled cross-over study on the effects of melatonin administered five hours before the individual dim light melatonin onset. *J Sleep Res* 1998;**7**:135–43.
9. van Geijlswijk IM, Korzilius HP, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. *Sleep* 2010;**33**:1605–14.
10. van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. *Psychopharmacology* 2010;**212**:379–91.
11. Braam W, van Geijlswijk I, Keijzer H, et al. Loss of response to melatonin treatment is associated with slow melatonin metabolism. *J Intellect Disabil Res* 2010;**54**:547–55.
12. Appleton RE, Gringras P. Melatonin: helping to MEND impaired sleep. *Arch Dis Child* 2013;**98**:216–7.
13. Owens JA, Rosen CL, Mindell JA. Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians. *Pediatrics* 2003;**111**:e628–35.

14. Owens JA. Pharmacotherapy of pediatric insomnia. *J Am Acad Child Adolesc Psychiatry* 2009;**48**:99–107.
15. Owens JA, Rosen CL, Mindell JA, Kirchner HL. Use of pharmacotherapy for insomnia in child psychiatry practice: a national survey. *Sleep Med* 2010;**11**:692–700.
16. Hartz I, Furu K, Bratlid T, Handal M, Skurtveit S. Hypnotic drug use among 0–17 year olds during 2004–2011: a nationwide prescription database study. *Scand J public health* 2012;**40**:704–11.
17. Heussler H, Chan P, Price AM, et al. Pharmacological and non-pharmacological management of sleep disturbance in children: an Australian paediatric research network survey. *Sleep Med* 2013;**14**:189–94.
18. Merchant NM, Azzopardi DV, Hawwa AF, et al. Pharmacokinetics of melatonin in preterm infants. *Br J Clin Pharmacol* 2013;**76**:725–33.
19. Sadeh A. Sleep and melatonin in infants: a preliminary study. *Sleep* 1997;**20**:185–91.
20. LeBourgeois MK, Carskadon MA, Akacem LD, et al. Circadian phase and its relationship to nighttime sleep in toddlers. *J Biol Rhythms* 2013;**28**:322–31.
21. Shinohara H, Kodama H. Relationship between circadian salivary melatonin levels and sleep–wake behavior in infants. *Pediatr Int off J Jpn Pediatr Soc* 2011;**53**:29–35.
22. Tauman R, Zisapel N, Laudon M, Nehama H, Sivan Y. Melatonin production in infants. *Pediatr Neurol* 2002;**26**:379–82.
23. Hartmann L, Roger M, Lemaitre BJ, Massias JF, Chaussain JL. Plasma and urinary melatonin in male infants during the first 12 months of life. *Clin Chimica Acta Int J Clin Chem* 1982;**121**:37–42.
24. Attanasio A, Rager K, Gupta D. Ontogeny of circadian rhythmicity for melatonin, serotonin, and N-acetylserotonin in humans. *J Pineal Res* 1986;**3**:251–6.
25. Waldhauser F, Weiszenbacher G, Frisch H, et al. Fall in nocturnal serum melatonin during prepuberty and pubescence. *Lancet* 1984;**1**:362–5.
26. Griefahn B, Brode P, Blaszkewicz M, Remer T. Melatonin production during childhood and adolescence: a longitudinal study on the excretion of urinary 6-hydroxymelatonin sulfate. *J Pineal Res* 2003;**34**:26–31.
27. Smits MG, van Stel HF, van der Heijden K, et al. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2003;**42**:1286–93.
28. van Maanen A, Meijer AM, Smits MG, Oort FJ. Termination of short term melatonin treatment in children with delayed dim light melatonin onset: effects on sleep, health, behavior problems, and parenting stress. *Sleep Med* 2011;**12**:875–9.
29. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *J Pineal Res* 2009;**47**:1–7.
30. van Geijlswijk IM, Mol RH, Egberts TC, Smits MG. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. *Psychopharmacology* 2011;**216**:111–20.
31. Burgess HJ, Revell VL, Molina TA, Eastman CI. Human phase response curves to three days of daily melatonin: 0.5 mg versus 3.0 mg. *J Clin Endocrinol Metab* 2010;**95**:3325–31.
32. EFSA. Panel on dietetic products NaAN. Scientific opinion on the substantiation of health claims related to melatonin and alleviation of subjective feelings of jet lag (ID 1953), and reduction of sleep onset latency, and improvement of sleep quality (ID 1953) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J* 2010;**8**:1467.
33. EFSA. Panel on dietetic products NaAN. Scientific Opinion on the substantiation of a health claim related to melatonin and reduction of sleep onset latency (ID 1698, 1780, 4080) pursuant to article 13(1) of regulation (EC) no 1924/2006. *EFSA J* 2011;**9**:2241.
34. van der Heijden KB, Smits MG, van Someren EJ, Boudewijn Gunning W. Prediction of melatonin efficacy by pretreatment dim light melatonin onset in children with idiopathic chronic sleep onset insomnia. *J Sleep Res* 2005;**14**:187–94.
35. Keijzer H, Smits MG, Peeters T, et al. Evaluation of salivary melatonin measurements for dim light melatonin onset calculations in patients with possible sleep–wake rhythm disorders. *Clin Chimica Acta Int J Clin Chem* 2011;**412**:1616–20.
36. Keijzer H, Smits MG, Duffy JF, Curfs LM. Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorders. *Sleep Med Rev* 2014;**18**:333–9.
37. Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. *J Biol Rhythms* 1999;**14**:72–6.
38. Ebisawa T, Uchiyama M, Kajimura N, et al. Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. *EMBO Rep* 2001;**2**:342–6.
39. Archer SN, Robilliard DL, Skene DJ, et al. A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 2003;**26**:413–5.
40. Gradisar M, Crowley SJ. Delayed sleep phase disorder in youth. *Curr Opin Psychiatry* 2013;**26**:580–5.
41. Micic G, de Bruyn A, Lovato N, et al. The endogenous circadian temperature period length (tau) in delayed sleep phase disorder compared to good sleepers. *J Sleep Res* 2013;**22**:617–24.
42. Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *J Gen Intern Med* 2005;**20**:1151–8.
43. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One* 2013;**8**:e63773.
44. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *J Child Neurol* 2001;**16**:86–92.
45. Eckerberg B, Lowden A, Nagai R, Akerstedt T. Melatonin treatment effects on adolescent students' sleep timing and sleepiness in a placebo-controlled crossover study. *Chronobiol Int* 2012;**29**:1239–48.
46. Wilhelmsen-Langeland A, Saxvig IW, Pallesen S, et al. A randomized controlled trial with bright light and melatonin for the treatment of delayed sleep phase disorder: effects on subjective and objective sleepiness and cognitive function. *J Biological Rhythms* 2013;**28**:306–21.
47. Saxvig IW, Wilhelmsen-Langeland A, Pallesen S, et al. A randomized controlled trial with bright light and melatonin for delayed sleep phase disorder: effects on subjective and objective sleep. *Chronobiol Int* 2014;**31**:72–86.
48. Braam W, Smits MG, Didden R, et al. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. *Dev Med Child Neurol* 2009;**51**:340–9.
49. Buscemi N, Vandermeer B, Hooton N, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006;**332**:385–93.
50. Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. *J Am Acad Child Adolesc Psychiatry* 2009;**48**:894–908.

