NEWSLETTER

INDICE:

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Congresso ADHD
PERCORSI DIAGNOSTICO-TERAPEUTICI CONDIVISI PER L'ADHD
UNA RISPOSTA ALLE CRITICITÀ E AI BISOGNI INEVASIE.
IRCCS Istituto di Ricerche Farmacologiche Mario Negri
Milano, 9-10 novembre 2015 pag. 64

BIBLIOGRAFIA ADHD SETTEMBRE 2015

ADHD Atten Deficit Hyperact Disord. 2015;7:177-78.
CONNECTIVE TISSUE PROBLEMS AND ATTENTION DEFICIT AND HYPERACTIVITY.
Baeza-Velasco C, Soussana M, Baghdadli A.

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Am J Psychiatry. 2015 Jul;172:638-46.
DIAGNOSTIC PRECURSORS TO BIPOLAR DISORDER IN OFFSPRING OF PARENTS WITH BIPOLAR DISORDER: A LONGITUDINAL STUDY.
Axelson D, Goldstein B, Goldstein T, et al.
OBJECTIVE: The authors sought to identify diagnostic risk factors of manic, mixed, or hypomanic episodes in the offspring of parents with bipolar disorder ("high-risk offspring").
METHOD: High-risk offspring 6-18 years old (N=391) and demographically matched offspring (N=248) of community parents without bipolar disorder were assessed longitudinally with standardized diagnostic instruments by staff blind to parental diagnoses. Follow-up assessments were completed in 91% of the offspring (mean follow-up interval, 2.5 years; mean follow-up duration, 6.8 years).
RESULTS: Compared with community offspring, high-risk offspring had significantly higher rates of subthreshold mania or hypomania (13.3% compared with 1.2%), manic, mixed, or hypomanic episodes (9.2% compared with 0.8%), and major depressive episodes (32.0% compared with 14.9%). They also had higher rates of attention deficit hyperactivity disorder (30.7% compared with 18.1%), disruptive behavior disorders (27.4% compared with 15.3%), anxiety disorders (39.9% compared with 21.8%), and substance use disorders (19.9% compared with 10.1%), but not unipolar major depressive disorder (major depression with no bipolarity; 18.9% compared with 13.7%). Multivariate Cox regressions showed that in the high-risk offspring, subthreshold manic or hypomanic episodes (hazard ratio=2.29), major depressive episodes (hazard ratio=1.99), and disruptive behavior disorders (hazard ratio=2.12) were associated with subsequent manic, mixed, or hypomanic episodes. Only subthreshold manic or hypomanic episodes (hazard ratio=7.57) were associated when analyses were restricted to prospective data.
CONCLUSIONS: Subthreshold manic or hypomanic episodes were a diagnostic risk factor for the development of manic, mixed, or hypomanic episodes in the offspring of parents with bipolar disorder and should be a target for clinical assessment and treatment research. Major depressive episodes and disruptive behavior disorders are also indications for close clinical monitoring of emergent bipolarity in high-risk offspring.

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

American Journal of Family Therapy. 2015 Aug;43:364-77.

USING THE 12-STEPS AS A PARENTING INTERVENTION WITH ADHD ADOLESCENTS.

Grogan M, Weitzman J.

This article describes a self-help model for adolescents with ADHD that draws on the 12-Steps. The model uses a modified form of the 12-Steps that incorporates parents into the process with the goal of inculcating some of the executive functioning that is absent in their adolescent by consistently using some of the 12-Steps as part of their daily routine. The model proposes that parents assume a coaching role with their adolescent to teach increased self-awareness, organization, accountability, and behavioral inhibition that, hopefully, will have a reparative effect on their child's immature neurological functioning.

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Amino Acids. 2014 Sep;46(9):2105-22.

PREPUBERAL INTRANASAL DOPAMINE TREATMENT IN AN ANIMAL MODEL OF ADHD AMELIORATES DEFICIENT SPATIAL ATTENTION, WORKING MEMORY, AMINO ACID TRANSMITTERS AND SYNAPTIC MARKERS IN PREFRONTAL CORTEX, VENTRAL AND DORSAL STRIATUM.

Ruocco LA, Treno C, Gironi Carnevale UA, et al.

Intranasal application of dopamine (IN-DA) has been shown to increase motor activity and to release DA in the ventral (VS) and dorsal striatum (DS) of rats. The aim of the present study was to assess the effects of IN-DA treatment on parameters of DA and excitatory amino acid (EAA) function in prepuberal rats of the Naples high-excitability (NHE) line, an animal model for attention-deficit hyperactivity disorder (ADHD) and normal random bred (NRB) controls. NHE and NRB rats were daily administered IN-DA (0.075, 0.15, 0.30 mg/kg) or vehicle for 15 days from postnatal days 28-42 and subsequently tested in the Làt maze and in the Eight-arm radial Olton maze. Soluble and membrane-trapped L-glutamate (L-Glu) and L-aspartate (L-Asp) levels as well as NMDAR1 subunit protein levels were determined after sacrifice in IN-DA- and vehicle-treated NHE and NRB rats in prefrontal cortex (PFc), DS and VS. Moreover, DA transporter (DAT) protein and tyrosine hydroxylase (TH) levels were assessed in PFc, DS, VS and mesencephalon (MES) and in ventral tegmental area (VTA) and substantia nigra, respectively. In NHE rats, IN-DA (0.30 mg/kg) decreased horizontal activity and increased nonselective attention relative to vehicle, whereas the lower dose (0.15 mg/kg) increased selective spatial attention. In NHE rats, basal levels of soluble EAAs were reduced in PFc and DS relative to NRB controls, while membrane-trapped EAAs were elevated in VS. Moreover, basal NMDAR1 subunit protein levels were increased in PFc, DS and VS relative to NRB controls. In addition, DAT protein levels were elevated in PFc and VS relative to NRB controls. IN-DA led to a number of changes of EAA, NMDAR1 subunit protein, TH and DAT protein levels in PFc, DS, VS, MES and VTA, in both NHE and NRB rats with significant differences between lines. Our findings indicate that the NHE rat model of ADHD may be characterized by (1) prefrontal and striatal DAT hyperfunction, indicative of DA hyperactivty, and (2) prefrontal and striatal NMDA receptor hyperfunction indicative of net EAA hyperactivty. IN-DA had ameliorative effects on activity level, attention, and working memory, which are likely to be associated with DA action at inhibitory D2 autoreceptors, leading to a reduction in striatal DA hyperactivity and, possibly, DA action on striatal EAA levels, resulting in a decrease of striatal EAA hyperfunction (with persistence of prefrontal EAA hyperfunction). Previous studies on IN-DA treatment in rodents have indicated antidepressant, anxiolytic and anti-parkinsonian effects in relation to enhanced central DAergic activity. Our present results strengthen the prospects of potential therapeutic applications of intranasal DA by indicating an enhancement of selective attention and working memory in a deficit model.

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BMC Med Genet. 2015;16:51.

FIRST DE NOVO KCND3 MUTATION CAUSES SEVERE KV4.3 CHANNEL DYSFUNCTION LEADING TO EARLY ONSET CEREBELLAR ATAXIA, INTELLECTUAL DISABILITY, ORAL APRAXIA AND EPILEPSY.

Smets K, Duarri A, Deconinck T, et al.

BACKGROUND: Identification of the first de novo mutation in potassium voltage-gated channel, shal-related subfamily, member 3 (KCND3) in a patient with complex early onset cerebellar ataxia in order to expand the genetic and phenotypic spectrum.

METHODS: Whole exome sequencing in a cerebellar ataxia patient and subsequent immunocytochemistry, immunoblotting and patch clamp assays of the channel were performed.

RESULTS: A de novo KCND3 mutation (c.877_885dupCGCGTCTTC; p.Arg293_Phe295dup) was found duplicating the RVF motif and thereby adding an extra positive charge to voltage-gated potassium 4.3 (Kv4.3) in the voltage-sensor domain causing a severe shift of the voltage-dependence gating to more depolarized voltages. The patient displayed a severe phenotype with early onset cerebellar ataxia complicated by intellectual disability, epilepsy, attention deficit hyperactivity disorder, strabismus, oral apraxia and joint hyperlaxity.

CONCLUSIONS: We identified a de novo KCND3 mutation causing the most marked change in Kv4.3's channel properties reported so far, which correlated with a severe and unique spinocerebellar ataxia (SCA) type 19/22 disease phenotype.

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BMJ Case Rep. 2015;2015.

QUETIAPINE-INDUCED MYOCARDITIS PRESENTING AS ACUTE STEMI.

Wassef N, Khan N, Munir S.

An 18-year-old man diagnosed with attention-deficit hyperactivity disorder was recently started on quetiapine in addition to regular methylphenidate, which he had been taking for a number of years. He presented with chest pain and inferolateral ST elevation, and underwent urgent coronary angiography, which showed normal coronary arteries. The initial troponin level was raised and an inpatient echocardiogram showed mild left ventricular systolic dysfunction with no evidence of regional wall motion abnormality. Cardiac MRI showed subepicardial late gadolinium enhancement, which was suggestive of myocarditis. Quetiapine and methylphenidate were discontinued and the patient was discharged home after 1 week. He was followed up within 8 weeks with complete recovery and no symptoms.

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Brain Sciences. 2015;5:369-86.

EMOTION REGULATION IN ADOLESCENT MALES WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER: TESTING THE EFFECTS OF COMORBID CONDUCT DISORDER.

Northover C, Thapar A, Langley K, et al.

Although attention-deficit hyperactivity disorder (ADHD) has been linked to emotion dysregulation, few studies have experimentally investigated this whilst controlling for the effects of comorbid conduct disorder (CD). Economic decision-making games that assess how individuals respond to offers varying in fairness have been used to study emotion regulation. The present study compared adolescent boys with ADHD (n = 90), ADHD + CD (n = 94) and typical controls (n = 47) on the Ultimatum Game and examined the contribution of ADHD and CD symptom scores and callous and unemotional traits to acceptance levels of unfair offers. There were no significant differences in acceptance rates of fair and highly unfair offers between groups, and only boys with ADHD did not significantly differ from the controls. However, the subgroup of boys with ADHD and additional high levels of aggressive CD symptoms rejected significantly more ambiguous (i.e., moderately unfair) offers than any other subgroup, suggesting impaired emotion regulation in those with ADHD and aggressive CD. Correlations within the CD group showed that the rejection rate to moderately unfair offers was predicted by aggressive CD symptom severity, but not callous and unemotional traits. These findings highlight the fact that ADHD is a heterogeneous condition from an emotion regulation point of view.

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Child Adolesc Psychiatry Ment Health. 2015;9.

AN OBJECTIVE MEASURE OF HYPERACTIVITY ASPECTS WITH COMPRESSED WEBCAM VIDEO.

Wehrmann T, M++ller JM.

Background: Objective measures of physical activity are currently not considered in clinical guidelines for the assessment of hyperactivity in the context of Attention-Deficit/Hyperactivity Disorder (ADHD) due to low and inconsistent associations between clinical ratings, missing age-related norm data and high technical requirements.

Methods: This pilot study introduces a new objective measure for physical activity using compressed webcam video footage, which should be less affected by age-related variables. A pre-test established a preliminary standard procedure for testing a clinical sample of 39 children aged 6-16years (21 with a clinical ADHD diagnosis, 18 without). Subjects were filmed for 6min while solving a standardized cognitive performance task. Our webcam video-based video-activity score was compared with respect to two independent video-based movement ratings by students, ratings of Inattentiveness, Hyperactivity and Impulsivity by clinicians (DCL-ADHS) giving a clinical diagnosis of ADHD and parents (FBB-ADHD) and physical features (age, weight, height, BMI) using mean scores, correlations and multiple regression.

Results: Our video-activity score showed a high agreement (r=0.81) with video-based movement ratings, but also considerable associations with age-related physical attributes. After controlling for age-related confounders, the video-activity score showed not the expected association with clinicians' or parents' hyperactivity ratings.

Conclusions: Our preliminary conclusion is that our video-activity score assesses physical activity but not specific information related to hyperactivity. The general problem of defining and assessing hyperactivity with objective criteria remains.

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Coll Antropol. 2015 Mar;39:27-31.

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN WITH INTELLECTUAL DISABILITY IN BOSNIA AND HERZEGOVINA.

Memisevic H, Sinanovic O.

Attention deficit hyperactivity disorder (ADHD) is very frequent in children with intellectual disability. The aim of this study was to examine the occurrence of ADHD in children with intellectual disability in Bosnia and Herzegovina with regard to their sex, etiology and level of intellectual disability. The method for data collection was the examination of the children's medical records. The sample consisted of 167 children attending two special education facilities in Sarajevo. Overall occurrence of the disorder was found to be 20.4%, a finding which is in accordance with existing studies. The results in this study revealed different male to female ratio (1.5:1) of the disorder as compared to existing studies. A difference in the prevalence of ADHD was found in relation to the level of intellectual disability. There are many children with dual diagnosis of intellectual disability and ADHD. It is necessary that multidisciplinary team is involved in the creation of behavioral and educational programs for these children.

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Cortex. 2015;73:62-72.

THE EXECUTIVE CONTROL NETWORK AND SYMPTOMATIC IMPROVEMENT IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Francx W, Oldehinkel M, Oosterlaan J, et al.

Background: One neurodevelopmental theory hypothesizes remission of attention-deficit/hyperactivity disorder (ADHD) to result from improved prefrontal top-down control, while ADHD, independent of the current diagnosis, is characterized by stable non-cortical deficits (Halperin & Schulz, 2006). We tested this theory using resting state functional MRI (fMRI) data in a large sample of adolescents with remitting ADHD, persistent ADHD, and healthy controls.

Methods: Participants in this follow-up study were 100 healthy controls and 129 adolescents with ADHD combined type at baseline (mean age at baseline 11.8 years; at follow-up 17.5 years). Diagnostic information was collected twice and augmented with magnetic resonance imaging (MRI) scanning at follow-up. We used resting state functional connectivity (RSFC) of the executive control network to investigate whether improved prefrontal top-down control was related to a developmental decrease in ADHD symptoms. In addition, we tested whether non-cortical RSFC, i.e., cerebellar and striatal RSFC, was aberrant in persistent and/or remittent ADHD compared to controls.
Results: Higher connectivity within frontal regions (anterior cingulate cortex) of the executive control network was related to decreases in ADHD symptoms. This association was driven by change in hyperactive/impulsive symptoms and not by change in inattention. Participants with remitting ADHD showed stronger RSFC than controls within this network, while persistent ADHD cases exhibited RSFC strengths intermediate to remittent ADHD cases and controls. Cerebellar and subcortical RSFC did not differ between participants with ADHD and controls.
Conclusions: In line with the neurodevelopmental theory, symptom recovery in ADHD was related to stronger integration of prefrontal regions in the executive control network. The pattern of RSFC strength across remittent ADHD, persistent ADHD, and healthy controls potentially reflects the presence of compensatory neural mechanisms that aid symptomatic remission.

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Drug Alcohol Depend. 2015 Apr;149:180-86.

SLEEP AND USE OF ALCOHOL AND DRUG IN ADOLESCENCE. A LARGE POPULATION-BASED STUDY OF NORWEGIAN ADOLESCENTS AGED 16 TO 19 YEARS.

Sivertsen B, Skogen JC, Jakobsen R, et al.

BACKGROUND: Changes in sleep patterns and increased substance involvement are common in adolescence, but our knowledge of the nature of their association remains limited. The aim of this study was to examine the association between several sleep problems and sleep behaviours, and use and misuse of alcohol and illicit drugs using data from a large population-based sample.
METHODS: A large population-based study from Norway conducted in 2012, the youth@hordaland study, surveyed 9328 adolescents aged 16-19 years (54% girls). Self-reported sleep measures provided information on sleep duration, sleep deficit, weekday bedtime and bedtime difference and insomnia. The main dependent variables were frequency and amount of alcohol consumption and illicit drug use, in addition to the presence of alcohol and drug problems as measured by CRAFFT.
RESULTS: The results showed that all sleep parameters were associated with substance involvement in a dose-response manner. Short sleep duration, sleep deficit, large bedtime differences and insomnia were all significantly associated with higher odds of all alcohol and drug use/misuse measures. The associations were only partly attenuated by sociodemographics factors and co-existing symptoms of depression and ADHD.
CONCLUSIONS: To the best of our knowledge, this is the first population-based study to examine the association between sleep, and alcohol and drug use, by employing detailed measures of sleep behaviour and problems, as well as validated measures on consumption of alcohol and illicit drug use. The findings call for increased awareness of the link between sleep problems and alcohol and drugs use/misuse as a major public health issue.

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Epilepsy Behav. 2015 Feb;43:109-16.

IMPAIRED PERFORMANCE ON ADVANCED THEORY OF MIND TASKS IN CHILDREN WITH EPILEPSY IS RELATED TO POOR COMMUNICATION AND INCREASED ATTENTION PROBLEMS.

Lunn J, Lewis C, Sherlock C.

Children with epilepsy (CWE) have social difficulties that can persist into adulthood, and this could be related to problems with understanding others' thoughts, feelings, and intentions. This study assessed children's ability to interpret and reason on mental and emotional states (Theory of Mind) and examined the

relationships between task scores and reports of communication and behavior. Performance of 56 CWE (8-16years of age) with below average IQ (n=17) or an average IQ (n=39) was compared with that of 62 healthy controls with an average IQ (6-16years of age) on cognition, language, and two advanced Theory of Mind (ToM) tasks that required children to attribute mental or emotional states to eye regions and to reason on internal mental states in order to explain behavior. The CWE-below average group were significantly poorer in both ToM tasks compared with controls.

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European Child & Adolescent Psychiatry. 2015 Aug;24:897-907.

SLEEP PROBLEMS PREDICT COMORBID EXTERNALIZING BEHAVIORS AND DEPRESSION IN YOUNG ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Becker SP, Langberg JM, Evans SW.

Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) experience high rates of sleep problems and are also at increased risk for experiencing comorbid mental health problems. This study provides an initial examination of the 1-year prospective association between sleep problems and comorbid symptoms in youth diagnosed with ADHD. Participants were 81 young adolescents (75 % male) carefully diagnosed with ADHD and their parents. Parents completed measures of their child's sleep problems and ADHD symptoms, oppositional defiant disorder (ODD) symptoms, and general externalizing behavior problems at baseline (Mage = 12.2) and externalizing behaviors were assessed again 1 year later. Adolescents completed measures of anxiety and depression at both time-points. Medication use was not associated with sleep problems or comorbid psychopathology symptoms. Regression analyses indicated that, above and beyond demographic characteristics, ADHD symptom severity, and initial levels of comorbidity, sleep problems significantly predicted greater ODD symptoms, general externalizing behavior problems, and depressive symptoms 1 year later. Sleep problems were not concurrently or prospectively associated with anxiety. Although this study precludes making causal inferences, it does nonetheless provide initial evidence of sleep problems predicting later comorbid externalizing behaviors and depression symptoms in youth with ADHD. Additional research is needed with larger samples and multiple time-points to further examine the interrelations of sleep problems and comorbidity.

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European Child & Adolescent Psychiatry. 2015 Aug;24:919-29.

MATERNAL SMOKING AND OFFSPRING INATTENTION AND HYPERACTIVITY: RESULTS FROM A CROSS-NATIONAL EUROPEAN SURVEY.

Kovess V, Keyes KM, Hamilton A, et al.

In utero exposure to tobacco smoke is associated with adverse neonatal outcomes; the association with later childhood mental health outcomes remains controversial. We used a strategy involving comparison of maternal and paternal smoking reports in a sample pooling data from six diverse European countries. Data were drawn from mother (N = 4,517) and teacher (N = 4,611) reported attention deficit and hyperactivity disorder (ADHD) symptoms in school children aged 6–11 in Turkey, Romania, Bulgaria, Lithuania, Germany, and the Netherlands, surveyed in 2010. Mothers report on self and husband's smoking patterns during the pregnancy period. Logistic regression used with control covariates including demographics, maternal distress, live births, region, and post-pregnancy smoking. In unadjusted models, maternal prenatal smoking was associated with probable ADHD based on mother [Odds Ratio (OR) = 1.82, 95 % Confidence Interval (CI) 1.45–2.29], teacher (OR = 1.69, 95 % CI 1.33–2.14) and mother plus teacher (OR = 1.49, 95 % CI 1.03–2.17) report. Paternal prenatal smoking was similarly associated with probable ADHD in unadjusted models. When controlled for relevant confounders, maternal prenatal smoking remained a risk factor for offspring probable ADHD based on mother report (OR = 1.44, 95 % CI 1.06–1.96), whereas the effect of paternal prenatal smoking diminished (e.g., mother report: OR = 1.17, 95 % CI 0.92–1.49). Drawing on data from a diverse set of countries across Europe, we document that the association between maternal smoking and offspring ADHD is stronger than that of paternal smoking during the pregnancy period and offspring ADHD.

To the extent that confounding is shared between parents, these results reflect a potential intrauterine influence of smoking on ADHD in children.

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European Child & Adolescent Psychiatry. 2015 Aug;24:887-95.

PEER DISLIKE AND VICTIMISATION IN PATHWAYS FROM ADHD SYMPTOMS TO DEPRESSION.

Roy A, Hartman CA, Veenstra R, et al.

The following hypotheses were tested in a longitudinal, population-based study: (1) Attention deficit hyperactivity disorder (ADHD) symptoms are associated with peer dislike and victimisation; (2) Peer dislike and victimisation increase the risk for subsequent depression; and (3) The effect of ADHD symptoms on depression is partly mediated through peer dislike and victimisation. Gender differences in mediating pathways through peer dislike and victimisation to depression were additionally explored. The Child Behaviour Checklist (CBCL), Youth Self Report (YSR) and Teacher's Checklist of Pathology (TCP) assessed ADHD symptoms in 728 adolescents. Peer nominations were used to assess peer dislike and victimisation. The Composite International Diagnostic Interview (CIDI) was used to assess depression. Effects of peer dislike, victimisation, and ADHD symptoms on depression were modelled using Cox regression. ADHD symptoms were associated with peer dislike ($rs = 0.17$, $p < 0.001$) and victimisation ($rs = 0.11$, $p = 0.001$). Dislike, victimisation, and ADHD symptoms increased risk for depression. Risk for depression associated with victimisation and ADHD symptoms reduced with time. Dislike and victimisation mediated 7 % of the effect of ADHD symptoms on depression. Pathways through dislike and victimisation were present in girls but not in boys. Peer dislike and victimisation explain, to a limited extent, the prospective association between ADHD and depression, particularly in girls.

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European Child & Adolescent Psychiatry. 2015 Jul;24:827-36.

GRIN2B PREDICTS ATTENTION PROBLEMS AMONG DISADVANTAGED CHILDREN.

Riva V, Battaglia M, Nobile M, et al.

It is well established that adversities and GRIN2B (coding an N-methyl-D-aspartate receptor subunit) are independently associated with behavioral and cognitive impairments in childhood. However, a high proportion of children exposed to adversities have good, long-term outcomes. We hypothesized that among children exposed to adversities, GRIN2B variants would predict the worst cognitive and behavioral outcomes. 6 single nucleotide polymorphisms of GRIN2B were genotyped in 625 children aged 6–11 years from an Italian community-based sample. The interacting effect of GRIN2B variants with 4 measures of adversities [low socioeconomic status (SES), preterm delivery, maternal smoking during pregnancy, and absence of breastfeeding] was investigated upon blindly assessed cognitive abilities (vocabulary, block design, digit spans of Wechsler's Intelligence Scale, and Rey complex figure) and parents-rated behavioral problems (Child Behavior Checklist/6–18). Rs2268119 × SES interaction (Hotelling's Trace = 0.07; $F(12,1154) = 3.53$; $p = 0.00004$) influenced behavior, with more attention problems among children in the 'either A/T or T/T genotype and low SES' group, compared to all other groups. This interaction effect was not significant in an independent, replication sample of 475 subjects from an Italian community-based sample. GRIN2B variants predict children with the worst outcome in attention functioning among children exposed to low SES. Our findings, if replicated, could help in the identification of children with the highest risk and may prompt cost-effective preventive/treatment strategies.

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Eur Child Adolesc Psychiatry. 2015;24:S251-S252.

EPIDEMIOLOGY OF AUTISM SPECTRUM DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN A COMMUNITY-BASED POPULATION SAMPLE OF FIVE-YEAROLDS CHILDREN.

Saito M, Kaneda-Osato A, Tanaka M, et al.

Background and Aims: In Japan, local governments are performing pregnant infants health checkup as fundamental maternal-and-childhealth service. However, that cannot be diagnosing developmental diseases, such as ASD. Furthermore, it is increased that undiagnosed children fall into secondary obstacle because of maladjustment after entering school. So, we underwent five-year-olds health checkup in cooperation with a city, aimed to help early diagnosis and early intervention. We report the prevalence and comorbidity of ASD and ADHD in DSM-5 criteria, and the difference of clinical data between ASD, ADHD and healthy control in a community-based population sample of five-year-olds children.

Methods: Subjects are 954/1310 children to become 5-year-old in April 2012 to March 2013. After primary screening (ASSQ, ADHD-RS, SDQ and DCDQ evaluated by parents) was performed, 226 secondly developmental health examination subjects were selected. Finally 159 children and their parents participated the examination. They completed questionnaires (AQ, Conners-3, PSI and CSHQ) evaluated by parents and we examined their intelligence and motor function by WISC-4 and M-ABC2 excepting severe developmental disorder. After examination, a pediatrician and psychiatrists diagnosed neuro developmental disorder using DSM-5 criteria. We calculated the prevalence and comorbidity of ASD and ADHD. Clinical data were statistically analyzed by multiple comparisons with Bonferroni correlation between ASD, ADHD and hearty control groups.

Results: 29 children were diagnosed as ASD. The prevalence of ASD was 3.04 % (95 % confidence interval: 1.95-4.13) and the comorbidities of ASD were ADHD (41.4 %) and ID (41.4 %). 30 children were ADHD only. They didn't have any comorbidity. 20/29 ASDs had not been diagnosed with ASD until this health checkup. Furthermore, the utilization of support systems in ADHDs was only 3.4 %. Mean birth weight of ASDs was significantly lower than ADHD and control groups. Mean age of mother at birth of ADHDs was significantly younger than control group. In mean CSHQ scores, Night Wakings of ASDs was higher than ADHD group and Sleep Duration of ADHDs was significantly lower than control group. In mean Conners 3 scores, Anxiety of ASDs and ADHDs was significantly higher than control group respectively, Depression of ADHDs were significantly higher than control group. In mean PSI of child side scores, ASD group and ADHD group was significantly higher than control group respectively.

Conclusion: These findings suggest that ASD and ADHD in 5-yearolds have more difficulties than healthy children and 40 % of them haven't yet received little support.

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Eur Child Adolesc Psychiatry. 2015;24:S251.

ENVIRONMENTAL FACTORS ASSOCIATED WITH SUSPECTED ADHD IN PRESCHOOLERS USING A SCREENING TOOL (ADHD-RS-IV-P).

J. Marin-Méndez, C. Borra-Ruiz, M. Alvarez-Gomez, C. Soutullo.

Introduction: ADHD is a neuro developmental disorder usually first diagnosed in school-age children, but symptoms frequently start in preschoolers. Its etiology is complex and involves both genetic and environmental factors.

Objective: The goal is to estimate the association between prenatal, perinatal and postnatal environmental factors and suspected ADHD in a large preschooler population.

Methods: From sample of children 3 to<7 years old both teachers and parents filled the ADHD-RS-IV-Preschool version as a screening tool. We chose the 93rd percentile in the ADHS-RS-IV-P in inattention, hyperactivity/impulsivity and total score as threshold cut-off points for suspected ADHD. Parents also filled a questionnaire about prenatal, perinatal and postnatal factors. To evaluate the association between factors and suspected ADHD we used a Chi square analysis.

Results: We evaluated of 1426 children (49.6 % males) in schools in Navarra and La Rioja. The average age 4.70 (IC95 % 4.65-4.74) years old. Prevalence of Suspected ADHD was 3.8 % (IC95 % 2.7-4.8). As far as environmental factors, only nicotine use during pregnancy was associated with suspected ADHD (p = 0.015). Other factors were not significant (Low birth weight, fetal distress, prematurity, need for incubator and

alcohol consumption during pregnancy). Suspected ADHD was also associated with familiar history of ADHD (p = 0.008).
Discussion: ADHD prevalence in our preschool epidemiological sample is similar to that published internationally. ADHD is commonly diagnosed at age older than 7 years old. At this age, ADHD is associated with environmental factor as tobacco consumption during pregnancy or low birth weight. In our sample we could see that suspect of ADHD at preschooler age is associates with tobacco consumption too. The familiar history of ADHD is also associated, which highlight the value of genetic factors in ADHD disorder. Our results indicate that assessment and prevention of ADHD could be started at preschooler age (before 7 years old). The suspect ADHD at this age is associated to environmental factors and familiar history like other developmental ages. More epidemiological studies are needed to replicate these results.

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Eur Child Adolesc Psychiatry. 2015;24:1129-38.
WHERE ARE THE STRONGEST ASSOCIATIONS BETWEEN AUTISTIC TRAITS AND TRAITS OF ADHD? EVIDENCE FROM A COMMUNITY-BASED TWIN STUDY.
Taylor MJ, Charman T, Ronald A.
Autism spectrum conditions (ASC) and attention-deficit/hyperactivity disorder (ADHD) regularly co-occur. Twin studies increasingly indicate that these conditions may have overlapping genetic causes. Less is known about the degree to which specific autistic traits relate to specific behaviours characteristic of ADHD. We hence tested, using the classical twin design, whether specific dimensional autistic traits, including social difficulties, communication atypicalities and repetitive behaviours, would display differential degrees of aetiological overlap with specific traits of ADHD, including hyperactivity/impulsivity and inattention. Parents of approximately 4,000 pairs of 12-year-old twins completed the Childhood Autism Spectrum Test and Conners' Parent Rating Scale. These measures were divided into subscales corresponding to different types of autistic and ADHD behaviours. Twin model fitting suggested that the degree of genetic overlap was particularly strong between communication difficulties and traits of ADHD (genetic correlations = .47-.51), while repetitive behaviours and social difficulties showed moderate (genetic correlations = .12-.33) and modest (.05-.11) genetic overlap respectively. Environmental overlap was low across all subscales (correlations = .01-.23). These patterns were also apparent at the extremes of the general population, with communication difficulties showing the highest genetic overlap with traits of ADHD. These findings indicate that molecular genetic studies seeking to uncover the shared genetic basis of ASC and ADHD would benefit from taking a symptom-specific approach. Furthermore, they could also help to explain why studies of the communication abilities of individuals with ASC and ADHD have produced overlapping findings.

