NEWSLETTER

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BIBLIOGRAFIA ADHD NOVEMBRE 2018

ADHD Atten Deficit Hyperact Disord. 2018.

HOW RELEVANT IS HIGHER-ORDER LANGUAGE DEFICIT (HOLD) TO CHILDREN WITH COMPLEX PRESENTATIONS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER?

Randell R, Somerville-Brown L, Chen W.

Attention-deficit hyperactivity disorder (ADHD) is frequently associated with language impairment, autism spectrum disorder (ASD) symptoms and higher-order language deficit (HOLD); yet, their complex relationship is poorly understood. HOLD encompasses deficits in using language for reasoning, problem-solving, causal and critical thinking. This study evaluates the roles of HOLD in children with ADHD. We hypothesise that both our subgroups (ADHD-only and ADHD + 'ASD traits') will have HOLD difficulties, though to a differing degree, as children with ADHD are compromised by executive function deficits, and those with additional ASD traits are further impaired by pragmatic language deficits. Data were reviewed from 36 children with ADHD (± 'ASD traits'), who attended the tier 4 statewide specialist clinic for ADHD patients non-responsive to community care. HOLD was assessed by the Test of Problem Solving-3 Elementary (TOPS-3). The age of the sample ranged from 6 to 12 years with a male-to-female ratio of 8:1. The rate of HOLD in our sample was 47.2% (published controls = 16%). Likewise, the rates of Making Inferences (50.0%, $p < 0.001$), Sequencing (44.4%, $p < 0.001$), Negative Questions (33.3%, $p = 0.278$), Problem-Solving (38.9%, $p = 0.022$), Predicting (27.8%, $p = 0.022$) and Determining Causes (30.6%, $p = 0.022$) were all elevated. When stratified, the rates in ADHD-only group and ADHD + 'ASD traits' group were 37.5% and 55.0%, respectively. Children with ADHD + 'ASD traits' had greater 'Sequencing' deficit. Our exploratory study confirms that HOLD is more common in children with ADHD, including deficits in Making Inferences, Sequencing, Problem-Solving, Predicting, Determining Causes and understanding Negative Questions. Our findings provide preliminary support for the potentially important role played by HOLD in neurodevelopmental disorders

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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.

ADHD Atten Deficit Hyperact Disord. 2018.

VITAMIN D LEVELS IN CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): A META-ANALYSIS.

Kotsi E, Kotsi E, Perrea DN.

The aim of this article was to assess the differences in serum 25(OH)D levels between children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and healthy controls. We used the PubMed (1966-2017), Scopus (2004-2017), ClinicalTrials.gov (2008-2017), Cochrane Central Register of Controlled Trials CENTRAL (2000-2017), and Google Scholar (2004-2017) databases. Statistical meta-analysis was performed with RevMan 5.3. Eight studies were finally included in the present meta-analysis with a total number of 11,324 children. Among them, 2655 were diagnosed with ADHD, while the remaining 8669 were recruited as healthy controls. All eight trials reported significantly lower serum concentrations of 25(OH)D in patients diagnosed with ADHD compared to healthy controls. The pooled data showed that there was a significant difference between the ADHD group and the control group (SMD = - 0.73, 95% CI [- 1.00, - 0.46]). The systematic review and meta-analysis of observational studies demonstrated an inverse association between serum 25(OH)D and young patients with ADHD. Large cohort studies are required to investigate whether vitamin D-deficient infants are more likely to develop ADHD in the future. Also, whether children with ADHD should be supplemented with higher doses of vitamin D3 remains to be confirmed through long-term controlled clinical trials

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ADHD Atten Deficit Hyperact Disord. 2018;10:285-95.

PARENT AND CHILD NEUROCOGNITIVE FUNCTIONING PREDICT RESPONSE TO BEHAVIORAL PARENT TRAINING FOR YOUTH WITH ADHD.

Fosco WD, Sarver DE, Kofler MJ, et al.

Parental cognitive functioning is thought to play a key role in parenting behavior and may inform response to behavioral intervention. This open-label pilot study examined the extent to which parent and child cognition impacted response to behavioral parent training for children with ADHD. Fifty-four participants (27 parent child dyads; Mages = 10.6 and 45.2 for children and parents, respectively) completed tasks assessing visuospatial and phonological working memory, inhibitory control, and choice-reaction speed at pre-treatment. Drift diffusion modeling decomposed choice-reaction time data into indicators of processing speed (drift rate) and response caution (boundary separation). Parents completed a 10-week manualized behavioral parent training program. Primary outcomes were pre- and post-treatment child ADHD and conduct problem severity, and parent-reported relational frustration and parenting confidence. Bayesian multiple regressions assessed parent and child cognitive processes as predictors of post-treatment outcomes, controlling for pre-treatment behavior. Better child visuospatial and phonological WM and higher parental response caution were associated with greater reductions in inattention. For conduct problems, better parental self-regulation (stronger inhibitory control and greater response caution) predicted fewer post-treatment conduct problems. Higher parental response caution also predicted lower post-treatment relational frustration and higher parental confidence. Bayesian evidence supported no relation between parent and child cognitive functions and treatment-related changes in hyperactivity. This pilot study demonstrates that cognitive processes central to etiologic theories of ADHD and models of parenting behavior can be successfully integrated into treatment outcome research to inform which families are most likely to benefit from behavioral interventions. This study demonstrates the feasibility of bridging the translational research gap between basic and applied clinical science and facilitates research on the role of cognition in psychosocial interventions

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Am J Med Genet Part B Neuropsychiatr Genet. 2018.

THE INVOLVEMENT OF THE CANONICAL WNT-SIGNALING RECEPTOR LRP5 AND LRP6 GENE VARIANTS WITH ADHD AND SEXUAL DIMORPHISM: ASSOCIATION STUDY AND META-ANALYSIS.

Grünblatt E, Nemoda Z, Werling AM, et al.

Wnt-signaling is one of the most abundant pathways involved in processes such as cell-proliferation, -polarity, and -differentiation. Altered Wnt-signaling has been linked with several neurodevelopmental disorders including attention-deficit/hyperactivity disorder (ADHD) as well as with cognitive functions, learning and memory. Particularly, lipoprotein receptor-related protein 5 (LRP5) or LRP6 coreceptors, responsible in the activation of the canonical Wnt-pathway, were associated with cognitive alterations in psychiatric disorders. Following the hypothesis of Wnt involvement in ADHD, we investigated the association of genetic variations in LRP5 and LRP6 genes with three independent child and adolescent ADHD (cADHD) samples (total 2,917 participants), followed by a meta-analysis including previously published data. As ADHD is more prevalent in males, we stratified the analysis according to sex and compared the results with the recent ADHD Psychiatric Genomic Consortium (PGC) GWAS. Meta-analyzing our data including previously published cADHD studies, association of LRP5 intronic rs4988319 and rs3736228 (Ala1330Val) with cADHD was observed among girls (OR = 1.80 with 95% CI = 1.07-3.02, p = .0259; and OR = 2.08 with 95% CI = 1.01-4.46, p = .0026, respectively), whereas in boys association between LRP6 rs2302685 (Val1062Ile) and cADHD was present (OR = 1.66, CI = 1.20-2.31, p = .0024). In the PGC-ADHD dataset (using pooled data of cADHD and adults) tendency of associations were observed only among females with OR = 1.09 (1.02-1.17) for LRP5 rs3736228 and OR = 1.18 (1.09-1.25) for LRP6 rs2302685. Together, our findings suggest a potential sex-specific link of cADHD with LRP5 and LRP6 gene variants, which could contribute to the differences in brain maturation alterations in ADHD affected boys and girls, and suggest possible therapy targets

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An Pediatr. 2018.

ASSESSMENT OF COMORBIDITY AND SOCIAL ANXIETY IN ADOLESCENTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: THE SELFIE STUDY.

***Mardomingo Sanz MJ, Sancho MC, Soler LpB, et al*.**

Introduction: Attention-deficit/hyperactivity disorder (ADHD) and its comorbidities have an impact on the social anxiety of children and adolescents, but there are practically no studies addressing this topic in adolescence. Our objective was to assess the degree of social anxiety and to analyse the presence of psychiatric comorbidities (PSCs) in adolescents with ADHD. Methodology: We conducted a cross-sectional observational study in patients aged 12 to 18 years with a confirmed diagnosis of ADHD (DSM-5). We collected data on the presence and type of PSCs and assessed social anxiety by means of the Social Anxiety Scale for Adolescents (SAS-A). Results: Forty-six child and adolescent psychiatrists and paediatric neurologists participated in the study and recruited 234 patients. Of the total patients, 68.8% (159) were male and 31.2% (72) female, with a mean age in the sample of 14.9 years (95% CI, 14.6-15.1). The type of ADHD was combined type (C) in 51.7% (121), predominantly inattentive (PI) in 37.2% (87), and predominantly hyperactive-impulsive (PH) in 9% (21). Of all patients, 97.9% (229) received pharmacological therapy: 78.6% (184) methylphenidate, 15% (35) lisdexamfetamine and 4.3% (10) atomoxetine. We found PSCs in 50.4% of the patients (118), of which the most frequent were learning and communication disorders (20.1%, n = 47) and anxiety disorders (19.2%, n = 45). The patients scored significantly higher in the SAS-A compared to reference values in the healthy population. The scores in the SAS-A were less favourable in adolescents with the PI type compared to those with the PH type (P =.015). The presence of a comorbid anxiety disorder was associated with worst scores in SAS-A (P <.001) showing an increased social anxiety. Conclusion: Adolescents with ADHD classified as PI and those with comorbid anxiety had a higher degree of social anxiety as measured by the SAS-A. This psychological aspect must be identified and controlled in adolescents with ADHD to promote their social adaptation

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Behav Genet. 2018;48:472-73.

GENETIC OVERLAP BETWEEN ADHD AND ASD: A REVIEW OF THE EVIDENCE FROM TWIN AND FAMILY STUDIES.

Ghirardi L, Kuja-Halkola R, Pettersson E, et al.

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are highly heritable neurodevelopmental disorders that frequently co-occur. Family studies have shown that relatives of individuals with ASD have an increased risk of receiving a diagnosis of ADHD (1-3) and that the magnitude of the risk is higher in relatives who are more genetically related (3). This implies that ADHD and ASD might be influenced by partially shared familial factors that are likely to be of genetic origin. This hypothesis is corroborated by twin studies, which have consistently found moderate genetic correlations between continuous traits of ADHD and ASD in the general population (4-7). In addition, because ADHD and ASD are considered heterogeneous disorders, researchers have relied on twin studies to examine associations among ADHD and ASD subscales. These studies have found that in children there were stronger phenotypic and genetic correlations between all ADHD subscales and ASD subscales related to communication and social difficulties (5-6). However, in adults, there was a stronger association between all ADHD subscales and ASD subscale related to restricted and repetitive behaviors (7). In this review, we are going to summarize the evidence from family and twin studies regarding the possible genetic overlap between ADHD and ASD. We will compare results from studies using data on clinical diagnoses and traits continuously measured in the population in childhood, adolescence, and adulthood. Furthermore, we will investigate how the magnitude of the correlations between ADHD and ASD subscales may differ by age

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Behav Genet. 2018;48:519.

RECONCEPTUALIZING PSYCHOPATHOLOGY FOR GENETIC STUDIES USING HIERARCHICAL DIMENSIONAL STRUCTURAL MODELS: THE EXAMPLE OF EXTERNALIZING AND AVPR1A.

Waldman I.

Recent trends in the psychopathology literature have reconceptualized psychopathology in terms of transdiagnostic or hierarchical dimensional perspectives. Despite these trends, the modal phenotypes used in psychiatric genetic studies (e.g., in GWASs of psychiatric disorders conducted through the Psychiatric Genetics Consortium) are single, specific psychiatric diagnoses. In this paper, I explore different conceptualizations of a higher-order Externalizing symptom dimension, as well as different analytic methods used to characterize this dimension, in its association with the Arginine Vasopressin 1a receptor gene (AVPR1a). I contrasted different models for characterizing the Externalizing symptom dimension with each other, as well as with models of its constituent diagnoses and symptom dimensions. In phenotypic analyses, data were available on parent ratings of DSM-IV symptoms of attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) fromΓêù2800 children whereas in genetic analyses data were available fromΓêù600 children, all aged 6-16 years old. In analyses of genetic association six SNPs in AVPR1a were used to characterize the gene in a series of gene-based tests. Comparisons of these phenotypic models used the percentage of variance explained and the relative fit of the alternative models to adjudicate among them. Results of these analyses highlight the benefits of construing psychopathology in terms of hierarchical dimensional models, as well as which conceptualizations and analytic methods are optimal

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Behav Genet. 2018;48:524.

ASSORTATIVE MATING AND INTERGENERATIONAL TRANSMISSION OF ADHD.

Ystrom E, Eilertsen EM, Gjerde L, et al.

ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning. Previous twin and family studies have shown moderate estimates of heritability for adult ADHD and high estimates of heritability of child ADHD. However, there is to date comparatively little knowledge on to what extent assortative mating on adult ADHD traits could change the genetic variation in the offspring generation. By using the Intergenerational Transmission of Risk (IToR) study, a twin-family

subsample of the Norwegian Mother and Child Cohort study, we will estimate the extent of assortative mating in adult ADHD. What is more, we will estimate the impact of assortative mating on, one, the heritability of adult ADHD, two, the heritability of child ADHD, and, three, the genetic transmission of adult ADHD to child ADHD. To estimate such parameters, we will apply an extended children of twin model on the IToR dataset comprising a large number of sibling/twinfamilies. If there is a strong assortative mating on adult ADHD, this could alter the prevalence and heritability in the offspring generation. What is more, the results will inform on the biological underpinnings of the similar phenomena of adult and child ADHD

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Behav Genet. 2018;48:471-72.

INHIBITORY CONTROL AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDHOOD: EVIDENCE FROM TWO MULTI-METHOD, LONGITUDINAL TWIN STUDIES.

Gagne J, Saudino K, Van HC, et al.

In childhood, low levels of inhibitory control (IC) are associated with externalizing behavior problems and Attention Deficit Hyperactivity Disorder (ADHD). Multiple twin studies indicate that IC is genetically influenced, however; findings depend somewhat on the age of the participants and the assessment methodology (Gagne and Saudino 2010, 2016; Gagne and Goldsmith 2011). For example, two of these studies show evidence for shared environmental influences and nonsignificant genetic influences on lab-based assessments of IC at age 3. However, parent-ratings of IC show a much more stable and consistent etiology and developmental trajectory. Genetic and environmental covariance between IC and externalizing behavior problems has also been noted in toddlers (Gagne, Saudino & Asherson 2011) and school age children (Lemery-Chalfant, Doelger, Goldsmith 2008). We investigated the development and etiology of IC and ADHD behavior problems and symptoms from a multi-method perspective in two independent twin samples. Using both datasets allows us the ability to examine IC development and behavioral maladjustment within early childhood and longitudinally from toddlerhood, through school transition, to early adolescence. Participants included 300 twin pairs (half MZ), 2 and 3 years of age, from the Boston University Twin Project (BUTP) and between 143 and 237 MZ and 237-401 DZ twin pairs (samples sizes differ) at 2.5 years, early school age, and early adolescence from the Wisconsin Twin Project (WTP). In the BUTP, parents rated IC and externalizing and ADHD behavior problems, and a lab-based assessment of IC was collected at both ages. In the WTP, mothers rated IC in todderhood and first grade, and ADHD symptoms in first grade and early adolescence. In first grade, an observational measure of IC similar to that used in the BUTP was obtained. Phenotypic correlations between IC and behavior problems and ADHD symptoms ranged from-.10 to-.68. MZ correlations exceeded DZ correlations for most traits, indicating genetic influences. In addition, MZ cross-twin, cross-trait twin correlations between IC and ADHD generally exceeded DZ correlations indicating significant genetic covariance between IC and ADHD across age. Initial bivariate Cholesky decompositions of BUTP age 2 IC (both parent-and lab-assessed) and ADHD behavior problems, WTP parent-rated toddler IC and first grade ADHD, and WTP parent-rated first grade IC and early adolescent ADHD yielded genetic and nonshared environmental variances and covariances. Toddler IC was phenotypically and etiologically associated with concurrent ADHD behavior problems and ADHD in first grade, as was first grade IC and early adolescent ADHD. Based on these findings, early IC can be considered a genetic risk factor for later ADHD symptoms. Future genetic analyses will include IC and ADHD behavior problems data from the BUTP at age 3, and laboratory-based behavioral assessments of IC and measures of home environment from WTP in early school age

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Behav Genet. 2018;48:473-74.

THE GENETIC AND ENVIRONMENTAL STRUCTURE OF PSYCHOPATHOLOGY SPECTRA IN MIDDLE CHILDHOOD.

Gjerde L, Eilertsen EM, Rosenstr+Âm T, et al.