51. Cortese S, Lecendreux M, Mouren MC, Konofal E. ADHD and insomnia. *J Am Acad Child Adolesc Psychiatry* 2006;**45**:384–5.
52. Kirov R, Brand S. Sleep problems and their effect in ADHD. *Expert Rev Neurother* 2014;**14**:287–99.
53. Cortese S, Brown TE, Corkum P, et al. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2013;**52**:784–96.
54. Van der Heijden KB, Smits MG, Van Someren EJ, Gunning WB. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. *Chronobiol Int* 2005;**22**:559–70.
55. Chaste P, Clement N, Botros HG, et al. Genetic variations of the melatonin pathway in patients with attention-deficit and hyperactivity disorders. *J Pineal Res* 2011;**51**:394–9.
56. Interventions CHfSRo. Cochrane Handbook for systematic reviews of interventions, Version 5.1.0 [updated March 2011]. In: Higgins JPT GS editor.
57. Owens J, Gruber R, Brown T, et al. Future research directions in sleep and ADHD: report of a consensus working group. *J Atten Disord* 2013;**17**:550–64.
58. Tjon Pian Gi CV, Broeren JP, Starreveld JS, Versteegh FG. Melatonin for treatment of sleeping disorders in children with attention deficit/hyperactivity disorder: a preliminary open label study. *Eur J Pediatr* 2003;**162**:554–5.
59. Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *J Am Acad Child Adolesc Psychiatry* 2006;**45**:512–9.
60. Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry* 2007;**46**:233–41.
61. Mohammadi MR, Mostafavi SA, Keshavarz SA, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. *Iran J psychiatry* 2012;**7**:87–92.
62. Krakowiak P, Goodlin-Jones B, Hertz-Picciotto I, Croen LA, Hansen RL. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. *J Sleep Res* 2008;**17**:197–206.
63. Sivertsen B, Posserud MB, Gillberg C, Lundervold AJ, Hysing M. Sleep problems in children with autism spectrum problems: a longitudinal population-based study. *Autism Int J Res Pract* 2012;**16**:139–50.
64. Tordjman S, Anderson GM, Pichard N, Charbuy H, Touitou Y. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. *Biol Psychiatry* 2005;**57**:134–8.
65. Goldman SE, Adkins KW, Calcutt MW, et al. Melatonin in children with autism spectrum disorders: endogenous and pharmacokinetic profiles in relation to sleep. *J Autism Dev Disord* 2014;**44**:2525–35.
66. Veatch OJ, Pendergast JS, Allen MJ, et al. Genetic variation in melatonin pathway enzymes in children with autism spectrum disorder and comorbid sleep onset delay. *J Autism Dev Disord* 2014. ePub ahead of print.
67. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Dev Med Child Neurol* 2011;**53**:783–92.
68. Braam W, Keijzer H, Struijker Boudier H, et al. CYP1A2 polymorphisms in slow melatonin metabolisers: a possible relationship with autism spectrum disorder? *J Intellect Disabil Res* 2013;**57**:993–1000.
69. Tordjman S, Najjar I, Bellissant E, et al. Advances in the research of melatonin in autism spectrum disorders: literature review and new perspectives. *Int J Mol Sci* 2013;**14**:2050 8–42.
70. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. Serotonin hypothesis of autism: implications for selective serotonin reuptake inhibitor use during pregnancy. *Autism Res off J Int Soc Autism Res* 2013;**6**:149–68.
71. Daly E, Ecker C, Hallahan B, et al. Response inhibition and serotonin in autism: a functional MRI study using acute tryptophan depletion. *Brain* 2014;**137**:2600–10.
72. Sajith SG, Clarke D. Melatonin and sleep disorders associated with intellectual disability: a clinical review. *J Intellect Disabil Res* 2007;**51**:2–13.
73. Gringras P, Gamble C, Jones AP, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 2012;**345**:e6664.
74. Hartter S, Ursing C, Morita S, et al. Orally given melatonin may serve as a probe drug for cytochrome P450 1A2 activity in vivo: a pilot study. *Clin Pharmacol Ther* 2001;**70**:10–6.
75. De Leersnyder H. Inverted rhythm of melatonin secretion in Smith-Magenis syndrome: from symptoms to treatment. *Trends Endocrinol Metab TEM* 2006;**17**:291–8.
76. Chik CL, Rollag MD, Duncan WC, Smith AC. Diagnostic utility of daytime salivary melatonin levels in Smith-Magenis syndrome. *Am J Med Genet A* 2010;**152A**:96–101.
77. Braam W, Didden R, Smits MG, Curfs LM. Melatonin for chronic insomnia in Angelman syndrome: a randomized placebo-controlled trial. *J Child Neurol* 2008;**23**:649–54.
78. Bruni O, Cortesi F, Giannotti F, Curatolo P. Sleep disorders in tuberous sclerosis: a polysomnographic study. *Brain Dev* 1995;**17**:52–6.
79. O'Callaghan FJ, Clarke AA, Hancock E, Hunt A, Osborne JP. Use of melatonin to treat sleep disorders in tuberous sclerosis. *Dev Med Child Neurol* 1999;**41**:123–6.
80. Hancock E, O'Callaghan F, Osborne JP. Effect of melatonin dosage on sleep disorder in tuberous sclerosis complex. *J Child Neurol* 2005;**20**:78–80.
81. McArthur AJ, Budden SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. *Dev Med Child Neurol* 1998;**40**:186–92.
82. De Leersnyder H, Zisapel N, Laudon M. Prolonged-release melatonin for children with neurodevelopmental disorders. *Pediatr Neurol* 2011;**45**:23–6.
83. Fraser J, Wraith JE, Delatycki MB. Sleep disturbance in mucopolysaccharidosis type III (Sanfilippo syndrome): a survey of managing clinicians. *Clin Genet* 2002;**62**:418–21.
84. Fraser J, Gason AA, Wraith JE, Delatycki MB. Sleep disturbance in Sanfilippo syndrome: a parental questionnaire study. *Arch Dis Child* 2005;**90**:1239–42.
85. Woolfenden S, Sarkozy V, Ridley G, Coory M, Williams K. A systematic review of two outcomes in autism spectrum disorder – epilepsy and mortality. *Dev Med Child Neurol* 2012;**54**:306–12.
86. Goldberg-Stern H, Oren H, Peled N, Garty BZ. Effect of melatonin on seizure frequency in intractable epilepsy: a pilot study. *J Child Neurol* 2012;**27**:1524–8.
87. Brigo F, Del Felice A. Melatonin as add-on treatment for epilepsy. *Cochrane Database Syst Rev* 2012;**6**:CD006967.
88. Jain S, Besag FM. Does melatonin affect epileptic seizures? Drug safety. *Int J Med Toxicol drug Exp* 2013;**36**:207–15.
89. Srinivasan V, Pandi-Perumal SR, Spence DW, et al. Potential use of melatonergic drugs in analgesia: mechanisms of action. *Brain Res Bull* 2010;**81**:362–71.
90. Reiter RJ, Tan DX, Galano A. Melatonin: exceeding expectations. *Physiology* 2014;**29**:325–33.
91. Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gogenur I. Analgesic effects of melatonin: a review of current evidence