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Eur Child Adolesc Psychiatry. 2015;24:S277.
THE IMPORTANCE OF MATERNAL WEIGHT FOR THE OCCURENCE OF ADHD AND AUTISM IN CHILDREN.
Andersen C, Thomsen P, Lemcke S.
Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (autism) are neuropsychiatric disorders, which appears in childhood with serious consequences for the affected children and their parents. The causes of ADHD and autism are not clear, but a significant genetic component are believed to be involved probably in combination with environmental influences. Among the environmental impacts that have been discussed is a possible association between maternal weight during pregnancy and the development of ADHD and autism in children. There are a number of studies showing different results, and causal relationships related to endocrine disruptions or immunological effects are hypothesized. The project aims to investigate the hypothesis that there is an association between the mother's BMI before pregnancy or weight gain during pregnancy and the occurrence of ADHD or autism in children. Denmark host one of the largest birth cohorts in the world, The Danish National Birth Cohort (DNBC). Between 1996 and 2002 Danish-speaking pregnant women were invited to take part in the DNBC by their general practitioners at the first antenatal visit and a total of 101,042 women consented to participate. The data about the mothers weight gain used in this project were collected via telephone interviews during weeks 12 and 30 of pregnancy, and

when the child was 6 months old. The children in the cohort are now between 11 and 16 years, and via the Danish registers it is possible to identify those children, who have been diagnosed with ADHD or autism. An investigation of correlations between the mother's weight during pregnancy and later ADHD or autism in the child will be a unique study because of the size and quality of the data collected. It could also add important news to the international search for causes of ADHD and autism. The project is ongoing and results are expected to be ready in May 2015 Authors: Christina Hebsgaard Andersen Per Hove Thomsen Sanne Lemcke Institutions: Research Department, Regional Centre for Child and Adolescent Psychiatry, Aarhus University Hospital, Denmark.

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Eur Child Adolesc Psychiatry. 2015;24:S48.

US GUIDELINES AND UPDATES ON SELECT PSYCHIATRIC DISORDERS.

Palyo S, Ivanov I, Pleak RR, et al.

Given the increase in prevalence in certain psychiatric diagnoses, it is important to highlight a set of guidelines for treatment and the benefits and obstacles of implanting these into clinical practice. Certain psychiatric illnesses such as Attention Deficit-Hyperactive Disorder (ADHD), Gender Dysphoria, and Substance Abuse experience great media publicity, which further stigmatizes children and adolescents with these disorders. With the increase in diagnoses, there are more numerous studies, more social media discussion, and more hurdles to implementing the best practice treatments with adolescents with these psychiatric symptoms. This panel of prominent New York based child and adolescent psychiatrists will discuss these issues and recommendations. ADHD is a debilitating neurobehavioral disorder affecting children and adolescents. Symptoms impact children and their families beyond the classroom yet many discussions focus primarily on treatment with medication alone or as a last resort after other interventions are exhausted. Dr. Oatis will discuss his extensive work on ADHD and best practices of implementing appropriate interventions with adolescents as well as the family role. Adolescent substance abuse presents clinicians with ongoing challenges regarding timely diagnosis and effective treatments. Dr. Ivanov will review and discuss risk factors for adolescent substance abuse, early warning signs and the clinical aspects of recreational drug use, misuse of prescription medications and clinical guidelines for screening and treatment of adolescents with problem drug use. The management of gender dysphoria has evolved to include diagnosis and treatment of children and adolescents with discussions regarding social transitioning, pubertal suspension, and hormonal interventions. There are issues with integration of children into schools as well as extracurricular activities and even in medical clinics. This presentation by Dr. Pleak will review U.S. and international guidelines for treating youth with gender dysphoria published between 2012-2015. The discussion following the presentations, chaired by Dr. Palyo, will aim to highlight the selected psychiatric diagnosis, the guidelines and updates on implementing these recommendations into a clinical setting. Each presenter will speak for 20 min with a 30-min discussion.

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Eur Child Adolesc Psychiatry. 2015;24:1075-90.

TWO NOVEL CBTS FOR ADOLESCENTS WITH ADHD: THE VALUE OF PLANNING SKILLS.

Boyer BE, Geurts HM, Prins PJM, et al.

Adolescents with ADHD have planning problems, often affecting school- and social functioning. Evidence-based treatments for adolescents with ADHD are scarce and treatment drop-out rates are substantial. The effectiveness of two new, individual, short-term cognitive behavioral therapies (CBT) was investigated: One with an aim on improving planning skills and one solution-focused treatment (SFT) without such an aim. Motivational Interviewing elements were added to both treatments to enhance treatment compliance. In a multi-center randomized clinical trial, 159 adolescents (12-17 years) with ADHD were randomly assigned to one of both treatments. Pre-, post- and 3-month follow-up data were gathered on five domains: Parent-rated ADHD, planning problems and executive functioning (primary outcomes), neuropsychological measures of planning, comorbid symptoms, general functioning, and teacher measures. Attrition was low in both treatments (5 %). Adolescents improved significantly between pre- and post-test with large effect sizes on all

domains. Improvements remained stable or continued to improve from post-test to follow-up, also when controlling for medication use. Marginally significant differences were found in favor of the planning-focused treatment: parents and therapists evaluated this treatment more positively than SFT and the planning-focused treatment showed more reduction of parent-rated planning problems. Two new CBTs with integrated motivational components were feasible and attrition was low. ADHD symptoms and co-existing problems of the adolescents improved from pre-test to 3 months after treatment. As the planning-focused treatment was evaluated more positive and had marginal additional beneficial effects to SFT, especially planning-focused CBT seems promising to fill the gap in available treatments for adolescents with ADHD.

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Eur Child Adolesc Psychiatry. 2015;24:S247-S249.

EFFECTS OF ATOMOXETINE AND OROS-MPHON EXECUTIVE FUNCTIONS IN PATIENTS WITH COMBINED TYPE ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Ince TB, Karakaya E, Oztop D.

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Eur Child Adolesc Psychiatry. 2015.

ASSOCIATIONS BETWEEN HIGH CALLOUSGÇÔUNEMOTIONAL TRAITS AND QUALITY OF LIFE ACROSS YOUTHS WITH NON-CONDUCT DISORDER DIAGNOSES .

Herpers PCM, Klip H, Rommelse NNJ, et al.

Research regarding callous-unemotional (CU) traits in non-conduct disorder (CD) diagnoses is sparse. We investigated the presence of high CU traits and their associations with quality of life (QoL) in a clinically referred sample of youths with non-CD diagnoses. Parents of 1018 children referred to a child and adolescent psychiatric clinic and rated their child's CU traits and QoL. Experienced clinicians derived DSM-IV-TR diagnoses based on systematic clinical evaluations of these children. High CU traits compared to low CU traits were present in 38.5 % of the sample, and more often in boys than girls (69.4 vs. 30.6 %, p = .004), and were associated with more police contacts (12.2 vs. 3.5 %, p < .001). Logistic regression analyses revealed that those with diagnoses of autism spectrum disorder (odds ratio; OR = 1.61; 95 % CI 1.24-2.09; p < .001) and disruptive behavior disorder not otherwise specified/oppositional defiant disorder (OR = 4.98; 95 % CI 2.93-8.64; p < .001), but not attention-deficit/hyperactivity disorder (OR = 1.01; 95 % CI .79-1.31; p = .94), were more likely to have high than low CU traits. Those with anxiety/mood disorders were more likely to have low than high CU traits (OR = .59; 95 % CI .42-82; p = .002). In all diagnostic groups, high CU compared to low CU traits were associated with significantly lower QoL, while controlling for gender, age, and comorbidity. As such, high CU traits significantly modify QoL in non-CD disorders.

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Exp Clin Psychopharmacol. 2015.

AN APPLICATION OF ANALYZING THE TRAJECTORIES OF TWO DISORDERS: A PARALLEL PIECEWISE GROWTH MODEL OF SUBSTANCE USE AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Mamey MR, Barbosa-Leiker C, McPherson S, et al.

Researchers often want to examine 2 comorbid conditions simultaneously. One strategy to do so is through the use of parallel latent growth curve modeling (LGCM). This statistical technique allows for the simultaneous evaluation of 2 disorders to determine the explanations and predictors of change over time. Additionally, a piecewise model can help identify whether there are more than 2 growth processes within each disorder (e.g., during a clinical trial). A parallel piecewise LGCM was applied to self-reported attention-deficit/hyperactivity disorder (ADHD) and self-reported substance use symptoms in 303 adolescents enrolled in cognitive-behavioral therapy treatment for a substance use disorder and receiving either oral-methylphenidate or placebo for ADHD across 16 weeks. Assessing these 2 disorders concurrently allowed us to determine whether elevated levels of 1 disorder predicted elevated levels or increased risk of the other disorder. First, a piecewise growth model measured ADHD and substance use separately. Next, a parallel

piecewise LGCM was used to estimate the regressions across disorders to determine whether higher scores at baseline of the disorders (i.e., ADHD or substance use disorder) predicted rates of change in the related disorder. Finally, treatment was added to the model to predict change. While the analyses revealed no significant relationships across disorders, this study explains and applies a parallel piecewise growth model to examine the developmental processes of comorbid conditions over the course of a clinical trial. Strengths of piecewise and parallel LGCMs for other addictions researchers interested in examining dual processes over time are discussed.

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FASEB J. 2015 May;29:1960-72.

DEVELOPMENTAL PESTICIDE EXPOSURE REPRODUCES FEATURES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Richardson JR, Taylor MM, Shalat SL, et al.

Attention-deficit hyperactivity disorder (ADHD) is estimated to affect 8-12% of school-age children worldwide. ADHD is a complex disorder with significant genetic contributions. However, no single gene has been linked to a significant percentage of cases, suggesting that environmental factors may contribute to ADHD. Here, we used behavioral, molecular, and neurochemical techniques to characterize the effects of developmental exposure to the pyrethroid pesticide deltamethrin. We also used epidemiologic methods to determine whether there is an association between pyrethroid exposure and diagnosis of ADHD. Mice exposed to the pyrethroid pesticide deltamethrin during development exhibit several features reminiscent of ADHD, including elevated dopamine transporter (DAT) levels, hyperactivity, working memory and attention deficits, and impulsive-like behavior. Increased DAT and D1 dopamine receptor levels appear to be responsible for the behavioral deficits. Epidemiologic data reveal that children aged 6-15 with detectable levels of pyrethroid metabolites in their urine were more than twice as likely to be diagnosed with ADHD. Our epidemiologic finding, combined with the recapitulation of ADHD behavior in pesticide-treated mice, provides a mechanistic basis to suggest that developmental pyrethroid exposure is a risk factor for ADHD.

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Front Human Neurosci. 2015;9.

ATTENTION DEFICITS REVEALED BY PASSIVE AUDITORY CHANGE DETECTION FOR PURE TONES AND LEXICAL TONES IN ADHD CHILDREN.

Yang M-T, Hsu C-H, Yeh P-W, et al.

Inattention (IA) has been a major problem in children with attention deficit/hyperactivity disorder (ADHD), accounting for their behavioral and cognitive dysfunctions. However, there are at least three processing steps underlying attentional control for auditory change detection, namely pre-attentive change detection, involuntary attention orienting, and attention reorienting for further evaluation. This study aimed to examine whether children with ADHD would show deficits in any of these subcomponents by using mismatch negativity (MMN), P3a, and late discriminative negativity (LDN) as event-related potential (ERP) markers, under the passive auditory oddball paradigm. Two types of stimuliΓÇöpure tones and Mandarin lexical tonesΓÇöwere used to examine if the deficits were general across linguistic and non-linguistic domains. Participants included 15 native Mandarin-speaking children with ADHD and 16 age-matched controls (across groups, age ranged between 6 and 15 years). Two passive auditory oddball paradigms (lexical tones and pure tones) were applied. The pure tone oddball paradigm included a standard stimulus (1000 Hz, 80%) and two deviant stimuli (1015 and 1090 Hz, 10% each). The Mandarin lexical tone oddball paradigmΓÇÖs standard stimulus was /yi3/ (80%) and two deviant stimuli were /yi1/ and /yi2/ (10% each). The results showed no MMN difference, but did show attenuated P3a and enhanced LDN to the large deviants for both pure and lexical tone changes in the ADHD group. Correlation analysis showed that children with higher ADHD tendency, as indexed by parentsΓÇÖ and teachersΓÇÖ ratings on ADHD symptoms, showed less positive P3a amplitudes when responding to large lexical tone deviants. Thus, children with ADHD showed impaired auditory change detection for both pure tones and lexical tones in both involuntary attention switching, and

attention reorienting for further evaluation. These ERP markers may therefore be used for the evaluation of anti-ADHD drugs that aim to alleviate these dysfunctions.

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Frontiers in Molecular Neuroscience. 2015;8.

TELOMERE LENGTH IS HIGHLY INHERITED AND ASSOCIATED WITH HYPERACTIVITY-IMPULSIVITY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Costa DS, Rosa DVF, Barros AGA, et al.

Telomere length (TL) is highly heritable, and a shorter telomere at birth may increase the risk of age-related problems. Additionally, a shorter TL may represent a biomarker of chronic stress and has been associated with psychiatric disorders. However, no study has explored whether there is an association between TL and the symptoms of one of the most common neurodevelopmental disorders in childhood: Attention Deficit/Hyperactive Disorder (ADHD). We evaluated 61 (range, 6ΓÇô16 years) ADHD children and their parents between 2012 and 2014. TL was measured with a quantitative polymerase chain reaction method with telomere signal normalized to the signal from a single copy gene (36B4) to generate a T/S ratio. Family data was processed through a generalized estimated equations (GEE) model to determine the effect of parental TL on children TL. Inattentive and hyperactive-impulsive symptoms were also evaluated in relation to TL. For the first time, we found general heritability to be the major mechanism explaining interindividual TL variation in ADHD (father-child: 95% CI = 0.35/0.91, p < 0.001; mother-child: 95% CI = 0.38/0.74, p < 0.001). The hyperactive-impulsive dimension of ADHD was related with childrenΓÇÖs TL (r = ΓêÆ339, p = 0.008) and maternal TL (r = ΓêÆ264, p = 0.047), but not with paternal TL (p > 0.05). The ADHD inattentive dimension was not significant associated with TL in this study (p > 0.05). TL was shown to be a potential biomarker of the ADHD symptoms burden in families affected by this neurodevelopmental disorder. However, it is crucial that future studies investigating the rate of telomere attrition in relation to psychiatric problems to consider the strong determination of TL at birth by inheritance.

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Frontiers in Neuroanatomy. 2015;9.

ABNORMAL SURFACE MORPHOLOGY OF THE CENTRAL SULCUS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Li S, Wang S, Li X, et al.

The central sulcus (CS) divides the primary motor and somatosensory areas, and its three-dimensional (3D) anatomy reveals the structural changes of the sensorimotor regions. Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is associated with sensorimotor and executive function deficits. However, it is largely unknown whether the morphology of the CS alters due to inappropriate development in the ADHD brain. Here, we employed the sulcus-based morphometry approach to investigate the 3D morphology of the CS in 42 children whose ages spanned from 8.8 to 13.5 years (21 with ADHD and 21 controls). After automatic labeling of each CS, we computed seven regional shape metrics for each CS, including the global average length, average depth, maximum depth, average span, surface area, average cortical thickness, and local sulcal profile. We found that the average depth and maximum depth of the left CS as well as the average cortical thickness of bilateral CS in the ADHD group were significantly larger than those in the healthy children. Moreover, significant between-group differences in the sulcal profile had been found in middle sections of the CSs bilaterally, and these changes were positively correlated with the hyperactivity-impulsivity scores in the children with ADHD. Altogether, our results provide evidence for the abnormity of the CS anatomical morphology in children with ADHD due to the structural changes in the motor cortex, which significantly contribute to the clinical symptomatology of the disorder.

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Frontiers in Psychology. 2015 Jul;6.

COGNITIVE TRAINING FOR CHILDREN WITH ADHD: A RANDOMIZED CONTROLLED TRIAL OF COGMED WORKING MEMORY TRAINING AND 'PAYING ATTENTION IN CLASS'.

van der Donk M, Hiemstra-Beernink AC, Tjeenk-Kalff A, et al.

The goal of this randomized controlled trial was to replicate and extend previous studies of Cogmed Working Memory Training (CWMT) in children with Attention-deficit/ hyperactivity disorder (ADHD). While a large proportion of children with ADHD suffer from academic difficulties, only few previous efficacy studies have taken into account long term academic outcome measures. So far, results regarding academic outcome measures have been inconsistent. Hundred and two children with ADHD between the age of 8 and 12 years (both medicated and medication naïve) participated in current randomized controlled trial. Children were randomly assigned to CWMT or a new active combined working memory- and executive function compensatory training called 'Paying Attention in Class.' Primary outcome measures were neurocognitive functioning and academic performance. Secondary outcome measures contained ratings of behavior in class, behavior problems, and quality of life. Assessment took place before, directly after and 6 months after treatment. Results showed only one replicated treatment effect on visual spatial working memory in favor of CWMT. Effects of time were found for broad neurocognitive measures, supported by parent and teacher ratings. However, no treatment or time effects were found for the measures of academic performance, behavior in class or quality of life. We suggest that methodological and non-specific treatment factors should be taken into account when interpreting current findings. Future trials with well-blinded measures and a third 'no treatment' control group are needed before cognitive training can be supported as an evidence-based treatment of ADHD. Future research should put more effort into investigating why, how and for whom cognitive training is effective as this would also potentially lead to improved intervention- and study designs.

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Inf Process Med Imaging. 2015;24:113-24.

BOOTSTRAPPED PERMUTATION TEST FOR MULTIRESPONSE INFERENCE ON BRAIN BEHAVIOR ASSOCIATIONS.

Ng B, Poline JB, Thirion B, et al.

Despite that diagnosis of neurological disorders commonly involves a collection of behavioral assessments, most neuroimaging studies investigating the associations between brain and behavior largely analyze each behavioral measure in isolation. To jointly model multiple behavioral scores, sparse multiresponse regression (SMR) is often used. However, directly applying SMR without statistically controlling for false positives could result in many spurious findings. For models, such as SMR, where the distribution of the model parameters is unknown, permutation test and stability selection are typically used to control for false positives. In this paper, we present another technique for inferring statistically significant features from models with unknown parameter distribution. We refer to this technique as bootstrapped permutation test (BPT), which uses Studentized statistics to exploit the intuition that the variability in parameter estimates associated with relevant features would likely be higher with responses permuted. On synthetic data, we show that BPT provides higher sensitivity in identifying relevant features from the SMR model than permutation test and stability selection, while retaining strong control on the false positive rate. We further apply BPT to study the associations between brain connectivity estimated from pseudo-rest fMRI data of 1139 fourteen year olds and behavioral measures related to ADHD. Significant connections are found between brain networks known to be implicated in the behavioral tasks involved. Moreover, we validate the identified connections by fitting a regression model on pseudo-rest data with only those connections and applying this model on resting state fMRI data of 337 left out subjects to predict their behavioral scores. The predicted scores significantly correlate with the actual scores, hence verifying the behavioral relevance of the found connections.

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Int J Orthod Milwaukee. 2015;26:21-24.

PSYCHO-NEUROLOGICAL STATUS IN CHILDREN WITH MALOCCLUSIONS AND MUSCLE PRESSURE HABITS.

Rubleva IA, Persin LS, Slabkovskaya AB, et al.

Non-nutritive sucking behaviors such as finger- and tongue-sucking, tongue thrust, lips- or cheek-sucking, nail-, lip- or tongue-biting and other pressure habits represent risk factors for malocclusion. The association between psycho-neurological disorders and different types of malocclusion in children with sucking habits was long studied. During neurological examination, many children with sucking habits are diagnosed as Minimal Cerebral Dysfunction or Attention Deficit Hyperactivity Disorder (ADHD) bearers. The aim of this study is to assess the psycho-neurological status and motor disorders in children with malocclusion and normal occlusion. 135 children, aged between 8 and 12 years old, were examined, 42 children with normal occlusion and 93 children with different types of malocclusion. Besides clinical examination, all children were studied by the following psychoneurological methods: 1) Parent's Questionnaire, 2) Diagnostic interview Kiddie-Sads 3) Physical and Neurological Exam for Subtle Signs and 4) stabilometric tests. This study shows as in presence of dentofacial anomalies, pressure habits, ADHD reports significant effects on the functional state of the motor system: increases are noted in all basic parameters of statokinesiograms (crossed distance, sway area and ellipse surface), which lead to increased physiologic energy costs to maintain the vertical position of the body.

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Int J Psychiatry Med. 2015;49:19-33.

SELF-IMAGE PROFILE IN CHILDREN AND ADOLESCENTS WITH ATTENTION DEFICIT/ HYPERACTIVITY DISORDER AND THE QUALITY OF LIFE IN THEIR PARENTS.

Gormez V, Forbes FC.

OBJECTIVE: We explored the impact of clinical response to treatment for Attention Deficit/Hyperactivity Disorder (ADHD) in children and adolescents on the subsequent changes in their self-image profile, the quality of life of their parents, and its effect on socio-demographic variables.

METHOD: Conners Rating Scales for Parents (CPRS-R) and for Teachers (CTRS-R) completed at the time of entry to the service were repeated to measure clinical response to treatment; the Self-image Profiles for Children (SIP-C) and Adolescents (SIP-A), the World Health Organization Quality of Life (WHOQoL) questionnaire and postcode data were used to evaluate other domains.

RESULTS: Data was collected for 53 boys (84%) and 10 girls (16%) with current mean age 11.5 years. Four-fifths (51/63) received pharmacological treatment and all parents were offered group parent training program. The only subscale in CPRS-R to show significance was the ADHD Index. The CTRS-R demonstrated statistically significant improvement ($p < 0.01$) in most subscales. On the Self-image Profile, children reported themselves as more Kind ($p < 0.012$), more Helpful ($p < 0.038$) and less Bossy ($p < 0.047$). Comparison of pre- and post-treatment scores on QoL revealed no significant changes; however, correlations of QoL responses against CPRS post-treatment revealed significant negative relationships in a number of instances. Parents living in less deprived areas felt their lives were more meaningful and less likely felt negatively about themselves ($p = 0.04$, $N = 26$, $rho = 0.405$).

CONCLUSION: Clinical improvement in ADHD symptoms was positively correlated with some improvement in the Self-image Profile of children and adolescents, but its impact on the QoL in parents was limited.

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J Affect Disord. 2015 May;177:28-35.

SUICIDAL IDEATION AND MENTAL HEALTH DISORDERS IN YOUNG SCHOOL CHILDREN ACROSS EUROPE.

Kovess-Masfety V, Pilowsky DJ, Goelitz D, et al.

INTRODUCTION: The aim of this study is to measure the prevalence of suicidal ideation and thoughts of death in elementary school children in a European survey and to determine the associated socio-demographic and clinical factors.

METHODS: Data refer to children aged 6-12 (N=7062) from Italy, Turkey, Romania, Bulgaria, Lithuania, Germany, and the Netherlands randomly selected in primary schools. Suicidal thoughts and death ideation

were measured using a computerized pictorial diagnostic tool from the Dominic Interactive (DI) completed by the children. The Strengths and Difficulties Questionnaire (SDQ) was administrated to teachers and parents along with a socio-demographic questionnaire.
RESULTS: Suicidal ideation was present in 16.96% of the sample (from 9.9 in Italy to 26.84 in Germany), death thoughts by 21.93% (from 7.71% in Italy to 32.78 in Germany). SI and DT were more frequent in single-parent families and large families. Externalizing disorders were strongly correlated with SI and DT after controlling for other factors and this was true for internalizing disorders only when reported by the children.
CONCLUSION: Recognizing suicidal ideation in young children may be recommended as part of preventive strategies such as screening in the context of the presence of any mental health problems whether externalizing or internalizing.

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J Cutan Med Surg. 2015 Mar;19:121-24.

DISEASES OF ABNORMAL SENSITIVITY TO COLD IN CHILDREN ON PSYCHOSTIMULANT DRUGS.

Coulombe J, Powell J, Hatami A, et al.

BACKGROUND: Oral psychostimulant (PS) drugs, the pharmacologic treatment of choice for attention-deficit/hyperactivity disorder (ADHD), have been associated with diseases of abnormal sensitivity to cold (DASC) such as Raynaud phenomenon and acrocyanosis.
OBJECTIVES: In a cohort of pediatric patients with DASC, we sought to identify prevalence and clinical features of patients on PS drugs.
METHODS: A 6-year retrospective chart review (2005-2011) of Ste-Justine University Hospital Center DASC patients with and without exposure to PS drugs was performed. Clinical data were analyzed with descriptive statistical methods.
RESULTS: Of 43 patients with DASC, 11 (25%) were exposed to PS drugs. In this group males were overrepresented, there was no evidence of collagen vascular diseases, serologic findings were not significant and the mean duration of PS intake was of 2.5 years. DASC age of onset was similar in both exposed and nonexposed patients. The incidence of more than one DASC type was greater in teenager patients with a positive family history of autoimmune and/or collagen vascular diseases.
LIMITATIONS: This study is limited by its small population size, short follow-up period and its retrospective nature.
CONCLUSION: Physicians should be aware of PS drugs as possible triggers for DASC.

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J Popul ther Clin Pharmacol. 2015;22:e59-e67.

MEDICATIONS USED IN THE TREATMENT OF DISRUPTIVE BEHAVIOR IN CHILDREN WITH FASD--A GUIDE.

Ozsarfati J, Koren G.

The majority of children with FASD suffer from disruptive behaviors and most of them need medications to modify these behaviors. The objective of this review is to familiarize professionals caring for children with FASD with stimulants and other drugs for ADHD, and the second generation antipsychotic risperidone - for aggressive and defiant behaviors

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J Psychiatr Pract. 2015 Jan;21:26-36.

USE OF ANTIPSYCHOTIC MEDICATIONS IN PEDIATRIC AND YOUNG ADULT POPULATIONS: FUTURE RESEARCH NEEDS.

Christian RB, Gaynes BN, Saavedra LM, et al.

The use of antipsychotics, particularly second generation antipsychotics, among children and adolescents has increased markedly during the past 20 years. Existing evidence gaps make this practice controversial and hinder treatment decision-making. This article describes and prioritizes future research needs regarding antipsychotic treatment in youth, focusing on within-class and between-class drug comparisons with regard to key population subgroups, efficacy and effectiveness outcomes, and adverse event outcomes. Using as

a foundation a recent systematic review of antipsychotic treatment among youth, which was completed by a different Evidence-based Practice Center, we worked with a diverse group of 12 stakeholders representing researchers, funders, health care providers, patients, and families to identify and prioritize research needs. From an initial list of 16 evidence gaps, we enumerated 6 high-priority research needs: 1) long-term comparative effectiveness across all psychiatric disorders; 2) comparative long-term risks of adverse outcomes; 3) short-term risks of adverse events; 4) differentials of efficacy, effectiveness, and safety for population subgroups; 5) comparative effectiveness among those with attention-deficit/hyperactivity disorder and disruptive behavior disorders and common comorbidities; 6) comparative effectiveness among those with bipolar disorder and common comorbidities. In this article, we describe these future research needs in detail and discuss study designs that could be used to address them.

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J Psychoactive Drugs. 2015 Apr;47:140-48.

NOVEL PSYCHOACTIVE SUBSTANCE AND OTHER DRUG USE BY YOUNG ADULTS IN WESTERN AUSTRALIA.

Goggin LS, Gately N, Bridle RI.

There is a lack of information regarding the use of novel psychoactive substances (NPS) in Western Australia. The aim of this study was to pilot-test an online survey to obtain data on the prevalence of NPS and other drug use by young Western Australians aged between 18 and 35 years. The Young Adult Drug and Alcohol Survey (YADAS) was a questionnaire deployed online for a period of six months. Participants were recruited via a combined targeted sampling and snowball methodology. There were 472 valid responses. Overall lifetime use of NPS was relatively high (17.6%), while use in the last year was lower (6.6%). These proportions were comparable to that of cocaine use. The most popular NPS were the synthetic cannabinoids. The proportions of respondents drinking alcohol at risky levels, mixing alcohol with energy drinks, and using pharmaceuticals such as ADHD medications for non-medical reasons were high. The YADAS is the first survey to ascertain the prevalence of use of numerous types of NPS in a large sample of young Western Australian adults. The utilization of an online survey methodology yielded valid results as compared to more intensive surveys, and enables researchers greater flexibility in being able to capture current trends.

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Journal of Attention Disorders. 2015 Aug;19:666-77.

AN EMPIRICAL EVALUATION OF ADHD COACHING IN COLLEGE STUDENTS.

Prevatt F, Yelland S.

Objective: This study evaluated a program for ADHD coaching in a sample of college students.

Method: ADHD coaching was conducted with 148 college students over a 5-year period. The theoretical orientation combined cognitive-behavioral therapy with psychoeducational techniques. Executive functioning served as a way of viewing both initial problem areas and outcomes.

Results: Clients who received an 8-week coaching program showed significant improvement in all 10 areas of study and learning strategies, on self-esteem, and on measures of symptom distress and satisfaction with school and work. These results were consistent across different semesters and time of semester, and with a variety of different coaches, all of whom were novice coaches.

Conclusion: This study provides important preliminary information about ADHD coaching, including coaching structure, processes, efficacy, and correlates of positive outcomes. Additional evaluations utilizing a randomized controlled design are needed.

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J Behav Ther Exp Psychiatry. 2015 Sep;48:27-32.

MIXING APPLES WITH ORANGES: VISUAL ATTENTION DEFICITS IN SCHIZOPHRENIA.

Caprile C, Cuevas-Esteban J, Ochoa S, et al.

Background & objectives: Patients with schizophrenia usually present cognitive deficits. We investigated possible anomalies at filtering out irrelevant visual information in this psychiatric disorder. Associations between these anomalies and positive and/or negative symptomatology were also addressed.