In recent years, there has been a renewed interest in understanding the causes of psychiatric comorbidity, and several studies have re-examined dimensionality using hierarchical or bi-factor modeling techniques. Previous reports from child and adolescence samples indicate that early psychopathology can be

conceptualized through two dimensional spectra: internalizing and externalizing risk. Evidence for a higher order general factor that accounts for comorbidity across the two specific spectra has also been found. Childhood and adolescence comprises several developmental stages where rapid changes can occur. A current limitation in understanding the structure of childhood psychopathology is that samples incorporating broad age spans are most common. Clearly defined age ranges are needed to understand the nature of comorbidity because factors leading to cooccurrence may differ throughout the lifespan. Although efforts have been made to assess associations between psychopathology spectra and personality, to the best of our knowledge, no studies have systematically incorporated normal personality traits into these models. Understanding the genetic and environmental structure of childhood psychopathology is important both for general knowledge and for designing intervention strategies. In this study, we aim to investigate the joint structure of common psychopathology symptoms (e.g. anxiety, depression, conduct disorder, and ADHD) and normal personality traits in children from a twin-sibling subsample of the Norwegian Mother and Child Cohort Study. Preliminary results will be presented at the conference

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Behav Genet. 2018;48:458-59.

PREDICTION OF AGGRESSION BY ADHD SUBSCALES IN CHILDREN AND ADULTS.

Boomsma D, Dolan C, Bartels M, et al.

Based on Bayesian machine learning analysis performed in the MATRICS consortium, in clinical adolescent ADHD and population cohorts, differential associations between aggression and hyperactivity and between aggression and inattention were suggested. We aimed to replicate these findings in the large population based Netherlands Twin Register in childhood (age 7-16 years) and in adulthood, employing both cross-sectional and longitudinal designs. In children and in adults outcome and predictor variables were assessed by comparable instruments. Aggression was assessed by the Achenbach System of Empirically Based Assessment (ASEBA) ageappropriate inventories, namely the Child behavior Check List (CBCL), the Youth or the Adult Self Report (YSR/ASR). Hyperactivity and inattention were assessed by the Conners Parent Rating Scale-Revised: Short version (CPRS-R:S) and the Adult ADHD Rating Scales (CAARS). Based on linear regression analyses in which hyperactivity and inattention predicted aggression, we observed different results in children and in adults in a series of cross-sectional and longitudinal analyses. In children, hyperactivity was a stronger predictor of aggression than inattention. However, in adults, inattention was the stronger predictor. As data were collected in twin families, we next will estimate the extent to which genetic correlations between aggression and these ADHD subscales explain the observed associations

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Behav Genet. 2018;48:454.

HARMONIZED PHENOTYPES FOR INTERNALIZING PROBLEMS AND ADHD.

Agarwal K, Whitehouse A, Van Den Berg SM.

The aim of this study is to harmonize questionnaire item data with an objective of having one phenotype, that is comparable across various cohorts. Our focus is on internalizing problems and ADHD symptoms. We used a total of 1330, 10-year-old children data available in the Western Australian Pregnancy Cohort study (RAINE) dataset, with complete data on the Child Behaviour Checklist (CBCL) and the Strength and Difficulties Questionnaire (SDQ). We carried out a varimax factor analysis on all items to identify relevant dimensions. We found two dimensions ('emotional problems' and 'ADHD') with high CBCL and SDQ loadings. We carried out an Item Response Theory (IRT) analysis using a Generalized Partial Credit Model to investigate the psychometric quality of these two dimensions. The results showed that particular subsets of CBCL and SDQ items can be used together but also separately to measure emotional problems and ADHD. We recommend to use these sets of items, rather than the original subscales, in order to work with commensurate phenotypes across various research groups

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Behav Genet. 2018;48:455-56.

GENETIC OVERLAP BETWEEN ADHD AND EXTERNALIZING, INTERNALIZING AND NEURODEVELOPMENTAL DISORDER SYMPTOMS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Andersson A, Tuvblad C, Kuja-Halkola R, et al.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder (Wilens, Biederman & Spencer 2002) and affects approximately 5% of children (Polanczyk, de Lima, Horta, Biederman & Rohde 2007). About half of those diagnosed in childhood continue to have the diagnosis and symptoms in adulthood (Kessler et al. 2006). The co-occurrence of ADHD with other psychiatric disorder symptoms (Burt et al. 2001; Cole et al. 2009; Polderman et al. 2014) has been suggested to be partly explained by a shared genetic vulnerability (Polderman et al. 2014). However, the strength of the genetic overlap is currently unclear. Also, no study has examined whether the genetic correlations differs between age groups (childhood versus adulthood), by rater (self-report, other informant, combined (parent-teacher, parent-twin, teacher-twin)), or by type of psychiatric disorder symptoms (externalizing, internalizing, neurodevelopmental). To address this gap, we conducted a systematic literature search to identify relevant twin studies, in PubMed, PsycINFO, and EMBASE. A total of 31 articles were identified and included in the present study. The pooled estimates showed that the comorbidity between ADHD and diverse psychiatric disorder symptoms were explained by shared genetic effects rg = 0.50 (0.43-0.56). A similar shared genetic overlap between ADHD and psychiatric disorder symptoms was observed in both childhood rg = 0.51 (0.42-0.61) and adulthood rg = 0.47 (0.40-0.53). Similar results were also found for self-reports rg = 0.49 (0.42-0.55), other informants rg = 0.50 (0.40-0.60), and combined raters rg = 0.51 (0.30-0.69). Further, the strength of the genetic correlations of ADHD with the externalizing rg = 0.49 (0.39-0.59), internalizing rg = 0.55 (0.40-0.68) and neurodevelopmental rg = 0.47 (0.40-0.53) spectrums were similar in magnitude. These findings emphasize the presence of a shared genetic liability between ADHD and externalizing, internalizing and neurodevelopmental disorder symptoms, independent of age and rater

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Behav Genet. 2018;48:480-81.

MULTIVARIATE GWAMA IN OVER 500K OBSERVATIONS ON AGGRESSIVE BEHAVIOR AND ADHD SYMPTOMS.

Ip H, Zafarmand H, Wedow R, et al.

We present the results of a multivariate genome-wide association (GWA) study of the developmental genetic etiology of aggressive behavior (AGG) and attention-deficit/hyperactivity disorder (ADHD). The project involves a collaboration among more than 20 international cohorts from Europe, Australia, New-Zealand and the USA. The cohorts are characterized by rich phenotyping in children and adolescents, including repeated measures at different ages and assessment by multiple informants and multiple instruments. In total, the meta-analysis includedΓêù526,000 observations and over 250 GWA studies. The data includes longitudinal measures of AGG and ADHD in children and adolescents aged 3-18 years, assessed by multiple informants (mother, father, teacher, and self) and multiple instruments. First, a series of univariate GWA studies was performed for every available combination of age, informant and instrument within cohort. This resulted in 1-52 analyses per cohort, with sample sizes ranging between 309 and 10,812. Next, results were pooled into age-by-informant combinations (e.g. mother-rated aged 3-5, teacherrated 8-11, etc.) that resulted in an excess of 10,000 independent observations, and then meta-analyzed. Genetic correlations between the age-by-informant meta-analyses, both within and across AGG and ADHD, were estimated with LD Score Regression. We then performed a multivariate meta-regression analysis across all GWA studies, correcting for dependency due to repeated measurements of the participants. We obtained an average SNP-heritability of 6.1% and 7.2% for AGG and ADHD, respectively, across the age-by-informant meta-analyses. After meta-analysis across age, genetic correlations between mother-and teacher-ratings was 0.54 for AGG and 0.51 for ADHD. Interestingly, the genetic correlation between teacher-ratings and self-report approached zero for both traits. Genetic correlation within rater, across phenotype ranged from 0.58 to 0.7. The multivariate meta-analysis across rater and phenotype revealed no significant loci for AGG/ADHD

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Behav Genet. 2018;48:469.

PARENTAL PRENATAL DEPRESSION AND OFFSPRING ADHD: A GENETICALLY INFORMED INTERGENERATIONAL STUDY.

Eilertsen EM, Hannigan L, McAdams T, et al.

Maternal prenatal depression has been associated with elevated levels of ADHD symptoms in offspring. This association could reflect detrimental effects of in-utero exposure to depression, but it could also be due to common genetic influences underlying depression and ADHD. The primary aim of the present study was to investigate whether an effect of maternal prenatal depression could be demonstrated while controlling for intergenerational transmission of genetic risk. In this study we use a children-of-twin design based on 17,070 sibling pairs, their partners and their children participating in the Norwegian Mother and Child Cohort Study. Self-ratings of prenatal depression were obtained from both mothers and fathers using the Symptom Checklist in week 17 and 30 during pregnancy. Maternal ratings of ADHD symptoms using Conner's Parent Rating Scale were obtained when the children were 5 years of age. Results will be presented at the conference

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Behav Neurol. 2018 Oct;2018.

ASSOCIATIONS BETWEEN ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD) TREATMENT AND PATIENT NUTRITIONAL STATUS AND HEIGHT.

Granato MF, Ferraro AA, Lellis DM, et al.

Attention-deficit hyperactivity disorder (ADHD) has been found to co-occur frequently with obesity, although the reasons for this association are unknown. The aim of this study was to compare the nutritional profile of a Brazilian cohort of ADHD patients with that of the general population and to analyze the association between ADHD drug treatment (with methylphenidate), nutritional status, and height of these individuals. In the first phase of the study, we designed the nutritional and height profile of 93 ADHD patients (5.1 to 13.8 years old) and compared it to a control group. In the second phase, we analyzed the association of the use of methylphenidate with nutritional status and height. The results showed that the prevalence of overweight/obesity was statistically higher in the cohort of ADHD patients compared to controls (40.9% vs. 34.7%; P < 0 05). After treating ADHD patients with methylphenidate, a statistically significant decrease in the BMI z-score was observed (0.695 vs. 0.305; P < 0 01). On the other hand, no significant impact on height was detected after treatment (0.189 vs. 0.248; P = 0 298). In conclusion, the results suggest that the use of methylphenidate in patients who have ADHD and obesity is relevant not only for controlling ADHD symptoms but also for improving the nutritional status of these individuals. Moreover, the treatment did not affect the patients height

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Biol Psychiatry. 2018.

POLYGENIC RISK SCORES DERIVED FROM A TOURETTE SYNDROME GENOME-WIDE ASSOCIATION STUDY PREDICT PRESENCE OF TICS IN THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN COHORT.

Abdulkadir M, Mathews CA, Scharf JM, et al.

Background: Tourette syndrome (TS) has a well-established genetic background, but its genetic architecture remains largely unknown. The authors investigated the role of polygenic risk scores (PRSs) derived from a TS genome-wide association study in relation to the occurrence of tics and associated traits in a general population cohort. Methods: Using the most recent TS genome-wide association study (n = 4819 cases; n = 9488 controls) as the discovery sample, PRSs were calculated in Avon Longitudinal Study of Parents and Children participants (n = 8941). Regression analyses were used to assess whether PRS predicted the presence and chronicity of tics, and symptom severity of obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder in Avon Longitudinal Study of Parents and Children participants. Results: Following correction for multiple testing, the PRS significantly predicted the presence (R2 = .48%, p empirical = .01, Q = .04) but not the chronicity (R2 = .16%, p empirical = .07, Q = .14) of tics in the Avon Longitudinal Study of Parents and Children cohort; it did not predict the severity of

obsessive-compulsive disorder (R2 = .11%, p empirical = .11, Q = .15), attention-deficit/hyperactivity disorder (R2 = .09%, p empirical = .19, Q = .21), or autism spectrum disorder (R2 = .12%, p empirical = .09, Q = .14). Conclusions: The authors found a significant polygenic component of tics occurring in a general population cohort based on PRS derived from a genome-wide association study of individuals with a TS diagnosis. This finding supports the notion that tics along a spectrum from nonclinical to clinical symptom levels share a similar genetic background

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2018;3:675-85.

FUNCTIONAL NEUROIMAGING EVIDENCE FOR DISTINCT NEUROBIOLOGICAL PATHWAYS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Stevens MC, Pearlson GD, Calhoun VD, et al.

Background: A challenge facing clinical neuroscientists is how best to synthesize diverse and sometimes inconsistent evidence for neuropsychological deficits and brain system dysfunction found in psychiatric disorders into models that guide etiological and treatment research. Multiple-pathway models suggest that psychiatric symptoms might arise from pathophysiology in different neural systems. This study tested dual-pathway model predictions for attention-deficit/hyperactivity disorder (ADHD) that reward and executive function cognitive deficits should be related to abnormalities in corresponding functionally specialized neural systems.

Methods: Behavioral inhibition and preference for immediate rewards were assessed in N = 251 adolescent boys and girls ages 12 to 18 diagnosed with DSM-IV combined-subtype ADHD or non-ADHD control subjects. Following taxometric analyses of test performance, the resulting subgroups were compared on a functional magnetic resonance imaging monetary incentive delay task probing reward anticipation and go/no-go task of motor response inhibition.

Results: Three ADHD subgroups were identified consistent with different proposed pathways ADHD with executive function/motor inhibition deficits, ADHD with both executive and reward deficits, and ADHD with relatively normal test performance. Each cognitive domain mapped to different ADHD brain dysfunction features as expected. However, no brain abnormalities were found common to all ADHD subgroups despite the fact they had nearly identical ADHD-related clinical characteristics.

Conclusions: The results suggest that combined-subtype ADHD is a collection of discrete disorders for which a comparable behavioral end point arises through different neurobiological pathways. The findings raise caution about applying common cause, single-deficit conceptual models to individual ADHD patients and should prompt researchers to consider biologically defined, multifactorial etiological models for other psychiatric diagnoses

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Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2018.

NEUROCOGNITIVE PATHWAYS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND WHITE MATTER MICROSTRUCTURE.

Bessette KL, Stevens MC.

Background: This study sought to identify attention-deficit/hyperactivity disorder (ADHD) abnormalities in relationships between brain white matter structure and individual differences in several types of impulsive behavior.

Methods: Adolescents, n = 67 with ADHD combined subtype and n = 68 without ADHD, were given neuropsychological tests and underwent diffusion tensor imaging scans. Principal component analysis reduced test scores into factors representing different types of impulsive behavior. Tract-based spatial statistics quantified white matter integrity in relationship to components of impulsive behavior. ADHD versus non-ADHD differences in the strength and nature of linear relationships between regional white matter and three impulsivity components were examined using multiple regression.