from experimental and clinical studies. *J Pineal Res* 2011;51:270–7.
92. Nagtegaal JE, Smits MG, Swart AC, Kerkhof GA, van der Meer YG. Melatonin-responsive headache in delayed sleep phase syndrome: preliminary observations. *Headache* 1998;38:303–7.
93. Bruni O, Galli F, Guidetti V. Sleep hygiene and migraine in children and adolescents. Cephalalgia. *Int J headache* 1999;19(Suppl. 25):57–9.
94. Rovers J, Smits M, Duffy JF. Headache and sleep: also assess circadian rhythm sleep disorders. *Headache* 2014;54:175–7.
95. Guidetti V, Dosi C, Bruni O. The relationship between sleep and headache in children: implications for treatment. *Cephalalgia Int J headache* 2014;34:767–76.
96. Miano S, Parisi P, Pelliccia A, et al. Melatonin to prevent migraine or tension-type headache in children. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol* 2008;29:285–7.
97. Fallah R, Shoroki FF, Ferdosian F. Safety and efficacy of melatonin in pediatric migraine prophylaxis. *Curr drug Saf* 2014. ePub ahead of print.
98. Lee AC, Kozuki N, Blencowe H, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. *Pediatr Res* 2013;74(Suppl. 1):50–72.
99. Alonso-Alconada D, Alvarez A, Arteaga O, Martinez-Ibarguen A, Hilario E. Neuroprotective effect of melatonin: a novel therapy against perinatal hypoxia-ischemia. *Int J Mol Sci* 2013;14:9379–95.
100. Carloni S, Perrone S, Buonocore G, et al. Melatonin protects from the long-term consequences of a neonatal hypoxic-ischemic brain injury in rats. *J Pineal Res* 2008;44:157–64.
101. Alonso-Alconada D, Alvarez A, Lacalle J, Hilario E. Histological study of the protective effect of melatonin on neural cells after neonatal hypoxia-ischemia. *Histol Histopathol* 2012;27:771–83.
102. Robertson NJ, Faulkner S, Fleiss B, et al. Melatonin augments hypothermic neuroprotection in a perinatal asphyxia model. *Brain* 2013;136:90–105.
103. Biran V, Phan Duy A, Decobert F, et al. Is melatonin ready to be used in preterm infants as a neuroprotectant? *Dev Med Child Neurol* 2014;56:717–23.
104. Ramanantsoa N, Fleiss B, Bouslama M, et al. Bench to cribside: the path for developing a neuroprotectant. *Transl stroke Res* 2013;4:258–77.
105. Eisermann M, Kaminska A, Berdougo B, Brunet ML. Melatonin: experience in its use for recording sleep EEG in children and review of the literature. *Neuropediatrics* 2010;41:163–6.
106. Ashrafi MR, Mohammadi M, Tafarroji J, et al. Melatonin versus chloral hydrate for recording sleep EEG. *Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc* 2010;14:235–8.
107. Wassmer E, Carter PF, Quinn E, et al. Melatonin is useful for recording sleep EEGs: a prospective audit of outcome. *Dev Med Child Neurol* 2001;43:735–8.
108. Sander J, Shamdeen MG, Gottschling S, et al. Melatonin does not influence sleep deprivation electroencephalogram recordings in children. *Eur J Pediatr* 2012;171:675–9.
109. Espezel H, Graves C, Jan JE, et al. Melatonin as a sedation substitute for diagnostic procedures. *Dev Med Child Neurol* 2000;42:646–7.
110. Schmidt CM, Bohlender JE, Deuster D, et al. The use of melatonin as an alternative to sedation in children undergoing brainstem audiometry. *Laryngo- Rhino- otologie* 2004;83:523–8.
111. Wassmer E, Fogarty M, Page A, et al. Melatonin as a sedation substitute for diagnostic procedures: MRI and EEG. *Dev Med Child Neurol* 2001;43:136.
112. Johnson K, Page A, Williams H, Wassemer E, Whitehouse W. The use of melatonin as an alternative to sedation in uncooperative children undergoing an MRI examination. *Clin Radiol* 2002;57:502–6.
113. Andersen IM, Kaczmarska J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. *J Child Neurol* 2008;23:482–5.
114. Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res* 2008;44:57–64.
115. Nagtegaal JE, Smits M, Van Der Meer YG, Fischer-Steenvoorden MG. Melatonin: a survey of suspected adverse drug reactions. *Sleep–Wake Res Netherl* 1996;7:115–8.
116. Zhdanova IV, Wurtman RJ, Regan MM, et al. Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab* 2001;86:4727–30.
117. Srinivasan V, Spence WD, Pandi-Perumal SR, et al. Melatonin and human reproduction: shedding light on the darkness hormone. *Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol* 2009;25:779–85.
118. Carrillo-Vico A, Reiter RJ, Lardone PJ, et al. The modulatory role of melatonin on immune responsiveness. *Curr Opin Investig Drugs* 2006;7:423–31.
119. Malow B, Adkins KW, McGrew SG, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *J Autism Dev Disord* 2012;42:1729–37. author reply 38.
120. Damiani JM, Sweet BV, Sohoni P. Melatonin: an option for managing sleep disorders in children with autism spectrum disorder. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Sys Pharm* 2014;71:95–101.
121. Ray CA. Melatonin attenuates the sympathetic nerve responses to orthostatic stress in humans. *J Physiol* 2003;551:1043–8.

Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Psychopathology, symptoms of attention-deficit/hyperactivity disorder, and risk factors in juvenile offenders

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
10 February 2015
Number of times this article has been viewed

Francesco Margari[1]
Francesco Craig[2]
Lucia Margari[2]
Emilia Matera[2]
Anna Linda Lamanna[2]
Paola Alessandra Lecce[2]
Donatella La Tegola[3]
Felice Carabellese[3]

[1]Psychiatry Unit, [2]Child Neuropsychiatry Unit, Department of Basic Medical Sciences, Neurosciences and Sense Organs of the Aldo Moro University of Bari, [3]Section of Criminology and Forensic Psychiatry, Department of Internal Medicine and Public Medicine, University of Bari, Bari, Italy

Background: The aim of this study was to assess the prevalence of potential environmental and psychopathological risk factors, with special focus on symptoms of attention-deficit/hyperactivity disorder (ADHD), in a sample of adolescent offenders in relation to the type of crime committed.

Methods: The assessment included data collection and administration of clinical standardized scales such as the Youth Self-Report and Conners' Adolescent Self-Report Scale. A total of 135 juvenile offenders participated in the study. In relation to the type of crime committed, we identified three groups matched for age and sex (crimes against people, property crimes, and alcohol-drug-related crimes).

Results: Fifty-two percent of juvenile offenders reported educational achievement problems and 34% reported a family history of psychiatric disorders. We detected a statistically significant difference between the three groups with regard to ADHD (P=0.01) and conduct problems (P=0.034). Juvenile offenders who had committed crimes against people showed more ADHD symptoms (18%) and conduct problems (20%) than adolescents who had committed property crimes and alcohol-drug-related crimes. Sixty percent of the juvenile offenders who had committed property crimes and 54% of those who had committed alcohol-drug-related crimes showed problems in academic achievement.

Conclusion: These findings suggest the need to implement specific interventions for prevention and treatment of specific criminal behavior.

Keywords: juvenile offenders, attention-deficit/hyperactivity disorder, conduct problems, academic achievement problems, peer relationships, family problems

Introduction

The alarming rate of criminal involvement among adolescents and young adults is a major concern in the USA and in many other European countries.[1,2] Moreover, it is not surprising that a majority of youth who have perpetrated violent crimes and are placed in detention have mental health difficulties. Although decades of scientific research aimed at understanding the phenomenon of juvenile offenders has resulted in the recognition of many environmental and individual risk factors, the relationship between adolescent delinquency and general psychopathology remains largely unexplored. One condition that is often neglected in forensic settings is attention-deficit/hyperactivity disorder (ADHD), which could be a precursor of later antisocial behavior.