Methods: A group of individuals with schizophrenia and a control group of healthy adults performed a Garner task. In Experiment 1, participants had to rapidly classify visual stimuli according to their colour while ignoring their shape. These two perceptual dimensions are reported to be “separable” by visual selective attention. In Experiment 2, participants classified the width of other visual stimuli while trying to ignore their height. These two visual dimensions are considered as being “integral” and cannot be attended separately.

Results: While healthy perceivers were, in Experiment 1, able to exclusively respond to colour, an irrelevant variation in shape increased colour-based reaction times (RTs) in the group of patients. In Experiment 2, RTs when classifying width increased in both groups as a consequence of perceiving a variation in the irrelevant dimension (height). However, this interfering effect was larger in the group of schizophrenic patients than in the control group. Further analyses revealed that these alterations in filtering out irrelevant visual information correlated with positive symptoms in PANSS scale. Limitations: A possible limitation of the study is the relatively small sample.

Conclusions: Our findings suggest the presence of attention deficits in filtering out irrelevant visual information in schizophrenia that could be related to positive symptomatology.

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Journal of Child Psychology and Psychiatry. 2015 Sep;56:949-57.

EARLY IDENTIFICATION OF ADHD RISK VIA INFANT TEMPERAMENT AND EMOTION REGULATION: A PILOT STUDY.

Sullivan EL, Holton KF, Nousen EK, et al.

Background: Attention deficit hyperactivity disorder (ADHD) is theorized to have temperamental precursors early in life. These are difficult to identify because many core features of ADHD, such as breakdowns in executive function and self-control, involve psychological and neural systems that are too immature to reliably show dysfunction in early life. ADHD also involves emotional dysregulation, and these temperamental features appear earlier as well. Here, we report a first attempt to utilize indices of emotional regulation to identify ADHD-related liability in infancy.

Methods: Fifty women were recruited in the 2nd trimester of pregnancy, with overselection for high parental ADHD symptoms. Measures of maternal body mass index, nutrition, substance use, stress, and mood were examined during pregnancy as potential confounds. Offspring were evaluated at 6 months of age using LABTAB procedures designed to elicit fear, anger, and regulatory behavior. Mothers completed the Infant Behavior Questionnaire about their child's temperament.

Results: After control for associated covariates, including maternal depression and prenatal stress, family history of ADHD was associated with measures of anger/irritability, including infant negative vocalizations during the arm restraint task ($p = .004$), and maternal ratings of infant distress to limitations ($p = .036$). In the regulation domain, familial ADHD was associated with less parent-oriented attention seeking during the still face procedure ($p < .001$), but this was not echoed in the maternal ratings of recovery from distress.

Conclusions: Affective response at 6 months of age may identify infants with familial history of ADHD, providing an early indicator of ADHD liability. These preliminary results provide a foundation for further studies and will be amplified by enlarging this cohort and following participants longitudinally to evaluate ADHD outcomes.

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Journal of Child Psychology and Psychiatry. 2015 Sep;56:966-75.

PRESCHOOL HYPERACTIVITY IS ASSOCIATED WITH LONG-TERM ECONOMIC BURDEN: EVIDENCE FROM A LONGITUDINAL HEALTH ECONOMIC ANALYSIS OF COSTS INCURRED ACROSS CHILDHOOD, ADOLESCENCE AND YOUNG ADULTHOOD.

Chorozoglou M, Smith E, Koerting J, et al.

Background: Preschool hyperactivity is an early risk factor for adult mental health problems and criminality. Little is known about; (a) the patterns of long-term service costs associated with this behavioural marker in the general population and (b) the specific factors predicting hyperactivity-related costs. We undertook a prospective study investigating associations between preschool hyperactivity and average individual annual service costs up to late adolescent and young adulthood.

Methods: One-hundred and seventy individuals rated as hyperactive by their parents and 88 nonhyperactive controls were identified from a community sample of 4,215 three years olds. Baseline information about behaviour/emotional problems and background characteristics were collected. At follow-up (when individuals were aged between 14 and 25 years) information was obtained on service use, and associated costs since the age of three. Based on this information we calculated the average cost per annum incurred by each individual.

Results: Compared to controls, preschoolers with hyperactivity had 17.6 times higher average costs per annum across domains (apart from nonmental health costs). These were £562 for each hyperactive individual compared with £30 for controls. Average annual costs decreased as a function of age, with higher costs incurred at younger ages. The effects of hyperactivity remained significant when other baseline factors were added to the model. Effects were fully mediated by later psychiatric morbidity. When the hyperactive group were examined separately, costs were consistently predicted by male gender and, for some cost codes, by conduct problems.

Conclusions: Preventative approaches targeting early hyperactivity may be of value. Services should be targeted towards high-risk individuals with careful consideration given to the cost-to-benefit trade-off of early intervention strategies.

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Journal of Child Psychology and Psychiatry. 2015 Sep;56:958-65.

LATENT PROFILE ANALYSIS OF NEUROPSYCHOLOGICAL MEASURES TO DETERMINE PRESCHOOLERS' RISK FOR ADHD.

Rajendran K, O'Neill S, Marks DJ, et al.

Background: Hyperactive/Inattentive preschool children show clear evidence of neuropsychological dysfunction. We examined whether patterns and severity of test scores could reliably identify subgroups of preschoolers with differential risk for ADHD during school-age.

Method: Typically developing (TD: n = 76) and Hyperactive/Inattentive (HI: n = 138) 3–4 year olds were assessed annually for 6 years (T1–T6). Latent profile analysis (LPA) was used to form subgroups among the HI group based on objective/neuropsychological measures (NEPSY, Actigraph and Continuous Performance Test). Logistic regression assessed the predictive validity of empirically formed subgroups at risk for ADHD diagnosis relative to the TD group and to each other from T2 to T6.

Results: Latent profile analysis yielded two subgroups of HI preschoolers: (a) selectively weak Attention/Executive functions, and (b) pervasive neuropsychological dysfunction across all measures. Both subgroups were more likely to have ADHD at all follow-up time-points relative to the TD group (OR range: 11.29–86.32), but there were no significant differences between the LPA-formed subgroups of HI children at any time-point.

Conclusions: Objective/neuropsychological measures distinguish HI preschoolers from their TD peers, but patterns and severity of neuropsychological dysfunction do not predict risk for ADHD during school-age. We hypothesize that trajectories in at-risk children are influenced by subsequent environmental and neurodevelopmental factors, raising the possibility that they are amenable to early intervention.

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Journal of Clinical Child and Adolescent Psychology. 2015 Sep;44:787-99.

PARENTING BEHAVIOR MEDIATES THE INTERGENERATIONAL ASSOCIATION OF PARENT AND CHILD OFFSPRING ADHD SYMPTOMS.

Tung I, Brammer WA, Li JJ, et al.

Although there are likely to be multiple mechanisms underlying parent attention-deficit/hyperactivity disorder (ADHD) symptoms as a key risk factor for offspring ADHD, potential explanatory factors have yet to be reliably identified. Given that parent ADHD symptoms independently predict parenting behavior and child ADHD symptoms, we tested whether individual differences in multiple dimensions of positive and negative parenting behavior (i.e., corporal punishment, inconsistent discipline, positive parenting behavior, observed negative talk, and observed praise) mediated the association between parental and offspring ADHD. We used a prospective design that featured predictors (i.e., parent ADHD symptoms) and mediators (i.e., parenting behavior) that temporally preceded the outcome (i.e., offspring ADHD symptoms). Using a well-characterized sample of 120 children with and without ADHD (ages 5–10 at Wave 1, 7–12 at Wave 2) and their biological parents, we examined multimethod (i.e., observed, self-report) measures of positive and negative parenting behavior as simultaneous mediators of the association of Wave 1 parent and Wave 2 offspring ADHD symptoms. Using a multiple mediation framework, consisting of rigorous bootstrapping procedures and controlling for parent depression, child's baseline ADHD and oppositional defiant disorder, and child's age, corporal punishment significantly and uniquely mediated the association of Wave 1 parent ADHD symptoms and Wave 2 offspring ADHD. We consider the role of parenting behavior in the intergenerational transmission of ADHD as well as implications of these findings for the intervention and prevention of childhood ADHD.

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Journal of Clinical Child and Adolescent Psychology. 2015 Sep;44:859-74.

ADHD SUBTYPE DIFFERENCES IN REINFORCEMENT SENSITIVITY AND VISUOSPATIAL WORKING MEMORY.

Dovis S, van der Oord S, Wiers RW, et al.

Both cognitive and motivational deficits are thought to give rise to the problems in the combined (ADHD-C) and inattentive subtype (ADHD-I) of attention-deficit hyperactivity disorder (ADHD). In both subtypes one of the most prominent cognitive weaknesses appears to be in visuospatial working memory (WM), which is composed of short-term memory (STM) and a central executive (CE). In children with ADHD-C, both STM and the CE seem impaired, and together with motivational impairments, give rise to their deficits in visuospatial WM. In children with ADHD-I, no studies investigated these WM components and their interplay with motivational impairments. Effects of a standard (feedback only) and a high level of reinforcement (feedback + 10 euros) on visuospatial WM-, STM-, and CE performance were examined in 27 children with ADHD-I (restrictive-subtype), 70 children with ADHD-C, and 40 typically developing controls (aged 9–12). In both ADHD-subtypes CE and WM performance was worse than in controls. STM performance of children with ADHD-I was, in contrast to that of children with ADHD-C, not different from controls. STM and WM performance was worse in ADHD-C than in ADHD-I, whereas CE-related performance did not differ. High reinforcement improved STM and WM performance in both subtypes but not in controls. This improvement was equally pronounced in both subtypes. High reinforcement did not improve CE-related performance. Both subtypes have equally pronounced motivational deficits, which have detrimental effects on their visuospatial STM and WM performance. In contrast to children with ADHD-C, children with ADHD-I seem unimpaired on visuospatial STM; only an impaired CE and motivational impairments give rise to their deficits in visuospatial WM.

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Journal of Inherited Metabolic Disease. 2015;38:S185.

ATTENTION DEFICIT-HYPERACTIVITY DISORDER AS A DOMINANT CLINICAL PRESENTATION IN OCTN2 DEFICIENCY.

Lamhonwah AM, Baric I, Lamhonwah J, et al.

Background: We report a novel OCTN2 mutation (novel in-frame deletion (p.T440-Y449) in a patient with ADHD.

Case report: This boy presented with Attention-Deficit/Hyperactivity Disorder (ADHD) at 3 years and at 8 1/2 years was notably hyperactive in the absence of hypoglycemic hypoketotic coma and had myopathy, cardiomyopathy, and very low serum carnitine. Formal psychological evaluation with the standardized ADHD Test, gave a score consistent with severe ADHD. He had elevated aminotransferases. His sister died of sudden infant death. On clinical suspicion of OCTN2 deficiency, he was treated with high dose oral L-carnitine (100 mg/kg/day) which led to significant improvements in his cardiomyopathy, exercise intolerance and behavioural problems. Studies and
Results: [3H]-L-carnitine uptake studies in his cultured skin fibroblasts confirmed OCTN2 deficiency. Molecular analysis of SLC22A5 gene in genomic DNA from the proband and his parents by PCR and Sanger sequencing revealed heterozygosity for a premature stop codon (p.R282X) (paternal inheritance) and a novel in-frame deletion (p.T440- Y449) (maternal inheritance) in a highly conserved putative caveolin-1 binding site. Immunoblot of fibroblasts with antimOctn2 antibody revealed a reduced truncated protein.
Conclusion: L-carnitine therapy not only reverses the myopathy and cardiomyopathy of OCTN2 deficiency, but may improve the neurological phenotype including ADHD.

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Journal of Inherited Metabolic Disease. 2015;38:S118.

A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF SAPROPTERIN TO TREAT SYMPTOMS OF ADHD AND EXECUTIVE DYSFUNCTION IN CHILDREN AND ADOLESCENTS WITH PHENYLKETONURIA.

Cohen-Pfeffer JL, Grant M, McCandless SM, et al.

Introduction: Children with phenylketonuria (PKU) may exhibit symptoms of neurocognitive impairment.
Methods: A sub-analysis was performed on pediatric subjects (< 18 years) with PKU from a larger cohort to determine the impact of sapropterin therapy on neurocognitive deficits. Subjects were randomized to blinded treatment with sapropterin (N = 43) or placebo (N = 43) for 13 weeks. Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Compos i te (GEC), Behavioral Regulation Index (BRI), and Metacognition Index (MI) T-scores were assessed at weeks 13 and 26. Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) was obtained at screening and weeks 4, 8, 13, and 26.
Results: For subjects on sapropterin after 13 weeks, average blood phenylalanine decreased from baseline of 501 -¦ 305 mmol/L to 394 -¦ 344 mmol/L. The least squares (LS) mean change differences from baseline between the sapropterin-treatment and placebo groups were significant for BRIEFGEC (p=0.04) and BRIEF-MI (p=0.04). The LS mean change differences in ADHD-RS from baseline between the sapropterin-treatment and placebo groups were significant for ADHD-RS Total Score (p=0.01), Hyperactivity/ Impulsivity (p=0.02), and Inattention (p=0.04).
Conclusions: In a double-blind, placebo controlled study, sapropterin use was associated with neurocognitive improvements in children and adolescents compared to placebo. Conflict of Interest declared.

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Journal of Neuropsychology. 2015 Sep;9:258-70.

EXECUTIVE FUNCTIONS IN PRESCHOOLERS WITH ADHD, ODD, AND COMORBID ADHD-ODD: EVIDENCE FROM ECOLOGICAL AND PERFORMANCE-BASED MEASURES.

Ezpeleta L, Granero R.

Executive functioning in 3-year-old preschoolers with attention-deficit hyperactivity disorder (ADHD), oppositional-defiant disorder (ODD), comorbid ADHD+ODD, and children without any of these conditions (control group) was examined. A community sample including 622 children was diagnosed using a diagnostic interview following DSM-IV criteria, and assessed using the Behavior Rating Inventory of Executive Function Preschool version (BRIEF-P) and the Kiddie-Conners' Continuous Performance Test. The children diagnosed with ADHD showed the poorest executive function (EF) profile in comparison with controls, and were closely followed up in this respect by the comorbid ADHD+ODD children. The ADHD and comorbid groups presented similar executive difficulties. The ODD group obtained mean scores statistically equal to those of controls in EF. These findings suggest that, in preschoolers, executive functioning deficits assessed with a performance-based measure or with behavioural descriptions are specific to children with ADHD, in

comparison with those with ODD. This study contributes knowledge about EFs in two prevalent and comorbid disorders in preschool children, ADHD and ODD, knowledge that can help our understanding of specific deficits and the design of specific early intervention initiatives.

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J Psychiatr Res. 2015 Sep;68:217-25.

ELUCIDATING X CHROMOSOME INFLUENCES ON ATTENTION DEFICIT HYPERACTIVITY DISORDER AND EXECUTIVE FUNCTION.

Green T, Bade Shrestha S, Chromik LC, et al.

Objective: To identify distinct behavioral and cognitive profiles associated with ADHD in Turner syndrome (TS), relative to idiopathic ADHD and neurotypical controls, in order to elucidate X-linked influences contributing to ADHD.

Methods: We used a multilevel-model approach to compare 49 girls with TS to 37 neurotypical females, aged 5–12, on established measures of behavior (BASC-2) and neurocognitive function (NEPSY). We further compared girls with TS to BASC-2 and NEPSY age-matched reference data obtained from children with idiopathic ADHD.

Results: Within the TS group, 51% scored at or above the "at-risk" range for ADHD-associated behaviors on the BASC-2 (TS/+ADHD). The BASC-2 behavioral profile in this TS/+ADHD-subgroup was comparable to a reference group of boys with ADHD with respect to attentional problems and hyperactivity. However, the TS/+ADHD-subgroup had significantly higher hyperactivity scores relative to a reference sample of girls with ADHD ($p = 0.016$). The behavioral profile in TS was associated with significantly lower attention and executive function scores on the NEPSY relative to neurotypical controls ($p = 0.015$); but was comparable to scores from a reference sample of children with idiopathic ADHD. Deficits in attention and executive function were not observed in girls with TS having low levels of ADHD-associated behavior (TS/-ADHD).

Conclusions: ADHD-associated behavioral and cognitive problems in TS are prevalent and comparable in severity to those found in children with idiopathic ADHD. The ADHD phenotype in TS also appears relatively independent of cognitive features typically associated with TS, like visuospatial weaknesses. These findings suggest that X-linked haploinsufficiency and downstream biological effects contribute to increased risk for ADHD.

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Journal of the American Academy of Child & Adolescent Psychiatry. 2015 Sep;54:745-52.

A POPULATION-BASED IMAGING GENETICS STUDY OF INATTENTION/HYPERACTIVITY: BASAL GANGLIA AND GENETIC PATHWAYS.

Mous SE, Hammerschlag AR, Polderman TJC, et al.

Objective: Although attention-deficit/hyperactivity disorder (ADHD) is 1 of the most common neurodevelopmental disorders, little is known about the neurobiology. Clinical studies suggest basal ganglia morphology plays a role. Furthermore, hyperactivity/impulsivity symptoms have recently been linked to genetic pathways involved in dopamine/norepinephrine and serotonin neurotransmission and neuritic outgrowth. We aimed to assess the association between ADHD symptoms, basal ganglia volume, and the 3 proposed genetic pathways in a pediatric population-based sample. With this, we aimed to investigate the generalizability of earlier clinical findings to the general population.

Method: This study included a population-based sample of 1,871 children with data on ADHD symptoms and genetic data, and 344 children with additional neuroimaging data. Regression analyses between ADHD symptom severity and volumetric data of the basal ganglia were performed. Also, gene-set analyses investigating the association between both ADHD symptom severity and basal ganglia volume with the dopamine/norepinephrine, serotonin, and neuritic outgrowth pathways were performed.

Results: More inattention and hyperactivity/impulsivity symptoms were associated with a smaller volume of the putamen (ß = –0.13, p = .034), which was regarded as trend-level after correction for multiple testing. Stratified analyses showed a stronger putamen–hyperactivity association in children with clinical scores,

although a similar trend was visible in the nonclinical subsample. The genetic pathways were not related to either ADHD symptoms or basal ganglia volume.
Conclusion: ADHD symptoms were marginally related to putamen volume in our population-based sample. We found no evidence for a role of dopamine/norepinephrine, serotonin, or neuritic outgrowth genetic pathways in ADHD symptom severity.

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Molecular Autism. 2015;6.
DISTINCT EFFECTS OF ASD AND ADHD SYMPTOMS ON REWARD ANTICIPATION IN PARTICIPANTS WITH ADHD, THEIR UNAFFECTED SIBLINGS AND HEALTHY CONTROLS: A CROSS-SECTIONAL STUDY.
Van Dongen EV, von RD, O'Dwyer L, et al.
Background: Autism spectrum disorder (ASD) traits are continuously distributed throughout the population, and ASD symptoms are also frequently observed in patients with attention-deficit/hyperactivity disorder (ADHD). Both ASD and ADHD have been linked to alterations in reward-related neural processing. However, whether both symptom domains interact and/or have distinct effects on reward processing in healthy and ADHD populations is currently unknown.
Method: We examined how variance in ASD and ADHD symptoms in individuals with ADHD and healthy participants was related to the behavioural and neural response to reward during a monetary incentive delay (MID) task. Participants (mean age: 17.7 years, range: 10-28 years) from the NeuroIMAGE study with a confirmed diagnosis of ADHD (n = 136), their unaffected siblings (n = 83), as well as healthy controls (n = 105) performed an MID task in a magnetic resonance imaging (MRI) scanner. ASD and ADHD symptom scores were used as predictors of the neural response to reward anticipation and reward receipt. Behavioural responses were modeled using linear mixed models; neural responses were analysed using FMRIB's Software Library (FSL) proprietary mixed effects analysis (FLAMEO).
Result: ASD and ADHD symptoms were associated with alterations in BOLD activity during reward anticipation, but not reward receipt. Specifically, ASD scores were related to increased insular activity during reward anticipation across the sample. No interaction was found between this effect and the presence of ADHD, suggesting that ASD symptoms had no differential effect in ADHD and healthy populations. ADHD symptom scores were associated with reduced dorsolateral prefrontal activity during reward anticipation. No interactions were found between the effects of ASD and ADHD symptoms on reward processing.
Conclusion: Variance in ASD and ADHD symptoms separately influence neural processing during reward anticipation in both individuals with (an increased risk of) ADHD and healthy participants. Our findings therefore suggest that both symptom domains affect reward processing through distinct mechanisms, underscoring the importance of multidimensional and multimodal assessment in psychiatry.
Keywords: ADHD; ASD; Comorbidity; Reward; Reward anticipation.

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Neuropsychopharmacology. 2015 Sep;40:2298-306.
REDUCED SYMPTOMS OF INATTENTION AFTER DIETARY OMEGA-3 FATTY ACID SUPPLEMENTATION IN BOYS WITH AND WITHOUT ATTENTION DEFICIT/HYPERACTIVITY DISORDER .
Bos DJ, Oranje B, Veerhoek ES, et al.
Attention deficit/hyperactivity disorder (ADHD) is one of the most common child psychiatric disorders, and is often treated with stimulant medication. Nonpharmacological treatments include dietary supplementation with omega-3 fatty acids, although their effectiveness remains to be shown conclusively. In this study, we investigated the effects of dietary omega-3 fatty acid supplementation on ADHD symptoms and cognitive control in young boys with and without ADHD. A total of 40 boys with ADHD, aged 8-14 years, and 39 matched, typically developing controls participated in a 16-week double-blind randomized placebo-controlled trial. Participants consumed 10 g of margarine daily, enriched with either 650 mg of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) each or placebo. Baseline and follow-up assessments addressed ADHD symptoms, fMRI of cognitive control, urine homovanillic acid, and cheek cell phospholipid sampling. EPA/DHA supplementation improved parent-rated attention in both children with ADHD and typically

developing children. Phospholipid DHA level at follow-up was higher for children receiving EPA/DHA supplements than placebo. There was no effect of EPA/DHA supplementation on cognitive control or on fMRI measures of brain activity. This study shows that dietary supplementation with omega-3 fatty acids reduces symptoms of ADHD, both for individuals with ADHD and typically developing children. This effect does not appear to be mediated by cognitive control systems in the brain, as no effect of supplementation was found here. Nonetheless, this study offers support that omega-3 supplementation may be an effective augmentation for pharmacological treatments of ADHD.

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Niger Postgrad Med J. 2014 Dec;21:273-78.

CO-MORBIDITY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND EPILEPSY IN CHILDREN SEEN IN UNIVERSITY OF NIGERIA TEACHING HOSPITAL ENUGU: PREVALENCE, CLINICAL AND SOCIAL CORRELATES.

Chidi IR, Chidi NA, Ebele AA, et al.

Aims and objectives: To determine the prevalence of ADHD, epilepsy co-morbidity and social and clinical correlates in Nigerian children.

Patients and Methods: A cross-sectional study of 113 children with epilepsy was carried out and assessed for ADHD prevalence using the home version of the ADHD Rating Scale IV. The presence of certain variables occurring in association with the co-morbidity was also determined.

Results: Sixteen (14.2%) children had ADHD, epilepsy co-morbidity. The inattentive subtype of ADHD was the most common (68.8%). The factors that were significantly associated with the co-morbidity were poor academic performance (p=0.01), living in rural areas (p=0.00), history of status epilepticus (p=0.00) and the presence of other associated neurological pathologies (p=0.00).

Conclusion: Children with the co-morbidity are more likely to be those that are underachieving academically, with history of status epilepticus, family history of epilepsy, and abnormal EEG. Children with the co-morbidity should be actively sought after and managed accordingly.

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OTJR: Occupation, Participation and Health. 2015 Jul;35:151-59.

MIXED-METHOD EXPLORATION OF SOCIAL NETWORK LINKS TO PARTICIPATION.

Kreider CM, Bendixen RM, Mann WC, et al.

The people who regularly interact with an adolescent form that youth's social network (SN), which may impact participation. We investigated the relationship of SNs to participation using personal network analysis and individual interviews. The sample included 36 youth, aged 11 to 16 years. Nineteen had diagnoses of learning disability, attention disorder, or high-functioning autism, and 17 were typically developing. Network analysis yielded 10 network variables, of which 8 measured network composition and 2 measured network structure, with significant links to at least 1 measure of participation using the Children's Assessment of Participation and Enjoyment (CAPE). Interviews from youth in the clinical group yielded description of strategies used to negotiate social interactions, as well as processes and reasoning used to remain engaged within SNs. Findings contribute to understanding the ways SNs are linked to youth participation and suggest the potential of SN factors for predicting rehabilitation outcomes.

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PLoS ONE. 2015 Jul;10.

PAIN SENSITIVITY IN ADOLESCENT MALES WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: TESTING FOR ASSOCIATIONS WITH CONDUCT DISORDER AND CALLOUS AND UNEMOTIONAL TRAITS.

Northover C, Thapar A, Langley K, et al.

Background: Reduced processing and experience of aversive emotional cues is a common component of theories on the development and persistence of aggression and antisocial behaviour. Yet physical pain, arguably the most basic aversive cue, has attracted comparatively little attention.

Methods: This study measured pain sensitivity and physiological response to painful stimuli (skin conductance level, SCL) in adolescent boys with Attention-Deficit/Hyperactivity Disorder (ADHD; n = 183), who are at high risk for antisocial behaviour. We compared boys with ADHD with and without a comorbid diagnosis of Conduct Disorder (CD) on pain sensitivity, and examined patterns of association between pain measures, on the one hand, and problem severity and callous and unemotional (CU) traits, on the other.
Results: Boys with comorbid CD exhibited a higher pain threshold and tolerance than boys with ADHD alone, but the groups did not differ in physiology at the time the pain threshold and tolerance were reported. Regression analyses showed that ADHD problem severity positively predicted pain sensitivity, whereas levels of CU traits negatively predicted pain sensitivity.
Conclusions: These findings on physical pain processing extend evidence of impairments in aversive cue processing among those at risk of antisocial behaviour. The study highlights the importance of considering comorbidity and heterogeneity of disorders when developing interventions. The current findings could be used to identify subgroups within those with ADHD who might be less responsive to interventions that use corrective feedback to obtain behaviour change.

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Psychiatry Res. 2015 Aug;228:312-17.

COMPULSIVE BUYING: EARLIER ILLICIT DRUG USE, IMPULSE BUYING, DEPRESSION, AND ADULT ADHD SYMPTOMS.

Brook JS, Zhang C, Brook DW, et al.

This longitudinal study examined the association between psychosocial antecedents, including illicit drug use, and adult compulsive buying (CB) across a 29-year time period from mean age 14 to mean age 43. Participants originally came from a community-based random sample of residents in two upstate New York counties. Multivariate linear regression analysis was used to study the relationship between the participant's earlier psychosocial antecedents and adult CB in the fifth decade of life. The results of the multivariate linear regression analyses showed that gender (female), earlier adult impulse buying (IB), depressive mood, illicit drug use, and concurrent ADHD symptoms were all significantly associated with adult CB at mean age 43. It is important that clinicians treating CB in adults should consider the role of drug use, symptoms of ADHD, IB, depression, and family factors in CB.

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Psychiatry Res. 2015 Aug;228:746-51.

DECREASED LEVELS OF SERUM OXYTOCIN IN PEDIATRIC PATIENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER.

Sasaki T, Hashimoto K, Oda Y, et al.

Attention Deficit/Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD) are highly comorbid, and both disorders share executive function deficits. Accumulating evidence suggests that ASD patients have significantly lower peripheral oxytocin (OXT) levels compared with their normal counterparts, and that the repetitive behavior seen in ASD is related to abnormalities in the OXT system. In this study, we investigated whether serum levels of OXT are altered in pediatric patients with ADHD. We measured serum OXT levels: drug naive ADHD (n = 23), medicated ADHD (n = 13), and age- and sex- matched, neurotypical controls (n = 22). Patients were evaluated using the ADHD-RS. Serum levels of OXT in total subjects with ADHD were significantly decreased compared with those of neurotypical controls, and serum levels of OXT in drug naive ADHD patients were significantly lower than those in medicated ADHD patients. Interestingly, there was a significant negative correlation between serum OXT levels and ADHD-RS total scores, as well as ADHD-RS inattentive scores in all ADHD patients. In conclusion, this study suggests that decreased levels of OXT may play a role in the pathophysiology of patients with ADHD and its inherent inattentiveness.

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Psychiatry Research: Neuroimaging. 2015 Aug;233:278-84.

NEURAL CORRELATES OF RESPONSE INHIBITION IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A CONTROLLED VERSION OF THE STOP-SIGNAL TASK.

Janssen TWP, Heslenfeld DJ, Mourik Rv, et al.

The stop-signal task has been used extensively to investigate the neural correlates of inhibition deficits in children with ADHD. However, previous findings of atypical brain activation during the stop-signal task in children with ADHD may be confounded with attentional processes, precluding strong conclusions on the nature of these deficits. In addition, there are recent concerns on the construct validity of the SSRT metric. The aim of this study was to control for confounding factors and improve the specificity of the stop-signal task to investigate inhibition mechanisms in children with ADHD. FMRI was used to measure inhibition related brain activation in 17 typically developing children (TD) and 21 children with ADHD, using a highly controlled version of the stop-signal task. Successful inhibition trials were contrasted with control trials that were comparable in frequency, visual presentation and absence of motor response. We found reduced brain activation in children with ADHD in key inhibition areas, including the right inferior frontal gyrus/insula, and anterior cingulate/dorsal medial prefrontal cortex. Using a more stringent controlled design, this study replicated and specified previous findings of atypical brain activation in ADHD during motor response inhibition.

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Psychiatry Research: Neuroimaging. 2015 Sep;233:488-95.

MOTOR OVERFLOW IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IS ASSOCIATED WITH DECREASED EXTENT OF NEURAL ACTIVATION IN THE MOTOR CORTEX.

Gaddis A, Rosch KS, Dirlikov B, et al.