Results: Principal component analysis found three separate impulsivity-related factors that were interpreted as motor response inhibition, impulsive choice, and delay aversion. Relationships between regional fractional

anisotropy and response inhibition or impulsive choice did not differ between ADHD and non-ADHD groups. There was a significant interaction between diagnostic group and delay aversion test performance relationships with regional fractional anisotropy. For youths without ADHD, greater anisotropy in numerous tracts predicted better delay aversion test performance. In contrast, anisotropy in regions including the corpus callosum, corona radiata, internal capsule, and corticospinal tracts had either a negative or no relationship with delay aversion test performance in ADHD.
Conclusions: The results provide additional support that different proposed etiological pathways to ADHD have discretely different neurobiological features. Large disorganization of white matter microstructure appears to contribute to reward-based ADHD pathways rather than motor inhibition

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BMJ Open. 2018;8.
YOUNG AGE AT SCHOOL ENTRY AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER-RELATED SYMPTOMS DURING PRIMARY SCHOOL: RESULTS OF A PROSPECTIVE COHORT STUDY CONDUCTED AT GERMAN RUDOLF STEINER SCHOOLS.
Wendt J, Schmidt MF, et al.
OBJECTIVES: Young age at school entry (ASE) for students has been related to their impaired mental health in higher grades. To avoid the negative health consequences of young ASE, preschool examinations and individual school entry deferral for young children are routinely performed by some school authorities. We aimed to investigate whether ASE was associated with attention-deficit hyperactivity disorder (ADHD)-related symptoms in pupils attending schools using a selective school enrolment procedure.
DESIGN: Prospective open cohort study with baseline assessments at school entry and two follow-ups in the second and fourth grades.
SETTING: Up to 128 Rudolf Steiner Schools (Waldorf Schools) located within Germany.
PARTICIPANTS: Of the 3079 children from whom data were gathered in the second or fourth grade, 2671 children born between 1 July 2001 and 31 October 2002 (age at baseline: mean 6.7, min 5.91, max 7.24 years, 50% girls) were selected for analysis to avoid bias introduced by individuals at the edges of the ASE distribution.
MAIN OUTCOME MEASURES: ADHD-related symptoms were assessed at school entry and second and fourth grades by parent-reported and teacher-reported versions of the Strengths and Difficulties Questionnaire (Hyperactivity-Inattention Subscale).
RESULTS: The agreement between parent-reported and teacher-reported symptoms was poor (intra-class correlation: 0.41 and 0.44 in second and fourth grade assessments, respectively). Regarding teacher reports, ASE was negatively associated with ADHD-related symptoms in the second grade (regression coefficient β=-0.66 per year, P=0.0006) and fourth grade (β=-0.56, P=0.0014). Associations remained after adjusting for potential confounders and pre-existing symptoms at baseline. Regarding parent reports, associations were markedly weaker in both grades (second grade: β=-0.22, P=0.12; fourth grade: β=-0.09, P=0.48).
CONCLUSIONS: Using a prospective study design and comprehensive adjustment for confounding and baseline symptoms, we confirmed prior evidence of the association between young ASE and teacher-reported ADHD symptoms in primary school

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Brain Dev. 2018.
NOVEL METHOD USING HJORTH MOBILITY ANALYSIS FOR DIAGNOSING ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN GIRLS.
Chow JC, Ouyang C-S, Chiang C-T, et al.
Background: Attention-deficit hyperactivity disorder (ADHD) is a common childhood neuropsychiatric disorder. Diagnosis of ADHD is based on core symptoms or checklists; however, practitioner subjectivity inevitably results in instances of over- or under-diagnosis. Although an elevated theta/beta ratio (TBR) of the electroencephalography (EEG) band has been approved by the Food and Drug Administration as a factor

that may be used in diagnosis of ADHD, several studies have reported no significant differences between the TBR of patients with ADHD and controls.
Purpose: In this study, a method was developed based on Hjorth Mobility (M) analysis of EEG to compare patients with ADHD and controls.
Methods: Differences in the presentations of ADHD between boys and girls are well established; therefore, separate investigations are required. The present study enrolled 30 girls with ADHD and 30 age-matched controls.
Results: The results revealed that the control group had significantly higher Hjorth M values in most brain areas in EEG readings compared with the values for the ADHD group. Compared with TBR, our method revealed a greater number of more significant differences between the girls in the ADHD group and the controls. Moreover, our method can produce the higher average sensitivity (0.796), average specificity (0.796), average accuracy (0.792), and average area under the curve of receiver operating characteristic curve (AUC) value (0.885). Therefore, compared with TBR, Hjorth M possessed the better potential for differentiating between girls with ADHD and controls.
Conclusion: The proposed method was more accurate than the TBR in diagnosing ADHD. Therefore, Hjorth M may be a promising tool for differentiating between children with ADHD and controls

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Child Care Health Dev. 2018 Nov;44:871-78.
INJURY AMONG CHILDREN AND YOUNG PEOPLE WITH AND WITHOUT ATTENTIONâ€• DEFICIT HYPERACTIVITY DISORDER IN THE COMMUNITY: THE RISK OF FRACTURES, THERMAL INJURIES, AND POISONINGS.
Prasad V, West J, Sayal K, et al.
Background: Injuries commonly cause morbidity and mortality in children and young people (CYP). Attention deficit hyperactivity disorder (ADHD) is the commonest neurobehavioural disorder in CYP and is associated with increased injury risk. However, large, population based estimates of the risk of specific injuries are lacking. We aimed to provide estimates of the risk of fractures, thermal injuries, and poisonings in CYP with and without ADHD.
Methods: In this population based cohort study, we used primary and secondary care medical records from England from the Clinical Practice Research Datalink. There were 15,126 CYP with ADHD frequencyâ€• matched to 263,724 without, aged 3- 17 years at diagnosis. The risk of (a) fractures, (b) thermal injuries, and (c) poisonings in CYP with ADHD was compared with those without.
Results: The absolute rate of injury per thousand person years at risk in CYP with versus without ADHD was fracture 28.9 (95% CI [27.5, 30.3]) versus 18.7 (95% CI [18.5, 19.0]), long bone fracture 17.7 (95% CI [16.7, 18.8]) versus 11.8 (95% CI [11.6, 12.0]), thermal injuries 4.4 (95% CI [3.9, 4.9]) versus 2.2 (95% CI [2.1, 2.3]), and poisonings 6.3 (95% CI [5.7, 6.9]) versus 1.9 (95% CI [1.9, 2.0]). Adjusting for age, sex, geographical region, deprivation, and calendar year, CYP with ADHD had 25% increase in risk of fracture (hazard ratio [HR] = 1.25; 95% CI [1.19, 1.31]), 21% increase in risk of long bone fracture (HR = 1.21; 95% CI [1.13, 1.28]), double the risk of thermal injury (HR = 2.00; 95% CI [1.76, 2.27]), and almost four times the risk of poisoning (HR = 3.72; 95% CI [3.32, 4.17]).
Conclusions: CYP with ADHD are at greater risk of fracture, thermal injury, and poisoning compared with those without. Paediatricians and health care professionals should provide injury prevention advice at diagnosis and reviews

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Compr Psychiatry. 2018;87:138-42.
INCREASED ZONULIN IS ASSOCIATED WITH HYPERACTIVITY AND SOCIAL DYSFUNCTIONS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Özyurt G, Öztürk Y, Appak YÇ, et al.
Background: In attention deficit hyperactivity disorder (ADHD), deteriorations of brain gut axis has been shown in previous studies. One area where the most important challenges are seen in ADHD is social functioning. Zonulin is a protein found in the intestinal intraepithelial component; it has been shown that the

level of zonulin increases when intestinal permeability is impaired. Changes in intestinal function were shown in ADHD. Zonulin has been shown to be associated with social impairment in children with autism spectrum disorder. In this study, it was aimed to evaluate the relationship between the ADHD symptoms and zonulin in children with ADHD. Secondarily relation of zonulin and difficulties in social functioning was examined in these children.
Methods: Forty children diagnosed with ADHD and forty-one healthy children similar age and gender to ADHD group and their mothers were included in the study. Children without any chronic systemic immunological or infectious diseases were included in the case and control group. The ADHD symptoms were scored by the DuPaul ADHD scale and the social functioning of the children was assessed by the Social Responsiveness Scale (SRS). Serum zonulin levels were analyzed by enzyme-linked immunosorbent assay.
Results: Children with ADHD had higher serum zonulin levels and were more impaired in social functioning compared to controls. The level of zonulin was independently predicted with hyperactivity symptoms and SRS scores in regression analysis.
Conclusion: In this sample of children with ADHD, elevated zonulin levels were associated with increased symptoms of hyperactivity and impairment of social functioning

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Dev Cognitive Neurosci. 2018;33:83-98.
MAKING AN UNKNOWN UNKNOWN A KNOWN UNKNOWN: MISSING DATA IN LONGITUDINAL NEUROIMAGING STUDIES.
Matta TH, Flournoy JC, Byrne ML.
The analysis of longitudinal neuroimaging data within the massively univariate framework provides the opportunity to study empirical questions about neurodevelopment. Missing outcome data are an all-to-common feature of any longitudinal study, a feature that, if handled improperly, can reduce statistical power and lead to biased parameter estimates. The goal of this paper is to provide conceptual clarity of the issues and non-issues that arise from analyzing incomplete data in longitudinal studies with particular focus on neuroimaging data. This paper begins with a review of the hierarchy of missing data mechanisms and their relationship to likelihood-based methods, a review that is necessary not just for likelihood-based methods, but also for multiple-imputation methods. Next, the paper provides a series of simulation studies with designs common in longitudinal neuroimaging studies to help illustrate missing data concepts regardless of interpretation. Finally, two applied examples are used to demonstrate the sensitivity of inferences under different missing data assumptions and how this may change the substantive interpretation. The paper concludes with a set of guidelines for analyzing incomplete longitudinal data that can improve the validity of research findings in developmental neuroimaging research

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Dev Med Child Neurol. 2018.
MENTAL HEALTH DISORDERS AND PHYSICAL RISK FACTORS IN CHILDREN WITH CEREBRAL PALSY: A CROSS-SECTIONAL STUDY.
Whitney DG, Warschausky SA, Peterson MD.
Aim: To examine the prevalence of mental health disorders among children with and without cerebral palsy (CP), and to examine how physical risk factors in children with CP might mitigate any elevated risk of mental health disorders in this population.
Method: Children from 6 years to 17 years of age with (n=111) and without (n=29 909) CP from the 2016 National Survey of Children's Health were included in this cross-sectional study. Mental health disorders included depression, anxiety, behavior/conduct problems, and attention deficit disorder/attention-deficit/hyperactivity disorder (ADHD). Physical risk factors included physical activity (number of active days 60min), sleep duration, and pain.
Results: Adjusting for sociodemographics, children with CP had higher odds of mental health disorders (odds ratio [OR]=2.7-7.1, $p<0.05$) except for attention deficit disorder/ADHD (OR=2.5; 95% confidence interval [CI]=0.9-7.1). Further adjusting for physical factors, the odds of depression were no longer increased (i.e. attenuated) in children with CP (OR=1.0; 95% CI=0.3-3.3); however, the odds of anxiety (OR=3.8; 95%

CI=1.9-7.8) and behavior/conduct problems (OR=3.8; 95% CI=1.3-11.1) remained elevated. Assessed individually, low physical activity and pain attenuated the odds of depression in children with CP (OR=1.9; 95% CI=0.7-5.3; OR=1.4; 95% CI=0.6-3.8 respectively).
Interpretation: Children with CP have an elevated prevalence of mental health disorders even after accounting for physical risk factors. Low physical activity and pain partially accounts for the association between CP and depression.
What this paper adds: Children with cerebral palsy (CP) have an elevated risk of developing mental health disorders. Physical factors do not fully account for higher mental health disorder prevalence. Physical activity partially accounts for the relationship between CP and depression. Pain partially accounts for the relationship between CP and depression

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Diabetes Care. 2018;41:2502-08.
MATERNAL GESTATIONAL DIABETES MELLITUS, TYPE 1 DIABETES, AND TYPE 2 DIABETES DURING PREGNANCY AND RISK OF ADHD IN OFFSPRING.
Xiang AH, Wang X, Martinez MP, et al.
OBJECTIVE To examine the relative importance of maternal preexisting type 1 diabetes (T1D), preexisting type 2 diabetes (T2D), and gestational diabetes mellitus (GDM) on risk of attention deficit/hyperactivity disorder (ADHD) in offspring.
RESEARCH DESIGN AND METHODS This retrospective birth cohort study included 333,182 singletons born in 1995-2012 within Kaiser Permanente Southern California hospitals. Children were prospectively followed through electronic medical records from age 4 years. Relative risks of ADHD associated with diabetes exposures in utero were estimated by hazard ratios (HRs) using Cox regression with adjustment for potential confounders. For GDM, timing of exposure was evaluated by gestational age at diagnosis and severity was assessed by the need for antidiabetes medication treatment during pregnancy.
RESULTS A total of 37,878 (11.4%) children were exposed to diabetes (522 exposed to T1D, 7,822 T2D, and 29,534 GDM). During a median of 4.9 years (interquartile range 2.2, 9.6) of follow-up after age 4 years, 17,415 (5.2%) children were diagnosed with ADHD. ADHD risk was not associated with GDM taken as a whole (P = 0.50) or with gestational age at GDM diagnosis (P = 0.16). However, the risk was significantly greater for the GDM requiring versus not requiring antidiabetes medications (P < 0.001). Compared with children unexposed to diabetes, the adjusted HRs for ADHD in children were 1.57 (95% CI 1.09-2.25) for exposure to T1D, 1.43 (1.29-1.60) for T2D, 1.26 (1.14-1.41) for GDM requiring antidiabetes medications, and 0.93 (0.86-1.01) for GDM not requiring medications.
CONCLUSIONS The hierarchy of risks suggests that severity of maternal diabetes (T1D vs. T2D vs. GDM requiring antidiabetes medications) influences the risk of ADHD in offspring of mothers with diabetes

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Dyslexia. 2018;24:276-93.
CO-MORBIDITIES IN CHINESE CHILDREN WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND READING DISABILITIES.
Wang L-C, Chung KKH.
The co-morbidity of attention deficit/hyperactivity disorder (ADHD) and reading disorder (RD) is more frequent than expected. This investigation assessed the potential uniqueness of the co-morbidity of ADHD and RD and extended existing findings to the Chinese language. A parallel group design with a post hoc analysis of group differences was employed to compare 4 groups of children (30 with ADHD, 33 with RD, 28 with ADHD-á+-áRD, and 30 typically developing) regarding their reading comprehension, attention, reading-related abilities, and cognitive abilities. The findings indicated that children with RD and/or ADHD symptom(s) exhibited diverse cognitive profiles, and the distinguishing factor contributed to different inhibitions. Additionally, Chinese-speaking children with the co-morbid symptoms of RD and ADHD demonstrated greater deficits in auditory working memory and rapid naming than did the pure-deficit groups. Furthermore, although problems with phonological awareness were similar between the 2 groups, the deficiency of

orthographic knowledge was more severe in children with RD than in the co-morbid group. The ADHD RD group's cognitive and reading-related abilities displayed a relatively complicated pattern that should be considered in the diagnosis of either RD or ADHD and their remediation design

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Emotion. 2018 Nov.

ARE EMOTION RECOGNITION ABILITIES INTACT IN PEDIATRIC ADHD?

Wells EL, Day TN, Harmon SL, et al.

Extant studies suggest that children with attention-deficit/hyperactivity disorder (ADHD) may make more errors and respond more slowly on tasks that require them to identify emotions based on facial affect. It is unclear, however, whether these findings reflect a unique deficit in emotion recognition, or more general difficulty with choice-response tasks (i.e., tasks that require participants to select among a set of competing options). In addition, ADHD is associated with executive dysfunction, but there is inconsistent evidence regarding the extent to which top-down cognitive control is involved in emotion recognition. The current study used a series of four counterbalanced tasks to systematically manipulate emotional content and working memory demands to determine (a) whether children with ADHD exhibit a unique facial affect recognition deficit and (b) the extent to which facial affect recognition is an automatic versus controlled process that depends in part on working memory. Bayesian results from a carefully phenotyped sample of 64 children ages 8 to 13 (M = 10.42, SD = 1.56; 26 girls; 67% Caucasian/non-Hispanic) with ADHD (n = 35) and without ADHD (n = 29) indicated that working memory is involved in children's ability to efficiently infer emotional state from facial affect (BF_{10}= 4.59 × 10^{14}). Importantly, there was significant evidence against deficits in emotion recognition for children with ADHD. The ADHD/non-ADHD groups were statistically equivalent in terms of recognition accuracy (BF_{01} = 1.32 × 10^{54}, d = -0.18), and the ADHD group's slower recognition speed was parsimoniously explained by difficulty with choice-response tasks rather than unique to emotional stimuli (BF_{10} = 3.23, d = 0.31). These findings suggest that emotion recognition abilities are intact in children with ADHD, and highlight the need to control for impaired bottom-up (choice-response) and top-down abilities (working memory) when investigating emotional functioning in ADHD. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

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Emot Behav Difficulties. 2018;23:389-409.

HAS SCHOOLING OF ADHD STUDENTS REACHED A CROSSROADS?

Malmqvist J.

The aim of the present study was to examine and describe educational leadersΓÇÖ mindset types related to schooling of students with ADHD in five municipalities with ADHD special education classes and in five pair-matched municipalities without such classes. Selection of the ten municipalities was based on the results from a nationwide survey (response rate 76%) aimed at investigating how Swedish municipalities organise schooling for ADHD students. Interview data was analysed with the use of a theoretical framework presented as a typology table describing mindsets more or less in line with either the neuropsychiatric paradigm or inclusion. The perceived neuropsychiatric influence on ADHD studentsΓÇÖ schooling seemed to affect educational leadersΓÇÖ decision making, leading to different schooling for ADHD students in different municipalities. The findings, presented as municipality profiles, are discussed in relation to the notion of inclusive education and alternative educational paths leading either towards inclusion or exclusion

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Encephale. 2018.

PSYCHOMETRIC PROPERTIES OF THE FRENCH VERSION OF THE SOCIAL RESPONSIVENESS SCALE IN AUTISM SPECTRUM DISORDER WITH OR WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Stordeur C, Boele A, Peyre H, et al.

Objectives: The Social Responsiveness Scale (SRS) is an instrument that is commonly used to screen for Autism Spectrum Disorder (ASD). Attention Deficit Hyperactive Disorder (ADHD) frequently occurs with ASD and both disorders share some phenotypic similarities. In the present study, we aimed to determine the psychometric properties of the French version of the Social Responsiveness Scale (SRS) and its 5 subscales (social awareness, social cognition, social communication, social motivation, and autistic mannerisms) to discriminate between children with ADHD and those with ASD (differential diagnosis) and children with ADHD from those with a dual diagnosis of ADHD and ASD (comorbid diagnosis).
Method: SRS total scores and the 5 subscores of the SRS were compared between 4 groups of children: ADHD (n = 32), ASD + ADHD (n = 30), ASD (n = 31) and typical neurodevelopment (TD; n = 30) children. The discriminant validity was estimated using the Area Under the ROC Curves (AUC).
Results: SRS Social cognition (AUC = 0.73) and Autistic mannerisms (AUC = 0.70) subscores were the most discriminating for differential diagnosis of ASD and ADHD. SRS total scores (AUC = 0.70), and Social communication (AUC = 0.66) and Autistic mannerisms (AUC = 0.75) subscores were the most discriminating for comorbid diagnosis of ASD among ADHD children.
Conclusion: The SRS autistic mannerisms subscore was found to be clinically relevant for both differential diagnosis of ASD and ADHD and comorbid diagnoses of ASD among ADHD children but with a modest discriminant power

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Environ Int. 2018;121:658-66.