Juvenile offenders and general psychopathology

Young offenders show high rates of psychosocial risk factors, such as impulsive temperament characteristics, emotional and behavior problems, low academic performance,

Correspondence: Lucia Margari
Child Neuropsychiatry Unit, Department of Basic Medical Sciences, Neurosciences and Sense Organs of the Aldo Moro University of Bari, Hospital Polyclinic of Bari, Piazza Giulio Cesare 1, Bari, Italy
Email lucia.margari@uniba.it

substance or alcohol abuse, poor relationships with parents and peers, and mental health problems.[3–6] Teplin et al showed that, excluding conduct disorder (common among detained youth), nearly 60% of males and over two thirds of females met diagnostic criteria and had diagnosis-specific impairment for one or more psychiatric disorders (affective disorder, anxiety, psychosis, ADHD, disruptive behavior disorders, and substance use disorders).[7] In a review study, Vermeiren et al found varied psychiatric disorders in offender samples, which included conduct and oppositional disorders, depressive and anxiety disorders, post-traumatic stress disorder, and ADHD.[8] Recently, Coker et al examined relationships between psychiatric disorders and self-reported crime involvement in a sample of youth representative of the US population.[9] The authors detected that youth with lifetime psychiatric disorders, compared with youth with no disorders, had significantly greater odds of crime, including violent crime, while for violent crime resulting in arrest, conduct disorder, alcohol use disorders, and drug use disorders had the greatest odds, with similar findings for violent crime with no arrest. These findings highlight the importance of developing mental health services for juvenile offenders and the necessity of adequate diagnostic and therapeutic interventions in these adolescents.

Juvenile offenders and ADHD

A considerable amount of evidence demonstrates that children diagnosed with ADHD are at high risk of criminality; however, the role of ADHD in the prediction of criminality remains unclear in both clinical and population-based studies.[10,11] Bulten et al revealed that 38% of adult offenders retrospectively received the diagnosis of ADHD during their childhood.[12] On the other hand, a significantly elevated risk for oppositional defiant disorder, conduct disorder, and many long-term adverse outcomes, including criminality, are frequently found in children with ADHD.[13–15] Barkley detected that children with ADHD were more likely to engage in a variety of antisocial activities in comparison with a control group, and that the frequency of such activities was largely predicted by the severity of ADHD in childhood and adolescence.[10] Prospective studies reported that children having high levels of ADHD often show disruptive behavior patterns, especially during adolescence, suggesting that hyperactivity could be a predictor of antisocial behavior.[14,15] In particular, Molina et al reported that, at age 13–18 years, approximately 25%–30% of ADHD youths were in the spectrum of clinically serious antisocial behavior, 26.8% had been arrested at least once, and 30% had engaged in moderately serious to serious delinquent behavior.[16] On the contrary, Pingault et al showed that although the contribution of childhood hyperactivity to criminality may be detected in large samples using multi-informant longitudinal designs, ADHD is not a strong predictor of later criminality.[17] An important gap in the current literature regarding the risk of antisocial and aggressive behavior in children and adolescents is that to date theoretical frameworks of early risk factors for violence and aggression have not effectively integrated social and biological factors. Further, mental health risk factors have been largely ignored in these frameworks. One exception is the model proposed by Moffitt, which distinguishes two main categories in the description of severity and continuity of antisocial behavior in the pediatric age group, ie, a "life-course persistent" (LCP) group, characterized by persistent antisocial behavior that starts early in life, and an "adolescent-limited" group, in which the antisocial behavior starts during adolescence and remains restricted to this period.[18] In particular, ADHD could play a crucial role in the development of LCP delinquency, which may also help to explain the genetic predisposition for LCP offending. In the same vein, Loeber et al suggested that in children in whom the onset of aggression occurs in the preschool period, antisocial behavior/criminal behavior is considered to be especially persistent when the child fulfils the diagnostic criteria for an ADHD diagnosis.[19] Nevertheless, even today in the criminal justice system, ADHD is a neglected vulnerability, which can leave a suspect disadvantaged during court proceedings and prevention or treatment of criminal behavior.[20] For these reasons, the aim of this study was to evaluate potential environmental and psychopathological risk factors, focusing especially on ADHD symptoms, in a sample of juvenile offenders in relation to the type of crime committed. We hypothesized that symptoms of ADHD could represent a prognostic factor for the development of specific criminal activity.

Materials and methods

Participants

The study was conducted by the Child Neuropsychiatry Unit in collaboration with the Section of Criminology and Forensic Psychiatry at the University of Bari Aldo Moro. The sample involved adolescents of both sexes, with an age range of 14–18 years, adjudicated by the Juvenile Court of Puglia for committing a first crime where the Public Prosecutor's Office considered that there was sufficient evidence of responsibility in committing the crime. Exclusion criteria included any other serious medical condition and migrant adolescents who did not have a complete understanding of the Italian language. In addition, individuals with a previous

psychiatric disorder were excluded from the study because the Italian justice system considers a suspect not punishable if he/she was suffering from a psychiatric disorder at the time of committing the offence. Consents of the legal authorities of the Juvenile Court were obtained. Written informed consent was obtained by adolescents and their parents after providing all the details of the study procedure.

Assessment

The assessment included collection of information regarding each subject enrolled in the study, obtained through a semi-structured interview developed ad hoc and administration of clinical standardized scales, including the Youth Self-Report (YSR) for age 11–18 years[21] and the Conners' Adolescent Self-Report Scale (CASS).[22]

Semistructured interview

A semistructured interview was developed in order to elicit a detailed account of each participant's experiences. This consisted of the following five main sections: criminal records, quality of family relationships, peer relationships, academic achievement, and antisocial behavior.

Criminal records

Criminal records involved three type of crimes: crimes against people, property crimes, and alcohol–drug-related crimes. The crimes against people group included adolescents who had been convicted of stalking, assault, physical injuries, sexual harassment, and bodily harm. The property crimes group included adolescents who had been convicted of theft from private property, architectural theft, damage to buildings or monuments, arson, graffiti, and other forms of antisocial behavior in proximity to heritage assets. The alcohol–drug-related crimes group included adolescents who had been convicted of alcohol and/or drug abuse, drug trafficking, or possession of drugs.

Quality of family relationships

Quality of family relationships was classified as adequate or poor. For adequate quality of family relationships, we referred to the presence of appreciation for one another, good communication skills, a large amount of time spent together, and good coping ability. For poor quality of family relationships, we referred to the presence of at least one of the following problems: poor appreciation for one another, low communication skills, a small amount of time spent together, poor coping ability, conflicting relationships, and low levels of family support.

Peer relationships

Peer relationships were classified as adequate or poor. For adequate peer relationships, we referred to the presence of stable interpersonal relationships, assertiveness and altruistic behaviors, and belonging to group dynamics. For poor peer relationships, we referred to the presence of at least one of the following problems: no friends, peer rejection, and social withdrawal.

Academic achievement

Academic achievement was classified as regular or irregular. For regular academic achievement, we referred to number of years of education appropriate to the age of the subject or completion of compulsory education that in Italy is from 6 to 16 years of age. For irregular academic achievement, we referred to the presence of at least one of the following problems: discontinuity of schooling, low academic performance, and dropout from school.

Antisocial behavior

The previous antisocial behavior section included failure to conform to social norms. The antisocial behavior was classified as absent or present. For the presence of antisocial behavior, we referred to the presence of at least one of the following problems: domestic violence, repeated physical fights or assaults, alcohol and substance abuse, reckless disregard for safety of self or others, and failure to comply with police officers.

Youth Self-Report

The YSR is a prominent and widely used measure for assessment of emotional and behavioral problems among youth aged 11–18 years. The 119 items on the YSR are rated as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true). The developers of the YSR intended it to be completed by youths with a mental age of 10 years and fifth-grade reading skills. Validity and reliability of the YSR broad band and *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)-oriented scales have been documented, and extensive normative data are available for children aged 11–18 years. The YSR contains the following subscales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. These subscales are grouped into two higher order factors, ie, internalizing and externalizing problems. The 2001 revision also added six DSM-oriented scales consistent with DSM diagnostic categories: affective problems, anxiety problems, somatic problems, ADHD, oppositional defiant

problems, and conduct problems. The YSR are also scored on competence scales for activities and competence in social relationships.