Motor overflow is a developmental phenomenon that typically disappears by late childhood. Abnormal persistence of motor overflow is often present in children with attention-deficit/hyperactivity disorder (ADHD). This study employed functional magnetic resonance imaging (fMRI) during a finger-sequencing task to examine whether excessive motor overflow in children with ADHD is associated with decreased extent of motor circuit activation. Thirty-four right-handed children (18 typically developing controls, 16 ADHD) completed fMRI while performing a finger-sequencing task. Motor overflow was evaluated during a finger-sequencing task and a motor examination (the PANESS) performed outside the scanner. Diagnostic differences in behavioral measures of overflow and extent of activation in the contralateral and ipsilateral motor network ROIs were examined, along with correlations between overflow and extent of activation. Children with ADHD demonstrated greater overflow and lesser extent of activation in left primary motor cortex (BA4) and bilateral premotor cortex (BA6) and supplementary motor area (SMA) during right-hand finger-sequencing compared to controls. Decreased extent of primary motor and premotor activation correlated with increased hand-related overflow movements in children with ADHD but not controls. These findings suggest that overflow movements in children with ADHD may reflect decreased recruitment of neural circuitry involved in active inhibition of homologous motor circuitry unnecessary to task execution.

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Psychiatry Research: Neuroimaging. 2015 Sep;233:458-65.

FAMILIAL RISK AND ADHD-SPECIFIC NEURAL ACTIVITY REVEALED BY CASE-CONTROL, DISCORDANT TWIN PAIR DESIGN.

Godinez DA, Willcutt EG, Burgess GC, et al.

Individuals with ADHD, as well as their family members who do not meet clinical criteria, have shown deficits in executive function. However, it remains unclear whether underlying neural alterations are familial or ADHD-specific. To investigate this issue, neural activation underlying executive function was assessed using functional magnetic resonance imaging during performance of a Stroop task in three groups of individuals: 20 young adults who were diagnosed with ADHD in childhood, their 20 dizygotic co-twins without ADHD in childhood, and 20 unrelated controls selected from dizygotic twin pairs in which neither twin had ADHD in childhood (total n = 60). Implicating the frontoparietal network as a location of effects specific to ADHD,

activation in the superior frontal (Brodmann's Area—BA 6) and parietal regions (BA 40) was significantly reduced in twins with childhood ADHD compared to both their control co-twins and unrelated control twins. Consistent with familial influences, activity in the anterior cingulate and insula was significantly reduced in both the twins with ADHD and their co-twins compared to the unrelated controls. These results show that both ADHD-specific and familial influences related to an ADHD diagnosis impact neural systems underlying executive function.

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Psychol Med. 2015 Sep;45:2633-46.

ATTENTION NETWORK FUNCTIONING IN CHILDREN WITH ANXIETY DISORDERS, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND NON-CLINICAL ANXIETY.

Mogg K, Salum GA, Bradley BP, et al.

Background: Research with adults suggests that anxiety is associated with poor control of executive attention. However, in children, it is unclear (a) whether anxiety disorders and non-clinical anxiety are associated with deficits in executive attention, (b) whether such deficits are specific to anxiety versus other psychiatric disorders, and (c) whether there is heterogeneity among anxiety disorders (in particular, specific phobia versus other anxiety disorders).

Method: We examined executive attention in 860 children classified into three groups: anxiety disorders (n = 67), attention-deficit/hyperactivity disorder (ADHD; n = 67) and no psychiatric disorder (n = 726). Anxiety disorders were subdivided into: anxiety disorders excluding specific phobia (n = 43) and specific phobia (n = 21). The Attention Network Task was used to assess executive attention, alerting and orienting.

Results: Findings indicated heterogeneity among anxiety disorders, as children with anxiety disorders (excluding specific phobia) showed impaired executive attention, compared with disorder-free children, whereas children with specific phobia showed no executive attention deficit. Among disorder-free children, executive attention was less efficient in those with high, relative to low, levels of anxiety. There were no anxiety-related deficits in orienting or alerting. Children with ADHD not only had poorer executive attention than disorder-free children, but also higher orienting scores, less accurate responses and more variable response times.

Conclusions: Impaired executive attention in children (reflected by difficulty inhibiting processing of task-irrelevant information) was not fully explained by general psychopathology, but instead showed specific associations with anxiety disorders (other than specific phobia) and ADHD, as well as with high levels of anxiety symptoms in disorder-free children.

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Res Autism Spectr Disord. 2015;20:58-66.

DO COMMUNICATION AND SOCIAL INTERACTION SKILLS DIFFER ACROSS YOUTH DIAGNOSED WITH AUTISM SPECTRUM DISORDER, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, OR DUAL DIAGNOSIS?

Salley B, Gabrielli J, Smith CM, et al.

Given the well-documented symptom overlap between autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), careful evaluation of potential differentiation and overlap is critical for accurate diagnostic decisions. Although research has considered the use of symptom checklists and parent/teacher report questionnaires for symptom differentiation, standardized observational methods, typically utilized in the context of ASD evaluation, have received less attention. The present study examined the continuum of communication and social interaction impairment for youth diagnosed with ASD and ADHD, as indexed by the Autism Diagnostic Observation Schedule (ADOS). Participants were 209 youth ages 3-18 years with ASD, ADHD, dual diagnosis (ASD + ADHD) or no diagnosis. Differences across diagnostic groups were observed for mean communication and social interaction total scores on the ADOS, with the highest scores (i.e., greater impairment) observed for the ASD group and lowest scores for the ADHD and no diagnosis groups. Results provide the first evidence for use of the ADOS for distinguishing youth who have

ADHD alone versus ASD alone or co-occurring ASD + ADHD. Findings are discussed in light of implications for clinical practice and future research.

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Res Dev Disabil. 2015;47:48-60.

VALIDATION OF DSM-5 AGE-OF-ONSET CRITERION OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN ADULTS: COMPARISON OF LIFE QUALITY, FUNCTIONAL IMPAIRMENT, AND FAMILY FUNCTION.

Lin Y-J, Lo K-W, Yang L-K, et al.

The newly published Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) elevates the threshold of the ADHD age-of-onset criterion from 7 to 12 years. This study evaluated the quality of life and functional impairment of adults with ADHD who had symptoms onset by or after 7 years and examined the mediation effect of family function and anxiety/depression symptoms between ADHD diagnosis and quality of life and functional impairment. We assessed 189 adults with ADHD and 153 non-ADHD controls by psychiatric interview and self-administered reports on the Adult ADHD Quality of Life Scale, Weiss Functional Impairment Rating Scale, Family APGAR, and Adult Self Report Inventory-4. The ADHD group was divided into early-onset ADHD (onset <7 years, n= 147) and late-onset ADHD (onset between 7 and 12 years, n= 42). The mediation analysis was conducted to verify the mediating factors from ADHD to functional impairment and quality of life. The late-onset ADHD had more severe functional impairment at work and poorer family support than early-onset ADHD while they had comparable impairment at other domains. Less perceived family support and current anxiety/depressive symptoms partially mediated the link between ADHD diagnosis and quality of life/functional impairment both in early- and late-onset ADHD. Our data support decreased quality of life and increased functional impairment in adult ADHD, regardless of age of onset, and these adverse outcomes may be mediated by family support and anxiety/depression at adulthood. Our findings also imply that the new DSM-5 ADHD criteria do not over-include individuals without impairment.

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Rev Bras Psiquiatr. 2015 Jan;37:67-70.

THE BRAZILIAN POLICY OF WITHHOLDING TREATMENT FOR ADHD IS PROBABLY INCREASING HEALTH AND SOCIAL COSTS.

Maia CR, Stella SF, Mattos P, et al.

Objective: To estimate the economic consequences of the current Brazilian government policy for attention-deficit/hyperactivity disorder (ADHD) treatment and how much the country would save if treatment with immediate-release methylphenidate (MPH-IR), as suggested by the World Health Organization (WHO), was offered to patients with ADHD.

Method: Based on conservative previous analyses, we assumed that 257,662 patients aged 5 to 19 years are not receiving ADHD treatment in Brazil. We estimated the direct costs and savings of treating and not treating ADHD on the basis of the following data: a) spending on ADHD patients directly attributable to grade retention and emergency department visits; and b) savings due to impact of ADHD treatment on these outcomes.

Results: Considering outcomes for which data on the impact of MPH-IR treatment are available, Brazil is probably wasting approximately R$ 1.841 billion/year on the direct consequences of not treating ADHD in this age range alone. On the other hand, treating ADHD in accordance with WHO recommendations would save approximately R$ 1.163 billion/year.

Conclusions: By increasing investments on MPH-IR treatment for ADHD to around R$ 377 million/year, the country would save approximately 3.1 times more than is currently spent on the consequences of not treating ADHD in patients aged 5 to 19 years.

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Technol Eval Cent Assess Program Exec Summ. 2014 Oct;29:1-6.

QUANTITATIVE ELECTROENCEPHALOGRAPHY AS A DIAGNOSTIC AID FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Anon.

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The Journal of Pediatrics. 2015 Aug;167:435-41.

PRENATAL LEAD EXPOSURE MODIFIES THE IMPACT OF MATERNAL SELF-ESTEEM ON CHILDREN'S INATTENTION BEHAVIOR.

Xu J, Hu H, Wright R, et al.

Objective: To prospectively evaluate the association of maternal self-esteem measured when their offspring were toddlers with the subsequent development of attention deficit hyperactivity disorder (ADHD)-like behavior in their school-age offspring and the potential modifying effects of prenatal lead exposure.

Study design: We evaluated a subsample of 192 mother-child pairs from a long-running birth-cohort project that enrolled mothers in Mexico from 1994-2011. Prenatal lead exposure was assessed using cord blood lead and maternal bone lead around delivery (tibia and patella lead, measured by K-x-ray-fluorescence). When children were 2 years old, maternal self-esteem was measured using the Coopersmith Self-Esteem Inventory. When children were 7-15 years old, children's blood lead levels and ADHD symptoms were assessed, and Conners' Parent Rating Scale-Revised and Behavior Rating Inventory of Executive Function-Parent Form were used as measures of ADHD-like behavior.

Results: Adjusting for family economic status, marital status, maternal education and age, child's age and sex, and children's current blood lead levels, increased maternal self-esteem was associated with reduced child inattention behavior. Compared with those among high prenatal lead exposure (P25-P100), this association was stronger among low prenatal lead exposure groups (P1-P25, P values for the interaction effects between prenatal lead exposure and maternal self-esteem levels of < .10). Each 1-point increase in maternal self-esteem scores was associated with 0.6- to 1.3-point decrease in Conners' Parent Rating Scale-Revised and Behavior Rating Inventory of Executive Function-Parent Form T-scores among groups with low cord blood lead and patella lead (P1-P25).

Conclusions: Children experiencing high maternal self-esteem during toddlerhood were less likely to develop inattention behavior at school age. Prenatal lead exposure may play a role in attenuating this protective effect.

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Transl Psychiatry. 2015;5:e500.

ASSOCIATION BETWEEN SNAP-25 GENE POLYMORPHISMS AND COGNITION IN AUTISM: FUNCTIONAL CONSEQUENCES AND POTENTIAL THERAPEUTIC STRATEGIES.

Braida D, Guerini FR, Ponzoni L, et al.

Synaptosomal-associated protein of 25 kDa (SNAP-25) is involved in different neuropsychiatric disorders, including schizophrenia and attention-deficit/hyperactivity disorder. Consistently, SNAP-25 polymorphisms in humans are associated with hyperactivity and/or with low cognitive scores. We analysed five SNAP-25 gene polymorphisms (rs363050, rs363039, rs363043, rs3746544 and rs1051312) in 46 autistic children trying to correlate them with Childhood Autism Rating Scale and electroencephalogram (EEG) abnormalities. The functional effects of rs363050 single-nucleotide polymorphism (SNP) on the gene transcriptional activity, by means of the luciferase reporter gene, were evaluated. To investigate the functional consequences that SNAP-25 reduction may have in children, the behaviour and EEG of SNAP-25(+/-) adolescent mice (SNAP-25(+/+)) were studied. Significant association of SNAP-25 polymorphism with decreasing cognitive scores was observed. Analysis of transcriptional activity revealed that SNP rs363050 encompasses a regulatory element, leading to protein expression decrease. Reduction of SNAP-25 levels in adolescent mice was associated with hyperactivity, cognitive and social impairment and an abnormal EEG, characterized by the occurrence of frequent spikes. Both EEG abnormalities and behavioural deficits were rescued by repeated exposure for 21 days to sodium salt valproate (VLP). A partial recovery of SNAP-25 expression content in

SNAP-25(+/-) hippocampi was also observed by means of western blotting. A reduced expression of SNAP-25 is responsible for the cognitive deficits in children affected by autism spectrum disorders, as presumably occurring in the presence of rs363050(G) allele, and for behavioural and EEG alterations in adolescent mice. VLP treatment could result in novel therapeutic strategies.

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Zhonghua Yi Xue Za Zhi. 2014 Nov;94:3387-91.

ALTERED ANATOMICAL ASYMMETRY IN CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER: A PILOT OPTIMIZED VOXEL-BASED MORPHOMETRIC STUDY.

Cao Q, Wang J, Sun L, et al.

Objective: Mounting evidence suggests that attention deficit/hyperactivity disorder (ADHD) is related with abnormal anatomical asymmetry in some brain regions, such as basal ganglia.However, few cross-sectional studies have examined the abnormalities of anatomical asymmetry in whole brain of ADHD. Thus this cross-sectional study was to explore the anatomical asymmetry in whole brain of ADHD with optimized voxel-based morphometry (OVBM).

Methods: Twenty-five boys with ADHD and 27 age and gender-matched controls were recruited. All participants were right-handed. The grey matter concentration of each voxel was calculated with OVBM. A statistical evaluation of grey matter asymmetry was then conducted on normalized grey matter images and their flipped counterparts.

Results: One-sample t-test revealed that the whole-brain anatomical asymmetry pattern was similar in two groups. Through group comparisons, ADHD showed reversed left-greater-than-right asymmetry in superior and middle frontal gyri versus controls.

Conclusion: Anatomical asymmetry of prefrontal cortex is abnormal in children with ADHD. And abnormal anatomical asymmetry may play an important role in the pathophysiology of ADHD.

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Zhonghua Yi Xue Za Zhi. 2014 Dec;94:3649-51.

INTENSITY OF FUNCTIONAL CONNECTION BETWEEN BILATERAL HEMISPHERES OF CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER BY FUNCTIONAL MAGNETIC RESONANCE IMAGING.

Jiang K, Dong X, Gao M, et al.

Objective: To explore the neural mechanisms of attention-deficit hyperactivity disorder (ADHD) through analyzing the intensity of functional connection between bilateral hemispheres of children with ADHD by resting-state functional magnetic resonance imaging (rs-fMRI).

Methods: The approach of voxel-mirrored homotopic connectivity (VMHC) was employed to analyze 31 school-age and 31 ADHD children by rs-fMRI scans.

Results: Positively activated brain regions were visualized when comparing ADHD and normal children, suggesting that ADHD children's VMHC scores were higher in bilateral frontal lobe ($t = 5.81$), bilateral occipital lobe ($t = 5.82$) and bilateral cerebellar posterior lobe ($t = 6.17$). Statistically significant differences existed between two groups (FDR correction, $Q<0.01$).

Conclusions: The increased intensity of functional connection between bilateral prefrontal lobes in children with ADHD reflects attention disorder and leads to a decline of working memory . The strengthening of bilateral occipital lobes slows down memory process. And the increased intensity of cerebellar connections may damage neural circuits and aggravate ADHD symptoms.

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ORIGINAL CONTRIBUTION

GRIN2B predicts attention problems among disadvantaged children

Valentina Riva · Marco Battaglia · Maria Nobile · Francesca Cattaneo · Claudio Lazazzera · Sara Mascheretti · Roberto Giorda · Chantal Mérette · Claudia Émond · Michel Maziade · Cecilia Marino

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Abstract It is well established that adversities and *GRIN2B* (coding an *N*-methyl-D-aspartate receptor subunit) are independently associated with behavioral and cognitive impairments in childhood. However, a high proportion of children exposed to adversities have good, long-term outcomes. We hypothesized that among children exposed to adversities, *GRIN2B* variants would predict the worst cognitive and behavioral outcomes. 6 single nucleotide polymorphisms of *GRIN2B* were genotyped in 625 children aged 6–11 years from an Italian community-based sample. The interacting effect of *GRIN2B* variants with 4 measures of adversities [low socioeconomic status (SES), preterm delivery, maternal smoking during pregnancy, and absence of breastfeeding] was investigated upon blindly assessed cognitive abilities (vocabulary, block design, digit spans of Wechsler's Intelligence Scale, and Rey complex figure) and parents-rated behavioral problems (Child Behavior Checklist/6–18). Rs2268119 × SES interaction (Hotelling's Trace = 0.07; $F(12,1154) = 3.53$; $p = 0.00004$) influenced behavior, with more attention problems among children in the 'either A/T or T/T genotype and low SES' group, compared to all other groups. This interaction effect was not significant in an independent, replication sample of 475 subjects from an Italian community-based sample. *GRIN2B* variants predict children with the worst outcome in attention functioning among children exposed to low SES. Our findings, if replicated, could help in the identification of children with the highest risk and may prompt cost-effective preventive/treatment strategies.

Keywords Socioeconomic status · *GRIN2B* · Gene–environment interaction

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V. Riva · M. Nobile · F. Cattaneo · C. Lazazzera · S. Mascheretti · C. Marino
Child Psychopathology Unit, Scientific Institute 'Eugenio Medea', Don L. Monza 20, Bosisio Parini (LC), Italy

V. Riva
The Academic Centre for the Study of Behavioural Plasticity, Vita-Salute San Raffaele University, 20 via Stamira d'Ancona, Milan, Italy

M. Battaglia · C. Mérette · C. Émond · M. Maziade · C. Marino (✉)
Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, 2601 Chemin de la Canardière, Quebec, Canada
e-mail: Cecilia.Marino@fmed.ulaval.ca

M. Battaglia · C. Mérette · C. Émond · M. Maziade · C. Marino
Department of Psychiatry and Neuroscience, Laval University, Quebec, Canada

R. Giorda
Molecular Biology Laboratory, Scientific Institute 'Eugenio Medea', Don L Monza 20, Bosisio Parini (LC), Italy

Introduction

For decades, disadvantaged socioeconomic status (SES) has been found related to impaired cognitive development, poor academic performance, and generally worse mental and physical health in children [1, 2]. Similar associations have been described for preterm delivery [3, 4], maternal smoking during pregnancy [5] and absence of breastfeeding, even though for the latter, mixed findings are reported and mainly related to childhood cognitive abilities [6, 7]. What is still unknown, however, is how to identify those children whose brain functions are vulnerable to such early adversities versus those who are more resilient to the same

hazards. Lack of knowledge at this level prevents public health decision makers and clinical practitioners to apply individually focused interventions, so that the goal of optimal cost-efficiency ratio is often missed. Indeed, a high proportion of children exposed to detrimental environments have good or even exceptional long-term outcomes [8], which bring about the crucial relevance of individual differences in responding to adversities during the developmental years.

Individual differences in developmental cognitive [9, 10] and behavioral traits [11–13] are not only influenced by environmental, but also by genetic factors. Accessibility to genetic polymorphisms makes it possible to link identified genes to phenotypic variability in human cognition and behavior; this can be done within the framework of clearly defined a priori hypotheses, provided that a basis of molecular, behavioral, and developmental neuroscience data is available [14]. Because of extensive evidence deriving from basic and clinical research, the *GRIN2B* gene, which codes for the Glun2B subunit of the *N*-methyl-D-aspartate receptor (NMDAR), seems particularly apt to predict children's vulnerability to cognitive and behavioral problems in presence of adversities and social disadvantage. NMDARs are involved in learning processes and memory formation [15, 16], and the Glun2B subunit plays a critical role in the experience-dependent, synaptic plasticity responses that are key to learning and memory [17–19]. Moreover, *GRIN2B* variants are involved in several human illnesses that share the core features of impaired cognition and memory including intellectual disability [20], Alzheimer's [21] and Parkinson's disease [22], schizophrenia [23], autism spectrum [24], bipolar [25], attention deficit/hyperactivity [26], obsessive–compulsive disorders [27], and developmental dyslexia [28]. Among an a priori selected panel of 47 genes with well-established molecular and biological functions in animal memory, *GRIN2B* variants associated with episodic memory in the general population [29]. However, association between *GRIN2B* variants and either neuropsychiatric disorders or cognitive/behavioral, common phenotypes did not emerge from genome-wide association studies. No functional variants of the GRIN2B gene have been reported up to the present.

Given the well-supported evidence that adversities and social disadvantage [1–7] as well as *GRIN2B* [20–29] are independently associated with behavioral and cognitive problems, we hypothesized that these factors could act jointly and have enhanced effects upon mental health in childhood. Our expectation was that among children grown up in an adverse environment, *GRIN2B* variants would predict the worst cognitive and behavioral outcomes. To control for inherited confounds, we checked for association between exposure to an adverse environment and genotype. Gene–environment correlations are of particular concern in the case of smoking during pregnancy, because in a novel, genetically sensitive design, it has been demonstrated that offspring of pregnant smokers were more likely to have attention deficit/hyperactivity disorder if they were biologically related rather than unrelated to their mother, consistent with a true, genetic risk effect [30]. Here, in a community-based cohort of 625 Italian children aged 6–11 years investigated by a well-established set of measures of adversities and extensive cognitive and behavioral indices, we show that *GRIN2B* variants predict the most severe attention impairments among disadvantaged children.

Methods

Sample

To obtain a general population sample, we targeted children aged 6–11 years in five elementary public schools of five Italian towns. Inclusion criteria were: (1) belonging to Caucasian families of Italian mother tongue for at least 1 generation; (2) having no certified visual, hearing, intellectual or motor disabilities; (3) having a written informed consent signed by both parents. After application of these criteria, 625 subjects who had completed the assessment and successful DNA collection were included in the study (mean age 8.20, standard deviation 1.51, female:male ratio 0.92). These children represented 84 % of those eligible to the study, without significant differences between participants and non-participants relative to age, sex, and education. The study protocol was approved by the Eugenio Medea Scientific Institute ethical and scientific committees.

Assessment

Cognitive measures

There were four measures of cognitive abilities: the vocabulary, block design, forward/backward digit spans subtests of the Wechsler Intelligence Scale for Children-III [31], and the Rey complex figure test [32]. Vocabulary and block design were chosen on the basis of their high correlation (r) with verbal and performance intelligent quotient (IQ; $r = 0.82$, and $r = 0.73$) [31]. Raw scores on the forward/backward digit spans were summed to produce a composite measure of memory abilities. For each IQ subtest, standardized scores based on age norms (mean 10; SD 3) were used as phenotypes in subsequent analyses.

The Rey complex figure is a test designed to measure encoding and retrieval of visual memory [32]. Each

participant was asked to copy a complex figure while in the presence of the stimulus, i.e., the Rey figure, and then to reproduce the same figure after 30 min without the stimulus being available. Delayed recall performance was scored based on the presence, placement, and accuracy of 18 items in the figure. Age-corrected *z*-scores were provided based on published norms on the Italian population [32], and were used as phenotypes in subsequent analyses.

Behavioral measures

Children's behavioral and emotional profiles were rated by the parent-administered Child Behavior Checklist (CBCL/6-18) [33, 34]. The Italian translation of the CBCL was found reliable and valid by previous epidemiological work [35]. We employed the eight CBCL/6–18 subscales (anxious/depressed; withdrawn/depressed; somatic complaints; rule-breaking and aggressive behavior; social, thought and attention problems). In this study, we used the *T*-scores based on the set of multicultural norms ''group 2'', which applied to the normative sample of the Italian population as suggested by the multicultural supplement to the manual for the ASEBA [36].

SES and environmental measures

By an ad hoc questionnaire, we assessed the presence of:

1. SES ("What was the father's/mother's employment during the child's first three years of life?");
2. maternal smoking during pregnancy ("Has the mother smoked more than one cigarette a day for more than one month during pregnancy?"); coded '0' when answer was 'no' and '1' otherwise;
3. gestational age ("At what week of pregnancy was your child born?");
4. breastfeeding ("Has the mother breastfed her child for at least one month?"); coded '0' if child was breastfed, '1' otherwise.

SES was based on parental occupation, which was scored according to the Hollingshead 9-point scale [37]; a score ranging 10–90 was assigned to each parental job, and the higher of two scores was used when both parents were employed. Since analysis and interpretation of interactions are more straightforward with dichotomous factors [38], we dichotomized gestational age, and SES based on cut-off points—as available from existent literature—respectively, at 36 weeks and 30 points [39–41].

Laboratory procedure

Saliva/mouth wash samples were collected to obtain DNA. We included the four most significantly associated SNPs with impaired cognition and memory in children reported by Ludwig et al. [28].

Table 1 Pairwise linkage disequilibrium analyses across pairs of 5 SNPs of the *GRIN2B* gene

SNP 1	SNP 2	D'	r^2
rs5796555	rs1012586	0.760	0.430
rs5796555	rs2268119	0.324	0.101
rs5796555	rs2216128	0.223	0.044
rs5796555	rs11609779	0.336	0.008
rs1012586	rs2268119	0.535	0.204
rs1012586	rs2216128	0.229	0.035
rs1012586	rs11609779	0.260	0.007
rs2268119	rs2216128	0.531	0.262
rs2268119	rs11609779	0.367	0.023
rs2216128	rs11609779	0.860	0.049

Amplification and sequencing of four regions of *GRIN2B* allowed typing of the following SNPs: rs5796555-/A; rs1012586 G/C; rs2268119 A/T; rs2216128 A/G; rs11609779 C/T; rs2192973 G/A. Amplifications were performed in 10-µl reactions using JumpStart Red ACCUTaq LA DNA polymerase (Sigma) and the following protocol: 30 s at 96 °C, 35 cycles of 15 s at 94 °C/20 s at 58 °C/30 s at 68 °C, 5 min final elongation time. Sequencing reactions were performed with a Big Dye Terminator Cycle Sequencing kit (Applied Biosystems) and run on an ABI Prism 3130xl Genetic Analyzer. Online Resource Table S1 shows allele and genotype frequencies, and Hardy–Weinberg equilibrium test for each SNP (HAPLOVIEW program; http://www.broad.mit.edu/mpg/haploview/); SNP rs2192973 was not in Hardy–Weinberg equilibrium and was therefore excluded from further analyses. Table 1 shows pairwise linkage disequilibrium analyses across pairs of SNPs; the value of r^2 (the square of the correlation coefficient) ranged between 0.007 and 0.43. D' values (a measure of linkage disequilibrium) ranged from 0.22 to 0.86. Although markers rs11609779 and rs2216128 showed high D' (0.86), r2 was low (0.049) and therefore included in subsequent analyses. When testing interactive effects, we tested the additive genetic model and for each SNP, genotypes were grouped into a three-level variable (coded '0', '1' and '2'), each level representing, respectively, 0, 1, and 2 minor frequency alleles.

Statistical analyses

Pearson's bivariate correlation analyses were employed to assess the degree of relatedness among cognitive and behavioral phenotypes. Independence among environmental variables and between genotypes and environmental factors was tested by Pearson's Chi-square statistics

Table 2 Descriptive statistics of cognitive and behavioral measures ($n = 625$)

	Min	Max	Mean (SD)	Skewness	Kurtosis
Cognitive measures					
IQ vocabulary[a]	3	19	9.93 (2.61)	0.25	0.14
IQ block design[a]	4	19	11.78 (2.57)	0.06	−0.12
IQ memory[a]	1	19	10.02 (3.11)	−0.12	0.12
Rey complex figure[b]	−2.58	3.54	−0.13 (1.04)	0.42	0.12
Behavioral measures[c]					
Anxious/depressed	50	84	55.84 (6.83)	1.13	0.56
Withdrawn/depressed	50	85	55.46 (6.51)	1.30	1.17
Somatic complaints	50	76	54.89 (5.62)	1.11	0.39
Social problems	50	93	54.41 (4.95)	1.86	6.71
Thought problems	50	79	54.01 (5.63)	1.70	2.40
Attention problems	50	87	54.96 (5.93)	1.64	2.84
Rule-breaking behavior	50	73	52.92 (4.06)	2.10	5.12
Aggressive behavior	50	81	53.99 (5.47)	1.79	3.17

[a] Wechsler Intelligence Scale for Children–III IQ subtests, expressed in age-normed standard scores (mean 10, SD 3)

[b] Age-normed *z*-scores (mean 0, SD 1)

[c] CBCL/6–18 subscales, expressed in age- and sex-normed *T*-scores (mean 50, SD 10)

applied to the contingency tables. By analysis of variance (ANOVA), we tested the interactive effects of each combination of *GRIN2B* marker and environmental factor (the independent variables) upon cognitive and behavioral phenotypes (the dependent variables). In the light of the observed degrees of intercorrelation among the dependent variables (see below "Results"), behavioral phenotypes were jointly analyzed by multivariate analysis of variance (MANOVA); cognitive phenotypes were instead analyzed by four separate ANOVAs. The Bonferroni-corrected threshold to infer significance in this set of analyses was set to 0.0005 (0.05/100; 5 outcomes, 5 markers and 4 environmental variables). Post hoc analyses were performed using the Least Squares Means method (LSMEANS statement of the GLM procedure of the SAS software (SAS/STAT Software [computer program]. Version 9.2 ed. Cary, NC, USA: SAS Institute Inc.) for specific pairwise comparisons. Given that 6 groups are present (3 genotypes × 2 SES status), up to 15 pairwise comparisons are possible but only the three comparisons involving the SES effect for each of the 3 genotypes will be considered, leading strictly to 3 comparisons. Corresponding effect sizes (ES) were calculated by subtracting two group's averages (for example, comparing SES ≤30 to SES >30 for subjects with genotype T/T at rs2268119) and dividing by a pooled standard deviation derived from the within mean square of the model. All other analyses were performed using SPSS version 21.0 software package.