PRENATAL FLUORIDE EXPOSURE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) SYMPTOMS IN CHILDREN AT 6-12YEARS OF AGE IN MEXICO CITY.

Bashash M, Marchand M, Hu H, et al.

Background: Epidemiologic and animal-based studies have raised concern over the potential impact of fluoride exposure on neurobehavioral development as manifested by lower IQ and deficits in attention. To date, no prospective epidemiologic studies have examined the effects of prenatal fluoride exposure on behavioral outcomes using fluoride biomarkers and sensitive measures of attention.
Objective: We aimed to examine the association between prenatal fluoride exposure and symptoms associated with attention-deficit/hyperactivity disorder (ADHD).
Method: 213 Mexican mother-children pairs of the Early Life Exposures to Environmental Toxicants (ELEMENT) birth cohort study had available maternal urinary samples during pregnancy and child assessments of ADHD-like behaviors at age 6-12. We measured urinary fluoride levels adjusted for creatinine (MUFcr) in spot urine samples collected during pregnancy. The Conners' Rating Scales-Revised (CRS-R) was completed by mothers, and the Conners' Continuous Performance Test (CPT-II) was administered to the children.
Results: Mean MUFcr was 0.85 mg/L (SD = 0.33) and the Interquartile Range (IQR) was 0.46 mg/L. In multivariable adjusted models using gamma regression, a 0.5 mg/L higher MUFcr (approximately one IQR higher) corresponded with significantly higher scores on the CRS-R for DSM-IV Inattention (2.84 points, 95% CI: 0.84, 4.84) and DSM-IV ADHD Total Index (2.38 points, 95% CI: 0.42, 4.34), as well as the following symptom scales: Cognitive Problems and Inattention (2.54 points, 95% CI: 0.44, 4.63) and ADHD Index (2.47 points; 95% CI: 0.43, 4.50). The shape of the associations suggested a possible celling effect of the exposure. No significant associations were found with outcomes on the CPT-II or on symptom scales assessing hyperactivity.
Conclusion: Higher levels of fluoride exposure during pregnancy were associated with global measures of ADHD and more symptoms of inattention as measured by the CRS-R in the offspring

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Epilepsy Behav. 2018;89:79-83.

BEHAVIOR PROBLEMS IN CHILDREN WITH EPILEPSY AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN CENTRAL CHINA.

Zhao Q, Wang M, Kang H, et al .

In this study, we aimed to evaluate the prevalence of attention-deficit hyperactivity disorder (ADHD) in children with epilepsy in Central China and compare the behavioral problems in children with epilepsy combined with and without ADHD. Children with epilepsy aged between 6 and 16 years were recruited for this study. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were administered for the diagnosis of ADHD and ADHD subtype in children with epilepsy. Children Behavior Checklist (CBCL) was administered by trained research assistants to evaluate children's behavior problems. Among 206 children diagnosed as having epilepsy, 51 had ADHD symptoms. Among them, 52.1% (29/51) were inattentive subtype (ADHD-I), 13.73% (7/51) were hyperactive/impulsive subtype (ADHD-HI), and 29.41% (15/51) were combined subtype (ADHD-C). Children with epilepsy and ADHD had significantly higher scores on attention problems, rule-breaking behavior, and aggressive behavior subscales ($P < 0.01$). Our results showed that children with epilepsy exhibited a significantly higher rate of ADHD compared with controls in Central China, with a predominant inattentive subtype. Children with epilepsy and ADHD showed more behavior problems such as attention-deficit, delinquent, and aggressive behaviors compared with children with epilepsy only

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European Annals of Allergy and Clinical Immunology. 2018;50:262-67.

IMPACT OF ALLERGY ON CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Abd El-Hamid ZB, Refaat MM, El-Shahawy HH, et al.

Attention deficit hyperactivity disorder (ADHD) has gained importance lately, because it has become common and has caused serious implication to those affected. DSM-IV-TR defined ADHD by symptoms of inattention, hyperactivity and impulsivity (1). Studies estimated that 4% to 8% of children worldwide have ADHD, which is more prevalent in boys than girls by three folds (2). In Egypt, the prevalence raised to 9.4% (3). There are many speculations about the possible relationship between ADHD and allergy, owing to the fact that ADHD children had allergic disorders. It is putative that ADHD might be a complication of allergy, as it was found that allergic reactions led to a sequence of imbalanced cholinergic/adrenergic activity in the central nervous system (4). On the other hand, ADHD can occur secondary to side effects of antiallergic drugs (5). The pathogenesis of allergy and ADHD both rely on gene-environment interaction, which is complex in nature (6). Surprisingly, ADHD and allergy share the hypersensitivity phenomenon. When exposed to certain stimuli which are tolerated by normal subjects, a sequence of symptoms occur. As inhalants like mite or ingestants like milk can trigger an allergic reaction, certain foods and pollens can activate ADHD symptoms (7). Due to this hypersensitivity concept in pathogenesis of both allergic disease and ADHD, integrated evaluation, proper diagnosis, prevention and management should be revised and put in consideration to improve quality of care of these patients (5). Therefore, the aim of this work was to investigate the percentage of allergic conditions among clinically diagnosed children with ADHD, and to study the effect of allergy on symptom patterns, severity and its association with demographic variables in ADHD children. Secondary outcomes were to detect the most common allergens in ADHD children with concurrent allergic disorders

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Eur Arch Psychiatry Clin Neurosci. 2018.

PRENATAL ALCOHOL USE AS A RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER .

Pagnin D, Zamboni Grecco ML, Furtado EF.

The objective of the study was to investigate the association between alcohol use during pregnancy and mental disorders in childhood, controlling for confounding risk factors by a longitudinal study of pregnant women and their offspring. The initial cohort comprised pregnant women attending an obstetric service. From the initial sample of 449 pregnant women, 81 mother child pairs agreed to participate. After 12 years, mother child pairs were assessed through self-administered questionnaires and semi-structured interviews. The

Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL) was used to assess the presence of any mental disorders in the children. The mothers were assessed by the Self-Reporting Questionnaire (SRQ) and the Alcohol Use Disorders Identification Test (AUDIT). Furthermore, data on the motherΓÇÖs alcohol use collected during pregnancy were analysed. A logistic regression tested the influence of alcohol consumption in all trimesters and binge drinking on the occurrence of attention-deficit/hyperactivity disorder (ADHD), controlling for covariates. Binge drinking at any time during pregnancy or low moderate alcohol consumption in all trimesters of pregnancy was associated with a fivefold increased odds of child ADHD. The combination of both patterns of alcohol use added an increase of 19% in the variance of ADHD s occurrence. The episodic use of at least four drinks or the regular use of low moderate alcohol doses during pregnancy was associated with significantly increased odds of subsequent child ADHD. Reducing binge drinking and regular alcohol use of pregnant women may lead to a significant decrease in their children developing ADHD

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Eur Child Adolesc Psychiatry. 2018.

ECOLOGICAL MODEL OF SCHOOL ENGAGEMENT AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN SCHOOL-AGED CHILDREN.

Nguyen MN, Watanabe-Galloway S, Hill JL, et al.

School engagement protects against negative mental health outcomes; however, few studies examined the relationship between school engagement and attention-deficit hyperactivity disorder (ADHD) using an ecological framework. The aims were to examine: (1) whether school engagement has an independent protective association against the risk of ADHD in children, and (2) whether environmental factors have an association with ADHD either directly or indirectly via their association with school engagement. This cross-sectional study used data from the 2011-2012 National Survey of Children's Health, which collected information about children's mental health, family life, school, and community. The sample contained 65,680 children aged 6-17 years. Structural equation modeling was used to estimate the direct association of school engagement and ADHD and indirect associations of latent environmental variables (e.g., family socioeconomic status (SES), adverse childhood experiences (ACEs), environmental safety, and neighborhood amenities) and ADHD. School engagement had a direct and inverse relationship with ADHD ($\beta = -0.35$, $p < 0.001$) such that an increase in school engagement corresponds with a decrease in ADHD diagnosis. In addition, family SES ($\beta = -0.03$, $p = 0.002$), ACEs ($\beta = 0.10$, $p < 0.001$), environment safety ($\beta = -0.10$, $p < 0.001$), and neighborhood amenities ($\beta = -0.01$, $p = 0.025$) all had an indirect association with ADHD via school engagement. In conclusion, school engagement had a direct association with ADHD. Furthermore, environmental correlates showed indirect associations with ADHD via school engagement. School programs targeted at reducing ADHD should consider family and community factors in their interventions

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Eur Child Adolesc Psychiatry. 2018.

LPHN3 GENE VARIATIONS AND SUSCEPTIBILITY TO ADHD IN CHINESE HAN POPULATION: A TWO-STAGE CASE-CONTROL ASSOCIATION STUDY AND GENEΓÇÔENVIRONMENT INTERACTIONS.

Huang X, Zhang Q, Gu X, et al.

Polymorphisms in latrophilin 3 (LPHN3) were recently reported to be associated with attention-deficit/hyperactivity disorder (ADHD), and subsequently other researchers tried to replicate the findings in different populations. This study was aimed to confirm the role of the LPHN3 in ADHD and explore the potential interactions with environmental risk factors in Chinese Han population. We examined the association of LPHN3 with ADHD in a population of 473 ADHD children and 585 controls. As a supplement of ADHD diagnosis, Conners Parent Symptom Questionnaire (PSQ) was used to evaluate ADHD symptoms. Blood lead levels (BLLs) were measured by atomic absorption spectrophotometry and other potential environmental risk factors were determined via a questionnaire filled out by the parents. Finally, after validation in an independent sample (284 cases and 390 controls), we observed significant associations

between LPHN3 variants rs1868790 and ADHD risk in combined stage within codominant model [TA/AA: OR (95% CI) = 1.636 (1.325ΓÇô2.021)], dominant model [OR (95% CI) = 1.573 (1.288ΓÇô1.922)], and additive model [OR (95% CI) = 1.535 (1.266ΓÇô1.862)]. Furthermore, rs1868790 significantly interacted with BLLs and maternal stress to modify ADHD susceptibility (P < 0.05), and rs1868790 was found to be related with ADHD symptoms (P < 0.05). Expression quantitative trait loci analysis further indicated that rs1868790 took part in the regulation of LPHN3 gene expression. As the first study to comprehensively explore the role of LPHN3 in ADHD in Chinese children, our research suggests that LPHN3 gene has a significant effect on the ADHD in a Chinese population

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Eur Child Adolesc Psychiatry. 2018.

PEER RELATIONSHIPS AND PROSOCIAL BEHAVIOUR DIFFERENCES ACROSS DISRUPTIVE BEHAVIOURS.

Milledge SV, Cortese S, Thompson M, et al.

It is unclear if impairments in social functioning and peer relationships significantly differ across common developmental conditions such as attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), and associated callousΓÇôunemotional traits (CU traits). The current study explored sex differences and symptoms of parent- and teacher-reported psychopathology on peer relationships and prosocial behaviour in a sample of 147 referred children and adolescents (aged 5ΓÇô17-áyears; 120-ám). The results showed that increases in parent-reported ADHD Inattentive symptoms and teacher-reported ADHD HyperactiveΓÇôImpulsive symptoms, CD, ODD, and CU traits were significantly associated with peer relationship problems across sex. At the same time, teacher-reported symptoms of ODD and both parent- and teacher-reported CU traits were related to difficulties with prosocial behaviour, for both boys and girls, with sex explaining additional variance. Overall, our findings show a differential association of the most common disruptive behaviours to deficits in peer relationships and prosocial behaviour. Moreover, they highlight that different perspectives of behaviour from parents and teachers should be taken into account when assessing social outcomes in disruptive behaviours. Given the questionable separation of conduct problem-related constructs, our findings not only point out the different contribution of those aspects in explaining peer relationships and prosocial behaviour, but furthermore the variance from different informants about those aspects of conduct problems

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Eur J Paediatr Neurol. 2018.

A SYSTEMATIC REVIEW OF COMORBIDITY BETWEEN CEREBRAL PALSY, AUTISM SPECTRUM DISORDERS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Craig F, Savino R, Trabacca A.

OBJECTIVES: The aim of this systematic review was to examine the incidence and prevalence of comorbidity between Cerebral Palsy (CP), Autism spectrum disorders (ASDs) and Attention-Deficit/Hyperactivity Disorder (ADHD).

METHODS: We searched for articles indexed in PubMed, EBSCOhost, Scopus, Web of Science and other potentially relevant internet sources using a combination of expressions including "cerebral palsy" AND "autism" OR "ASD" OR "pervasive development disorder" AND "Attention Deficit Hyperactivity Disorder" OR "ADHD".

RESULTS: We identified 2542 studies on CP and ASD and 998 studies on CP and ADHD. After screening titles and abstracts and removing duplicated studies, 47 full papers (CP and ASD n = 28; CP and ADHD n = 19) were downloaded and screened for eligibility. Twenty-eight (CP and ASD n = 16; CP and ADHD n = 12) studies were identified in the peer-review literature. Based on this systematic review, ASD and ADHD seem to be more common in people with CP than in the general population, yet the gold standard methods for diagnosing ASD or ADHD are not suitable for children with motor problems.

CONCLUSIONS: Assessing the occurrence of ASD and ADHD would improve the significant cost of healthcare, therapies, and overall daily living for families with children affected by CP. However, psychometric studies are needed in the future to promote development of measures suitable for individuals with CP. In

addition, this review highlights the paucity of peer-reviewed studies investigating the occurrence of ASD and ADHD in children with different CP subtypes or functional abilities, and there are still some open questions about pathogenic mechanisms common to CP, ASD and ADHD

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Eur Neuropsychopharmacol. 2018.

CHILDHOOD SEROTONERGIC FUNCTION AND EARLY ADULT OUTCOMES IN YOUTH WITH ADHD: A 15-YEAR FOLLOW-UP STUDY.

Ivanov I, Flory J, Newcorn JH, et al.

Longitudinal studies have shown that clinical precursors of antisocial personality disorder (ASPD) include attention-deficit/hyperactivity disorder (ADHD) and more notably comorbid ADHD and conduct disorder (CD). Despite existing evidence for the purported role of abnormal serotonergic function in aggressive youth and adults, little evidence exists on the role of serotonin in the progression from childhood disruptive behavior disorders to adult psychopathology, including ASPD. This study examined the relation between serotonergic function in children diagnosed with ADHD and the development of ASPD in early adulthood. We hypothesized that low serotonin response to a pharmacological probe in childhood would predict the development of adult ASPD. Towards this goal we divided 40 adults (M = 37, F = 3), ages 23ΓÇô26 (m-24.57, sd-2.33) diagnosed with childhood ADHD into 2 groups: participants with (n = 21) and without (n = 19) ASPD. We used logistic regression to assess whether serotonergic measures in childhood assessed via prolactin and cortisol responses to a fenfluramine challenge, would selectively predict the development of ASPD in early adulthood. Logistic regression models showed that low central serotonergic response in childhood indexed by cortisol response significantly predicted adult ASPD (Wald = 4.427, p =.035) but not ADHD diagnosis in adulthood. Adults without ASPD had the highest serotonergic response whereas adults with adolescent ASPD (i.e. early onset ASPD) had the lowest response. Thus we provide new evidence of the link between low serotonergic function in childhood and the development of ASPD in adulthood, particularly for boys with adolescent onset of ASPD. These findings are relevant for understanding the contribution of childhood neurobiology to risk for later ASPD

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Eur Psychiatry. 2019;55:18-22.

FIRST EPISODE PSYCHOSIS AND COMORBID ADHD, AUTISM AND INTELLECTUAL DISABILITY.

Strålin P, Hetta J.

Background: Comorbidity between neurodevelopmental disorders and psychotic disorders is common, but little is known about how neurodevelopmental disorders influence the presentation and outcome of first episode psychosis.

Methods: A nation-wide cohort (n = 2091) with a first hospitalization for psychosis between 2007-2011 and at ages between 16-25 at intake was identified from Swedish population registries. Comorbid diagnoses of neurodevelopmental disorders were identified at first psychosis hospitalization and for ADHD also by dispensations of psychostimulants before the first psychosis hospitalization. Data from the registers on hospitalizations and dispensations of antipsychotic and psychostimulant medications during the year before and 2 years after the first psychosis hospitalization were analysed. Self-harm and substance use disorders were identified by ICD10 codes at hospitalizations.