Conners' Adolescent Self-Report Scale

The CASS is the adolescent form of the Conners' Rating Scales-Revised (CRS-R). The CRS-R was designed to address the need for a multimodal assessment of behavioral difficulties in children and adolescents and contains a parent form and teacher form, as well as an adolescent self-report form. The adolescent self-report form, ie, CASS, is appropriate for adolescents aged 12–17 years, although some studies have examined its utility with children younger than 12 years. The CASS is designed to provide a self-report evaluation of various symptoms associated with ADHD. The CASS contains the following subscales: family problems, conduct problems, anger control problems, emotional problems, cognitive problems, hyperactive–impulsive symptoms, DSM-IV symptoms, and an ADHD Index.

Statistical analysis

Descriptive statistics were used to summarize the variables studied and the characteristics of the juvenile offenders. The Kuder–Richardson Formula 20 was used to check the internal consistency and reliability of the semistructured interview with dichotomous choices. Values can range from 0.00 to 1.00. A value of at least 0.70 is desirable. We found a Kuder–Richardson 20 Index of 0.80, indicating that the items show good internal consistency and reliability.

Raw scores obtained for each subscale of the YSR and CASS were transformed to *t*-scores to allow for consideration of how an individual's response compares with that of the population norms. In the statistical analysis, we detected the performance of mean values of the YSR and CASS. For the YSR, the borderline (*t*-score >65) and clinical (*t*-score >70) groups were put together. In line with the interpretive guidelines for CASS, participants with a *t*-score of 66 on a subscale represent individuals who score well above average and are categorized as symptomatic for that trait. The sample was divided in relation to the type of crime committed, and we identified three groups. In order to analyze the frequency of the psychopathology with a qualitative analysis, we reported the frequencies in terms of presence or absence in reference to the cut-off of each scale on the YSR and CASS respectively. Chi-square (χ^2) independence was used to examine the differences between the three groups. The analysis of variance test was used to evaluate the mean differences on the YSR and CASS scales between the three groups. In addition, Bonferroni correction was used to conduct the post hoc analysis. Variables showing a *P*-value <0.05 in the univariate analyses were included as associated factors in the multiple linear regression analysis. The multiple regression analysis was used to analyze the relationship between the statistically significant dependent variable (ADHD and conduct problems) and a combination of dichotomous predictor variables, such as quality of family relationships, peer relationships, academic achievement, and antisocial behavior.

A *P*-value of <0.05 was considered to be statistically significant for all the tests. For statistical processing, we used Statistical Package for the Social Sciences version 20 software (IBM Corporation, Armonk, NY, USA).

Results

A total of 135 juvenile offenders with a mean age of 16.28±0.8 years participated in the study. A crime against people was committed by 37% of the participants, property crimes by 37%, and alcohol–drug-related crimes by 26%. The features of the study sample are summarized in Table 1.

The YSR results showed that internalizing problems were present in 23% of the juvenile offenders, manifesting

Table 1 Sociodemographic and criminal features of juvenile offenders

n	135
Sex	
Male	89%
Female	11%
School	
Junior	63%
High	36%
Family composition	
Nuclear	90%
Single-parent	10%
Family relationships	
Poor	15%
Good	85%
Psychiatric family history	34%
Type of crime*	
Against people	37%
Property crimes	37%
Alcohol–drug-related	26%
Educational achievement	
Regular	48%
Irregular	52%
Peer relationships	
Poor	28%
Good	72%
Antisocial behavior	34%

Notes: *Age F=485, P=0.617; sex F=957, P=0.387.

mainly as anxious/depressed (12%) and withdrawn/depressed (13%) problems. Thirty-one percent of the participants showed externalizing problems; in particular we found higher percentages in the presence of ADHD (10%), oppositional defiant problems (19%), conduct problems (11%), and rule-breaking behavior (13%).

The CASS results showed that 4% of the juvenile offenders exceeded the cut-off on the hyperactive–impulsive and DSM-IV symptoms scale, while 5% exceeded the cut-off on the ADHD Index scale. All YSR and CASS scores for the juvenile offenders are reported in Table 2.

In relation to the type of crime committed, we identified three groups that showed no statistically significant differences in age (P=0.617) or sex (P=0.387). Comparing these three groups, we detected a statistically significant difference in problems of academic achievement (P=0.03) and peer relationships (P=0.04). In particular, adolescents who had committed a crime against people reported more peer relationship problems (34%) than the other two groups, while adolescents who had committed property crimes (60%) and alcohol–drug-related crimes (54%) showed a greater irregularity in their school career compared with the crime against people group. Analyzing the results obtained from the YSR, no statistically significant differences were found between the type of crime groups with regard to internalizing and externalizing problems, while statistically significant differences were found between the three groups with regard to ADHD (P=0.02) and conduct problems (P=0.03). Post hoc analysis showed that adolescents who had committed crimes against people had more ADHD symptoms and conduct problems when compared with adolescents who have committed property crimes and alcohol–drug-related crimes. In addition, the CASS results showed a higher percentage of hyperactive–impulsive symptoms, DSM-IV Symptoms and ADHD Index in adolescents who had committed crimes against people compared with the other groups, but no statistically significant differences were found. The differences between the three groups are summarized in Table 3.

Table 2 YSR and CASS scores for juvenile offenders

	Percent above cutoff	Mean ± SD
YSR		
Activities	41	35±8.2
Social relationships	11	41±7.2
Anxious/depressed	12	55±7.9
Withdrawn/depressed	13	54±8.7
Somatic complaints	6	53±7.3
Social problems	5	52±7.1
Thought problems	2	52±6.3
Attention problems	13	54±8.9
Rule-breaking behavior	13	55±8.5
Aggressive behavior	12	56±9.4
Internalizing problems	23	51±11.1
Externalizing problems	31	52±12.1
Total problems	25	50±11.5
Affective problems	9	54±7.3
Anxiety problems	5	54±7.2
Somatic problems	10	54±7.7
ADHD	10	53±7.7
Oppositional defiant problems	19	55±8.5
Conduct problems	11	54±8.5
CASS		
Family problems	2	45±6.8
Conduct problems	4	48±8.8
Anger control problems	5	45±8.3
Emotional problems	2	45±6.8
Cognitive problems	4	45±9.3
Hyperactive–impulsive	4	44±8.8
DSM-IV symptoms	4	45±8.9
ADHD Index	5	45±9.5

Abbreviations: YSR, Youth Self-Report; CASS, Conners' Adolescent Self-Report Scale; SD, standard deviation; ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders.

Multiple regression was used to evaluate the impact of predictor variables such as academic achievement, family relationships, antisocial behavior, and peer relationships on the ADHD and conduct problem scores (Table 4). In the crime against people group, we found that problems in academic achievement (P=0.003) and peer relationships (P=0.002) were significant predictors of ADHD score. In addition, the presence of problems in academic achievement were significant predictors of conduct problem score (P=0.016) in the same group. In the crime against property group, we detected that problems in family relationships (P=0.001; P=0.001) and peer relationships (P=0.003; P=0.004) were significant predictors of ADHD score and conduct problems, respectively. In the alcohol–drug-related crimes group, the presence of antisocial behavior was a significant predictor of conduct problems (P=0.009).