Results

The descriptive statistics of the cognitive and behavioral measures are shown in Table 2. All measures displayed acceptable distribution, except for attention, social and thought problems, and rule-breaking and aggressive behaviors (skewness and/or kurtosis ≥|2|). To account for deviation from normality of some behavioral phenotypes, we log-transformed variables with skewness and/or kurtosis ≥|2|. Descriptives of the log-transformed variables are reported in Online Resource Table S2. Social problems and rule-breaking behavior still showed skewness and/or kurtosis ≥|2| and were therefore excluded from further analyses. Online Resource Table S3 shows the relationships among cognitive and behavioral phenotypes. Bonferroni-corrected threshold to infer significance in this set of analyses was set to 0.0011 (0.05/45). Correlations were small to moderate (0.14–0.28) among cognitive measures, and more substantial (0.32–0.60), as typically found [34], among behavioral problems. Table 3 shows the distributions of environmental measures. Pearson's Chi-square statistics applied to contingency tables showed no interrelationship among all these measures of environment, except for gestational age and breastfeeding, which were moderately associated with each other ($\chi^2 = 15.77$; p values = 0.0002; Bonferroni corrected, p value threshold for significance = 0.05/6 = 0.0083). Online Resource Table S4 shows the relationship between genotypes and environmental variables: Chi-square analyses showed no significant p values, suggesting negligible G–E correlations in our data set (Bonferroni-corrected threshold to infer significance was set to 0.0025 (0.05/20). Results from the ANOVAs upon cognitive phenotypes are shown in Online Resource Table S5. No interactive effects were above the Bonferroni-corrected threshold for any combination of markers and environmental variables. Results from the MANOVAs upon behavioral phenotypes are shown in Table 4. We found a significant interactive effect of

Table 3 Descriptive statistics of socioeconomic status and other measures of environment ($n = 625$)

	Mean (SD)	Skewness	Kurtosis	Minor category (%)	Missing values (%)
Socioeconomic status	56.39 (19.01)	0.05	−0.81	16.5[a]	1.0
Maternal smoking during pregnancy				8.8	1.9
Gestational age at birth	38.67 (2.39)	−1.58	3.92	16.7[b]	8.2
Breastfeeding				22.3	1.9

[a] Cut-off points were 30 for socioeconomic status

[b] Cut-off points were 36 for gestational age at birth

Table 4 Interaction effects between *GRIN2B* markers and environmental factors from 20 two-way MANOVAs upon behavioral phenotypes ($n = 625$)

Marker	F statistic[a]	p value	Effect size[b]
Socioeconomic status			
rs5796555	1.70	0.0622	0.017
rs1012586	1.20	0.2747	0.012
rs2268119	3.53	0.00004	0.040
rs2216128	2.25	0.0081	0.022
rs11609779	1.08	0.3738	0.011
Maternal smoking during pregnancy			
rs5796555	0.51	0.9010	0.005
rs1012586	0.35	0.6845	0.007
rs2268119	0.97	0.4752	0.010
rs2216128	1.95	0.0254	0.020
rs11609779	0.57	0.8689	0.006
Gestational age			
rs5796555	0.37	0.9754	0.004
rs1012586	1.66	0.0696	0.018
rs2268119	1.16	0.3061	0.013
rs2216128	1.19	0.0834	0.020
rs11609779	1.08	0.3772	0.012
Breastfeeding			
rs5796555	0.70	0.7510	0.007
rs1012586	0.33	0.9838	0.003
rs2268119	1.83	0.0396	0.019
rs2216128	1.90	0.0310	0.019
rs11609779	0.25	0.9953	0.003

Dependent variables in each MANOVA were the 6 CBCL/6–18 subscales: anxious/depressed, withdrawn/depressed, somatic complaints, thought problems (*log-transformed*) attention problems (*log-transformed*), aggressive behavior (*log-transformed*). The Bonferroni-corrected threshold to infer significance was set to 0.0005

[a] Hotelling's Trace

[b] Partial eta-squared

rs2268119 and SES (Hotelling's Trace = 0.07; $F(12,1154) = 3.53$; $p = 0.00004$). The ANOVAs revealed a significant interaction effect of rs2268119 and SES upon the CBCL/6–18 attention problem subscales ($F = 8.63$; $df = 2$; $p = 0.0002$). Post hoc analyses of this interaction showed that subjects with genotype T/T and A/T had significantly more attention problems when they belonged to SES ≤30 (respectively, 61.0 ± 9.4 and 57.8 ± 8.7) relative to SES >30 (respectively, 54.4 ± 6.1 and 53.9 ± 5.2; Table 5).

Table 5 p values and effect sizes from post hoc analyses of the significant interaction between rs2268119 and SES upon attention problems in the initial, replication and combined samples

	Initial sample		Replication sample		Combined sample	
	ES	p value	ES	p value	ES	p value
Low (≤30) vs high (>30) socioeconomic status (SES) for each genotype at rs2268119:						
A/A	0.02	0.876	0.26	0.099	0.14	0.179
A/T	0.87	3E−06	0.43	0.032	0.66	1E−06
T/T	1.29	0.002	1.14	0.022	1.20	1E−04

We attempted to replicate the significant interaction of rs2268119 and SES upon the CBCL/6–18 attention problems subscale. The replication sample consisted of subjects drawn from 2 epidemiological studies of mental health in Italian youth, aged 10–14 years. Subjects from study 1 ($n = 460$) were from the Italian Project on Pre-adolescent Mental Health [PrISMA; 34, 35]. Subjects from study 2 ($n = 171$) were participants in a longitudinal study of emotional and behavioral problems in childhood [PL; 39]. At the time of the present study, the DNA of 129 subjects was out of stock, leaving 502 subjects available for genetic analyses, who were genotyped for SNP rs2268119. Eventually, complete information on CBCL/6–18 attention problems subscale, SES and rs2268119 was available for 475 subjects (Table 6). There were no differences in sociodemographic and CBCL/6–18 subscales between the PrISMA/PL sample and the replication sample. Attention problems' distribution deviated from normality and was therefore log-transformed reaching acceptable scores (mean 1.74 and standard deviation 0.04; skewness 1.20; kurtosis 1.21). Rs2268119 was in Hardy–Weinberg equilibrium ($p = 0.4150$) and alleles frequencies did not statistically differ between the initial and the replication samples ($\chi^2 = 2.58$; $df = 2$; p value = 0.2752). SES displayed a normal distribution and dichotomized SES's minor category had a frequency of 18.3 %. SES distribution was not significantly different in the initial and

Table 6 Socio-demographic characteristics in the replication sample

Sex (males %)	Replication sample ($n = 475$)		
	48.63 %		
	Mean (SD)	Skewness	Kurtosis
Age	12.00 (0.88)	−0.01	−0.75
Socioeconomic status	57.20 (22.17)	−0.21	0.11
Anxious/depressed[a]	56.46 (7.16)	1.27	1.57
Withdrawn/depressed[a]	56.21 (6.88)	1.44	2.49
Somatic complaints[a]	55.51 (5.59)	1.04	0.58
Social problems[a]	55.36 (6.10)	1.25	0.94
Thought problems[a]	54.32 (5.66)	1.44	1.25
Attention problems[a]	55.89 (6.58)	1.55	2.99
Rule-breaking behavior[a]	52.70 (4.00)	2.09	4.55
Aggressive behavior[a]	54.42 (5.40)	1.36	1.46

[a] Child Behavior Checklist/6–18 subscales, expressed in normed *T*-scores

replication samples ($\chi^2 = 0.64$; $df = 1$; p value $= 0.4259$). Chi-square analyses between rs2268119 and SES showed no significant p values, suggesting negligible G–E correlation in the replication data set ($\chi^2 = 1.07$; $df = 2$; p value $= 0.5850$). The ANOVA in the replication sample revealed a non-significant interaction effect of rs2268119 and SES upon the CBCL/6–18 attention problems subscale ($F = 1.51$; $df = 2$; $p = 0.2223$). The ANOVA in the combined samples, i.e., the initial and replication samples, yielded a significant interaction effect of rs2268119 and SES upon the CBCL/6–18 attention problems subscale ($F = 7.96$; $df = 2$; $p = 0.0004$). Effect sizes and p values of post hoc comparisons in the initial, replication and combined samples are shown in Table 5. For genotype T/T, comparisons between SES ≤30 and SES >30 yielded strong and consistent effect sizes across the initial, replication and combined samples, and consistently, p values were all significant and were lower in the combined sample compared to the initial one. Figure 1 shows the CBCL/6–18 attention problems *T*-scores in the initial, replication and combined samples according to rs2268119 genotypes and SES.

The significant finding in the initial sample, based on continuous phenotypic measures, provides an exhaustive picture of the relationships in this study. However, an estimation of the odds ratios of developing cognitive or behavioral problems given the presence of, respectively, 'genetic', 'environmental', and 'both genetic and environmental' risk elements can provide a more direct appraisal of the public health significance of our findings. To do so, we dichotomized CBCL/6–18 attention problems T-scores

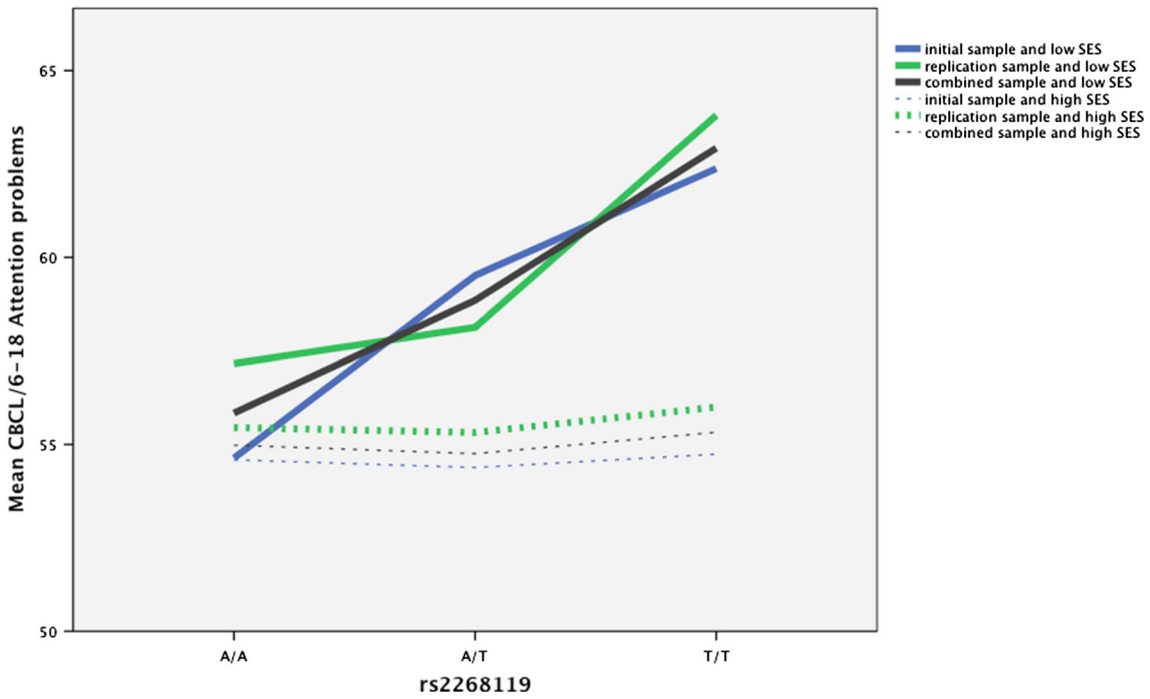

Fig. 1 CBCL/6–18 attention problems according to socioeconomic status and *GRIN2B*/rs2268119 in the initial, replication and combined samples. Initial sample: among 98 subjects with SES ≤30, 55 were A/A, 35 were A/T and 8 were T/T. Among 505 subjects with SES >30, 296 were A/A, 186 were A/T, and 23 were T/T. Replication sample: among 87 subjects with SES ≤30, 50 were A/A, 32 were A/T and 5 were T/T. Among 388 subjects with SES >30, 246 were A/A, 122 were A/T, and 20 were T/T. For attention problems, age- and sex-normed *T*-scores are shown (mean 50; SD 10)

into 'impaired' versus 'non-impaired'. The cut-off was set at 65, i.e., 1.5 standard deviation above the mean, so that the 'impaired' category pooled subjects with scores ≥65 ($n = 49$). The risk of developing an attention's impairment doubles when a child, grown up in a low SES, is also a carrier of rs2268119 T/T or A/T (odds ratio from 1.99 to 4.72; Online Resource Table S6).

Discussion

Based on extensive evidence [1–7, 20–29], we posited that *GRIN2B* variants would predict, among children exposed to adversities, those who developed the worst outcomes in cognitive or behavioral domains. Consistent with our hypothesis, we found that among children who had been exposed to low SES, those who developed the most impaired attention problems scores were carriers of the *GRIN2B* variants rs2268119 T/T or A/T (Fig. 1).

The interactive effect between rs2268119 and SES was significant in the initial and in the combined (initial plus replication) samples, but not in the replication sample.

The overall non-significant interaction effect of rs2268119 and SES upon attention problems in the replication sample may not be considered an outright refutation of the initial finding for a number of reasons. First, although the replication sample had geographical and ethnic origin similar to the initial sample, confounds due to population stratification might still have contributed to different results in the two samples. Second, complex behavioral traits have been shown to be etiologically heterogeneous, and, therefore, the two samples might have different pools of genetic and environmental risk factors [14]. Finally, effect sizes of SES conditioned on genotypes across the initial and replication samples were strong and consistent for genotype T/T while varied inconsistently for the other genotypes (Table 5), suggesting that the interaction effect, while truly present, may not have been detectable in the overall analysis of variance due to the smaller sample sizes of the 'T/T and SES ≤30′ group in the initial relative to the replication sample, i.e., 8 and 5 subjects, respectively [42].

Overall, our findings show that the ability to predict children with impaired behavioral outcome is considerably enhanced when risk elements are considered jointly in their interplay rather than separately, in that jointly analyzed 'genetic' and 'environmental' effects account for more than the sum of their separate effects on risk. All this confirms the importance of studying genetic and non-genetic risk factors simultaneously.

Our findings are visibly consistent with previous knowledge; *GRIN2B* variants and low SES have been found to affect human behavior by several groups who studied genetic or environmental risk factors separately. The *GRIN2B* gene has been related to childhood inattention [26]. In this study, authors investigated 9 SNPs of *GRIN2B* in 205 nuclear families ascertained through a proband affected by attention deficit/hyperactivity disorder. Family-based association analyses revealed an association of both the affection status and quantitative-related traits, i.e., inattention and hyperactivity/impulsivity, with several markers of *GRIN2B*, i.e., rs2268115, rs2300256, rs2284411 and rs2284407. Noteworthy, rs2268115 is located in intron 3 and is adjacent to rs2268119. Low SES—alone or in interaction with genes—has been found to influence several behavioral traits/disorders, including attention [1, 2, 39, 40].

While our more comprehensive analysis of interactive effects adds new and stronger insights into the relationships of *GRIN2B* variants across differential environmental niches in humans, it replicates the essence of what has been found in animal, environmentally controlled studies of the role of the Glun2B subunit on learning and development. Basic science thus provides support to, and mechanistic interpretations for our present findings. The Glun2B-containing NMDARs are involved in experience-dependent synaptic plasticity and are predominant at early embryonic stages of brain development [43, 44]. Postnatally, Glun2B-containing NMDARs are found in the fronto-parieto-temporal cortex and the hippocampus [45]. Interestingly, two recent animal studies showed behavioral changes in rats following gestation-related insults via Glun2B-containing NMDARs modifications [46, 47]. Son et al. [46] demonstrated that animals that had been exposed to stress during gestation show reduced hippocampal expression of Glun2B, together with impaired spatial learning and memory. Fumagalli et al. [47] showed that glutamatergic responsiveness can be increased via the phosphorylation of the Glun2B subunit in adult rats, but the effect is attenuated among prenatally stressed animals. It is also important to note that only two studies assessed *GRIN2B* interplays with adversities in humans [48, 49]. Demontis et al. [48] showed that the risk of developing schizophrenia associated with *GRIN2B* variants is moderated by prenatal maternal seropositivity for herpes simplex. Sokolowski et al. [49] showed an association of *GRIN2B* with suicidal attempts, but no interaction effects with stressful life events, or physical assault.

Our results must also be viewed in the light of some limitations. First, while cognitive functioning was assessed with a battery of tests, behavioral measures were collected from parents via questionnaires. Although the CBCL is a worldwide-adopted measure of childhood problem behavior, and questionnaires represent a practical tool to reach and assess such a large sample, the CBCL dimensions may be less valid and reliable than directly assessed behavior.

Second, SES is likely to incorporate other measures/indexes, and may also be indirectly related to many other variables, some of which may be partially genetic in origin. Therefore, the possibility remains that part of what we have interpreted as gene-by-environment interactions in fact encompasses gene-by-gene interactions. Third, correction for multiple comparisons accounted for the selected SNPs only, which did not cover the entire region of *GRIN2B*; for this reason, although appropriate, the corrective procedure was underpowered and, therefore, caution in the interpretation of findings is warranted, until further replication is obtained. Fourth, while gene-by-environment interactions are biologically sensitive and commonly found in experimental organisms, some quantitative biometric studies of human behavioral disorders questioned the veracity and/or the importance of such effects [50, 51]. On the other hand, recent reviews emphasize the importance of ''measured and identified'' approaches [52] as compared to biometric-quantitative studies [53] of gene-by-environment interactions. We believe that a conceptual guide toward adopting or discarding any new findings in this field should posit upon their biological value and meaning [54]: our investigation of the interplay between the *GRIN2B* gene and early adversities was primed by solid neuroscience evidence of a role of experience-dependent synaptic plasticity at the basis of learning and memory, [15–19] and by several genetic and environmental studies in man [20–29].

Our findings, if replicated, could influence the practice of medicine. By genotyping *GRIN2B* variants, it is possible to predict children with the highest risk for attention impairment among disadvantaged children exposed to low SES, respectively. This yields considerable advantages in terms of cost-effective strategies for targeted preventive/therapeutic programs. The now-reduced costs of the genetic analyses make this approach even more doable and relevant for public health knowledge, and translatable to the practice of general practitioners, pediatricians, and child psychiatrists. While these findings need both replication in independent samples and consideration of the potential limitations, our study may prompt further research and more efficient strategies in the transition toward better and personalized medicine.

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Conflict of interest The authors declare that they have no conflict of interest

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ORIGINAL ARTICLE

Prepuberal intranasal dopamine treatment in an animal model of ADHD ameliorates deficient spatial attention, working memory, amino acid transmitters and synaptic markers in prefrontal cortex, ventral and dorsal striatum

L. A. Ruocco · C. Treno · U. A. Gironi Carnevale · C. Arra · C. Mattern · J. P. Huston · M. A. de Souza Silva · S. Nikolaus · A. Scorziello · M. Nieddu · G. Boatto · P. Illiano · C. Pagano · A. Tino · A. G. Sadile

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Abstract Intranasal application of dopamine (IN-DA) has been shown to increase motor activity and to release DA in the ventral (VS) and dorsal striatum (DS) of rats. The aim of the present study was to assess the effects of IN-DA treatment on parameters of DA and excitatory amino acid (EAA) function in prepuberal rats of the Naples high-excitability (NHE) line, an animal model for attention-deficit hyperactivity disorder (ADHD) and normal random bred (NRB) controls. NHE and NRB rats were daily administered IN-DA (0.075, 0.15, 0.30 mg/kg) or vehicle for 15 days from postnatal days 28–42 and subsequently tested in the Làt maze and in the Eight-arm radial Olton maze. Soluble and membrane-trapped L-glutamate (L-Glu) and L-aspartate (L-Asp) levels as well as NMDAR1 subunit protein levels were determined after sacrifice in IN-DA- and vehicle-treated NHE and NRB rats in prefrontal cortex (PFc), DS and VS. Moreover, DA transporter (DAT) protein and tyrosine hydroxylase (TH) levels were assessed in PFc, DS, VS and mesencephalon (MES) and in ventral tegmental area (VTA) and substantia nigra, respectively. In NHE rats, IN-DA (0.30 mg/kg) decreased horizontal activity and increased nonselective attention relative to vehicle, whereas the lower dose (0.15 mg/kg) increased selective spatial attention. In NHE rats, basal levels of soluble EAAs were reduced in PFc and DS relative to NRB controls, while membrane-trapped EAAs were elevated in VS. Moreover, basal NMDAR1 subunit protein levels were increased in PFc, DS and VS relative to NRB controls. In addition, DAT protein levels were elevated in PFc and VS relative to NRB controls. IN-DA led to a number of changes of EAA, NMDAR1 subunit protein, TH and DAT protein levels in PFc, DS, VS, MES and VTA, in both NHE and NRB rats with significant differences between lines. Our findings indicate that the NHE rat model of ADHD may be characterized by (1) prefrontal and striatal DAT hyperfunction, indicative of DA hyperactivty, and (2)

L. A. Ruocco · C. Treno · U. A. Gironi Carnevale · A. G. Sadile
Department of Exptl. Med., School of Medicine, Second University of Naples, Naples, Italy

C. Arra
Animal Facility, I.N.T.G. Pascale, Naples, Italy

C. Mattern
M et P Pharma AG, Emetten, Switzerland, and Oceanographic Center, Nova Southeastern University, Florida, USA

J. P. Huston · M. A. de Souza Silva (✉)
Center for Behavioral Neuroscience, Institute of Experimental Psychology, University of Düsseldorf, Düsseldorf, Germany
e-mail: desouza@uni-duesseldorf.de

S. Nikolaus
Clinic of Nuclear Medicine, University Hospital Düsseldorf, Düsseldorf, Germany

A. Scorziello
Department of Neuroscience, Reproductive and Odontostomatological Sciences, Second University of Naples, Naples, Italy

M. Nieddu · G. Boatto
Department of Chemistry and Pharmacy, Sassari University, Sassari, Italy

P. Illiano · C. Pagano · A. Tino
Istituto di Cibernetica "Eduardo Caianiello" ICIB CNR, Pozzuoli, Italy

prefrontal and striatal NMDA receptor hyperfunction indicative of net EAA hyperactivty. IN-DA had ameliorative effects on activity level, attention, and working memory, which are likely to be associated with DA action at inhibitory D2 autoreceptors, leading to a reduction in striatal DA hyperactivity and, possibly, DA action on striatal EAA levels, resulting in a decrease of striatal EAA hyperfunction (with persistence of prefrontal EAA hyperfunction). Previous studies on IN-DA treatment in rodents have indicated antidepressant, anxiolytic and anti-parkinsonian effects in relation to enhanced central DAergic activity. Our present results strengthen the prospects of potential therapeutic applications of intranasal DA by indicating an enhancement of selective attention and working memory in a deficit model.

Keywords ADHD · Intranasal dopamine · L-Glutamate · L-Aspartate · NMDA receptor · Dopamine transporter · Tyrosine hydroxylase · Working memory · Attention

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a chronic, behavioral disorder characterized by inattention, impulsivity, and hyperactivity (for review see Steinhoff 2008). Pathophysiologically, ADHD is mainly ascribed to dopamin(DA)ergic dysfunctions in mesocorticolimbic regions (for review see Del Campo et al. 2011). In vivo imaging studies have shown that ADHD patients display an increased availability of striatal DA transporters (DAT), while D2 receptor binding as well as DA synthesis and release in the majority of investigations have been unaltered (for reviews see Krause 2008; Nikolaus et al. 2009). The pivotal role of DAT binding sites is supported by the therapeutic efficacy of DAT inhibitors, such as methylphenidate (for review see Volkow et al. 2005). Recently, also disturbance of glutamate(Glu)ergic function has been implied (for review see Lesch et al. 2013), which is based on the effectiveness of the *N*-methyl-D-aspartate (NMDA) antagonists amantadine (for review see Hosenbocus and Chahal 2013a) and memantine (for review see Hosenbocus and Chahal 2013b) in treating pediatric as well as adult ADHD.

Animal models for studying ADHD can be of the genetic and nongenetic type (for review see Russell 2011). Examples of genetic models are (1) the spontaneously hypertensive rat (SHR) (for review see Sagvolden 2000) and (2) the Naples high-excitability (NHE) line (for review see Viggiano et al. 2002a, 2003). These models reproduce two specific subtypes of the syndrome (for review see Purper-Ouakil et al. 2004), which are characterized by the key symptoms of delay aversion and hyperactivity, respectively. Delay aversion is considered to be due to a dysfunctional mesolimbic branch of the DA system and is modeled by the SHR (for review see Sonuga-Barke 2003), while hyperactivity, along with alterations of executive functions, are linked to a dysfunctional mesocortical branch of the central DA system and is modeled by the NHE rats (for review see Viggiano et al. 2002a, b, 2003). D-Amphetamine and methylphenidate reduce hyperactivity and ameliorate attention deficit in both animal models, as well as in ADHD patients (for review see Solanto 1998).

Because DA does not cross the blood brain barrier, its intranasal application (IN-DA) has emerged as a promising alternative for targeting the central nervous system (Graff and Pollack 2005; Illum 2007; Thorne and Frey 2001; Tayebati et al. 2013). There is evidence that IN-DA can be transported directly from the nasal mucosa into the brain, bypassing the blood brain barrier (Chemuturi et al. 2006; Dahlin et al. 2000, 2001). IN-DA application in rats has been shown to increase DA release in the neostriatum and nucleus accumbens, to reduce anxiety, increase activity and have antidepressant-like effects (Buddenberg et al. 2008; De Souza Silva et al. 2008), as well as to ameliorate parkinsonian-related behavior in the hemiparkinsonian rat (Pum et al. 2009).

We have demonstrated that subchronic IN-DA, administered during the prepuberal period in NHE rats, reduced behavioral hyperactivity and improved both nonselective and selective attention/working memory in this animal model of ADHD (Ruocco et al. 2009a). These results suggested the potential of employing IN-DA for therapeutic purposes. The aim of the present study was to enhance our understanding of the mechanisms responsible for the behavioral effects of IN-DA in this model. For this purpose, prepuberal NHE rats again received repeated applications of IN-DA during the fifth and sixth week of postnatal life, i.e., the prepuberal period that corresponds to adolescence in children. Male rats were employed, based on the high male-to-female ratio (4:1) of ADHD (Sergeant et al. 2003). We employed the Làt maze to measure nonselective attention towards environmental stimuli and the Eight-arm radial Olton maze to assess selective spatial attention/working memory (Aspide et al. 1998).

L-Glutamate (L-Glu) and L-aspartate (L-Asp) neurotransmission between prefrontal cortex (PFc) and both dorsal (DS) and ventral striatum (VS) plays a major role in information processing (Errico et al. 2008; D'Aniello 2007). Previous studies have demonstrated higher levels of L-Glu and L-Asp in the PFc of NHE rats (Ruocco et al. 2009b). Moreover, as tyrosine hydroxylase (TH) is the rate limiting enzyme for DA synthesis (for review see, Tolleson and Claassen 2012), also TH levels might play a role in the pathophysiology of ADHD. This is supported by previous findings showing an increase in TH in PFc and ventral tegmental area (VTA) of young adult NHE rats (Viggianao and Sadile 2000; Viggiano et al. 2002a, b, 2003). DAT

function is crucial to determine the duration of DA action and to maintain DA homeostasis in the central nervous system (for review see, Chen and Reith 2000). Previous studies have revealed increased DAT levels in the PFc of NHE rats, which can be related to the hyperactive state of the mesocortical DA system (Viggiano et al. 2002a, 2003; Ruocco et al. 2009c). This finding is consistent with the elevation of DAT binding observed in ADHD patients (for review see, Krause 2008). Furthermore, an elevation of both NMDA- and quisqualate-sensitive [3H]glutamate binding was detected in the neostriatum, thalamus, frontal cortex, occipital cortex, dentate gyrus and hippocampus of NHE rats (Sadile et al. 1996).

The present study aimed to assess the influence of prepuberal long-term treatment with IN-DA on activity and selective attention/working memory and nonselective attention in the NHE rat model of ADHD using both the Làt maze and the Eight-arm radial Olton maze. Moreover, we aimed to determine the effects of IN-DA on the levels of the excitatory amino acids (EAAs) L-Glu and L-Asp, and of the NMDAR1 subunit protein in prefrontal cortex (PFc), DS and VS, as well as on the levels of the DAT protein in PFc, DS, VS and mesencephalon (MES) and of TH in VTA and substantia nigra (SN). The expected results were considered as important to further our understanding of the plasticity of the mesocortical system and long-term changes in its functional state as well as to assess the potential of intranasal delivery of dopamine for therapeutic purposes.

Materials and methods

Animals

The subjects were 28 day old male rats of the Sprague–Dawley-derived Naples High-Excitability line (NHE; $n = 32$) and the random bred line (NRB; $n = 24$) from which the selective inbreeding started in 1976. The experiments were carried out at the end of the sixth postnatal week. Rats were housed in groups of four in standard Makrolon cages and maintained in a reversed 12:12 light–dark cycle (lights on from 7 PM to 7 AM) with food and water freely available. All experiments were authorized by the Ministero della Salute. Ethical advice was issued from the Istituto Superiore di Sanità.

Drug treatment

The animals were randomly assigned to treatment and control groups receiving vehicle or dopamine hydrochloride (DA-HCl, Sigma, USA) in doses of 0.075, 0.15, or 0.3 mg/kg. DA-HCl was suspended in a volume of 10 µl of gel composed of a viscous castor oil mixture (M & P Pharma, Emmetten, Switzerland), and applied into both nostrils (5 µl each) by the use of a micropipette for viscous media (Transferpettor, Brand GMBH +CO KG, Wertheim, Germany). Treatments were given daily at the beginning of the dark phase for 14 days from postnatal day 29 onward. One hour after the last application of drug or vehicle, rats were tested for activity and nonselective attention in the Làt maze and 24 h later, in the Eight-arm radial Olton maze. This interval was chosen on the basis of neurochemical and behavioral effects of IN-DA reported in previous studies (Buddenberg et al. 2008; De Souza Silva et al. 2008).

Behavior

Làt maze

The Làt maze consisted of a 60 × 60 × 40 cm box made of PVC material (KÖMACEL^R), closed by a cover. A smaller plastic transparent 30 × 30 × 40 cm box was inserted in the middle of the latter, thus providing a 60 cm long, 15 cm wide and 40 cm high corridor, which the animals could traverse (for details see Sadile et al. 1988). The box was illuminated by a white, cold 4 W lamp placed 60 cm above the floor in the centre of the cover, providing 0.1–0.2 µW/cm^2. Two such boxes were located in a sound-attenuated room.