Results: 2.5% of the cohort was identified with a diagnosis of intellectual disability, 5.0% with autism and 8.1% with ADHD. A larger proportion of cases with Autism (OR = 1.8, $p < 0.05$) and intellectual disability (OR = 3.1, $p < 0.01$) were using antipsychotic medication year 2 compared to the rest of the cohort. Delusional disorder was more common in the autism group (OR = 2.3, $p < 0.05$) at first psychosis hospitalization. ADHD was associated with higher risks for substance use disorders and self-harm both before and after the first psychosis hospitalization. Year 2 substance use disorder had a OR = 2.6 ($p < 0.001$) and self-harm OR = 4.1 ($p < 0.001$).

Conclusions: Psychosis with comorbid ADHD is associated with high risks for substance use disorders and for self-harm, while psychosis with comorbid autism and intellectual disability is associated with longer treatment and higher doses of antipsychotic medication

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Fizyoterapi Rehabilitasyon. 2017;28:S20.

COMPARISON OF THE BALANCE SITUATIONS OF CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER TO TYPICALLY DEVELOPING PEER.

Atasavun US, et al.

Purpose: It is known that to be difficult to perform motor activities in school-aged children with Attention Deficit Hyperactivity Disorder (ADHD). Muscle strength, flexibility, endurance and coordination with balance are important to do motor activity in children. So we aimed to compare the balance children with ADHD than healthy children in our study.

Methods: Thirteen healthy children and 12 children with ADHD were included in the study. Children's balance status was assessed by the balance sub-parameter of Bruininks-Oseretsky Test of Motor Proficiency - Short Form.

Results: The mean age of the children in the healthy group was 9.54-¦1.04 years while the mean age of children with ADHD was 8.58-¦2.1 years. A statistically significant difference was found when the balance status of both groups were compared (Z=-2.26, p=0.02). The mean balance score of the children in the healthy group was 7.31.37, while the balance score of the children with ADHD was 5.66-¦2.05.

Conclusion: As a result of our study, children with ADHD were found to have worse balance status than healthy children. This has been linked to some hypotheses that in some studies in children with ADHD are either smaller than the cerebellum in children with normal motor development or lack of stimuli necessary for planning motor activity. More advanced study to be done in this regard is needed. We also think that it is important to determine the loss of balance in children with ADHD at an early age and to be included in physiotherapy programs

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Heroin Addiction and Related Clinical Problems. 2018;20:48-49.

AFFECTIVE TEMPERAMENT IN PATIENTS WITH PERSISTENT ADHD AND SUBSTANCE USE DISORDER (COCAINE).

Caloro M, de RP, et al.

INTRODUCTION: Attention Deficit Hyperactivity Disorder (ADHD) is characterized by hyperactivity, memory disturbances, distractibility, impulsivity and/ or attention deficit. Although sideways thinking has its onset and maximum expression during childhood, it commonly occurs in adolescence and adulthood. In adolescence, in fact, there is a high risk of trauma and accidents, inability to follow the rules, learning difficulties, reckless behaviour, conduct disorders, and alcohol and substance abuse. ADHD is accompanied in 80% by psychiatric comorbidity, like Substance Use Disorder (SUD) and Bipolar Disorder (BD), which in turn negatively impact quality of life.

METHODS: We selected 128 consecutive outpatients referring to the psychiatric clinic of the Sant'Andrea Hospital, U.O.C. of Psychiatry at Sapienza University, Rome, and at the Va.R.Co. (Regional Evaluation for Cocaine) of the Rome RM1 Dependency Service (SerD) during the span of 12 months. We divided patients into three groups, i.e., patients with SUD (n = 66), with ADHD (n = 31), and comorbid SUD + ADHD (n = 31). Clinical data were collected through a semistructured interview. To evaluate persistent ADHD in adulthood, patients completed the Adult ADHD Self- Scale Report (ASRS-v1.1) and clinicians conducted the DIVA 2.0 semi-structured interview. To evaluate temperament we used the Italian TEMPS-A self-rated questionnaire.

RESULTS: Age at first substance use was significantly lower in the SUD + ADHD group compared to SUD alone, while the weekly use frequency was similar. As regards ASRS, we observed significant differences in the two diagnostic groups; in fact, in the SUD + ADHD, the mean values were higher than in the ADHD group. Moreover, the prevalent diagnosis was ADHD persistent in adult age of the combined inattention/motor-verbal hyperactivityimpulsivity subtype in the SUD + ADHD, while in the ADHD alone group, the inattentive

subtype prevailed. In SUD-only patients, the most represented temperament was dysthymic, in the SUD + ADHD group hyperthymic, finally in the ADHD-only group, the most represented temperament was anxious. **CONCLUSIONS**: Most adults with ADHD have another associated psychiatric disorder, which can mask ADHD; comorbidity in turn influences the clinical picture, severity, natural history, prognosis, and treatment of the disorder. SUD and mood disorders are the conditions with which ADHD is most frequently associated. SUD is widespread in the general population, and a significant proportion of people with SUD show symptoms of ADHD. In our case series, almost 30% of patients diagnosed with cocaine use had a history of ADHD since childhood and presented ADHD symptoms at the time of evaluation. Our data appear to agree with the observation that the association between SUD and ADHD would favour earlier onset of substance use. The relationship between adult ADHD and SUD is likely to be mediated by affective temperament, which would contribute to mood fluctuations and impulsive behaviours with substances abuse

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Heroin Addiction and Related Clinical Problems. 2018;20:20-21.

CAUSALITY OR CASUALITY. ADHD AND SUBSTANCE USE DISORDERS.

Martinez-Raga J.

INTRODUCTION: Attention deficit hyperactivity disorder (ADHD) is a complex and multifactorial neurodevelopmental disorder, characterized by a persistent pattern of inattention, hyperactivity and/or impulsivity. ADHD is the most frequent psychiatric disorder of childhood onset, with a worldwide prevalence of 3,4-7,2%. Studies show that about two-thirds of children diagnosed with ADHD continue with symptomatology in adulthood, so that it is estimated that 3-5% of the adult population have the disorder. Clinically, ADHD is a heterogeneous disorder, partly as a result of the high comorbidity rates with other mental disorders that often hinders its diagnosis, its treatment and the outcome. Substance use disorders (SUDs) are among the most frequent concurrent psychiatric disorders in adolescent or adult patients with ADHD.

METHODS: It is aimed to explore the interrelationship between substance use disorder and ADHD and gain a better understanding of risk factors and complications of this common comorbidity.

RESULTS: Due to the very nature of ADHD, among other factors the high association with other psychiatric disorders, is a notably underdiagnosed, particularly in adults, more often in women. Children, adolescents, and adults with ADHD have a high prevalence of other comorbid psychiatric disorders. At least 60- 80% of people with ADHD have another associated psychiatric disorder. SUDs are among the most frequent concurrent psychiatric disorders in the adolescent or adult patient with ADHD. Studies have shown that ADHD is an independent risk factor for developing a SUD; thus, individuals with ADHD have up to 1.8 times the risk of developing nicotine or alcohol dependence and up to 5.2 increased risk of developing addiction to illicit substances. Furthermore, a review with meta-analysis and meta-regression analysis showed that the Overall prevalence in clinical samples is 23% regardless of age, gender or ethnic background, duration of abstinence, and time or scope of study. It as also been shown a linear relationship between the severity of ADHD and the risk or severity of SUD. The existence of a conduct disorder in childhood seems to increase the risk of developing a TCS in people with ADHD, although several systematic reviews with meta-analyses suggest that the existence of ADHD in childhood alone would be associated with a significant higher risk of developing a SUD, the presence of an oppositional defiant disorder or a conduct disorder would explain the emergence of more severe problems associated with substance use among individuals with ADHD. Use, misuse and addiction to nicotine, alcohol or other substances is higher in subjects with ADHD due to the combination of various risk factors , including common neurobiological mechanisms, a shared deterioration in psychosocial, academic and labour functioning or comorbidity with other psychiatric disorders, although certain character traits and symptoms that often appear with ADHD and SUDs such as impulsivity or low self-esteem appear to be of great importance as well, as is also the case of the neuropsychological alterations characteristic of ADHD, particularly deficits in executive function or the self-medication hypothesis. Mounting evidence suggest that pharmacotherapies commonly used for ADHD are also effective in adolescents and adults with dual disorders, usually in association with various psychological interventions, with an overall good safety and tolerability profile. However, while most studies coincide in showing the efficacy of these drugs on the symptoms of ADHD in dual patients, their actions on substance use are much more limited.

CONCLUSION: The evidence form multiple studies and guidelines of good clinical practice indicate that all patients who attend treatment for their SUD should be assessed or at least screened to rule out the presence of an associated ADHD and vice versa

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Horm Res Paediatr. 2018;1-10.

RELATION BETWEEN EARLY OVER- AND UNDERTREATMENT AND BEHAVIOURAL PROBLEMS IN PREADOLESCENT CHILDREN WITH CONGENITAL HYPOTHYROIDISM.

Bongers-Schokking JJ, Resing WCM, Oostdijk W, et al.

Objective: Congenital hypothyroidism (CH) per se, when not treated or undertreated, may lead to severe behavioural problems (cretinism), whereas overtreatment of CH seems associated with attention problems.

Design and Methods: For 55 CH patients, prospectively followed from birth until 11 years, parents rated the Child Behaviour Checklist and teachers the Teacher's Report Form at children's ages 6 and 11 years. We related scores regarding Attention, Delinquency, and Aggression (ADA scores, indicative for attention deficit hyperactivity syndrome, ADHD), and scores regarding Withdrawn, Anxious, Social, and Thought problems (WAST scores, indicative for autism) to the occurrence of over- and undertreatment in five age periods. Over- and undertreatment were defined as free thyroxine (fT4) concentrations above/below the range of the patient's individual fT4 steady state concentration.

Results: ADA scores at 6 and 11 years for patients overtreated in the period 1-3 months postnatally were higher than those for patients who were not overtreated. Patients with severe CH undertreated in the period 3-6 months postnatally had higher WAST scores at 6 and 11 years than all other patients.

Conclusions: This is the first study suggesting that permanent ADHD as well as autism in CH patients at ages 6 and 11 years are the result of early overtreatment and undertreatment, respectively

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Human Reproduction. 2015;30:2129-37.

MENTAL DISORDERS IN CHILDHOOD AND YOUNG ADULTHOOD AMONG CHILDREN BORN TO WOMEN WITH FERTILITY PROBLEMS.

Svahn MF, Hargreave M, Nielsen TSS, et al.

STUDY QUESTION Is the risk of hospital admission or outpatient contact for mental disorders increased in children born to women with fertility problems compared with children born to women without fertility problems?

SUMMARY ANSWER We found an increased risk of hospital admission or outpatient contact for mental disorders in children born to women with fertility problems.

WHAT IS KNOWN ALREADY Few studies have investigated the risk of mental disorders in children born after fertility treatment and although some studies have pointed to an increased risk, others found no association. The inconsistent results may be due to methodological constraints in many previous studies, including small sample size and short follow-up, resulting in imprecise risk estimates and lack of information on risk patterns of mental disorders in adulthood.

STUDY DESIGN, SIZE, DURATION This nationwide retrospective register-based cohort study included all 2 412 721 children born in Denmark between 1969 and 2006. All children were followed from date of birth until date of hospital contact for a mental disorder, date of emigration, date of death or 31 December 2009, whichever occurred first.

PARTICIPANTS/MATERIALS, SETTING, METHODS Information concerning maternal fertility status for all children in the cohort was obtained by linkage to the Danish Infertility Cohort, which contains data on nearly all women with fertility problems in Denmark since 1963. A total of 124 269 (5%) children were born to women with fertility problems and 2 288 452 (95%) to women without fertility problems. To identify children hospitalized for a mental disorder, the cohort was linked to the Danish Psychiatric Central Research Registry. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between maternal fertility status and the risk of hospital admission or outpatient

contact for various groups of mental disorders, including any mental disorder and all 11 main discharge diagnostic groups, classified according to the International Classification of Diseases, version 10. MAIN
RESULTS AND THE ROLE OF CHANCE During a mean follow-up period of 21 years (range, 0-40 years), 168 686 (7%) children were admitted to hospital or had an outpatient contact for a mental disorder. Children born to women with fertility problems had a significantly higher risk of any mental disorder (HR 1.23; 95% CI 1.20-1.26) and for most of the 11 main discharge groups, including schizophrenia (HR 1.16; 95% CI 1.07-1.27), mood (affective) disorders (HR 1.21; 95% CI 1.15-1.28) and disorders of psychological development (HR 1.15; 95% CI 1.09-1.21) as well as the subgroup of attention-deficit/hyperactivity disorders (HR 1.36; 95% CI 1.29-1.45) compared with children born to women without fertility problems. The risk estimates did not change markedly when analyses were performed separately for mental disorders diagnosed during childhood (0-19 years) and in young adulthood (20-40 years).
LIMITATIONS, REASON FOR CAUTION The true risk of mental disorders may be somewhat underestimated, as only severe disorders requiring hospital admission or outpatient contact were considered as events. Furthermore, we could not determine whether the increased risks observed were due to factors related to the underlying infertility or to fertility treatment procedures.
WIDER IMPLICATIONS OF THE FINDINGS This is the first report on mental disorders in adulthood among children born to women with fertility problems. Furthermore, we have assessed the risk of several severe mental disorders not previously studied (e.g. neurotic, stress-related and somatoform disorders and disorders of adult personality and behaviour). These important findings should be investigated further in large epidemiological studies designed to differentiate between factors related to fertility treatment and to the underlying infertility

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Int J Epidemiol. 2018;47:1082-97.

PRENATAL AND POSTNATAL EXPOSURE TO PERSISTENT ORGANIC POLLUTANTS AND ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER: A POOLED ANALYSIS OF SEVEN EUROPEAN BIRTH COHORT STUDIES.

Forns J, Stigum H, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is increasing worldwide for reasons largely unknown and environmental chemicals with neurotoxic properties, such as persistent organic pollutants (POPs), have been proposed to play a role. We investigated the association between prenatal and postnatal exposure to polychlorinated biphenyl-153 (PCB-153), p-β¦ò-dichlorodiphenyldichloroethylene (p-β¦ò-DDE) and hexachlorobenzene (HCB) and ADHD in childhood.
Methods: We pooled seven European birth cohort studies encompassing 4437 mother- child pairs from the general population with concentrations of PCB-153, p-β¦ò-DDE and HCB measured in cord blood, maternal blood or milk. We then calculated prenatal (birth) and postnatal (3, 6, 12 and 24months) POP concentrations using a pharmacokinetic model. The operational definition of ADHD varied across cohorts and ranged from doctor diagnosis obtained from patient registries to maternal or teachers reports. We used multilevel (mixed) logistic regression models to estimate the associations between exposure to POPs at birth, 3, 6, 12 and 24 months and ADHD.
Results: The global prevalence of ADHD in our study was 6%. The mean age at assessment of ADHD was 5.8 years (range: 3.8-9.5 years). We found no association between exposure to PCB-153, p-β¦ò-DDE and HCB at any age point between birth and 24months and ADHD, in the pooled analyses (pooled odds ratios ranging from 1.00 to 1.01). A number of sensitivity analyses gave basically the same results.
Conclusions: In the largest study to date of 4437 children in seven European birth cohorts, we did not observe any association between either pre- or postnatal exposure (up to 24 months) to PCB-153, p-β¦ò-DDE and HCB and the risk of ADHD before the age of 10 years

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Int J Mol Sci. 2018;19.

THE DECREASE IN HUMAN ENDOGENOUS RETROVIRUS-H ACTIVITY RUNS IN PARALLEL WITH IMPROVEMENT IN ADHD SYMPTOMS IN PATIENTS UNDERGOING METHYLPHENIDATE THERAPY.

Chiara C, Bernanda PM, Claudia M, et al.

Increasing scientific evidence demonstrated the deregulation of human endogenous retroviruses (HERVs) expression in complex diseases, such as cancer, autoimmune, psychiatric, and neurological disorders. The dynamic regulation of HERV activity and their responsiveness to a variety of environmental stimuli designate HERVs as genetic elements that could be modulated by drugs. Methylphenidate (MPH) is widely used in the treatment of attention deficit hyperactivity disorder (ADHD). The aim of this study was to evaluate the time course of human endogenous retrovirus H (HERV-H) expression in peripheral blood mononuclear cells (PBMCs) with respect to clinical response in ADHD patients undergoing MPH therapy. A fast reduction in HERV-H activity in ADHD patients undergoing MPH therapy was observed in parallel with an improvement in clinical symptoms. Moreover, when PBMCs from drug-na+»ve patients were cultured in vitro, HERV-H expression increased, while no changes in the expression levels were found in ADHD patients undergoing therapy. This suggests that MPH could affect the HERV-H activity and supports the hypothesis that high expression levels of HERV-H could be considered a distinctive trait of ADHD patients

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Int J Psychophysiol. 2018;131:S42.