Discussion

Juvenile offenders are a very complex population, where it becomes important to have a global vision of the adolescent, including family and individual risk factors. Several family risk factors for delinquent behavior have been reported, including weak bonding with parents, inadequate parenting, abandonment by parents, family stress, family antisocial behavior, and family history of psychiatric disorders.[23–25] Other risk factors related to delinquent behavior include difficulty in social relationships, little interest in school, and low

Table 3 Features and clinical outcome for offenders divided by type of crime

	Against people		Property		Alcohol–drug-related		F	*P*-value
	%	Mean ± SD	%	Mean ± SD	%	Mean ± SD		
Sex (male)	84	–	92	–	91	–	0.96	0.38
Academic achievement	36	–	60	–	54	–	3.53	0.03*
Family relationships	10	–	22	–	5	–	2.78	0.24
Antisocial behavior	36	–	28	–	37	–	1.14	0.43
Peer relationships	34	–	30	–	11	–	2.97	0.04*
YSR								
Activities	48	34.54±9.274	44	34.68±8.17	28	36.26±6.73	0.52	0.60
Social relationships	14	40.26±7.703	6	42.02±5.71	14	42.83±8.25	1.46	0.24
Anxious/depressed	10	56.24±6.912	14	54.54±9.9	11	55.51±6.12	0.57	0.68
Withdrawn/depressed	18	54.90±7.043	8	53.34±9.72	11	55.71±7.63	0.93	0.40
Somatic complaints	6	53.88±5.363	6	53.50±9.9	5	53.77±5.51	0.03	0.97
Social problems	8	53.04±6.673	4	51.98±9.0	3	52.63±4.04	0.03	0.97
Thought problems	6	52.64±4.388	8	51.60±8.4	5	53.09±5.38	0.28	0.76
Attention problems	16	55.72±8.602	18	54.50±11.32	3	53.49±4.23	0.66	0.52
Rule-breaking behavior	16	56.10±6.947	8	54.36±10.68	14	56.89±7.12	1.00	0.37
Aggressive behavior	22	57.38±8.88	14	54.74±11.43	14	55.94±6.61	0.98	0.38
Internalizing problems	22	52.08±10.05	20	51.02±12.28	28	50.40±11.18	0.25	0.78
Externalizing problems	32	53.10±11.9	26	51.58±12.83	37	52.91±11.66	0.22	0.80
Total problems	26	51.86±10.9	24	50.22±11.98	25	50.31±11.77	0.30	0.74
Affective problems	8	54.34±5.7	8	53.42±9.51	11	54.89±6.0	0.43	0.65
Anxiety problems	6	55.24±5.9	6	53.08±9.24	2	54.54±5.59	1.14	0.32
Somatic problems	8	54.70±6.2	12	53.74±10	8	53.74±5.79	0.24	0.79
ADHD	18	55.80±7.38	8	53.00±9.42	0	54.06±4.67	2.91	0.02*[a]
Oppositional defiant problems	22	56.88±7.7	14	54.58±10.1	22	56.43±6.96	1.00	0.37
Conduct problems	20	55.88±8.2	4	53.08±10.35	8	54.17±5.13	3.05	0.03*[a]
CASS								
Family problems	4	47.68±8.23	2	45.32±5.82	0	44.31±5.39	0.01	0.99
Conduct problems	4	48.60±9.27	0	48.80±7.86	0	48.86±6.8	2.91	0.06
Anger control problems	4	45.34±9.3	4	45.58±7.71	3	45.34±7.88	0.01	0.99
Emotional problems	4	46.10±7.91	0	45.96±7.41	0	45.09±5.61	0.23	0.80
Cognitive problems	6	46.48±10.31	4	45.14±9.67	3	43.97±7	0.76	0.47
Hyperactive–impulsive	6	46.24±10.2	2	44.04±7.95	9	42.60±7.65	1.86	0.16
DSM-IV symptoms	4	45.28±11.01	2	43.70±8.50	0	45.71±7.9	0.72	0.49
ADHD Index	10	47.38±10.8	4	45.90±9.97	0	43.29±5.92	1.94	0.15

Notes: *$P<0.05$; [a]Bonferroni correction, against people > property; against people > alcohol-drug-related.
Abbreviations: YSR, Youth Self-Report; CASS, Conners' Adolescent Self-Report Scale; SD, standard deviation; ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders.

Table 4 Risk factors predicting increased ADHD and conduct problem scores in juvenile offenders

		Against people			Property			Alcohol-drug-related		
		b	t	*P*-value	b	t	*P*-value	b	t	*P*-value
ADHD	Family relationships	−4.62	−1.83	0.074	13.51	4.22	0.001*	−0.39	−0.11	0.91
	Academic achievement	5.88	3.14	0.003*	−0.16	−0.65	0.94	−1.79	−1.02	0.31
	Antisocial behavior	0.14	0.078	0.938	4.04	1.47	0.14	2.41	1.36	0.18
	Peer relationships	6.46	3.22	0.002*	11.5	3.18	0.003*	3.55	1.38	0.17
Conduct	Family relationships	−5.47	−1.45	0.085	12.33	3.56	0.001*	0.69	0.22	0.82
	Academic achievement	5.77	2.5	0.016*	−1.27	−0.46	0.64	−1.66	−1.1	0.28
	Antisocial behavior	−2.81	−1.19	0.23	−0.81	−0.27	0.78	4.22	3.01	0.009*
	Peer relationships	4.04	1.63	0.1	−12.04	−3.07	0.004*	10.54	0.86	8.42

Notes: b, standardized coefficient; *$P<05$.
Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

academic performance.[26] In our sample, we found that 52% had educational achievement problems while 34% had a family history of psychiatric disorders. Unexpectedly, we found that 85% of juvenile offenders showed good family relationships, with only 15% showing poor family relationships. This finding differs from previous research reporting poor family relationships as a risk factor for future delinquency or crime.[27] However, several studies detected a higher rate of delinquency in juveniles living in a single-parent family compared with juveniles living in a nuclear family, probably due to weaker parental control and supervision.[28,29] Thus, the discrepancy between our finding and the data in the literature could be attributed to the fact that the 90% of our participants lived in a nuclear family. On the other hand, in the present study we also found that 72% of the participants reported good peer relationships, with only 28% reporting poor peer relationships. This finding could be linked to the previous data, considering the fact that good early family relationships promote good relationships within the family and with peers later in life, as suggested by attachment theory.[30] In fact, a body of knowledge suggests that early family relationships as well as living in a nuclear family are important in the development of peer relationships.[31,32]

Recently, there has been an increasing amount of literature reporting internalizing and externalizing problems in juvenile offenders, such as anxiety, depression, substance abuse, conduct problems, ADHD, and oppositional defiant disorder;[7,8,19] however studies that have evaluated the presence of externalizing and internalizing problems in juvenile offenders are lacking in Italy. In the present study, emotional and behavioral problems assessed by the YSR showed that juvenile offenders reported both externalizing (in 31%) and internalizing problems (in 23%). Internalizing problems were mainly represented by withdrawn/depressed (13%), followed by anxious/depressed (12%), somatic problems (10%), and affective problems (9%). Externalizing problems were mainly represented by oppositional defiant problems (19%), followed by the rule-breaking behavior (13%), conduct problems (11%) and ADHD (10%). The findings of the current study are consistent with other research which found that most adolescent offenders exhibit more externalizing behaviors (conduct disorder, ADHD, drug abuse) than typical internalizing mental health problems (depression, panic disorder, anxiety).[33–35]

In the present study, the CASS scores showed that 4% of adolescents exceeded the cut-off of the hyperactive–impulsive and DSM-IV symptoms scale, while 5% of adolescents exceeded the cut-off of the ADHD Index scale. These findings seem to be consistent with three epidemiological studies in Italy which reported the prevalence of ADHD to be about 4% during childhood and adolescence.[36–38] However, the presence of ADHD symptoms may have been underestimated for several reasons. The hyperactivity symptoms decrease during adolescence,[39] since our sample involves adolescents, the hyperactivity could be less detected than earlier assessments. In addition, since self-report questionnaires were used, these young offenders might not have reported behavioral problems, such as the presence of ADHD symptoms, for fear of providing negative information on himself/herself. Another aim of this study was to evaluate the environmental risk factors (family, social, and school difficulties) and psychopathology in relation to the type of crime committed. Mallett et al suggested that the broad array of offences classified under personal crimes can be caused or motivated by very different means. A youth who commits a sex offence or causes physical injury or bodily harm will undoubtedly differ in motivation from a youth who commits a robbery, theft on private property, or alcohol and drug abuse.[40] For these reasons, we identified in our sample three groups in relation to the type of crime committed (crime against people, property crime, and alcohol-drug-related crimes). Previous longitudinal studies reported that ADHD could contribute more to drug-related and/or to non-violent crimes, but a recent study found that hyperactivity is not a strong predictor of later non-violent or mixed crime.[16,41] In our study, adolescents who committed crimes against people reported more peer relationship problems, ADHD symptoms, and conduct disorders compared with the other two groups. These problems could lead to reduced ability to evaluate social events objectively and commit subsequent aggressive behaviors.