Procedure

At the beginning of the dark phase of the inverted light/dark cycle (between 9 AM and 4 PM) the rats were individually exposed to the Làt maze and allowed to explore the corridor for 10 min. Pairs of rats from the same cage were tested at the same time. The behaviors were registered with a high-resolution charge-coupled device (CCD) camera and stored on a video tape recorder to be analyzed offline. Measures of activity were: horizontal activity (number of corner crossings) and vertical activity (frequency of rearing on hind limbs or leaning against the walls with one or both forepaws). Nonselective attention was operationalized as the duration of rearing and leaning episodes (Aspide et al. 1998). Behaviors were measured in 1-min blocks. The reliability index was reasonably high ($r = 0.914$; $df = 198$; $p < 0.001$). At the end of the behavioral test, the fecal boluses were counted and the floor was cleaned with a wet sponge.

Eight-arm radial (Olton) maze

The apparatus consisted of eight arms (8 × 60 cm) extending from an octagonal centre platform (diameter 18.5 cm). The distance from the centre platform to the end

of each arm was 69.25 cm. The apparatus was constructed of gray poly-vinylchloride with a smooth surface and 14 cm high side walls of transparent Plexiglas. The maze was placed on the floor in a dimly lit room, surrounded by a circular higher wall without visual cues. Behavior was monitored by a high-resolution CCD camera and stored on DVD to be analyzed offline.

Procedure

In the Eight-arm radial Olton maze each rat was placed on the centre platform into a cardboard cylinder to avoid immediate escape into an arm. The trial commenced with removal of the cylinder, allowing the animal to explore. The parameters assessed in the Olton maze were horizontal activity (frequency of alley visits) and frequency of rearings on the hind limbs as well as duration of rearing as measures of nonselective attention. The number of arms visited before occurrence of the first repetition occurred (first error [FE]) and the number of arms visited before completion of visits to all eight arms (NVTC) were also recorded. The latter two indices were considered as measures of selective spatial attention as well as of working memory.

Dissection of brain areas

The animals were killed and the brain was removed and put in ice-cold saline. After removal of the olfactory tubercles, the first coronal cut was made at 4.20 AP from Bregma, using the stereotaxic coordinates of a brain atlas as a reference (Paxinos and Watson 2007). Thus, small remnants of the PFc and cingulate cortex area1 were included. The entire upper portion of the DS was removed by a sagittal pinch extending between 2.20 and −3.8 AP, up to 7 mm DV in depth, which included putamen and globus pallidus. The VS was removed by a sagittal pinch between 2.70 and 0.48 AP, at 1 mm from the midline and at about 1 mm in depth, thus incorporating the nucleus accumbens. After removing the cerebellum and the lamina quadrigemina at the level of the fourth ventricle, the MES was dissected out including both medial and lateral portions. The rectangular strip of tissue extended from −5.20 to −6.80 AP.

Excitatory amino acids

Extraction procedure

Groups treated with IN-DA (0.150 and 0.300 mg/kg) and vehicle were analyzed; the 0.075 mg/kg IN-DA dose was excluded because it did not show any significant effect in the behavioral analysis. Brain samples were homogenized in 1 ml ice-cold saline in Eppendorf vessels and centrifuged at 7,500*g* at +4 °C for 20 min. The supernatant was filtered and used for the analysis of the soluble fraction (SF). The precipitate was shocked in bidistilled water and centrifuged at 7,500*g* at 4 °C for 20 min to obtain the membrane-trapped form (MTF). For both SF and MTF forms of the free aminoacids L-Glu, L-Asp and L-Leu were measured employing the LC/MS/MS technique.

Table 1 Liquid chromatography-tandem mass spectrometry parameters

Analyte	Retention time (min)	Selected reaction monitoring transitions (m/z)	Collision energy (eV)
Aspartate	1.36	134.0 → 134.0	4.0
		134.0 → 116.0	4.0
Glutammate	1.38	148.0 → 148.0	4.0
		148.0 → 130.0	7.5
Leucine	1.42	132.2 → 132.2	4.0
		132.2 → 86.0	10.0

Liquid chromatography/tandem mass spectrometry

The analysis was performed using an Varian 310-MS triple quadrupole mass spectrometer (Varian, Palo Alto, CA, USA) in positive ionization mode and selected reaction monitoring (SRM) mode (Table 1). The settings of the electrospray ionization (ESI) source were as follows: spray voltage, 5,000 V; capillary temperature 300 °C; sheath gas pressure (spraying), 20 arbitrary units; auxiliary gas pressure (desolvating), 10 arbitrary units; ion sweep gas pressure (curtain), 5 arbitrary units. The collision cell (Q2) pressure was 2.2 m Torr of argon. The collision energies were optimized for a maximum detection of each product ion (Table 1). Chromatographic separation was performed with a ProStar™ 300 HPLC system (Varian, Palo Alto, CA, USA) on an Varian Polaris® C_{18}column (5 µm, 2.1 mm × 100 mm) at a flow rate of 0.3 mL/min. The mobile phase consisted of aqueous 0.1 % formic acid (A) and acetonitrile (B). Samples were eluted with a linear gradient from 10 to 90 % B in 5 min. At 5:01 min, solvent B was decreased from 90 to 10 % and remained constant for 5 min. The total run time was 10 min.

Morphological analysis

Tissue preparation

Animals ($n = 6$ per group) were deeply anaesthetized with sodium pentobarbital (50 mg/kg i.p.) and perfused transcardially with saline (NaCl 0.9 %) for 2 min followed by 4 % paraformaldehyde in phosphate buffered saline (PBS; pH 7.4) for 5 min. The brain was quickly removed and

post-fixed in the same fixative for 2 h. After washing in PBS for 30 min, the brain was placed in a sucrose solution (18 % sucrose in PBS) at 4 °C. After equilibration in sucrose, forebrain and MES were divided from brainstem and cerebellum and sagittally cut in half along the midline. Each half was frozen on dry ice and stored at −80 °C. For this experiment, only one half of the prosencephalon was used. Frozen prosencephali were sagittally cut (slice thickness, 50 μm) using a cryostat. Random sampling took place every four sections. Before washing and staining, cryostat sections were left floating in cold PBS. All the sections were stained in the same run, to reduce experimental variability.

Tyrosine hydroxylase immunohistochemistry

Sections were washed in Tris buffered saline (TBS) and incubated with mouse monoclonal antibody against TH (Diasorin, Stillwater, USA) at a 1:5,000 dilution in 10 % normal bovine serum and 0.2 % triton X-100 in PBS at 4 °C. After overnight incubation, sections were washed three times in PBS and then incubated for 1 h with anti-mouse-biotin conjugated antibody (Vector, USA) at a 1:200 dilution in 10 % normal bovine serum and 0.2 % Triton X-100 in PBS at room temperature. Subsequently, sections were washed three times in TBS and incubated in ABC (Vector lab, USA) for 1 h. After three further washings in TBS, the reaction was visualized with 0.1 % diaminobenzidine and 0.02 % hydrogen peroxide in TB (0.05 M; pH 7.4) for 10 min in the dark. The reaction was terminated with cold TBS and the sections were flattened on to nontreated glass slides, air-dried and coverslipped with Permount. Slides were analyzed with a Zeiss Axioscope equipped with a CCD high-resolution camera (Hamamatsu Photonic Italy, C5405). The images were converted by a microcomputer-assisted analysis system (MCID-M2; Imaging Res. Inc. Canada) to a 640 × 512 pixel file and quantitatively analyzed according to the guidelines by Capowski (Capowski 1989). The following areas were considered [according to the atlas by Paxinos and Watson (2007)] for TH immunocytochemistry: DS (caudateputamen), VS (nucleus accumbens and olfactory tubercle), VTA and SN pars compacta. The sections from different animals corresponding to the same level were aligned using neuroanatomical markers. Measurements were taken at low magnification (objective 2.5× Plan-Neofluar, Zeiss). The number of sections was 8–10 for each animal per staining technique. The region of interest was outlined in each section and the relative optical density (ROD % log10 (256/observed gray levels) of the TH signal was measured. To obtain digital pictures of brain preparations from different groups, slices were photographed with a CCD digital camera (C-5985, Hamamatsu Photonics, Milan, Italy) and Image Pro-Plus software (Media Cybernetics, Silver Springs, MD, USA).

NMDAR1 subunit and DAT protein

Preparation of protein extracts

Membrane and cytosolic protein fractions were prepared as previously described (Fumagalli et al. 2008) with minor modifications. Tissues were homogenized in a glass-Teflon potter in cold 0.32 M sucrose buffer (pH 7.4) containing 1 mM HEPES, 0.1 mM EGTA, 0.1 mM phenylmethylsulfonyl fluoride and commercial cocktails of protease (Roche, Monza, Italy) and phosphatase (Sigma-Aldrich) inhibitors. The homogenate was clarified at 1,000*g* for 10 min obtaining a pellet (P1) corresponding to the nuclear fraction. The supernatant (S1) was then centrifuged at 13,000*g* for 15 min to obtain a clarified fraction of cytosolic proteins (S2) and a pellet (P2) corresponding to the crude membrane fraction that was homogenized in a glass potter in 1 % Triton X-100 buffer containing 50 mM Tris–HCl (pH 7.4), 300 mM NaCl, 5 mM EDTA and 0.02 % sodium azide. Total protein content was measured according to the Bradford Protein Assay procedure (Bio-Rad, Milan, Italy), using bovine serum albumin as calibration standard.

Gel electrophoresis and immunoblotting

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and transfer of proteins to nitrocellulose membranes were performed using conventional methods with minor modifications. The proteins were solubilized in loading buffer at 54 °C for 45 min, separated on 10 % polyacrylamide gels and transferred to PVDF membranes (GE Healthcare, Munich, Germany) in transfer buffer (25 mM Tris [pH 8.3], 192 mM glycine, 20 % methanol). The membranes were incubated with blocking buffer (5 % ECL blocking agent [GE Healthcare] in PBST [0.1 M phosphate buffered saline {pH 7.0}, 0.1 % Tween-20]) for 1 h at room temperature. The conditions for the primary antibodies were as follows: overnight incubation at 4 °C with the antibodies of either NMDAR1 (1:300 anti-NMDAR1 Chemicon-Millipore AB9864), DAT (1:500 anti Dopamine Transporter Millipore AB2231), Actin (1:500 anti-Actin Sigma A2066) or Actin (1:3000 anti-Actin clone C4 Chemicon-Millipore MAB1501). After three 10-min washings in PBST, the blots were incubated for 1 h at room temperature with horseradish peroxidase-conjugated secondary antibody (antirabbit or antimouse ECL antirabbit IgG HRP-linked whole Ab; GE Healthcare NA934, NA931). After washing, immunocomplexes were visualized with chemiluminescence using the ECL Western

blotting kit (GE Healthcare). All protein bands were within linear range of standard curves, and were normalized for actin level in the same membrane. Quantity One software (BioRad Laboratories, Hercules, CA) was used for standardization and quantification of protein bands obtained with Western blot analysis.

Statistics

All data were tested for fulfillment of the requirements for parametric analysis (Levene's test for univariate analysis and Box test of equality of covariance matrices for repeated measures analysis) using SPSS software (Version 11.0). For body weight and each behavioral parameter, a separate two-way repeated measures analysis of variance (ANOVA) was carried out, with treatment as between-group factor and time as repeated measures factor. Duration of leaning and rearing as measures of nonselective attention were evaluated by two-way ANOVAs with treatment as between-group factor and time as covariate. For selective attention, emotionality index and regional levels of soluble and membrane-trapped L-Glu/L-Leu and L-Asp/L-Leu ratios one-way ANOVAs were calculated with treatment as between-groups factor. The level of significance was set at $p_{\text{two-sided}} < 0.05$. Post hoc analysis was performed by Tukey's or LSD tests. Regional DAT protein levels and TH levels (expressed as percentage of baseline) after In-DA were compared between rat lines using the independent t test (two-tailed, $p_{\text{two-sided}} < 0.05$). NMDAR1 subunit levels could not be statistically analyzed due to the small sample sizes.

Results

Body weight

During the entire treatment period, the body weight of animals receiving IN-DA in different doses did not differ from vehicle-treated controls. Two-way repeated measures ANOVA (treatment × time) showed a significant main effect only for time ($F = 618.0$, $df = 2/50$, $p < 0.000$) with no interaction. Thus, all groups exhibited a similar increase in body weight (data not shown).

Behavior

Làt maze

Horizontal activity In the NHE rats, two-way ANOVA revealed significant main effects for treatment ($F = 3.01$, df 3/28, $p < 0.046$) and for time ($F = 16.27$, df 5/140, $p < 0.000$), with no interaction effects. Post hoc analysis with Tukey's test showed that the treatment effect—the reduction in horizontal activity—was due to the high dose of 0.3 mg/kg DA ($p < 0.028$). In contrast, in the NRB rats no significant differences were obtained for either treatment or time. As shown in Fig. 1a, only the dose of 0.3 mg/kg significantly reduced horizontal activity in the NHE rats. Horizontal activity over time of testing was similar across groups, as demonstrated by a significant main effect for time (see above) in the absence of a significant treatment per time interaction.

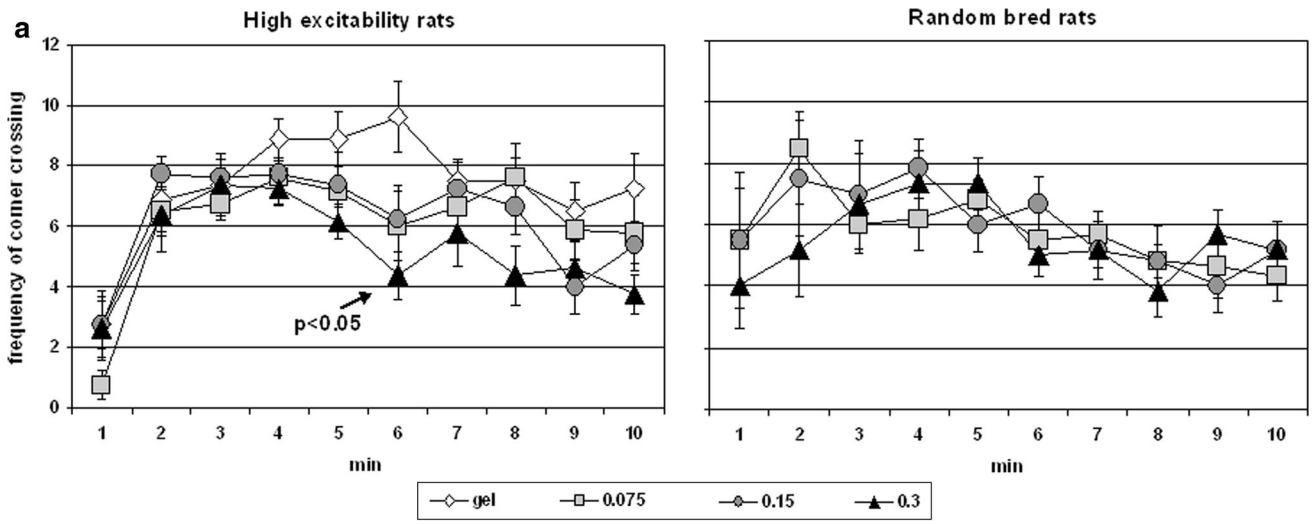
Frequency of leaning and rearing IN-DA treatments did not affect the orienting frequency, as measured by the frequency of leaning on the hind limbs against the wall in either NHE or NRB rats. Two-way ANOVAs yielded significant main effects only for time in leaning frequency in the NHE rats ($F = 8.11$, df 9/252, $p < 0.0001$) with a treatment per time interaction effect ($F = 1.66$, df 27/250, $p < 0.024$) and for time in rearing frequency in NRB controls ($F = 1.98$, df 9/180, $p < 0.043$) with no interaction.

Duration of leaning and rearing (measure of non-selective attention) IN-DA treatment with 0.3 mg/kg increased the duration of leaning against the wall in the NHE but not NRB rats, as demonstrated by one-way ANOVA ($F = 3{,}175$, $df = 3/28$, $p < 0.039$) (Fig. 1b). Two-way ANOVAs for treatment × time yielded significant main effects in both NHE ($F = 2.48$, df 5/139, $p < 0.034$) and NRB ($F = 3{,}011$, $df = 9/144$, $p < 0.003$) rats only for time without interaction.

Eight-arm radial Olton maze

Horizontal activity A two-way ANOVA for treatment and for rat line was carried out for frequency of horizontal activity in the radial maze. This analysis revealed significant main effects only for rat line in horizontal activity ($F = 12.41$, df 1/45, $p < 0.001$) (Fig. 2a), but not for treatment without interaction. This result confirms the higher horizontal activity typically exhibited by NHE rats, which has been interpreted to be of allocentric origin in the Olton maze (Berke et al. 2009).

FE and NVTC (measures of selective spatial attention/working memory) Perfect performance on this working memory task would entail exploration of each of the eight arms only once. The analysis of FE revealed a significant effect only for treatment ($F = 3.88$, df 3/45, $p < 0.015$). Separate one-way ANOVAs for each rat line revealed a significant treatment effect only in the NHE rats ($F = 5.73$, df 3/28, $p < 0.004$). Tukey's test showed that the treatment with 0.15 mg/kg significantly increased the FE value. In



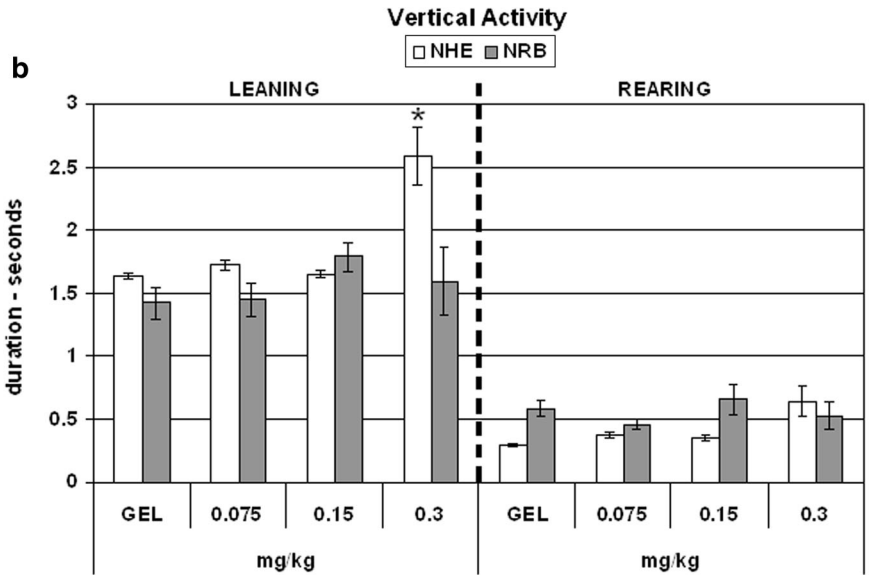


Fig. 1 Làt maze: behavioral effects of IN-DA on activity and nonselective attention in prepuberal NHE and NRB rats. Frequency of corner crossings plotted over the 10-min exposure per-min blocks. **a** Mean duration of rearing and leaning, **b** data are given as mean ± SEM (*$p < 0.05$)

fact, NHE rats typically re-entered a previously visited alley, whereas the control rats did this after having visited eight alleys in a row ($p < 0.045$) (Fig. 2b). This result indicates that the intermediate dose of IN-DA improved spatial attention/working memory in the NHE rats.

Emotionality index

The defecation score, indexed by the number of fecal boli laid down during testing in the Làt maze and Eight-arm radial Olton maze, yielded no significant differences across treatment groups. Separate one-way ANOVAs showed no treatment effect in the two mazes (data not shown).

Basal levels of glutamate and aspartate

Prefrontal cortex

The values of Glu and Asp corrected for Leu (which does not participate in neurotransmission) for NHE and NRB rats for the soluble and membrane-trapped form under basal conditions are shown in Fig. 3a. A one-way ANOVA demonstrated a lower level of soluble L-Glu/L-Leu in NHE rats relative to NRB controls ($F = 26.19$; $df = 1/4$, $p < 0.007$). Moreover, the level of membrane-trapped L-Glu/L-Leu was lower in NHE rats relative to NRB controls ($F = 88.47$; $df = 1/4$, $p < 0.001$). Soluble L-Asp/L-Leu

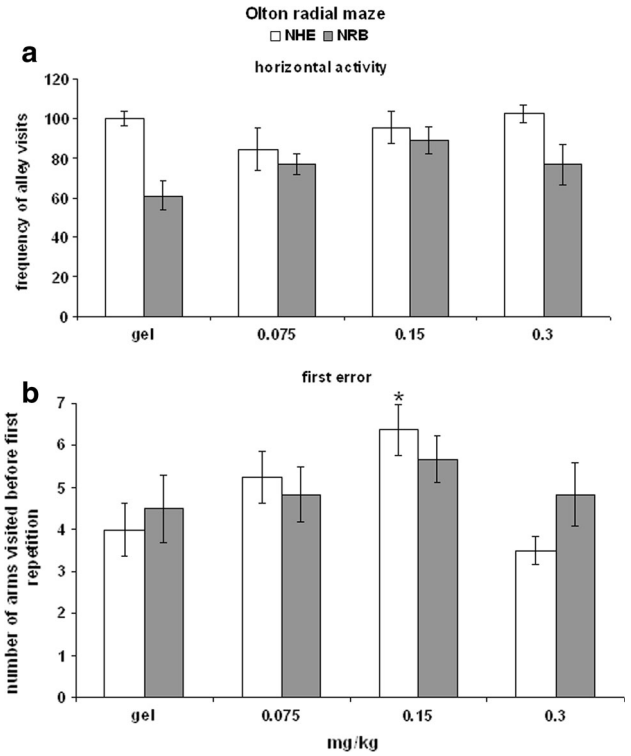


Fig. 2 Eight-arm radial Olton maze: effects of prepuberal IN-DA on indices of horizontal activity (**a**) and selective spatial attention/working memory (FE values, i.e., number of arms visited before repetition error) (**b**) in adult NHE and NRB rats. An efficient rat would explore the eight arms only one time; thus, the best possible score would be 9 for first error. Data given as mean ± SEM (*$p < 0.05$)

was also lower in NHE than in NRB rats ($F = 219.81$; $df = 1/4$, $p < 0.001$), whereas no significant difference of the membrane-trapped form of L-Asp/L-Leu was observed between rat strains.

Dorsal striatum

Levels of soluble and membrane-trapped L-Glu/L-Leu were lower in the DS of NHE rats relative to NRB controls ($F = 186.80$; $df = 1/4$, $p < 0.001$ and $F = 171.68$; $df = 1/4$, $p < 0.001$, respectively) as shown in Fig. 3b. Soluble L-Asp/L-Leu was lower in the DS of NHE as compared to NRB rats ($F = 3.352$; $df = 1/4$; $p < 0.027$), whereas membrane-trapped L-Asp/L-Leu was higher in the DS of NHE rats relative to NRB controls ($F = 250.50$; $df = 1/4$; $p < 0.001$).

Ventral striatum

Soluble L-Glu/L-Leu was lower in the VS of NHE rats compared to NRB controls ($F = 20.72$; $df = 1/4$, $p < 0.010$). No significant difference was evident for soluble L-Asp/L-Leu, as shown in Fig. 3c. Membrane-trapped L-Glu/

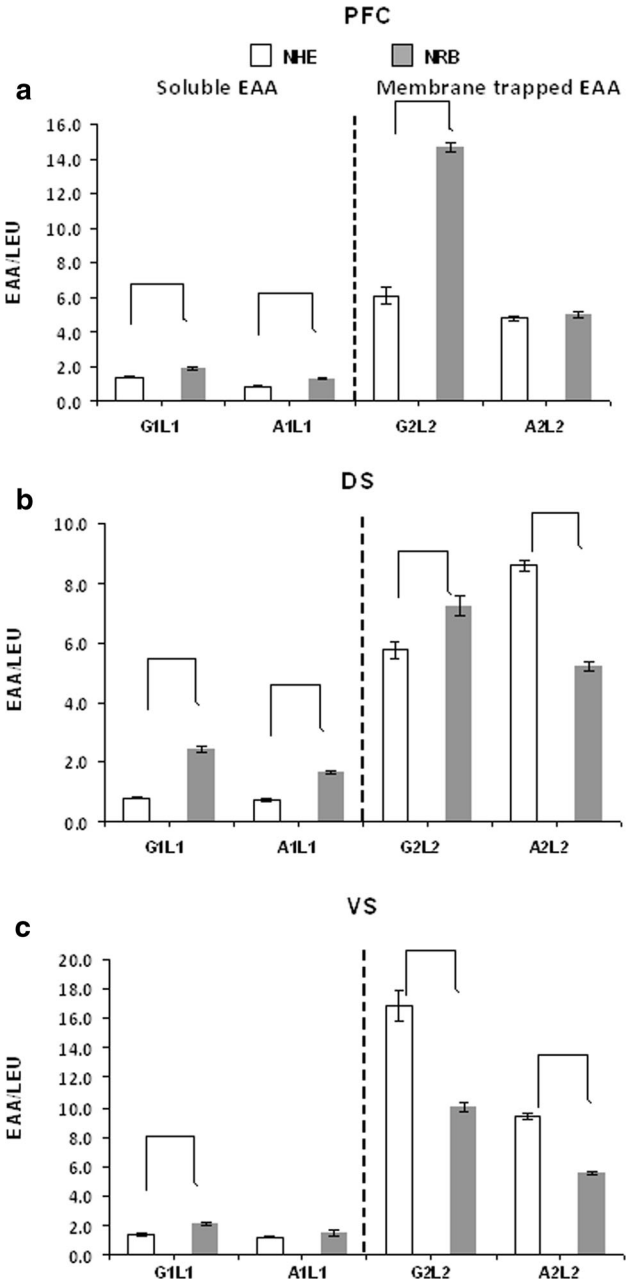


Fig. 3 L-Glu/L-Leu and L-Asp/L-Leu ratios for soluble and membrane-trapped forms in **a** prefrontal cortex (PFC), **b** dorsal striatum (DS) and **c** ventral striatum (VS) of NHE and NRB rats under basal conditions. Data given as mean ± SEM (*$p < 0.05$)

L-Leu and L-Asp/L-Leu were higher in the VS of NHE rats relative to NRB controls ($F = 38.53$; $df = 1/4$, $p < 0.003$ and $F = 268.588$; $df = 1/4$, $p < 0.001$, respectively).

Glutamate and aspartate after IN-DA

Prefrontal cortex

An one-way ANOVA on NHE rats showed an increase of soluble L-Glu/L-Leu ($F = 7.90$; $df = 2/6$, $p < 0.021$).

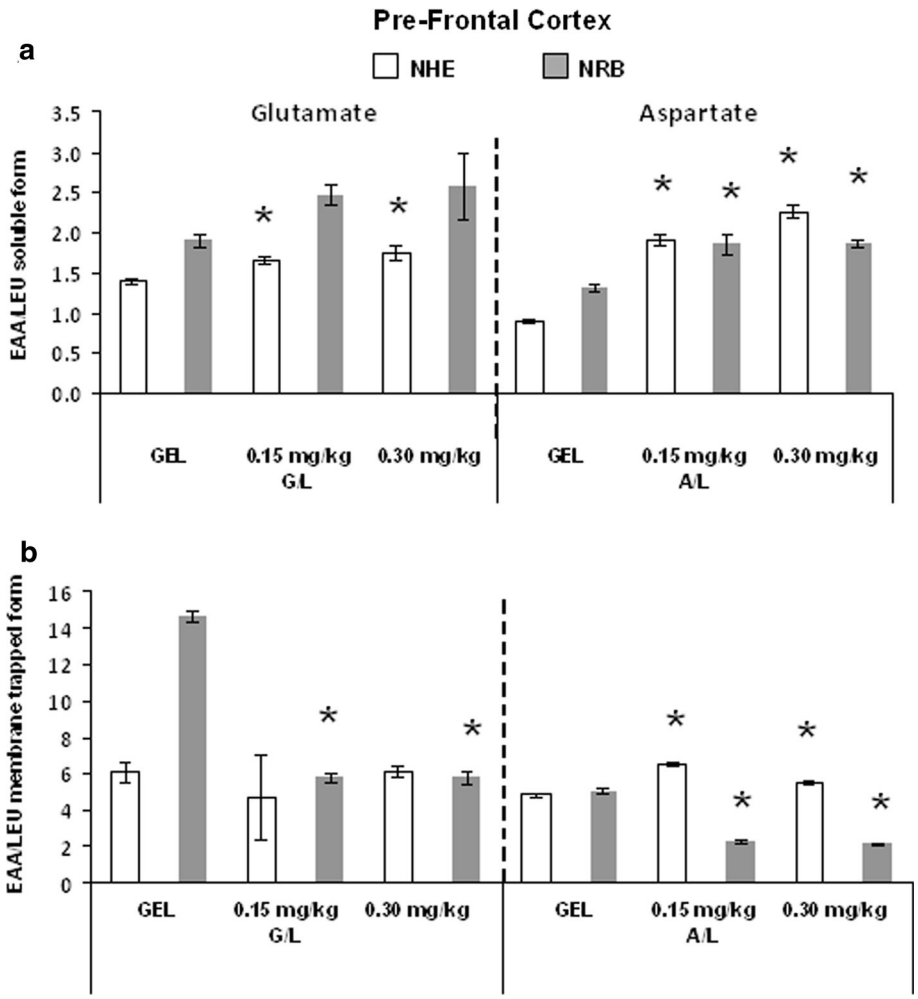


Fig. 4 L-Glu/L-Leu (G/L) and L-Asp/L-Leu (A/L) ratios in the soluble form (**a**) and in the membrane-trapped form (**b**) in the prefrontal cortex of NHE and NRB rats for each dose of IN-DA treatment. Data given as mean ± SEM (*$p < 0.05$)

Moreover, increases of both soluble ($F = 143.85$; $df = 2/6$, $p < 0.000$) and membrane-trapped L-Asp/L-Leu ($F = 39.85$; $df = 2/6$, $p < 0.000$) were observed. The LSD test revealed that this was due to both the 0.15 and the 0.3 mg/kg doses (soluble L-Glu/L-Leu, 0.15 mg/kg, $p < 0.028$; 0.3 mg/kg, $p < 0.009$; soluble L-Asp/L-Leu, $p < 0.0001$ both; membrane-trapped L-Asp/L-Leu, $p < 0.0001$ both).