INTERACTION BETWEEN PRE-STIMULUS AND POST-STIMULUS OSCILLATIONS DIFFERENTIATES ADHD AND ASD.

McLoughlin G.

Oscillatory activity in the brain has been shown to be a key factor in regulating attention. Neural oscillations measured using EEG can index attentional processes both before and after a stimulus appears. Accumulating evidence suggests that activity occurring during the pre-stimulus period is a reliable index of attentional engagement and plays a significant role in modulating post-stimulus behavioural and neurophysiological responses. Attentional impairments have been proposed as a common mechanism for the development of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). In this talk, I will introduce concepts underlying pre-stimulus oscillatory activity in relation to attentional processes and present findings that demonstrate differential associations between pre-stimulus alpha, task performance and post-stimulus oscillatory activity and event-related potentials, in a cross-disorder study of children with ASD and ADHD. Alpha (9-12 Hz) power and phase at stimulus onset were measured in the pre-stimulus period, and compared to behavioural responses, amplitude of early event-related potentials (ERPs; P1, N2) and post-stimulus theta (5-8 Hz), derived from EEG sources separated using independent component analysis (ICA). Children with ASD showed increased attentional engagement, or preparation for the upcoming stimulus (greater alpha desynchronisation) compared to children with ADHD. Children with ADHD showed impaired attention and cognitive control (N2 and P3) compared to ASD and TDC. A clear distinction between the disorders was found in the relationship between desynchronisation of pre-stimulus alpha and early ERP components and post-stimulus theta. Alpha desynchronisation was positively correlated with both P1 amplitude and theta synchronisation in ADHD and TDC, but negatively correlated in ASD. That is, in ASD, greater preparation for the upcoming stimulus unexpectedly resulted in poorer attentional processing post-stimulus. These findings may explain inconsistent attention deficits reported in previous studies in ASD and demonstrate the importance of objective brain measures in distinguishing pathophysiological mechanisms between ADHD and ASD

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Int J Psychophysiol. 2018;131:S108-S109.

DEFICIT OF VISUAL MEMORY IN DELAYED RECALL CONDITION IN PRESCHOOL CHILDREN WITH ADHD.

Kiselev S.

Introduction: It is known that children with ADHD have deficit in prefrontal cortex functions including deficit in working memory (Martinussen et al., 2012). In our previous research we have revealed that ADHD children have deficit in memory for faces and for names in delayed recall condition (Kiselev & Lvova, 2014; Kiselev

& Lvova, 2016). The goal of this research was to examine the hypothesis that children with ADHD have deficit in visual memory in delayed recall condition.
Methods: The experimental group included 19 children with ADHD (M= 5.97 years, SD = 0.35, 16 boys and 3 girls). The control group included 19 typically developing children (M= 5.75 years, SD = 0.41, 16 boys and 3 girls). The children from both groups were matched for IQ, gender and age. Children from both groups were assessed with visual memory subtest from Luria's child neuropsychological assessment battery (Glozman, 2013). This subtest is designed to assess the ability to perform visual memory task for objects in immediate and delayed recall conditions. The subtest includes 3 stages. At first stage child need to remember and recall 6 pictures. Then child performed visuospatial task for 5 minutes. At third stage child was asked to recall these 6 pictures.
Results: ANOVA with repeated measurements was used to reveal group differences in reproducing the objects in two conditions, with the amount of correct reproduced objects as the dependent variable, with group as between-participants factors and the task condition type as levels of repeated within-participant factors. The main effect of group was significant F(1,36)=100.44, indicating that typically developing children had better results in this task in comparison to children with ADHD. Most interestingly, the interaction of condition type and group was significant F(1,36)=98.15. ADHD children were less successful in reproducing the objects in delayed recall condition in comparison to typically developing children.
Conclusions: This study has shown that preschool children with ADHD have deficit in visual memory in delayed recall condition. However, they do not have the same deficit in immediate recall condition. In view of these results and results from our previous research concerning memory for faces and for names (Kiselev & Lvova, 2014; Kiselev & Lvova, 2016), it can be assumed that preschool children with ADHD have not global deficit in memory, but they have specific deficit in memory in delayed recall condition. Funding: The research was supported by Russian Foundation for Basic Research, grant '- 15-06-06491ðÉ

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Int J Psychophysiol. 2018;131:S104.

TIME-FREQUENCY ANALYSIS OF DELTA AND THETA OSCILLATORY ACTIVITY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER*.

Karakas S, Dogutepe E, Yilmaz M.

The aim was to search for oscillatory biomarkers that would serve as auxiliary criteria for diagnosis. The task was undertaken through the study of event-related oscillatory responses during cognitive processing. Participants were 70 unmedicated ADHD cases and 38 normal controls who were between 6 and 11 years of age (ADHD: 115.46-¦18.26 months, control: 119.186-¦17.75 months). All participants were right-handed and were within the normal IQ range (90-129). In ADHD, comorbidity served as an exclusion criterion. Tasks consisted of computerized Go/No Go (response selection) and Reversal Task (response inhibition). Event-related responses were recorded (prestimulus: 500 msec, poststimulus: 1200 msec; Dt= 1 ms; cutoff between DC and 100 Hz, 3 dB, 12 dB/c) and preprocessed for baseline shifts, eye movements and muscular movements). Multivariate Analysis of Covariance (covariate: age) with Repeated Measures on the last factor showed a significantly longer reaction time in the ADHD group in the Go/No Go task. In both tasks, the error rate of the ADHD group was significantly higher. The extraction and identification of the oscillatory components were performed using time-frequency analysis technique (TFHA). Delta amplitude and theta duration discriminated the clinical from the healthy group. Findings suggest that the ADHD Group suffers not only from attentional processing (as represented by the theta oscillatory component) but also from cognitive processing (as represented by the delta oscillatory component). *The study was supported by Do-ƒus University Scientific Projects (BAB-2016-17-D1-B01)

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Int J Psychophysiol. 2018;131:S64.

THE QUANTIFIED EEG CHARACTERISTICS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVE DISORDERS WITH LONG-TERM TREATMENT WITH ATOMOXETINE.

Chiarenza GA.

Objective: The aim of this study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are Responders and Non-Responders to long-term treatment with Atomoxetine at baseline and after 6 and 12 months of treatment. Patients with Attention Deficit Hyperactivity Disorder (ADHD) received atomoxetine titrated, over 7 days, from 0.5 to 1.2 mg/kg/day. QEEG and Swanson, Nolan, and Pelham IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy.

Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked earlobes. Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values.

Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values.

Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta

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Int J Psychophysiol. 2018;131:S146.

PSYCHOPHYSIOLOGICAL CORRELATES OF COLOR FUNCTION IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Savchuk LV, Polevaia SA, Fedotchev AI, et al.

Introduction: ADHD is one of the most common disorders in children and adolescents. It occurs in about 5% of the child population. This makes research of psychophysiological correlates of ADHD very important. Objective physiological indices of ADHD can be applied not only for preclinical diagnostics, but also for monitoring the dynamics of the state with ADHD.

Methods: In our work, to assess selective attention and activity level, the Toulouse-Pieron test was applied. It represents a variant of the proof test a nonverbal test which reveals ability of the respondent to voluntary concentrate the attention. The test took 10 minutes per volunteer. Processing of the results was manual, with the use of special keys. Instrumental quantitative assessment of emotiogenic changes of function of color discrimination was performed. To assess color discrimination thresholds in the framework of HLS color model the computer campimetry test was applied. The test took 5 minutes for each participant, and the assessment was performed automatically.

Results: A total of 41 subjects between 7 to 12 years of age participated in the study: 18 children with ADHD and 23 children without diagnosis. In hyperactive children the color discrimination thresholds in all shades are significantly higher than in healthy children ($p= 0,001$, t-tests). In 91% of healthy children the function of color discrimination with the maximum differential threshold in green shades range prevails, in 70% of children with ADHD in blue shades range. The indices of computer campimetry which are closely related to indices of accuracy ($r= - 0.87$; $p < 0.05$) and speed ($r= - 0.93$; $p < 0.05$) according to the Toulouse-Pieron test are revealed. The regression analysis was performed to calculate parameters of selective attention and speed: $K = -0.0118 * dH190 + 0.9083$ ($R2 = 0.79$) $V = -3.656 * dH160 + 57.562$ ($R2 = 0.6$), where K - accuracy according to the Toulouse-Pieron test, dH190 - differential threshold for shade 190; V - speed according to the Toulouse-Pieron test, dH160 - differential threshold for shade of 160.

Conclusions: Deterioration of color discrimination in shades of blue can be considered as possible markers of the increased risk of clinical ADHD development in children aged 7-12. Computer campimetry can be used

as a simple and reliable method to aid ADHD assessment along with the classical proof test for preclinical diagnosis. It can also be useful for monitoring of the dynamics of ADHD in children

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Int J Psychophysiol. 2018;131:S59.

QUANTITATIVE EEG AND ERPS IN CHILDREN AND ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Markovska-Simoska S, Pop-Jordanova N.

Introduction: In recent decades, resting state electroencephalographic (EEG) measures have been widely used to document underlying neurophysiological dysfunction in attention deficit hyperactivity disorder (ADHD). Although most EEG studies focus on children, there is a growing interest in adults with ADHD too. The aim of this study is to objectively assess and compare the absolute and relative EEG power as well as the theta/beta ratio, coherence and ICA ERPs components in children and adults with ADHD.

Methods: Studied sample included ADHD children and adults as well as control group. The resting EEG activity in eyes open and eyes closed condition for the four EEG spectral bands (delta, theta, alpha and beta) was evaluated in examined groups. The Visual and Emotional Continuous Performance Tests as modifications of GO/NOGO paradigm were applied in order to obtain cognitive ERPs as indexes of executive functions. Beside behavioral parameters of test performance, amplitude and latency of several cognitive ERPs reflecting different stages of information processing were explored.

Results: The findings obtained for ADHD children are increased absolute power of slow waves (theta and delta), whereas adults exhibited no differences compared with normal subjects. For the relative power spectra there were no differences between the ADHD and control groups. Across groups, the children showed greater relative power than the adults in the delta and theta bands, but for the higher frequency bands (alpha and beta) the adults showed more relative power than children. Classification analysis showed that ADHD children could be differentiated from the control group by the absolute theta values and theta/beta ratio at Cz, but this was not the case with ADHD adults. The ERPs results point out that there is disturbance in executive functioning in investigated ADHD group obtained by the significantly lower amplitude and longer latency for the engagement, motor inhibition and monitoring components.

Conclusions: Nowadays, QEEG parameters and independent components of ERPs have been applied in order to objectively discriminate ADHD population from norms. Their application is very important for choosing the right medication and type of psychotherapy or choosing the right location for neurofeedback treatment and localizing the area for TMS or tDCS. Thus, EEG and ERPs measures used as a diagnostic add-on in ADHD may be of interest in guiding a personalized medicine approach in particular regarding treatment outcomes

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Int J Psychophysiol. 2018;131:S162.

EFFICACY OF EEG BIOFEEDBACK PROCEDURES IN CORRECTING ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN.

Savchuk LV, Polevaia SA, Fedotchev AI, et al.

Introduction: Attention deficit hyperactivity disorder (ADHD) is affecting about 5% of children worldwide. The alternative to medical treatment, which induces adverse reaction in over 20% of cases, is the method of EEG biofeedback (EEGBF). There are two most substantiated EEGBF training protocols for children with ADHD: 1- increases beta activity (16-20Hz) while suppressing theta activity (4-8Hz); 2 - suppresses theta activity and simultaneously increases sensorimotor rhythm (SMR; 12-14Hz).

Methods: In this study, a double biofeedback from patients EEGs was used. The first loop was the auditory feedback stimuli from the EEG (4ΓÇô8Hz). Sound was delivered via headphones (sound intensity 0-40dB; frequency100-2000Hz), and served as a reference for the conscious manipulation of the EEG by the patient. The second feedback loop was the rhythmic light stimulation using lightemitting diode eyeglasses (under 100++W). Its parameters were automatically modulated by the narrowband component of the EEG +¦-SMR rhythm (8-14Hz) for the patient in order to activate it in resonance. The volunteers were instructed to try to decrease the sound intensity while paying no attention to light stimulation.

Results: A total of 23 subjects between 11 to 12 years of age participated in the study: 11 children with ADHD and 12 healthy children. EEG at rest was recorded for 5 minutes before asnd after stimulation. A two-loop feedback stimulation was recorded for 10 minutes. The Mann Whitney U test and the Wilcoxon signed-rank test were used for analysis. The power levels of the +© rhythm in children with ADHD is significantly higher (p = 0,00006). The total power in the +¦ range in healthy children is significantly higher (p = 0,02). The power of +¦ rhythmsignificantly increased after the stimulation in both groups (p = 0,01). When comparing the power in theta and alpha range in healthy children before the stimulation, and in ADHD group after the procedure, there is no significant difference in the alpha range, which indicates the shift in this index in children with ADHD to the normal value. The absence of significant differences in theta rhythm in both groups before and after the procedure is most likely due to the impossibility to learn after one procedure to consciously manipulate this EEG component.
Conclusion: There is a significant difference in EEG parameters of healthy children and children with ADHD. EEGBF training is a promising method to aid ADHD correction in children

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Iran J Med Sci. 2018;43:596-604.

EFFECTS OF MINDFUL PARENTING TRAINING ON CLINICAL SYMPTOMS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER AND PARENTING STRESS: RANDOMIZED CONTROLLED TRIAL.

Behbahani M, Zargar F, Assarian F, et al.

Background: Children with attention deficit hyperactivity disorder (ADHD) are at risk of impairment in multiple domains. This study aimed to investigate the effectiveness of mindful parenting training in reducing clinical symptoms in children with ADHD and parenting stress of their parents.
Methods: This randomized clinical trial was conducted on 2 groups (experimental and control) in 3 phases (pretest, posttest, and 8 weeksΓÇÖ follow-up). Sixty children with ADHD, who had been referred by the child psychiatrist in the Iranian city of Kashan in the second half of the year 2016, were selected along with their mothers. The mothers were assigned to one of the 2 groups via permuted blocked randomization. The mothers completed the parenting stress index short form (PSI SF 36) and the Swanson, Nolan, and Pelham Parent and Teacher rating scale (SNAP-IV). All the children in both groups received pharmacotherapy with either risperidone or Ritalin. The intervention group received 8 sessions (1 session each week, each session lasting 90 minutes) of mindful parenting training based on the Kabat-Zinn protocol. The data were analyzed using SPSS, version 20, via the t test, 2 test, repeated measures analysis of variance, and nonparametric Friedman test.
Results: This study showed a reduction in parenting stress, negative parent-child interactions, and children's problematic characteristics in the mindful parenting training group compared with the control group in the posttest and follow-up. Our results also demonstrated a significant improvement in ADHD symptoms in the experimental group by comparison with the control group in the posttest and follow-up.
Conclusion: Mindful parenting training was effective in reducing parenting stress and ADHD symptoms in our intervention group

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JAMA Pediatr. 2018.

GRANDMATERNAL DIETHYLSTILBESTEROL AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN.

Ryan M, Smith B.

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JAMA Pediatr. 2018.
GRANDMATERNAL DIETHYLSTILBESTROL AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN - REPLY.
Kioumourtzoglou M-A, Weisskopf MG.