The present findings seem to be consistent with those of Bagwell et al who found that ADHD children reported fewer close friendships and more peer rejection when compared with a non-ADHD group, suggesting that the long-term effects of ADHD on social functioning were more pronounced for children with persistent ADHD or conduct disorder in adolescence.[42] Moreover, we found that academic achievement problems were more frequent in adolescents who committed property crimes (60%) and alcohol-drug-related crimes (54%) compared with adolescents who committed crimes against people. This finding supports previous research describing a relationship between low academic performance and delinquency.[43,44] There is evidence that the intellectual functioning of young offenders is in the low–average range and that they have significant deficits

in reading, mathematics, and written and oral language compared with their non-offending peers,[45] while higher academic performance was associated with desistance from offending.[46] In addition, multiple regression was used to evaluate the impact of predictor variables, such as academic achievement, family relationships, antisocial behavior, and peer relationships, on the ADHD and conduct problem scores in the three groups. In the crimes against people group, academic achievement and peer relationship problems were associated with ADHD symptoms and problems in academic achievement was also associated with conduct problems. In the property crimes group, we found that the presence of family relationships and peer relationships difficulties were associated with ADHD and conduct problems, while antisocial behavior was a significant predictor of conduct problems in the alcohol–drug-related crimes group. This finding underscores the relevance of psychosocial risk factors in addition to possible genetic risk factors for increased ADHD symptoms in adolescents displaying antisocial behavior. In fact, an association with serotonergic gene expression has been described for several psychiatric disorders related to a general lack of impulse control and impulsive aggression, such as ADHD.[47,48] In particular, Retz et al examined the relationship between serotonergic dysfunction and violent behavior, and demonstrated genetic regulation of violent behavior in a subgroup of male offenders with a history of childhood ADHD, suggesting a significant role of serotonin transporter functionality in violent behavior.[47]

Several limitations to this study need to be acknowledged. First, the reliance on a semistructured interview schedule for the measurement of qualitative variables raises concern about the validity of causal conclusions for a range of reasons, including systematic response distortions, different research methods, and the psychometric properties (reliability and validity) of questionnaire scales. Another limitation lies in the fact that the impact of ADHD on the continuation or amelioration of antisocial behavior in delinquent adolescents remains unclear. Several studies have reported that attention problems and impulsivity/hyperactivity constitute two genetically distinct groups, suggesting that differentiation of inattention from hyperactivity/impulsivity may be important, and also that different pathways towards delinquency may exist.[49] Fletcher et al suggest that people with inattentive-type symptoms are more likely to commit crimes that might require some planning, such as selling drugs or burglary compared with individuals with no ADHD symptoms, whereas individuals with impulsive symptoms have the highest increase in criminal activity of all the ADHD types, and are more likely to be arrested and convicted of a crime. Individuals with the combined-type of ADHD symptoms had weaker associations with crime compared with individuals who have only inattentive or only hyperactive symptoms. Surprisingly, individuals with the combined-type of ADHD symptoms are not at a multiplicative risk of criminal activities.[50]

In conclusion, this is the first Italian study to examine the association between environmental and psychopathological risk factors, focusing especially on ADHD symptoms, and type of crime committed in a sample of adolescent offenders. The findings confirm the presence of family, social, and school difficulties in juvenile offenders. Moreover, ADHD and conduct disorders contribute to more crimes against people when compared with property and alcohol–drug-related crimes, suggesting that ADHD could represent a risk factor to engage in specific crime, and this probability rises dramatically for ADHD children with conduct disorder. This finding suggests the need to implement interventions based on specific risk factors and psychopathologies for the treatment of criminal behavior. In addition, extended collaboration between the child, the adolescent psychiatrist, and the judicial system would be beneficial in preventing later criminality in children with ADHD. Further research is certainly needed to clarify this issue.

Acknowledgments

We thank the following personnel for their generous support: Manuela Tamma, Egle Alfarano, Andrea Lisi, Ignazio Grattagliano, Maria Elena Lafortezza, Foloriana Pinto, Francesca Perrini, Francesca Montemiglio, Rosanna Viale, Paola Cuna, Giuseppe Tucci, and Ermenegilda Scardaccione.

Disclosure

None of the authors has any conflict of interest to disclose. All authors have seen and approved the final version of the paper and accept responsibility for the data presented.

References

1. Junger-Tas J, Marshall I, Ribeud D. *Delinquency in an International Perspective: The International Self-Reported Delinquency Study*. New York, NY, USA: Kugler; 2003.
2. Junger-Tas J, Marshall I, Enzmann D, Killias M, Steketee M, Gruszczynska B. *Juvenile Delinquency in Europe and Beyond: Results of the Second International Self-Report Delinquency Study*. Berlin, Germany: Springer eBook; 2010.
3. Herrenkohl TI, Maguin E, Hill KG, Hawkins JD, Abbott RD, Catalano RF. Developmental risk factors for youth violence. *J Adolesc Health*. 2000;26(3):176–186.