A reduced level of L-Glu/L-Leu only in the membrane-trapped form was observed in the NRB rat line ($F = 302.90$; $df = 2/6$, $p < 0.000$), whereas increased and decreased levels of L-Asp/L-Leu were observed in soluble ($F = 14.31$; $df = 2/6$, $p < 0.005$) and membrane-trapped ($F = 177.40$; $df = 2/6$, $p < 0.000$) form, respectively. The LSD test showed that both 0.15 and 0.3 mg/kg doses affected the EEA levels (soluble L-Asp/L-Leu, $p < 0.004$ both; membrane-trapped L-Glu/L-Leu, $p < 0.0001$ both; membrane-trapped L-Asp/L-Leu, $p < 0.0001$ both) as shown in Fig. 4a, b.

Dorsal striatum

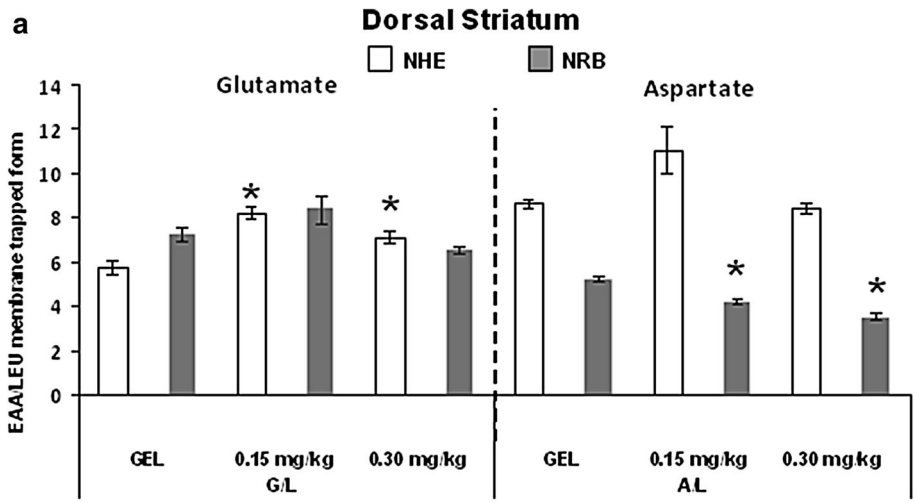
One-way ANOVA on NHE rats showed an increased ratio of L-Glu/L-Leu only for the membrane-trapped form ($F = 17.83$; $df = 2/6$, $p < 0.03$; Fig. 5a). LSD tests evidenced that this was due to either the 0.15 mg/kg dose (L-Glu/L-Leu, $p < 0.01$) or the 0.300 mg/kg dose (L-Glu/L-Leu, $p < 0.016$). A reduced ratio of L-Asp/L-Leu only in the membrane-trapped form ($F = 4.70$; $df = 2/6$, $p < 0.001$) was observed in the NRB rat line. The LSD test showed that both 0.15 and 0.3 mg/kg dose affected EEA levels (L-Glu/L-Leu, $p < 0.003$ and L-Asp/L-Leu, $p < 0.0001$).

Ventral striatum

One-way ANOVA on NHE rats evidenced no differences of L-Glu/L-Leu levels between either dose of IN-DA and vehicle. An increase of soluble L-Glu/L-Leu ($F = 6.72$; $df = 2/6$, $p < 0.029$) was obtained for NRB controls with the LSD test revealing that this was due to the 0.150 mg/kg dose ($p < 0.026$; Fig. 5b).

Levels of tyrosine hydroxylase

The ratio of TH levels obtained after IN-DA (0.015 and 0.3 mg/kg) and vehicle in the VTA is shown in Fig. 6



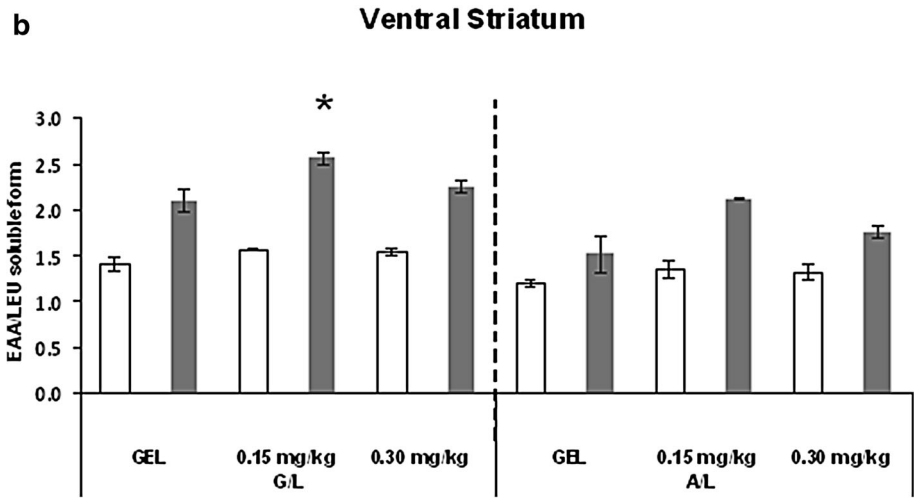


Fig. 5 L-Glu/L-Leu a (G/L) and L-Asp/L-Leu (A/L) ratios in the membrane-trapped form in the dorsal striatum (**a**) and in the soluble form in the ventral striatum (**b**) of NHE and NRB rats for each dose of IN-DA treatment. Data given as mean ± SEM (*$p < 0.05$)

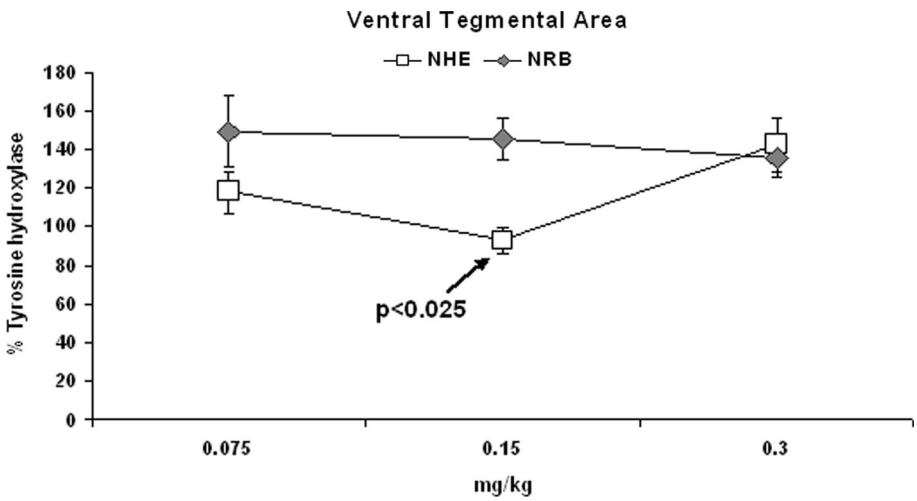


Fig. 6 Tyrosine hydroxylase levels after IN-DA (expressed as percentage of gel) for NHE and NRB rat lines in the ventral tegmental area for each dose of IN-DA. Data are given as mean ± SEM (*$p < 0.05$)

for both NHE and NRB rats. In NHE rats, TH was decreased after 0.15 mg/kg IN-DA, but increased after 0.3 mg/kg IN-DA ($t = 3.19$; *df* 8/10; $p < 0.025$). On the contrary, in the NRB rats treated with IN-DA no significant changes of TH levels were observed for either dose. Moreover, no significant changes were found in the SN of either NHE or NRB rats after any dose of IN-DA (Table 2).

Table 2 Tyrosine hydroxylase levels as percentage of vehicle with standard error of mean (SEM) in NHE and NRB rats after IN-DA treatment

Tyrosine hydroxylase in ventral tegmentum (VTA)				
Dose IN-DA	NRB		NHE	
	% Vehicle	Sem %	% Vehicle	Sem %
0.075	149.36	18.24	117.92	11.10
0.150	145.48	10.86	92.65	7.01
0.300	135.37	9.48	142.42	13.88
SN				
Dose IN-DA	NRB		NHE	
	% Vehicle	Sem %	% Vehicle	Sem %
0.075	137.40	26.09	117.97	12.29
0.150	122.47	13.62	92.04	6.58
0.300	162.64	15.48	144.35	14.90

Basal DAT protein levels

Prefrontal cortex

The levels of DAT protein in the PFc of NHE and NRB rats are shown in Fig. 7a. The present preliminary analysis indicated that in the NHE rat line the DAT protein levels were higher relative to NRB controls e ($\approx$143 %; $p < 0.0001$).

Dorsal striatum

In the DS, no differences between strains were observed (Fig. 7b).

Ventral striatum

In the VS of NHE rats, DAT protein levels were higher relative to NRB controls ($\approx$156 %; $p < 0.057$; Fig. 7c.

Mesencephalon

DAT protein levels were lower in the MES of NHE compared to NRB rats (about 41 %; $p < 0.013$; Fig. 7d).

DAT protein levels after IN-DA

Prefrontal cortex

An increased DAT protein level was observed in NHE rats (Fig. 8a) treated both with IN-DA 0.15 mg/kg (+79 %, *t* test, $p < 0.037$) and 0.300 mg/kg (+120 %, $p < 0.004$) compared to vehicle. In NRB controls (Fig. 8b) the 0.15 mg/kg dose increased l DAT protein levels (+62 %; $p < 0.029$), whereas no significant differences were observed after 0.3 mg/kg IN-DA.

Dorsal striatum

DAT protein levels of NHE rats (Fig. 8a) treated with IN-DA at 0.150 and 0.3 mg/kg did not differ relative to vehicle. In NRB rats (Fig. 8b) treatment with 0.15 mg/kg yielded increased DAT protein levels (+48 %, *t* test, $p < 0.0194$) whereas no significant differences were observed after the 0.3 mg/kg dose.

Ventral striatum

In neither NHE nor NRB rats IN-DA treatment produced a significant effect on DAT protein levels (Fig. 8a, b).

Mesencephalon

In neither NHE nor NRB rats IN-DA treatment produced a significant effect on DAT protein levels (Fig. 8a, b).

NMDAR1 subunit protein levels

In the present study, IN-DA was only injected in a small sample ($N = 3$/group) of prepuberal NHE rats. Although the group size did not allow for statistical analysis, the results may be indicative of action (Fig. 9).

In the PFc of NHE rats the NMDAR1 subunit protein level increased from 0.12 to 0.15, whereas in NRB controls it decreased from 0.06 to 0.03 starting, however, from a lower baseline level. In the DS of NHE rats the NMDAR1 subunit protein level decreased from 0.15 to 0.07, whereas in the NRB rats, it increased from 0.04 to 0.08 after the 0.15 mg/kg dose (starting from a lower baseline level) and remained at 0.04 after the 0.30 mg/kg dose. In the VS of NHE rats the NMDAR1 subunit protein level increased from 0.12 to 0.20, and in the VS of NRB rats from 0.03 to 0.09.

Discussion

NHE vs NRB—basal conditions

Findings showed reduced levels of soluble L-Glu in the PFc, DS and VS of NHE rats relative to NRB controls, while membrane-trapped L-Glu levels were decreased in PFc and DS, but elevated in VS. Levels of soluble L-Asp were lowered in PFc and DS of NHE rats relative to NRB controls, but unaltered in the VS. In contrast, membrane-trapped Asp levels were unaltered in the PFc, but elevated

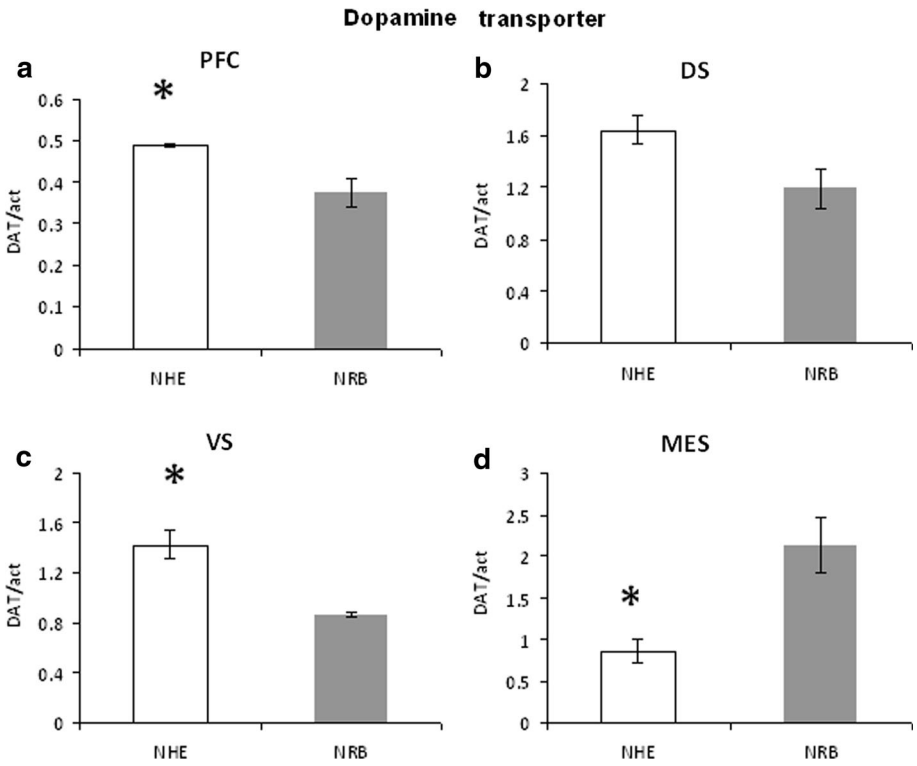


Fig. 7 Basal dopamine transporter (DAT) protein levels in **a** prefrontal cortex (PFC), **b** dorsal striatum (DS), **c** ventral striatum (VS) and **d** mesencephalon (MES) of NHE and NRB rats. Data given as mean ± SEM of DAT over actine (DAT/act). Data are given as mean ± SEM (*$p < 0.05$)

in the DS and VS of NHE rats relative to controls. Taken together, findings evidence a reduction of soluble EAAs in the PFc and DS and an elevation of membrane-trapped EAAs in the VS of NHE rats. Moreover, NMDAR1 subunit proteins were elevated in PFc, DS and VS of NHE rats, and DAT protein levels were increased in PFc and VS, decreased in MES and unaltered in DS.

The results obtained on EAA levels in PFc correspond to previous findings of higher EAA levels in the PFc of NHE rats (Ruocco et al. 2009b; however, see below). Likewise, findings obtained on NMDAR1 subunit protein levels in PFc and DS are consistent with previous findings of increased NMDA-sensitive [3H]glutamate binding in these regions (Sadile et al. 1996). Moreover, the relevance of EAA hyperactivity in neuropsychiatric disorders is underlined by the recent findings of increased Glu levels in the anterior cingulate of ADHD and borderline patients (Hoerst et al. 2010; Rüsch et al. 2010). The finding of increased prefrontal DAT protein levels corroborates previous findings on NHE rats (Viggiano et al. 2002a, 2003; Ruocco et al. 2009c). Moreover, results obtained on DAT protein levels in DS and MES of NHE rats relative to NRB controls are consistent with findings of unaltered neostriatal DAT (van Dyck et al. 2002; Jucaite et al. 2005) and decreased midbrain DAT binding in ADHD patients (Jucaite et al. 2005). They do not correspond, however, to the increases of neostriatal DAT binding observed in the majority of in vivo investigations (Dougherty et al. 1999; Krause et al. 2000; Dresel et al. 2000; la Fougere et al. 2006; Larisch et al. 2006; Spencer et al. 2007).

If we proceed from the assumption that regulatory mechanisms aim to maintain functional homeostasis throughout the central nervous system, the decrements of soluble L-Glu in PFc, DS and VS and of soluble L-Asp in PFc and DS are in agreement with the observed increases of the NMDAR1 subunit protein in these regions, which may be interpreted in terms of a compensatory up-regulation of available binding sites. This also holds for the decrease in membrane-trapped L-Glu in PFc and DS, but, interestingly, not for membrane-trapped L-Glu in VS, as well as membrane-trapped L-Asp in PFc, DS and VS. Therefore, it may rather be inferred that the concentrations of membrane-trapped EAAs have increased in response to the increased availability of NMDA binding sites. If this be the case, then NHE rats may be hypothesized to have more NMDA receptors relative to NRB controls, leading to, first, an increase in L-Glu binding in the VS as well as of L-Asp binding in both DS and VS, and, secondly, to corresponding decreases of soluble L-Glu and L-Asp in these regions. It remains to be seen, however, in as much NMDAR1 subunit protein levels correspond to the final expression of NMDA receptor molecules. Yet, for the time being, the role of NMDA dysfunction in human ADHD is underlined by the association of ADHD with variations of the NMDA-type Glu receptor subunit genes (GRIN1, 2A-D; Dorval et al. 2007).

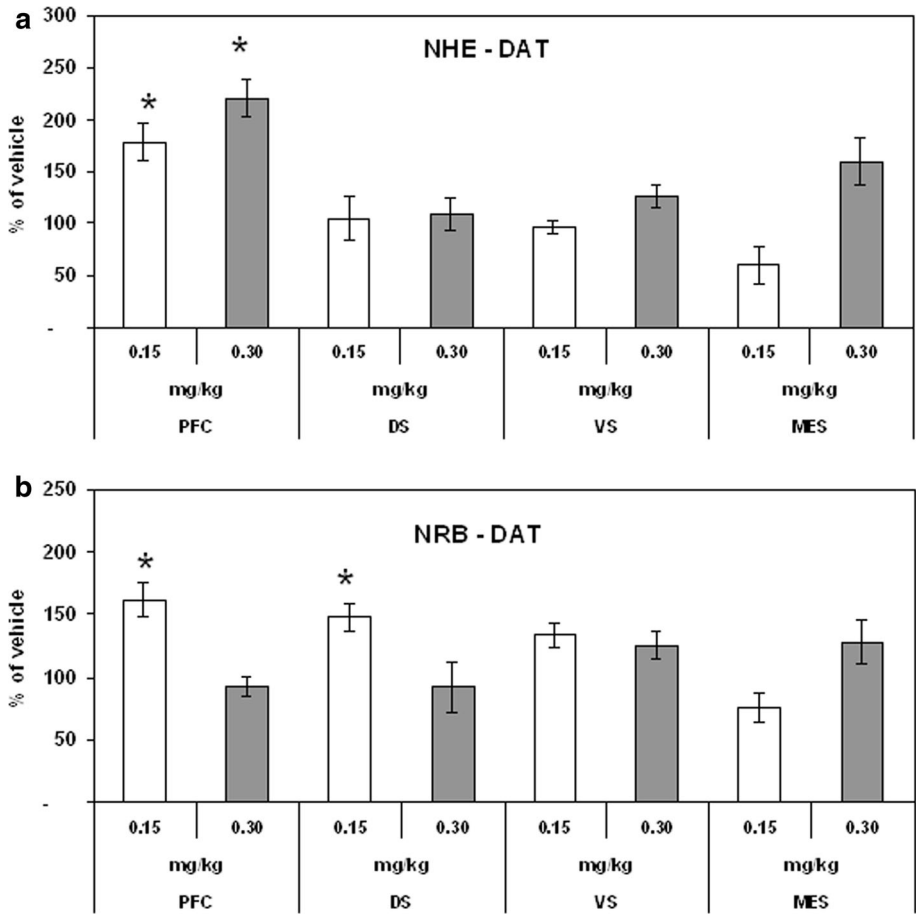


Fig. 8 DAT protein levels (as percent of vehicle) in prefrontal cortex (PFC), dorsal striatum (DS), ventral striatum (VS) and mesencephalon (MES) of NHE (**a**) and NRB (**b**) rats after IN-DA (0.15 and 0.30 mg/kg). Data are given mean ± SEM (*$p < 0.05$)

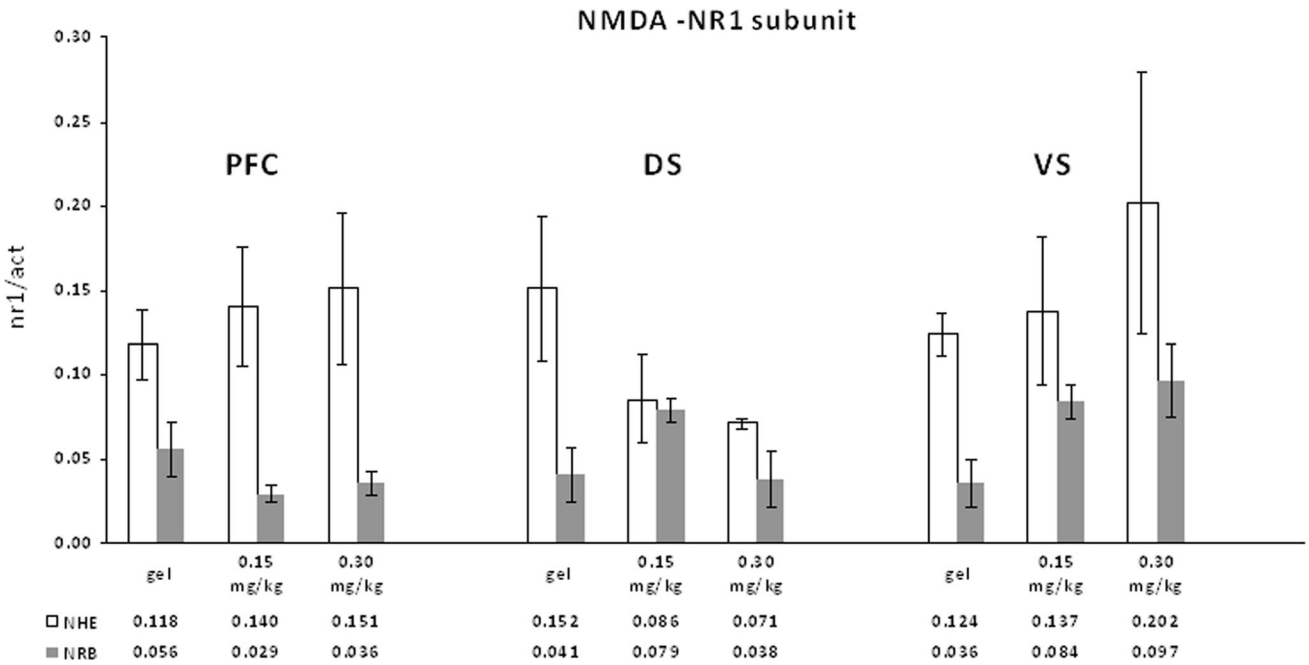


Fig. 9 NMDAR1 subunit protein levels in prefrontal cortex (PFC), dorsal striatum (DS) and ventral striatum (VS) in NHE and NRB rats after IN-DA (0.15 and 0.30 mg/kg) and vehicle. Data given as mean ± SEM of NMDA-R1/nr1 over actine (nr1/act)

Taken together, NHE rats may be characterized by both elevated prefrontal NMDAR1 subunit proteins and elevated prefrontal and ventral striatal DAT protein levels. Glu is known to stimulate DA release (Clow and Jhamandas 1989), while Glu release is inhibited by the D2 receptor subtype (Yamamoto and Davy 1992). Thus, it may be hypothesized that the elevation of excitatory input to the prefrontal target region of mesostriatal efferents in NHE rats induces an increase of DA efflux, which, in turn, diminishes EAA concentrations. This conjecture is consistent with the observed increases of DAT protein in both the VS and the prefrontal target region of mesolimbic DAergic projections. It remains to be elucidated, however, in as much the level of transporter protein corresponds to the final expression of DAT molecules on the presynaptic terminal, and whether human ADHD and the rat NHE model of this disease basically differ with respect to the impact of DAT function in DS and VS (the latter of which in NHE rats displayed a significant increase of DAT protein levels relative to NRB controls).

NHE versus NRB—IN-DA treatment

Firstly, in the PFc of NHE rats, IN-DA elicited an increase of both soluble L-Glu and L-Asp, whereas in NRB controls prefrontal soluble L-Asp was increased, but prefrontal soluble Glu remained unaltered. Moreover, both membrane-trapped L-Glu and L-Asp were decreased in the PFc of NRB rats, whereas they were unaltered and augmented, respectively, in prefrontal tissues of NHE controls. Secondly, in the DS of NHE rats, IN-DA elicited an increase in membrane-trapped L-Glu with no alterations of soluble L-Glu, soluble L-Asp and membrane-trapped L-Asp in this region, whereas in the DS of NRB controls membrane-trapped L-Asp was elevated and soluble L-Asp, soluble L-Glu and membrane-trapped L-Glu remained unaltered. Thirdly, in the VS of NHE rats, no effect was exerted on EAA concentrations by IN-DA, whereas in the VS of NRB controls concentrations of soluble L-Glu were elevated with no alterations of soluble L-Asp and both membrane-trapped L-Glu and L-Asp. From this, it follows that NHE and NRB lines differ as to the regional effects of IN-DA on soluble and membrane-trapped EAAs. It may be hypothesized that the varying effects on soluble and membrane-trapped EAA levels in NHE rats and NRB controls are associated with between-strain differences of regional DA and EAA function.

The application of IN-DA can be assumed to increase DA levels in the mesocorticolimbic system (de Souza Silva et al. 2008). If DA is applied to NRB controls, DAT protein levels, therefore, may be expected to rise in both striatum and prefrontal target regions of mesostriatal efferents, as was the case in the present investigation. In the NHE rat model, basal striatal DAT binding sites may be expected to be higher relative to normal animals; thus, an increase of available DA is not likely to lead to a further elevation of striatal DAT protein levels. Accordingly, in the present investigation, both dorsal and ventral striatal DAT protein levels were unaltered after IN-DA relative to vehicle. Findings indicate, however, that prefrontal DAT protein levels had risen, presumably as an adaptive response to the increased availability of DA in the prefrontal target regions of striatal efferents.

DA synthesis and release are modulated by a negative feedback loop, which is established by DA acting upon presynaptic terminal autoreceptors of the inhibitory D2/3 receptor subtype (for review see Langer 1997). In NRB controls, the elevation of DA levels by 0.15 and 3 mg/kg IN-DA had no effect on ventral tegmental TH levels. Apparently, these doses did not augment mesostriatocortical DA levels to an extent requiring the onset of regulatory feedback mechanisms in SN or VTA. In contrast, in NHE rats a biphasic action was observed in the VTA with a decrease of TH after 0.15 mg/kg and an increase of TH after 0.3 mg/kg IN-DA. From this it may be concluded that DA concentrations after 0.3 mg/kg IN-DA at the time of sacrifice and brain dissection were lower compared to the 0.15 mg/kg dose. Evidently, the application of the higher dose had resulted in DA concentrations sufficient to activate feedback inhibition at the presynaptic terminal resulting in reduced levels of TH, which catalyzes the conversion of L-tyrosine to the DA precursor L-3,4-dihydroxyphenylalanine. The subsequent reduction of DA levels, then, is likely to have disinhibited presynaptic D2 autoreceptors leading again to an enhancement of DA synthesis (indicated by the increase of TH levels) and release.

The application of IN-DA can be expected to enhance both inhibitory and excitatory DAergic neurotransmission in the mesocorticolimbic system. As Glu release is inhibited by DA (Yamamoto and Davy 1992), an elevation of available DA is likely to lead to an inhibition of EAA efflux in both DS and VS. This conjecture is in agreement with the increases of NMDAR1 subunit protein levels observed in both NHE and NRB rats in these regions, which may be interpreted in terms of a compensatory up-regulation of available NMDA receptor binding sites. As a matter of fact, the inhibition of striatal EAA efflux by the increased availability of striatal DA offers a more extensive explanation for the efficacy of methylphenidate treatment of human ADHD beyond the elevation of DA levels via blockade of re-uptake sites (for review see Volkow et al. 2005). In NHE rats also prefrontal NMDAR1 subunit protein levels were found to be increased, while they were decreased in NRB controls. From the increase of striatal NMDAR1 subunit protein levels a net elevation of

EAAergic input to prefrontal projection areas may be inferred, which is likely to be compensated by the decrease of NMDAR1 subunit protein levels in this area. This adaptive mechanism of prefrontal NMDA receptor function could not be detected in NHE rats, supporting our hypothesis of NMDA hyperfunction in this ADHD animal model. Moreover, in NHE rats prefrontal soluble L-GLu and L-Asp as well as membrane-trapped L-Asp levels were elevated, which may also be interpreted in terms of prefrontal EAA hyperactivity relative to NRB controls.

The regional differences between both soluble and membrane-trapped EAAs in both baseline and after IN-DA imply that EAA function is severely disturbed in the NHE rat model of ADHD also after long-term IN-DA treatment. Basal prefrontal and dorsal striatal levels of both soluble and membrane-trapped EAA levels appear to be lowered relative to normal rats, which may be causally related to an increased availability of NMDA binding sites (as indicated by the elevation of baseline prefrontal and both dorsal and ventral striatal NMDAR1 subunit protein levels relative to NRB controls) and, possibly, a compensatory net EAA hyperfunction. A further decrease of EAA levels as induced by IN-DA, then may be surmised to result in a further increase of prefrontal and (ventral) striatal NMDAR1 subunit protein levels (and probably also NMDA binding sites). However, also the levels of soluble and membrane-trapped EAAs appear to rise adding to the effect of net EAA and NMDA hyperfunction.

Behavioral results

Horizontal activity assessed with the Làt maze was significantly reduced in NHE rats after 0.3 mg/kg IN-DA, while nonselective attention (vertical activity in terms of duration of leaning against the wall with one or both forepaws) was significantly increased after the same dose. Moreover, selective spatial attention (in terms of FE values), as obtained with the Eight-arm radial Olton maze, were significantly elevated after 0.15 mg/kg IN-DA. Interestingly, IN-DA produced no effect in NRB controls.

Findings show that IN-DA significantly influenced activity and attention in NHE rats relative to vehicle. Thereby, results on horizontal activity and FE values were consistent with previous findings on NHE rats after the same doses of IN-DA (Ruocco et al. 2009a). In contrast, however, to the present investigation, IN-DA exerted no effect on vertical activity. This might be due to the fact that the previous study did not differentiate between rearing on hind limbs and leaning against the wall with one or both forepaws, which may have led to disparate findings.