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J Affective Disord. 2019;245:335-39.
RISKS OF BIPOLAR DISORDER, DEPRESSIVE DISORDER, AND TRAUMATIC BRAIN INJURY AMONG SIBLINGS OF PATIENTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Wei H-T, Pan T-L, Hsu J-W, et al.
Background: Previous studies have suggested that the unaffected siblings of patients with attention-deficit hyperactivity disorder (ADHD) experience deficits in attention, impulsivity control, and behavior inhibition, which are associated with health-risk behaviors. However, risks to mental and physical health among the unaffected siblings of ADHD probands have rarely been investigated.
Methods: Using the Taiwan National Health Insurance Research Database, 5128 unaffected siblings of ADHD probands born between 1980 and 2000 were included in our study along with 20,512 age- and sex-matched controls, and they were followed from 1996 or birth until the end of 2011. Mental and physical health risks, including affective disorders, traumatic brain injury (TBI), and sexually transmitted infection were identified during the follow-up period.
Results: Logistic regression analyses with adjustments for demographic data showed that the unaffected siblings were more likely to develop unipolar depression (odds ratio [OR]: 1.76, 95% confidence interval [CI]: 1.39-2.22), bipolar disorder (OR: 2.10, 95% CI: 1. 09-4.05), and TBI (OR: 1.24, 95% CI: 1.14-1.36) than were the control group.
Discussion: The unaffected siblings of patients with ADHD were prone to developing unipolar depression, bipolar disorder, and TBI later in life

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J Child Adolesc Psychopharmacol. 2018;28:582-605.
A FOCUSED REVIEW ON THE TREATMENT OF PEDIATRIC PATIENTS WITH ATYPICAL ANTIPSYCHOTICS.
Lee ES, Vidal C, Findling RL.
Objectives: The use of atypical antipsychotic medications in pediatric patients has become more prevalent in recent years. The purpose of this review is to provide a clinically relevant update of recent selected key publications regarding the use of atypical antipsychotics in this population.
Methods: Studies reviewed included randomized, double-blind, placebo-controlled medication trials conducted within the past 5 years. A PubMed search was conducted for each of the 11 second-generation antipsychotic medications currently approved by the Food and Drug Administration for use in the United States: Clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, paliperidone, asenapine, iloperidone, lurasidone, and cariprazine. Trials published in English with subjects 18 years of age and younger were included in this review. Additional studies, chosen for their significance to clinical practice, were also included at the discretion of the authors.
Results: This review demonstrates that more empiric data are available regarding both the acute efficacy and, to a lesser extent, the longer-term efficacy and tolerability for several of the considered antipsychotic medications. The clinical conditions for which these medications have been studied include schizophrenia, bipolar disorder, Tourette's disorder, and autism spectrum disorder. They have also been used as an adjunctive treatment for disruptive behavior disorders with aggression, which have not responded to treatment with stimulants.
Conclusion: Evidence regarding the efficacy and tolerability of antipsychotic medications for mental health disorders in children and adolescents has expanded exponentially in recent years. However, more information is needed so that evidence-based comparisons between medications can be made. In the future, data enabling the selection of medications based upon individual patient characteristics could potentially lead to greater efficacy and efficiency in treating what are frequently debilitating medical conditions. Maladaptive

aggression in children, often treated with antipsychotics, is one such area in which there is a dearth of actual information available to the clinician. It is to be hoped that additional, longer-term studies of these medications will further inform evidence-based practice in clinical settings

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J Child Adolesc Psychopharmacol. 2018;28:606-14.

DIAGNOSIS AND TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN PRESCHOOL-AGED CHILDREN.

Childress AC, Stark JG .

Objectives: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined as a persistent pattern of inactivity and/or hyperactivity that interferes with behavioral function or development. Diagnosis and treatment of ADHD in the preschool-aged population (children 3-5 years old) is more complicated compared with older children because of developmental and physiological differences. This article reviews the available literature regarding the challenges associated with ADHD diagnosis and treatment in preschool-aged children, as well as the unmet needs of preschool-aged children with ADHD.

Methods: Key considerations for ADHD diagnosis and treatment patterns in preschool-aged children are summarized in this review, including the need for early intervention, the association with comorbidities, and the differences in pharmacokinetic profiles between preschool-aged children and older children.

Results: Efficacy and safety data are lacking, as clinical trial design and execution pose unique challenges in this population. Preschool-aged children often have difficulty with pill swallowing and tolerating phlebotomy necessary for the collection of pharmacokinetic and safety data. However, early diagnosis and treatment are essential to mitigate ADHD symptoms and comorbidities that may develop during childhood and adolescence in patients with persistent ADHD.

Conclusion: This review describes the established diagnostic and treatment modalities, along with the unmet needs of preschool-aged children with ADHD

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J Clin Psychiatry. 2018;79.

IMPACT OF DRUG ADHERENCE ON OPPOSITIONAL DEFIANT DISORDER AND CONDUCT DISORDER AMONG PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

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

Objective: Attention-deficit/hyperactivity disorder (ADHD) may be a predecessor of oppositional defiant disorder (ODD) and conduct disorder (CD), and medication is an effective treatment option for ADHD. This study aims to examine whether adherence to medication treatment is associated with developing ODD and CD among youths with ADHD.

Methods: A total of 33,835 youths (4 years age of diagnosis 18 years) with ADHD (ICD-9-CM code 314.X) undergoing medication treatment for at least 90 days were selected from Taiwan's National Health Insurance Research Database during the period of January 2000 through December 2009. Patients' medical records were monitored through December 31, 2011, or until they had a diagnosis of ODD or CD. We categorized participants as compliant or noncompliant on the basis of a medication possession ratio (MPR) of 50%.

Results: The patients with better drug adherence (MPR 50%) exhibited a significantly decreased probability of developing ODD (53% reduction, P < .001) or CD (58% reduction, P < .001) when compared to the patients with poor drug adherence (MPR < 50%). The results in our sensitivity analyses showed that good drug adherence consistently exerted protective effects on ODD or CD, irrespective of patients' characteristics. Moreover, the patients with the best drug adherence (MPR 75%) had the lowest risks of developing ODD or CD.

Conclusion: Among patients with ADHD undergoing drug therapy, a better drug adherence is associated with a lower likelihood of their developing ODD or CD in later life

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J Clin Psychiatry. 2018;79.

FURTHER EVIDENCE OF MORBIDITY AND DYSFUNCTION ASSOCIATED WITH SUBSYNDROMAL ADHD IN CLINICALLY REFERRED CHILDREN.

Biederman J, Fitzgerald M, Kirova A-M, et al.

Background: While the diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) have evolved over the years, some children with impairing ADHD symptoms fail to meet the full diagnostic threshold for the disorder. The main aim of this study was to evaluate the morbidity and dysfunction of subsyndromal ADHD in the clinical setting.

Methods: Subthreshold and full ADHD subjects were derived from consecutive referrals (n = 2,947) to a pediatric psychopharmacology program at a major academic center. Subjects were diagnosed with subthreshold ADHD if they met at least 1 of the following criteria: (1) their age at onset for ADHD was 7 years; (2) they had 5 but < 8 ADHD symptoms using the DSM-III-R or 4 but < 6 ADHD inattentive or hyperactive/impulsive symptoms using the DSM-IV. Healthy controls were derived from 2 identically designed longitudinal casecontrol studies of youth with and without ADHD. Psychiatric assessments relied on clinical structured interviews and measures of psychopathology, social functioning, cognitive ability, and academic achievement.

Results: Of the 1,931 children diagnosed with ADHD, 140 (7%) were diagnosed with subthreshold ADHD. 48% of subthreshold ADHD subjects had an age at onset 7 years, and 73% had insufficient symptoms. Reanalysis of findings using DSM-5 criteria showed that only 21% of our subthreshold ADHD subjects would have met DSM-5 criteria based on age at onset of < 12 years, while 79% would have maintained their subthreshold diagnoses. Subjects with subthreshold ADHD differed from controls in the mean number of comorbid disorders; rates of mood, anxiety, and elimination disorders (all P < .001) and substance use disorders (P < .05); scores on all Child Behavior Checklist clinical and social functioning scales; scores on 7 of the 10 Social Adjustment Inventory for Children and Adolescents scales; rates of requiring extra help in school and being placed in a special class; and scores on 4 of the 5 Wechsler Intelligence Scale for Children-Revised Version subscales (excluding Digit Span) as well as in Freedom from Distractibility Index score (P < .001). Subthreshold and full ADHD subjects had similarly elevated Global Assessment of Functioning scores versus controls (P < .001), but subjects with subthreshold ADHD had fewer perinatal complications and better family functioning scores and were more likely to be female and older and to come from families of higher socioeconomic status than subjects with full ADHD.

Conclusions: Clinically referred children failing to meet full-threshold diagnosis for ADHD due to either insufficient symptoms or later age at onset have patterns of clinical features highly similar to those with the full syndrome. These results extend to previously reported findings in nonreferred samples documenting the high morbidity and disability associated with subthreshold ADHD

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Journal of Clinical Psychology in Medical Settings. 2018.

BRIEF BEHAVIORAL INTERVENTION FOR DISRUPTIVE BEHAVIOR IN A CHILD WITH A HYPOTHALAMIC HAMARTOMA: A CASE REPORT.

Fein RH, Banks GG, Gragert MN, et al.

Most children with hypothalamic hamartoma (HH) manifest symptoms of epilepsy and associated cognitive deficits and behavioral difficulties as well as central precocious puberty (CPP). However, there is little to no research examining behavioral difficulties in children with HH without epilepsy, nor is there research examining treatments to address the behavioral difficulties of patients with HH without epilepsy. In the current case report, the authors implemented a validated parent management training program [the Brief Behavioral Intervention (BBI)], to treat symptoms of ADHD and disruptive behavior in a 6-year-old female patient with HH and CPP. The family participated in six BBI sessions over a period of 8-áweeks. Parent behavioral ratings suggested significant reductions of symptoms of ADHD and disruptive behaviors to the normal range. The current case report demonstrates the effectiveness of the BBI program in the treatment of behavioral difficulties in a patient with HH and CPP. Further, the present study explores behavioral manifestations rarely explored in patients with HH without epilepsy

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J Fluency Disord. 2018.

ELEVATED ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS IN CHILDREN WHO STUTTER.

Druker K, Hennessey N, Mazzucchelli T, et al.

Purpose: This study described the proportion of children who stutter who exhibit Attention Deficit Hyperactivity Disorder (ADHD) symptoms, manifesting in inattentive and hyperactive/impulsive behaviours. Children who stutter with these challenging behaviours may not respond as quickly and successfully to stuttering treatment. A preliminary exploration of differences in treatment responsiveness for children with and without ADHD symptoms was undertaken.

Method: Participants were 185 preschool children who stutter who had completed stuttering therapy within 3 months prior to study commencement. Differences between groups of children who stutter with and without elevated ADHD symptoms were investigated, in terms of pre-treatment stuttering features (stuttering severity and typography), demographic variables (age at onset, time between onset and commencement of therapy, family history and sex) and treatment data (post-treatment stuttering severity and number of sessions to achieve discharge criteria).

Results: One-half (50%) of participants exhibited elevated ADHD symptoms. These children required 25% more clinical intervention time to achieve successful fluency outcomes than children without elevated ADHD symptoms. Findings suggest that more ADHD symptoms, increased pre-treatment stuttering severity, and male sex were associated with poorer responsiveness to stuttering treatment.

Conclusion: The large proportion of children exhibiting elevated ADHD symptoms, and the increase in clinical contact time required in this subgroup to achieve successful fluency outcomes, is suggestive of the need for clinicians to tailor stuttering intervention to address these concomitant behaviour challenges. Findings support the use of careful caseload management strategies to account for individual differences between children, and strengthen prognostic information available to parents and clinicians

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Journal of Managed Care and Specialty Pharmacy. 2015;21:S37.

OFF-LABEL USE OF ANTIDEPRESSANTS FOR CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD).

Lai L, Margolles M, Lobitz A, et al.

BACKGROUND: Off-label drug use attributed to 21% of prescriptions written annually. Of all off-label drug use, antidepressant is one of the most common practices. Antidepressants can be an alternative pharmacotherapy when tolerance or abuse of a CNS stimulant is a problem for ADHD treatment. However, this off-label prescription has been controversial especially to children.

OBJECTIVE: The study aims to investigate the prevalence and pattern of off-label antidepressants use for children with ADHD.

METHODS: A retrospective population-based study was conducted by analyzing a national database from the U.S. National Ambulatory Medical Care Survey (NAMCS). The NAMCS is a national probability sample survey conducted annually by the National Center for Health Statistics. Patients 17 years of age or younger with a diagnosis of ADHD were included in the study. A series of weighted descriptive analyses were used to estimate the prevalence of ADHD prescriptions. A weighted logistic regression was performed to examine antidepressants practice patterns across various patient and physician characteristics. All analyses utilized SAS PROC SURVEY applications and incorporated sample weights and standard errors to adjust for the complex sampling design.

RESULTS: Among 1.01 billion outpatient visits that took place in 2010, 7.03 million visits were encountered from children with ADHD diagno sis. Children aged 7-12 years (50%), accounted for the highest frequency of ADHD outpatient visits than those aged 13-17 years (37.7%), and aged 0-6 years (12.3%). Male accounted for more than twice of ADHD visits than female (69.04% vs. 30.96%). FDA-approved CNS stimulants were the most widely prescribed ADHD drugs during 3.33 million visits (60%). FDA-approved non-CNS stimulants were the second most widely prescribed ADHD drugs during 1.71 million visits (30 %). Off-label antidepressants were the third widely prescribed ADHD drugs during 0.32 million visits (10%) The results of the weighted logistic regression showed gender is the only significant factor associated with off-label antidepressant use after controlling race, region, payment type, and physician specialty, Male is 5.28 times (OR: 5.28, 95% CI: 2.257-12.330) as likely to be prescribed antidepressants as female.

CONCLUSIONS: This study found off-label antidepressants were commonly prescribed to the children with ADHD. Literature has reported that off-label prescribing is widespread but may not always be inappropriate. However, antidepressant use in children must be monitored carefully because it may cause severe side effects

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Journal of Managed Care and Specialty Pharmacy. 2015;21:S37-S38.

IMPACT ANALYSIS OF AN IMPLEMENTED ADD/ADHD CLINICAL EDIT IN A MEDICAID POPULATION.

DeRuiter A, Donald C, Counts K, et al.

BACKGROUND: Attention deficit disorder (ADD) and attention deficit/ hyperactivity disorder (ADHD) have been diagnosed in approximately 11% of children ages 4-17 years in the U.S. as of 2011. The rising trend of medication-based therapy has made appropriate use of these agents a concern for payers and prescribers.
OBJECTIVE: To determine the impact on utilization and reimbursement of a recently-implemented ADD/ADHD clinical edit in a Medicaid population.
METHODS: A clinical edit for ADD/ADHD was implemented for a Medicaid population in February 2014. The edit was applied to the feefor-service (FFS) population, while the managed care organizations (MCOs) had the option to implement the edit as written or apply their own variation. The edit was designed to ensure proper utilization by applying daily dosage limits, age restrictions, and diagnosis requirements based on ADD/ADHD medication classes. Data was collected for six months pre-and post-implementation for clients enrolled in FFS and MCOs, and included diagnosis, pharmacy claims, and reimbursement data. A comparison of the pre and post data was performed.
RESULTS: Implementation of the edit improved appropriate utilization in three areas: use of extended-release (ER) stimulants in clients with a history of substance abuse, inappropriate use of ER stimulant and non-stimulant (NS) medications in clients less than 6 years of age, and use of IR stimulants in children 3-5 years of age. A decrease in claim volume was seen in clients with a history of substance abuse using ER stimulants (FFS -28.7%, MCO -6.1%). The claims cost for these clients decreased in the FFS population and increased slightly in the MCO population (FFS -28.1%, MCO +0.8%). For clients less than 6 years of age, ER claims volume decreased (FFS -37.3%, MCO -19.3%) as did claims volume for NS medications (FFS -61.1%, MCO -34.6%). The claims cost for these clients decreased in the ER stimulant group (FFS -34.8%, MCO -12.1%), as well as the NS group (FFS -58.6%, MCO -13.9%). For clients 3-5 years of age, a decrease in claims volume was seen in the FFS group (-18.9%), while the MCO group showed an increase (+61.7%). Likewise, the claims cost decreased for the FFS group (-14.9%) and increased for the MCO group (+127.6%).
CONCLUSIONS: Implementing an edit that applies restrictions on maximum daily doses, age, and diagnoses for ADD/ADHD medications can help ensure appropriate utilization of the medications. In addition, cost savings related to the medications may be realized

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Journal of Managed Care and Specialty Pharmacy. 2017;23:S49.

ACADEMIC DETAILING FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN OKLAHOMA MEDICAID.

Bulkley C, Travers J, Holderread B, et al.