4. Nagin DS, Tremblay RE. Parental and early childhood predictors of persistent physical aggression in boys from kindergarten to high school. *Arch Gen Psychiatry*. 2001;58(4):389–394.
5. Abram KM, Teplin LA, McClelland GM, Dulcan MK. Comorbid psychiatric disorders in youth in juvenile detention. *Arch Gen Psychiatry*. 2003;60(11):1097–1108.
6. Carswell K, Maughan B, Davis H, Davenport F, Goddard N. The psychosocial needs of young offenders and adolescents from an inner city area. *J Adolesc*. 2004;27(4):415–428.
7. Teplin LA, Abram KM, McClelland GM, Dulcan MK, Mericle AA. Psychiatric disorders in youth in juvenile detention. *Arch Gen Psychiatry*. 2002;59(12):1133–1143.
8. Vermeiren R. Psychopathology and delinquency in adolescents: a descriptive and developmental perspective. *Clin Psychol Rev*. 2003;23(2):277–318.
9. Coker KL, Smith PH, Westphal A, Zonana HV, McKee SA. Crime and psychiatric disorders among youth in the U.S. population: an analysis of the national comorbidity survey – adolescent supplement. *J Am Acad Child Adolesc Psychiatry*. 2014;53(8):888–898.
10. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: antisocial activities and drug use. *J Child Psychol Psychiatry*. 2004;45(2):195–211.
11. Mannuzza S, Klein RG, Moulton JL, III. Lifetime criminality among boys with attention deficit hyperactivity disorder: a prospective follow-up study into adulthood using official arrest records. *Psychiatry Res*. 2008(3);160:237–246.
12. Bulten E, Nijman H, van der Staak C. Psychiatric disorders and personality characteristics of prisoners at regular prison wards. *Int J Law Psychiatry*. 2009;32(2):115–119.
13. Belcher JR. Attention deficit hyperactivity disorder in offenders and the need for early intervention. *Int J Offender Ther Comp Criminol*. 2012;58(1):27–40.
14. Babinski LM, Hartsough CS, Lambert NM. Childhood conduct problems, hyperactivity-impulsivity, and inattention as predictors of adult criminal activity. *J Child Psychol Psychiatry*. 1999;40(3):347–355.
15. Taylor E, Chadwick O, Heptinstall E, Danckaerts M. Hyperactivity and conduct problems as risk factors for adolescent development. *J Am Acad Child Adolesc Psychiatry*. 1996;35(9):1213–1226.
16. Molina BS, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):484–500.
17. Pingault JB, Côté SM, Lacourse E, Galéra C, Vitaro F, Tremblay RE. Childhood hyperactivity, physical aggression and criminality: a 19-year prospective population-based study. *PLoS One*. 2013;8(5):e62594.
18. Moffitt TE, Caspi A. Adolescent-limited delinquency and life-course persistent offending. *Psychol Rev*. 2001;100(4):674–701.
19. Loeber R, Slot W, Stouthamer-Loeber M. *A Cumulative Developmental Model of Risk and Promotive Factors*. Hampshire, UK: Ashgate Publishing Ltd; 2008.
20. Gudjonsson GH, Young S. An overlooked vulnerability in a defendant: attention deficit hyperactivity disorder and a miscarriage of justice. *Legal and Criminological Psychology*. 2006;11(2):211–218.
21. Achenbach TM. *Manual for the Young Adult Self-Report and Young Adult Behavior Checklist*. Burlington, VT, USA: Department of Psychiatry, University of Vermont; 1997.
22. Conners CK. *Conners' Rating Scales-Revised*. North Tonawanda, NY, USA: Multi-Health Systems; 1997.
23. Hoeve M, Blokland A, Dubas JS, Loeber R, Gerris JR, van der Laan PH. Trajectories of delinquency and parenting styles. *J Abnorm Child Psychol*. 2008;36(2):223–235.
24. Sentse M, Veenstra R, Lindenberg S, Verhulst FC, Ormel J. Buffers and risks in temperament and family for early adolescent psychopathology: generic, conditional, or domain-specific effects? The trails study. *Dev Psychol*. 2009;45(2):419–430.
25. Perdue TR, Williamson C, Ventura LA, et al. Offenders who are mothers with and without experience in prostitution: differences in historical trauma, current stressors, and physical and mental health differences. *Womens Health Issues*. 2012;22(2):195–200.
26. Mulder E, Vermunt J, Brand E, Bullens R, van Marle H. Recidivism in subgroups of serious juvenile offenders: different profiles, different risks? *Crim Behav Ment Health*. 2012;22(2):122–135.
27. Petrosino A, Derzon J, Lavenberg J. The role of family in crime and delinquency: evidence from prior quantitative reviews. *Southwest Journal of Criminal Justice*. 2009;6(2):108–132.
28. Schroeder RD, Osgood AK, Oghia MJ. Family transitions and juvenile delinquency. *Sociol Inq*. 2010;80(4):579–604.
29. Demuth S, Brown S. Family structure, family processes, and adolescent delinquency: the significance of parental absence versus parental gender. *Journal of Research in Crime and Delinquency*. 2004;41(1):58–81.
30. Ainsworth MD. Attachments beyond infancy. *Am Psychol*. 1989;44(4):709–716.
31. Thienneman M, Shaw RJ, Steiner H. Defense style and family environment. *Child Psychiatry Hum Dev*. 1998;28(3):189–198.
32. Pallini S, Baiocco R, Schneider BH, Madigan S, Atkinson L. Early child–parent attachment and peer relations: a meta-analysis of recent research. *J Fam Psychol*. 2014;28(1):118–123.
33. Rayner J, Kelly TP, Graham F. Mental health, personality and cognitive problems in persistent adolescent offenders require long-term solutions: a pilot study. *Journal of Forensic Psychiatry and Psychology*. 2005;16(2):248–262.
34. Imbach D, Aebi M, Metzke CW, Bessler C, Steinhausen HC. Internalizing and externalizing problems, depression, and self-esteem in non-detained male juvenile offenders. *Child Adolesc Psychiatry Ment Health*. 2013;27(1):7–14.
35. Vieno A, Nation M, Perkins DP, Pastore M, Santinello M. Social capital, safety concerns, parenting, and early adolescents' antisocial behavior. *J Community Psychol*. 2010;38(3):314–328.
36. Gallucci F, Bird HR, Berardi C, Gallai V, Pfanner P, Weinberg A. Symptoms of attention-deficit hyperactivity disorder in an Italian school sample: findings of a pilot study. *J Am Acad Child Adolesc Psychiatry*. 1993;32(5):1051–1158.
37. Camerini GB, Coccia M, Caffo E. [Attention deficit-hyperactivity disorder: frequency analysis in a school population through questionnaires to teachers]. *Psichiatria dell'Infanzia e dell'Adolescenza*. 1996;63:587–594. Italian.
38. Mugnaini D, Masi G, Brovedani P, et al. Teacher reports of ADHD symptoms in Italian children at the end of first grade. *Eur Psychiatry*. 2006;21(6):419–426.
39. Fergusson DM, Horwood LJ, Ridder EM. Show me your child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. *J Child Psychol Psychiatry*. 2005;46(8):837–849.
40. Mallett C, Stoddard-Dare P, Workman-Crenshaw L. Special education disabilities and juvenile delinquency: a unique challenge for school social work. *School Social Work Journal*. 2011;36(1):26–40.
41. Sourander A, Elonheimo H, Niemela S, et al. Childhood predictors of male criminality: a prospective population-based follow-up study from age 8 to late adolescence. *J Am Acad Child Adolesc Psychiatry*. 2006;45(5):578–586.
42. Bagwell CL, Molina BS, Pelham WE, Hoza B. Attention-deficit hyperactivity disorder and problems in peer relations: predictions from childhood to adolescence. *J Am Acad Child Adolesc Psychiatry*. 2001;40(11):1285–1292.
43. Loeber R, Farrington DP. Young children who commit crime: epidemiology, developmental origins, risk factors, early interventions, and policy implications. *Dev Psychopathol*. 2000;12(4):737–762.
44. Reinke WM, Herman KC. A research agenda for school violence prevention. *Am Psychol*. 2002;57(10):796–797.

45. Leone PE, Christle CA, Nelson CM, Skiba R, Frey A, Jolivette K. *School Failure, Race, and Disability: Promoting Positive Outcomes, Decreasing Vulnerability for Involvement with the Juvenile Delinquency System*. Baltimore, MD, USA: National Center on Education, Disability, and Juvenile Justice, University of Maryland; 2003.
46. Flannery RB Jr, Everly GS Jr, Eyler V. The Assaulted Staff Action Program (ASAP) and declines in assaults: a meta-analysis. *Int J Emerg Ment Health*. 2000;2(3):143–148.
47. Retz W, Thome J, Blocher D, Baader M, Rösler M. Association of attention deficit hyperactivity disorder-related psychopathology and personality traits with the serotonin transporter promoter region polymorphism. *Neurosci Lett*. 2002;319(3):133–136.
48. Seeger G, Schloss P, Schmidt MH. Marker gene polymorphisms in hyperkinetic disorder – predictors of clinical response to treatment with methylphenidate? *Neurosci Lett*. 2001;313(1–2):45–48.
49. Willcutt EG, Pennington BF, DeFries JC. Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *Am J Med Genet*. 2000;96(3):293–301.
50. Fletcher J, Wolfe B. Long-term consequences of childhood ADHD on criminal activities. *J Ment Health Policy Econ*. 2009;12(3):119–138.

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

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