As stated above, DA synthesis and release are modulated by a negative feedback loop, which is established by DA acting upon presynaptic terminal autoreceptors of the inhibitory D2/3 receptor subtype (for review see Langer 1997). In the present study, a biphasic action was observed after IN-DA with a decrease of TH in the VTA after 0.15 mg/kg and an increase after 0.3 mg/kg IN-DA. From this may be concluded that DA concentrations after 0.3 mg/kg IN-DA at the time of killing and brain dissection were lower compared with the 0.15 mg/kg dose, as the application of the higher dose, in contrast to the lower one, had resulted, firstly, in DA concentrations sufficiently high to activate feedback inhibition at the presynaptic terminal leading to a reduction of DA synthesis and release, and then, secondly, in DA concentrations sufficiently low to disinhibit presynaptic D2 autoreceptors, leading again to an enhancement of DA synthesis (indicated by the increase of TH levels) and release. The reduction in horizontal activity, as well as the increase in nonselective attention at 1 h after IN-DA administration are, thus, likely to be related to the action of DA occurring first in order at the inhibitory D2 autoreceptor binding sites and leading to an activation of feedback inhibition and subsequent reduction in DA synthesis and release.

With the improvement of selective spatial attention (or working memory), matters are different, as here the lower IN-DA dose of 0.15 mg/kg proved to be effective. Moreover, in the Eight-arm radial Olton maze, data were acquired 24 h instead of 1 h after the last administration of IN-DA or vehicle. It follows that 0.15 mg/kg IN-DA exerted long-term effects on selective attention/working memory which was not the case for the 0.3 mg/kg dose. The fact that 0.3 mg/kg, but not 0.15 mg/kg was effective in reducing horizontal activity and increasing nonselective attention in the Làt maze suggests that the lower dose was not sufficient to induce feedback inhibition at D2 autoreceptor binding sites and reduce DA levels. The increased availability of DA in both DS and VS (elicited by the disinhibition of presynaptic D2 autoreceptors occurring second in order), however, may have induced a lasting decline of EAA levels, which may have acted back on striatal and mesostriatocortical DA neurons. Thereby, it may not be dismissed, that also the reduction of horizontal activity as well as the improvement of nonselective attention may be additionally related to the inhibition of EAA release.

Our findings may have been confounded by the fact the basal level of both EAAs were strikingly lower in NHE rats across all brain areas compared to a previous study (Ruocco et al. 2009b). This could be explained in several ways. First, in the present study, EAAs were expressed as ratio over L-Leu; as L-Leu levels were higher in NHE rats, this may have decreased the levels of soluble EAAs relative to NRB controls. Secondly, in the present study, we attempted to probe the functional compartmentalization of L-Glu and L-Asp, whereas in the previous study we considered whole

brain levels. Thirdly, discrepancies might be due to methodological differences, such as extraction from brain samples, sensitivity and selectivity of detection system (LC/MS/MS vs. HPLC). Fourthly, the higher sensitivity of LC/MS/MS allowed detection of EAAs in individual samples versus average content from pooled areas. Lastly, animal handling before the beginning of the experiment and the intranasal route of administration are likely to have resulted in milder stress (Ruocco et al. 2009d).

In addition, it must be considered that DA and EAAs not only interact with each other, but also with a variety of other neurotransmitters, including noradrenaline (NA), serotonin (5-HT), μ-aminobutyric acid (GABA) and histamine (Flint et al. 1985; Peris and Dunwiddie 1985; Barbeito et al. 1989; Rodriguez et al. 1997). The far-reaching impact of neurotransmitter interactions has been demonstrated for a variety of neuropsychiatric conditions including anxiety disorder, major depression, bipolar disorder and schizophrenia (Nikolaus et al. 2010, 2012, 2014). Also in ADHD and the NHE rat model of this disorder, the disturbances of DA and EAA function are likely to induce alterations of NAergic, 5-HTergic, GABAergic and/or histaminergic neurotransmission, which may be expected to positively or negatively influence human as well as animal behaviors. Therefore, investigations are needed, which specifically assess NA, 5-HT, GABA and/or histamine function in NHE rats. Moreover, in addition to NMDA receptor dysfunction, also disturbances of Glu signaling via metabotropic receptor subtypes is implied in the pathophysiology of ADHD (for review see Lesch et al. 2013). Thus, future efforts should be also directed towards assessing the contribution of other EAA receptor subtypes to the behavioral abnormalities of the NHE rat.

Taken together, the findings obtained in the present investigation indicate that the NHE rat model of ADHD may be characterized by (1) prefrontal and striatal DAT hyperfunction, indicative of DA hyperactivty, and (2) prefrontal and striatal NMDA receptor hyperfunction, indicative of net EAA hyperactivty. IN-DA has ameliorative effects on activity, attention and working memory, which are likely to be associated (1) with DA action at inhibitory D2 autoreceptor binding sites, leading to a reduction in striatal DA hyperactivity and, possibly, (2) with DA action on striatal EAA levels leading to a reduction in striatal EAA hyperfunction (with persistence of prefrontal EAA hyperfunction). Previous studies on IN-DA treatment in rodents have indicated antidepressant, anxiolytic and anti-parkinsonian effects in relation to enhanced central dopaminergic activity (Buddenberg et al. 2008; De Souza Silva et al. 2008; Pum et al. 2009). Our present results strengthen the prospects of potential therapeutic application of IN-DA by indicating an enhancement of selective attention and working memory in a deficit model.

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Conflict of interest None of the authors declare any conflict of interest, except for C. Mattern, who is employed by M & P Pharma AG, Emmetten, Switzerland.

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Direttori del Corso
Maurella Della Seta, Corrado Di Benedetto
SIDBAE - Istituto Superiore di Sanità, Roma
Alessandro Antonietti
Università Cattolica del Sacro Cuore, Milano

Segreteria Scientifica
Scilla Pizzarelli
Settore Documentazione – SIDBAE
Istituto Superiore di Sanità, Roma
Tel.: 06 49902520
e-mail: scilla.pizzarelli@iss.it
Tania Lopez
Dipartimento di Medicina Clinica
Sapienza Università di Roma
Tel.: 06 49902426
e-mail: tania.lopez@guest.iss.it
Elisa Zugno
Università Cattolica del Sacro Cuore, Milano
Tel.: 02 72342284
e-mail: spaee@unicatt.it

Segreteria Tecnica
Antonietta Monaco, Vincenza Elena Virgallita
Settore Documentazione – SIDBAE
Istituto Superiore di Sanità, Roma
Tel: 06 49902534
Fax: 06 49387117
e-mail: documentazione@iss.it

INFORMAZIONI GENERALI

Sede
Università Cattolica del Sacro Cuore di Milano,
Cripta Aula Magna

Ingresso
Largo A. Gemelli 1 - 20123 Milano

Per ogni informazione attinente al Corso si prega di contattare la Segreteria Scientifica:
Scilla Pizzarelli, Tania Lopez
Tel: 06 49902520, 06 49902426
e-mail: scilla.pizzarelli@iss.it, tania.lopez@guest.iss.it

Destinatari e numero massimo partecipanti
Il corso è rivolto a rappresentanti delle associazioni di pazienti, genitori, insegnanti e operatori che si confrontano con le difficoltà di attenzione, l'iperattività e l'impulsività dei bambini e ragazzi verso cui sono chiamati a svolgere un ruolo di accudimento e/o educativo e che avvertono il bisogno di orientarsi nel campo delle informazioni, multiformi e controverse, che circolano in rete.
Il corso è aperto anche a esperti di problematiche evolutive (psicologi, neuropsichiatri, psichiatri, pediatri), interessati ad aggiornare e approfondire le proprie conoscenze sull'ADHD attraverso l'analisi delle conoscenze disponibili tramite la comunicazione mediatica e le reti sociali.
Saranno ammessi un massimo di **50 partecipanti**.

Modalità di iscrizione
La partecipazione al corso è gratuita.
La domanda di iscrizione, scaricabile dal sito dell'Istituto (www.iss.it), dovrà essere compilata, firmata e trasmessa via fax al n. 06 49387117, oppure via e-mail all'indirizzo documentazione@iss.it, **entro e non oltre il 12 ottobre 2015**, al fine di permettere la selezione dei partecipanti. Si intendono ammessi a partecipare solo coloro che ne riceveranno comunicazione (via e-mail). Al partecipante è richiesto di inviare conferma o disdetta della propria partecipazione.

Modalità per la selezione dei partecipanti
La selezione delle domande verrà effettuata sulla base dei seguenti criteri:
- appartenenza ad uno dei profili dei destinatari
- equa distribuzione geografica sul territorio nazionale
- pari opportunità tra i generi
- ordine di arrivo delle domande

Viaggio e soggiorno
Le spese di viaggio e soggiorno sono a carico del partecipante

Attestati
Al termine del corso, ai partecipanti che avranno frequentato almeno tre quarti del programma sarà rilasciato l'attestato di frequenza (che include il numero di ore di formazione). La chiusura del corso e la consegna dei relativi attestati non verranno anticipate per nessun motivo ed i partecipanti sono pregati di organizzare il proprio rientro di conseguenza.

Accreditamento ECM
Non è previsto l'accreditamento ECM

Il progetto
"Alfabetizzazione sanitaria ed empowerment del paziente attraverso lo sviluppo di un sistema informativo elettronico nel campo della salute"
(# GR-2010-2313824)
è finanziato dal Ministero della Salute

Corso

MEDUSA
(MEDicina Utenti SAlute in rete)
Navigare informati per una partecipazione consapevole:
il Disturbo da Deficit di Attenzione e Iperattività (ADHD)
(come valutare le fonti di informazione e giudicare le opinioni su diagnosi e trattamento dell'ADHD)

30 ottobre 2015

Università Cattolica Del Sacro Cuore di Milano

Corso

MEDUSA
(MEDicina Utenti SAlute in rete)
Navigare informati per una partecipazione consapevole:
il Disturbo da Deficit di Attenzione e Iperattività (ADHD)
(come valutare le fonti di informazione e giudicare le opinioni su diagnosi e trattamento dell'ADHD)

co-organizzato da
Settore Documentazione, Settore Informatico
ISTITUTO SUPERIORE DI SANITA'
e
Servizio di Psicologia dell'Apprendimento e dell'Educazione in Età Evolutiva (SPAEE)
UNIVERSITÀ CATTOLICA DEL SACRO CUORE DI MILANO

30 ottobre 2015

N.ID Corso: 133C15

Rilevanza per il SSN: Tra le finalità del Piano Sanitario Nazionale 2011-2013 la diffusione dell'informazione e l'incremento della partecipazione del cittadino occupano un posto di rilievo. L'alfabetizzazione sanitaria ha un ruolo fondamentale nella promozione della salute, aumentando il livello di consapevolezza e ponendo il paziente nella condizione di comprendere come mantenersi in buona salute. I cittadini con un buon livello di informazione sanitaria hanno un ruolo fondamentale nella realizzazione di strategie di ricerca clinica incentrate sul paziente, nei processi decisionali, nell'accesso alle terapie, così come dichiarato nella European Health strategy 2008-2013.

Obiettivi generali:
Promozione dell'empowerment del cittadino e del paziente, quale mezzo per migliorare la qualità, l'efficienza e il risultato dell'assistenza sanitaria, riducendo le disuguaglianze nel campo della salute. Il corso intende offrire ai partecipanti l'opportunità di acquisire dei criteri e degli strumenti per valutare l'attendibilità dei dati disponibili in rete..

Obiettivi specifici:
1. apprendere le modalità pertinenti di ricerca e di interrogazione delle fonti informative;
2. individuare i canali informativi attendibili;
3. formulare le corrette e adeguate domande di informazione;
4. presentare lo stato attuale delle conoscenze scientifiche disponibili circa l'ADHD;
5. chiarire la linea di demarcazione tra dati e loro interpretazioni;
6. passare dalla raccolta delle informazioni alla valutazione e alle decisioni.

Metodo didattico:
Il corso prevede lezioni frontali ed esercitazioni pratiche.

Venerdì 30 ottobre 2015

9.00	Registrazione dei partecipanti
9.30	Presentazione del progetto e del portale MEDUSA **C. Di Benedetto**
9.45	Il cittadino e l'informazione medica: conoscenze, credenze, epistemologie personali **A. Antonietti**
10.00	Internet per la salute **M. Della Seta**
10.30	L'empowerment del cittadino **L. Sampaolo**
11.00	Coffee break
11.15	ADHD: che cosa possono dire oggi la ricerca e la clinica **A. Costantino**
11.45	Gli invii ai servizi per l'ADHD: informati/disinformati? **E. Zugno**
12.15	La tecnologia wireless al servizio del cittadino: le app sulla salute **T. Lopez**
12.45	Risorse informative per il cittadino **S. Pizzarelli**
13.15	Buffet
14.15	ADHD: l'educativo, il sociale, il culturale **V. Perucca**
14.45	ADHD: le domande dei genitori **F. Sgroi**
15.15	Prove di ricerca in rete **F. Danisi, C. Valenti**
16.00	Dal Registro Regionale per l'ADHD alle pratiche dei cittadini **M. Bonati**
16.30	Test di valutazione dell'apprendimento
16.45	Conclusioni

Docenti ed Esercitatori

Alessandro Antonietti
Università Cattolica del Sacro Cuore, Milano

Maurizio Bonati
Istituto di Ricerche Farmacologiche Mario Negri, Milano

Federica Danisi
Università Cattolica del Sacro Cuore, Milano

Antonella Costantino
Fondazione IRCCS Policlinico, Mangiagalli e Regina Elena, Milano

Maurella Della Seta
Settore Documentazione, Istituto Superiore di Sanità, Roma

Corrado Di Benedetto
Settore Informatico, Istituto Superiore di Sanità, Roma

Tania Lopez
Dipartimento di Medicina Clinica, Sapienza Università di Roma

Valeria Perucca
Università Cattolica del Sacro Cuore, Milano

Scilla Pizzarelli
Settore Documentazione, Istituto Superiore di Sanità, Roma

Letizia Sampaolo
Settore Documentazione, Istituto Superiore di Sanità, Roma

Francesca Sgroi
Associazione Italiana Famiglie ADHD (AIFA) e Associazione Italiana Disturbi Attenzione e Iperattività (AIDAI)

Chiara Valenti
Università Cattolica del Sacro Cuore, Milano

Elisa Zugno
Università Cattolica del Sacro Cuore, Milano

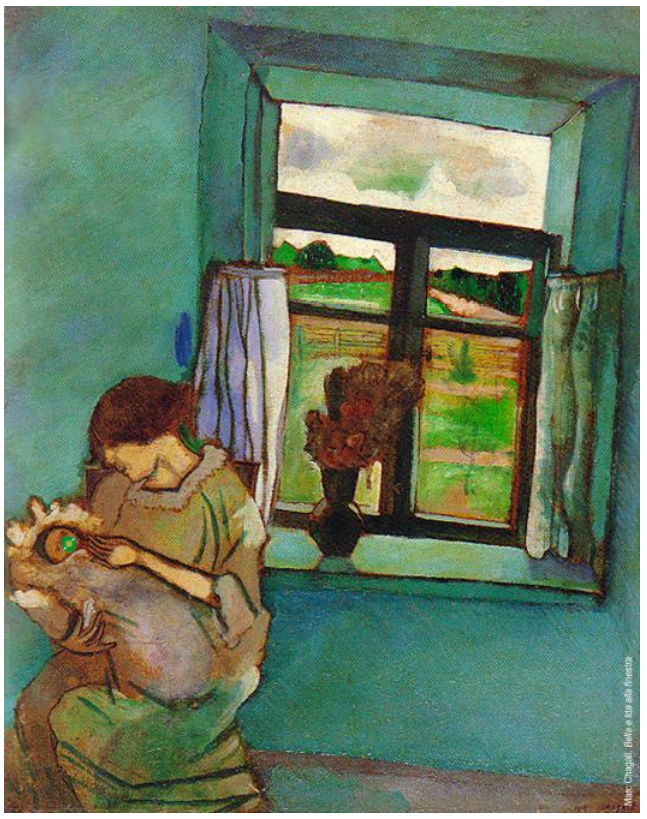
I.R.C.C.S. Fondazione Istituto Neurologico Nazionale C. Mondino
Direttore Scientifico Prof. G. Nappi

UNIVERSITÀ DEGLI STUDI DI PAVIA
Magnifico Rettore Prof. F Rugge

NUOVE PROSPETTIVE NELLA PSICOFARMACOTERAPIA DEI DISTURBI PSICHIATRICI IN NEUROPSICHIATRIA INFANTILE

Responsabile Scientifico
Umberto Balottin, S.C. Neuropsichiatria Infantile, IRCCS C. Mondino

Pavia, sabato 14 novembre 2015
IRCCS Mondino, Pavia - Aula Berlucchi



Con il patrocinio di: **ASSNPIA e AO della Provincia di Pavia**

Il convegno è organizzato nell'ambito delle attività formative per il Progetto Regionale "Presa in carico della fase post-acuta della psicopatologia dell'adolescente".

Presentazione

Il congresso ha lo scopo di fornire un aggiornamento sulle più recenti acquisizioni sul tema della psicofarmacoterapia nell'area della psicopatologia grave dell'adolescente. Le caratteristiche farmacodinamiche e farmacocinetiche delle varie sostanze utilizzabili in adolescenza e nell'infanzia sono del tutto peculiari e spesso poco studiate. Così modalità di somministrazione, dosaggi, indicazioni sono spesso completamente differenti rispetto a quanto è possibile fare in età adulta. Come ben noto i dati di efficacia e di sicurezza di farmaci utilizzabili in infanzia e adolescenza sono molto specifici e differenti da quelli dell'adulto. È perciò necessaria una specifica conoscenza di tali problematiche per poter utilizzare in modo efficace e sicuro farmaci nella psicofarmacoterapia dei disturbi gravi dell'adolescenza. Questo convegno, che nasce dalla collaborazione di tre principali centri ospedalieri di neuropsichiatria infantile della Regione Lombardia, cerca di offrire un contributo significativo per la comprensione di queste difficili tematiche del resto particolarmente cruciali per l'esito delle terapie in adolescenza.

Data e Sede

Sabato 14 novembre 2015
IRCCS C. MONDINO - Aula Berlucchi

Quote di iscrizione

Il Convegno è gratuito.
Iscrizioni on line all'indirizzo www.mondino.it

Accreditamento

È in atto la pratica di accreditamento per la certificazione dell'evento finalizzata all'attribuzione di Crediti Formativi Regionali Lombardi ECM/CPD, secondo il programma Educazione Continua in Medicina per **le seguenti figure professionali:**
Medico chirurgo (Genetica medica, Laboratorio di genetica medica, Medicina generale, Neonatologia, Neurologia, Neuropsichiatria Infantile, Pediatria, Pediatri di libera scelta, Psichiatria); **Psicologo** (psicologia, psicoterapia); **Terapista della Neuro e Psicomotricità dell'età evolutiva, Educatore Professionale, Fisioterapista, Infermiere, Infermiere Pediatrico, Logopedista, Tecnico della riabilitazione psichiatrica, Tecnico di neurofisiopatologia, Terapista occupazionale.**
L'assegnazione dei crediti è subordinata all'effettiva partecipazione al programma formativo. Sono stati preassegnati **n. 2,8 crediti ECM-CPD.**

Coordinamento e segreteria Organizzativa

Ufficio Formazione & Informazione IRCCS C. Mondino
formazione.informazione@mondino.it

Programma

8.15 – 8.45	**Registrazione partecipanti**
8.45 – 9.00	**Saluti delle autorità e introduzione ai lavori**
Moderatori:	F. Neri (Milano-Monza), E. Fazzi (Brescia), Pierangelo Veggiotti (Pavia)
9.00 – 9.25	**Alcuni nuovi quesiti nella ricerca in psicofarmaco terapia dell'età evolutiva** *M. Bonati (Milano)*
9.25 – 9.55	**La prescrizione del farmaco e il significato relazionale** *F. Petrella (Pavia)*
9.55 – 10.30	**Strategie, rischi e benefici delle associazioni farmacologiche: interazioni farmacocinetiche e farmaco-dinamiche** *A. Fagiolini (Siena)*
10.30 – 11.00	*Pausa caffè*
Moderatori: M.	P. Canevini, A. Costantino (Milano); E. Perucca (Pavia)
11.00 – 11.25	**ADHD e psicofarmacoterapia in età evolutiva** *B. Vitiello (Bethesda)*
11.25 – 11.55	**Psicosi, La terapia farmacologica** *R. Nacinovich, F. Neri (Milano-Monza)*
11.55 – 12.25	**Disturbi dell'umore e psicofarmacoterapia** *U. Balottin, M. Chiappedi, (Pavia)*
12.25 – 12.55	**La terapia farmacologica dei disturbi di aggressività e del comportamento dirompente** *G. Rossi, C. Termine (Varese)*
12.55 - 13.20	**Disturbi del comportamento alimentare e psico-farmacoterapia** *A. Albizzati, F. Cantini (Milano)*
13.20 – 13.30	**Conclusioni finali**

****

Segreteria scientifica
Umberto Balottin, Pavia
umberto.balottin@unipv.it

Francesca Neri, Milano/Monza
Matteo Chiappedi, Pavia
Giulia Castellani, Pavia
Renata Nachinovich, Milano/Monza
Giorgio Rossi, Varese
Cristiano Termine, Varese
Pierangelo Veggiotti, Pavia

WebCenter

Questionario per la valutazione della Newsletter ADHD

Gent.mi lettori,

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

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

http://givitiweb.marionegri.it/Centres/Customs/adhd/Publics/ValutazioneNewsletter.aspx?project=adhd

Si confida nella Vs preziosa collaborazione.

RELATORI

Daniele Arisi
UONPIA, A.O. Ist. Ospedalieri di Cremona
Claudio Bissoli
UONPIA, IRCCS "Ca'Granda" Ospedale Maggiore Policlinico di Milano
Maurizio Bonati
Dipartimento Salute Pubblica, IRCCS Ist. "Mario Negri" di Milano
Gianluigi Casadei
CESAV, IRCCS Ist. "Mario Negri" di Milano
Serafino Corti
Dipartimento Disabili, Fondazione Ist. Ospedaliero di Sospiro (CR)
Antonella Costantino
UONPIA, IRCCS "Ca' Granda" Osp. Maggiore Policlinico di Milano
Gianluca Daffi
UONPIA, A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Paola Effedri
UONPIA, A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Elisa Fazzi
UONPIA, A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Emiddio Fornaro
UONPIA, A.O. Ospedale Niguarda "Ca'Granda" di Milano
Ottaviano Martinelli
Neuropsichiatria Infantile, A.O. Provincia di Lecco
Dino Maschietto
Neuropsichiatria Infantile, ASL di San Donà di Piave (VE)
Luigi Mazzone
Neuropsichiatria Infantile, IRCCS Ospedale Pediatrico Bambino Gesù, Roma
Massimo Molteni
IRCCS, Ist. Scientifico Eugenio Medea di Bosisio Parini
Annalisa Monti
Direttore UOC NPI ASL 11 (Empoli); Membro del consiglio Direttivo SINPIA
Paola Morosini
UONPIA, A.O. della Provincia di Lodi
Laura Reale
Scuola di Specialità, Univ. degli Studi di Milano; Ist. "Mario Negri" di Milano
Monica Saccani
UONPIA, A.O. San Paolo, Univ. degli Studi di Milano
Laura Vanzin
Neuropsichiatria Infantile, IRCCS Eugenio Medea, Bosisio Parini (LC)
Davide Villani
Neuropsichiatria Infantile, A.O. Provincia di Lecco
Edda Zanetti
UONPIA A.O. Spedali Civili Presidio Ospedaliero dei Bambini di Brescia
Alessandro Zuddas
Clinica di Neuropsichiatria infantile, Univ. degli Studi di Cagliari

Con il patrocinio della:

SINPIA
Società Italiana di Neuropsichiatria dell'Infanzia e dell'Adolescenza

L'IRCCS – Istituto di Ricerche Farmacologiche Mario Negri si trova a Milano in zona Bovisa nelle vicinanze del Campus Politecnico (Ingegneria) e della Triennale Bovisa.
E' facilmente raggiungibile con il passante ferroviario, scendendo alle fermate di Bovisa (FNM) o Villapizzone (FS).
Se fermate a Bovisa ricordatevi di scendere le scale che si trovano sul lato destro della stazione.

Segreteria organizzativa:
Laboratorio per la Salute Materno Infantile
Dipartimento di Salute Pubblica
IRCCS - Istituto di Ricerche Farmacologiche Mario Negri
Via Giuseppe La Masa, 19. Milano
Tel. 02 39014511 – fax 02 3550924
ADHD@marionegri.it

La partecipazione è gratuita e prevede l'assegnazione di 12 crediti ECM.
L'iscrizione al Convegno è obbligatoria e deve essere effettuata entro il 31 ottobre 2015 accedendo al link:

ADHD.marionegri.it

PERCORSI DIAGNOSTICO-TERAPEUTICI CONDIVISI PER L'ADHD

Una risposta alle criticità e ai bisogni inevasi

Milano, 9-10 novembre 2015
Ore 9.00-18.00 - AULA A

IRCCS
Istituto di Ricerche Farmacologiche Mario Negri
Via G. La Masa 19 - 20156 Milano

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

Azienda Ospedaliera
SPEDALI CIVILI BRESCIA

RegioneLombardia

Il Progetto: "Condivisione dei percorsi diagnostico-terapeutici per l'ADHD in Lombardia" è stato in parte finanziato dalla Regione Lombardia con Decreto DG Salute n 3798 del 08.05.2014 e n 778 del 05.02.2015. Il progetto coinvolge 18 Centri di Riferimento per l'ADHD e il Laboratorio per la Salute Materno Infantile dell'IRCCS - Istituto di Ricerche Farmacologiche Mario Negri.
Coordinatore del Progetto è la UONPIA degli Spedali Civili di Brescia.

PERCORSI DIAGNOSTICO-TERAPEUTICI CONDIVISI PER L'ADHD

Una risposta alle criticità e ai bisogni inevasi

Il Progetto Condivisione dei percorsi diagnostico terapeutici per l'ADHD ha permesso nel triennio 2011-2013 di strutturare un raccordo tra i Centri di Riferimento per l'ADHD in Lombardia e di attivare momenti di formazione e confronto condivisi. Il Registro ha rappresentato un essenziale strumento di monitoraggio continuo e sistematico che ha permesso di programmare e usare in modo appropriato le risorse sulla base dei bisogni (gravità e tipo di domanda), attivando progressivi e significativi miglioramenti nella pratica clinica e garantendo un'efficiente e omogenea qualità delle cure.
Permangono tuttavia significative disomogeneità delle risposte tra i Centri (tempi di attesa per la prima visita, tempi del percorso diagnostico, offerta terapeutica, etc.). L'attività del gruppo formazione/informazione ha evidenziato il bisogno di iniziative continue per le professionalità diversamente implicate nella presa in carico del paziente con ADHD. Anche le famiglie e gli insegnanti dei pazienti necessitano di percorsi informativi e formativi condivisi e partecipati.

Alla luce di queste considerazioni la fase 2014-2015 del Progetto prevedeva di:

- **Migliorare** la struttura della rete curante per l'ADHD: ottimizzando il raccordo e il coordinamento tra i nodi della rete, aumentando il coinvolgimento del territorio, diminuendo e governando la migrazione sanitaria, definendo i livelli di qualità richiesti per i diversi nodi della rete, migliorando l'omogeneità e appropriatezza delle risposte diagnostiche e terapeutiche, definendo la struttura/articolazione della rete regionale dell'ADHD sulla base della qualità delle cure.
- **Implementare** le azioni informative/formative migliorando l'informazione e formazione rivolte alle famiglie, scuole e operatori sulle modalità di presa in carico, gli aggiornamenti normativi e la conoscenza scientifica relativi all'ADHD.
- **Garantire** risposte terapeutiche omogenee e appropriate in tutto il territorio regionale migliorando la capacità di risposta terapeutica dei servizi, sia nell'ambito dei Centri di riferimento che dei Poli territoriali.

LUNEDÌ 9 NOVEMBRE 2015

***Mattina** 09.00 – 13.00*

LA PREVALENZA DEI BISOGNI: LA SAGA ADHD
Maurizio Bonati

PERCORSO DIAGNOSTICO CONDIVISO PER L'ADHD
Massimo Molteni

dal Progetto
Daniele Arisi

e ancora …
Comorbilità — ***Emiddio Fornaro***

Guardando oltre
ADHD-disturbi dirompenti-autismo: appropriatezza, qualità e utilità dei percorsi diagnostici — ***Luigi Mazzone***

DISCUSSIONE

***Pomeriggio** 14.30 – 18.00*

INTERVENTI TERAPEUTICI CONDIVISI PER L'ADHD
Ottaviano Martinelli

dal Progetto — ***Monica Saccani***

e ancora … dubbi e criticità
Parent training — ***Claudio Bissoli***

Teacher training — ***Gianluca Daffi***

Child training
- ✓ Coping Power Program: evidenze, limiti, prospettive — ***Laura Vanzin***
- ✓ Esperienze in età scolare e prescolare — ***Davide Villani***

Guardando oltre
Strategie di interventi tra ieri e oggi — ***Dino Maschietto***

DISCUSSIONE

MARTEDÌ 10 NOVEMBRE 2015

***Mattina** 09.00 – 13.00*

FORMAZIONE E AGGIORNAMENTO PERMANENTE DEGLI OPERATORI
Edda Zanetti

dal Progetto
Formazione — ***Paola Effedri***
Centro ADHD vs territorio — ***Paola Morosini***

e ancora …
Luoghi e contesti di educazione continua — ***Elisa Fazzi***

Guardando oltre
Quale formazione per quale operatore — ***Serafino Corti***

DISCUSSIONE

***Pomeriggio** 14.30 – 18.00*

STRUTTURA DELLA RETE CURANTE PER L'ADHD
Antonella Costantino

dal Progetto
Monitoraggio e valutazione del funzionamento della rete — ***Ottaviano Martinelli***

e ancora …
Al compimento della maggiore età — ***Laura Reale***

La spesa dei percorsi ADHD per i Servizi — ***Gianluigi Casadei***

Guardando oltre
Organizzazione dei Servizi vs garanzia dei diritti — ***Annalisa Monti***

DISCUSSIONE

RICERCA-AZIONE IN NEUROPSICHIATRIA DELL'ETÀ EVOLUTIVA
Alessandro Zuddas

DISCUSSIONE GENERALE E CONCLUSIONI

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

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