PROBLEM DESCRIPTION: Recent CDC reports demonstrate no significant improvements in ADHD over-prescribing in the primary care setting. Over-prescribing of ADHD medications remain a significant issue for the Oklahoma Healthcare Authority (OHCA).
GOAL: Academic Detailing (AD) disseminates evidence-based, best practice guidelines. OHCA uses its AD program to (1) reduce ADHD medication prescribing, prescription costs, and prior authorizations; (2) improve patient outcomes; and (3) assess provider satisfaction with the AD program.
PROGRAM DESCRIPTION: Program information was obtained from the 2011 American Academy of Pediatrics Attention-Deficit/ Hyperactivity Disorder (ADHD) guidelines. A pharmacist facilitated AD sessions, which involved discussions with prescribers focusing on practice paradigms for ADHD treatment and highlighting of potential benefits of guideline implementation. Sessions varied in attendance from one to eight

prescribers and were performed from January 2016 to May 2017. A questionnaire regarding program satisfaction was given immediately after each session to all who participated.
OBSERVATIONS: ADHD prescribing observed through pharmacy claims declined Γê+9% in comparison to non-detailed providers. The predicted cost savings was $3,700 per provider detailed. ADHD medication prior authorization requests also declined by approximately 13% since detailing. Eighty individuals responded to the questionnaire. The majority were family practitioners (43%) and general pediatricians (22%) who spent on average 40% of their time caring for pediatric and/or ADHD patients. In regards to satisfaction, 75% reported they would make practice changes and 89% would recommend this program to colleagues and participate in future AD topics. In regards to session information 88% of respondents agreed it was relevant to their practice; 91% agreed it was evidence-based; 94% agreed it was new and/or different; 92% agreed it was easily understood; and 82% agreed it was clearly presented. More than 70% strongly agreed that the AD facilitator was knowledgeable and engaging.
FINDINGS/RECOMMENDATIONS: Providers who attended the program will likely continue to use AD services given their positive appraisal and response in their prescribing patterns. To demonstrate value, AD interventions that are measurable and provide meaningful benchmarks will facilitate justification of such services. Measurements that can elicit value are monitoring of prescription claims, costs, and prior authorizations as well as assessing provider satisfaction. Future considerations for the AD program include expanding to more providers and addressing other disease topics

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Journal of Mental Health. 2018.
THE ROLE OF MOTHERS' AFFILIATE STIGMA AND CHILD'S SYMPTOMS ON THE DISTRESS OF MOTHERS WITH ADHD CHILDREN.
Charbonnier E, Caparos S, et al.
BACKGROUND: Mothers of ADHD children often display high levels of distress. Understanding the origin of such distress in a view to reducing it is an essential part of the clinical management of ADHD children. Studies have shown that children's symptoms are linked to mothers' stigma and that such stigma can cause mothers' distress. However, no study has explored the links between symptoms, stigma and distress.
AIM: We tested (1) whether children's symptoms are sources of affiliate stigma, which in turn contributes to generating mothers' distress and (2) whether such relationship is stronger in mothers of male ADHD children.
METHOD: 159 French mothers of an ADHD child were recruited. Four indices were used to assess mothers' distress: anxiety, depression, self-esteem and life satisfaction. Children's ADHD symptoms and mothers' affiliate stigma were also measured and contrasted with distress.
RESULTS: Mothers' distress was positively related with both affiliate stigma and children's ADHD symptoms, but this was only true in mothers of male ADHD children. The relationship between children's symptoms and mothers' distress was mediated by affiliate stigma.
CONCLUSIONS: Psychosocial interventions in mothers of ADHD children must integrate affiliate stigma and should be adjusted according to child's gender

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J Nerv Ment Dis. 2018;206:859-64.
MATERNAL PRENATAL THYROID FUNCTION AND OFFSPRING ADHD: FINDINGS FROM THE ALSPAC COHORT.
Fetene DM, Betts KS, Alati R.
Thyroid hormone plays a pivotal role in the developing brain and may affect the development of attention deficit hyperactivity disorder (ADHD). This study aimed to examine the role of maternal thyroid function during pregnancy on offspring ADHD. A total of 2912 mother-child pairs were included from the Avon Longitudinal Study of Parents and Children. Thyroid parameters were assessed during the first trimester of pregnancy. Offspring ADHD was assessed using the Development and Well-Being Assessment at the ages of 7.5 and 15 years. The odds of presenting with ADHD were estimated using generalized estimating equations. Levels of thyroid-stimulating hormone (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.48-1.75), free thyroxine (OR, 1.07; 95% CI, 0.87-1.32), and thyroid peroxidase antibodies (OR, 1.00; 95% CI, 0.80-1.25) were not

associated with ADHD in children aged 7.5 and 15 years. This study showed no association between maternal thyroid function and offspring ADHD

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J Neural Transm. 2018.

HAIR CORTISOL CONCENTRATION IN MOTHERS AND THEIR CHILDREN: ROLES OF MATERNAL SENSITIVITY AND CHILD SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Schloß S, Müller V, Becker K, et al.

Associations between mothers' and children's cortisol secretion parameters are well established. According to the bio-behavioral synchrony model, these associations reflect influences of the mother child relationship, the child's social adjustment, and might also reflect shared genetic dispositions. From the bio-behavioral synchrony model, we predicted a stronger mother-child hair cortisol concentration (HCC) link in mothers showing highly adequate (compared to those showing less adequate) parenting behaviors and in children showing low (compared to those showing high) ADHD symptoms. From a genetic perspective, no such moderator effects, or a stronger mother-child HCC link in children with high ADHD symptoms, can be expected. The study sample consisted of 111 4-5-year-old children (64 of whom screened positive for increased ADHD symptoms) and their mothers. ADHD symptoms were assessed by a clinical interview and parent and teacher questionnaires. Maternal sensitive/responsive parenting behavior was assessed by an at-home behavior observation procedure. In mothers and children, HCC in the most proximal 3-cm scalp hair segment was analyzed using luminescence immunoassay. Overall HCCs of mothers and their children correlated significantly. Maternal sensitivity/responsiveness and child ADHD symptoms proved to be significant moderator variables of this association: High maternal sensitivity/responsiveness and low ADHD symptoms of the child were associated with a stronger mother-child link in HCC. The findings are in line with the bio-behavioral synchrony model in the mother-child relationship, and are less compatible with a genetic perspective. The results might hint at environmental events influencing the development of stress axis functioning in subgroups of preschoolers with high ADHD symptoms

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J Neurodevelopmental Disord. 2018;10.

AN EMOTION RECOGNITION SUBTYPING APPROACH TO STUDYING THE HETEROGENEITY AND COMORBIDITY OF AUTISM SPECTRUM DISORDERS AND ATTENTION-DEFICIT/HYPERACTIVITY DISORDER 17 PSYCHOLOGY AND COGNITIVE SCIENCES 1701 PSYCHOLOGY.

Waddington F, Hartman C, De BY, et al.

Background: Emotion recognition dysfunction has been reported in both autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD). This suggests that emotion recognition is a cross-disorder trait that may be utilised to understand the heterogeneous psychopathology of ASD and ADHD. We aimed to identify emotion recognition subtypes and to examine their relation with quantitative and diagnostic measures of ASD and ADHD to gain further insight into disorder comorbidity and heterogeneity.

Methods: Factor mixture modelling was used on speed and accuracy measures of auditory and visual emotion recognition tasks. These were administered to children and adolescents with ASD (N = 89), comorbid ASD + ADHD (N = 64), their unaffected siblings (N = 122), ADHD (N = 111), their unaffected siblings (N = 69), and controls (N = 220). Identified classes were compared on diagnostic and quantitative symptom measures.

Results: A four-class solution was revealed, with the following emotion recognition abilities: (1) average visual, impulsive auditory; (2) average-strong visual and auditory; (3) impulsive/imprecise visual, average auditory; (4) weak visual and auditory. The weakest performing class (4) contained the highest percentage of patients (66.07%) and the lowest percentage controls (10.09%), scoring the highest on ASD/ADHD measures. The best performing class (2) demonstrated the opposite: 48.98% patients, 15.26% controls with relatively low scores on ASD/ADHD measures.

Conclusions: Subgroups of youths can be identified that differ both in quantitative and qualitative aspects of emotion recognition abilities. Weak emotion recognition abilities across sensory domains are linked to an

increased risk for ASD as well as ADHD, although emotion recognition impairments alone are neither necessary nor sufficient parts of these disorders

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Journal of Neurosurgery. 2017;126:A1399-A1400.

PSYCHIATRIC DISORDERS IN CHILDREN WITH CHIARI MALFORMATION TYPE I: PREVALENCE AND RISK FACTORS.

Frim DM, DeDios-Stern S, Fredrickson S, et al.

Introduction: This cross-sectional study investigates prevalence and risks of psychiatric illnesses in a large cohort of children with Chiari malformation type 1 (CM1). To our knowledge, no study of this size has been previously undertaken.

Methods: Children with CM1 between the ages of 6 and 17 years were identified after receiving the diagnosis of CM1 during a neurosurgery clinic visit. Eighty-six participants were recruited between 2010-2016 [Age M = 11 years, 3 months (SD = 3 years, 5 months); 44 males, 42 females]. Parents of participants completed a pediatric medical history questionnaire and a semi-structured interview regarding the child's psychiatric, developmental, medical history, and family characteristics. A review of medical records was completed to complement interview data.

Results: Results revealed elevated rates of psychiatric conditions, including attention deficit hyperactivity disorder (22.1%), anxiety (12.8%) and depression (10.5%) when compared to the general population (attention deficit hyperactivity disorder, 3.4%; anxiety, 6.5%; depression, 2.6%). A two-step binary logistic regression analysis revealed that having problems during pregnancy (Wald = 6.98, p = 0.01) increased your risk of psychiatric disorder 9-fold. Being born premature (Wald = 6.90, p = 0.01) or having seizures (Wald = 3.72, p = 0.05) also significantly predicted psychiatric history among participants.

Conclusion: The current findings suggest a high prevalence of psychiatric illness in children with CM1. Pregnancy complications were associated with a high risk of a psychiatric diagnosis. CNS vulnerabilities during pregnancy may explain this relationship. Seizures and prematurity only slightly improved the prediction model

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J Psychopathol Behav Assess. 2018;40:586-92.

ASSOCIATIONS BETWEEN CONDUCT DISORDER, NEURODEVELOPMENTAL PROBLEMS AND PSYCHOPATHIC PERSONALITY TRAITS IN A SWEDISH TWIN YOUTH POPULATION.

Svensson O, et al.

Previous research has found a complex relationship between psychopathic traits, neurodevelopmental problems (NDPs), and conduct disorder (CD) in children. This study explores associations between psychopathic traits, assessed with the Child Problematic Traits InventoryΓÇöShort Version (CPTI-SV), and CD in children with and without coexisting NDPs (i.e., attention deficit/hyperactivity disorder [ADHD] and autism spectrum disorder [ASD]) in a community-based sample of Swedish twins (n = 8762). Findings indicate weak to moderately strong correlations between psychopathic traits and CD, ADHD, and ASD, respectively. Furthermore, in univariable analyses, both psychopathic traits and NDPs displayed significant positive associations with being screened positive for CD, though only the grandiose-deceitful dimension of CPTI-SV and the ADHD domain concentration and attention deficits remained significantly associated with CD in a multivariable regression model. The results are relevant to screening and assessment in child and youth psychiatry, as a grandiose and deceitful interpersonal style may also be a valid sign of children at risk of developing CD

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Lancet Psychiatry. 2018;5:870-71.
UNBALANCED RISK-BENEFIT ANALYSIS OF ADHD DRUGS.
Wang S, Zheng Y.

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Mitochondrion. 2018.
ASSESSMENT OF ASSOCIATIONS BETWEEN MITOCHONDRIAL DNA HAPLOGROUPS AND ATTENTION DEFICIT AND HYPERACTIVITY DISORDER IN KOREAN CHILDREN.
Hwang IW, Kwon BN, Kim HJ, et al.
Attention deficit hyperactivity disorder (ADHD) is a multifactorial disorder with multiple environmental and biological etiologies, including genetic factors. Until now, several genetic variants have been reported to be significantly associated with ADHD. Recently, the relationship between mitochondrial DNA (mtDNA) haplogroups and psychiatric disorders such as schizophrenia has also been reported. However, currently there are no reports pertaining to the genetic association between mtDNA haplogroups and ADHD. Therefore, we performed an mtDNA haplogroup analysis of a total of 472 Korean children (150 Children with ADHD and 322 controls). The 20 East Asian specific mtDNA haplogroups were determined using the SNaPshot assay. We also sequenced the displacement loop (D-loop) region, position 15,971ΓÇô613. Our results showed that haplogroup B4 was significantly associated with ADHD (OR, 1.90; 95% CI, 1.055ΓÇô3.429; p = 0.031). A marginally significant association was found in subjects with ADHD and haplogroup B5 (OR, 0.26; 95% CI, 0.059ΓÇô1.139; p = 0.041). When stratified based on gender, an association was also observed between haplogroup B5 and boys diagnosed with ADHD (OR, 0.17; 95% CI, 0.022ΓÇô1.340; p = 0.048). Compared with boys, girls with ADHD carried an excess of the haplogroup D4b (OR, 4.83; 95% CI, 1.352ΓÇô17.272; p = 0.014). Stratified analysis of subtypes also showed significant results (combined: haplogroup B4, p = 0.007; inattentive: haplogroup F, p = 0.022). Our results showed a possible role of mtDNA haplogroups in the genetic etiology of ADHD and ADHD symptoms in Korean children

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Mol Psychiatry. 2018;23.
PHARMACOGENETICS PREDICTORS OF METHYLPHENIDATE EFFICACY IN CHILDHOOD ADHD.
Myer NM, Boland JR, Faraone SV.
Stimulant medication has long been effective in treating attention-deficit/hyperactivity disorder (ADHD) and is currently the first-line pharmacological treatment for children. Both methylphenidate and amphetamine modulate extracellular catecholamine levels through interaction with dopaminergic, adrenergic and serotonergic system components; it is therefore likely that catecholaminergic molecular components influence the effects of ADHD treatment. Using meta-analysis, we sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. We identified 36 studies (3647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 ADRA2A (odds ratio: 1.69; confidence interval: 1.12 2.55), rs4680 COMT (odds ratio (OR): 1.40; confidence interval: 1.04 1.87), rs5569 SLC6A2 (odds ratio: 1.73; confidence interval: 1.26 2.37) and rs28386840 SLC6A2 (odds ratio: 2.93; confidence interval: 1.76ΓÇô4.90), and, repeat variants variable number tandem repeat (VNTR) 4 DRD4 (odds ratio: 1.66; confidence interval: 1.16 2.37) and VNTR 10 SLC6A3 (odds ratio: 0.74; confidence interval: 0.60ΓÇô0.90), whereas the following variants were not statistically significant: rs1947274 LPHN3 (odds ratio: 0.95; confidence interval: 0.71 1.26), rs5661665 LPHN3 (odds ratio: 1.07; confidence interval: 0.84 1.37) and VNTR 7 DRD4 (odds ratio: 0.68; confidence interval: 0.47-1.00). Funnel plot asymmetry among SLC6A3 studies was identified and attributed largely to small study effects. Egger's regression test and Duval and Tweedie's trim and fill were used to examine and correct for publication bias. These findings have major implications for advancing our therapeutic approach to childhood ADHD treatment

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NeuroImage Clin. 2018.

CAN WE USE NEUROIMAGING DATA TO DIFFERENTIATE BETWEEN SUBGROUPS OF CHILDREN WITH ADHD SYMPTOMS: A PROOF OF CONCEPT STUDY USING LATENT CLASS ANALYSIS OF BRAIN ACTIVITY.

Lecei A, van Hulst BM, de ZP, et al.

Background: Multiple pathway models of ADHD suggest that multiple, separable biological pathways may lead to symptoms of the disorder. If this is the case, it should be possible to identify subgroups of children with ADHD based on distinct patterns of brain activity. Previous studies have used latent class analysis (LCA) to define subgroups at the behavioral and cognitive level and to then test whether they differ at the neurobiological level. In this proof of concept study, we took a reverse approach. We applied LCA to functional imaging data from two previously published studies to explore whether we could identify subgroups of children with ADHD symptoms at the neurobiological level with a meaningful relation to behavior or neuropsychology.

Methods: Fifty-six children with symptoms of ADHD (27 children with ADHD and 29 children with ASD and ADHD symptoms) and 31 typically developing children performed two neuropsychological tasks assessing reward sensitivity and temporal expectancy during functional magnetic resonance imaging. LCA was used to identify subgroups with similar patterns of brain activity separately for children with ADHD-symptoms and typically developing children. Behavioral and neuropsychological differences between subgroups were subsequently investigated.

Results: For typically developing children, a one-subgroup model gave the most parsimonious fit, whereas for children with ADHD-symptoms a two-subgroup model best fits the data. The first ADHD subgroup (n = 49) showed attenuated brain activity compared to the second subgroup (n = 7) and to typically developing children (n = 31). Notably, the ADHD subgroup with attenuated brain activity showed less behavioral problems in everyday life.

Conclusions: In this proof of concept study, we showed that we could identify distinct subgroups of children with ADHD-symptoms based on their brain activity profiles. Generalizability was limited due to the small sample size, but ultimately such neurobiological profiles could improve insight in individual prognosis and treatment options

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NeuroImage Clin. 2018.

LARGE-SCALE BRAIN FUNCTIONAL NETWORK TOPOLOGY DISRUPTIONS UNDERLIE SYMPTOM HETEROGENEITY IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Qian X, Castellanos FX, Uddin LQ, et al.

Accumulating evidence suggests brain network dysfunction in attention-deficit/hyperactivity disorder (ADHD). Whether large-scale brain network connectivity patterns reflect clinical heterogeneity in ADHD remains to be fully understood. This study aimed to characterize the differential within- and between-network functional connectivity (FC) changes in children with ADHD combined (ADHD-C) or inattentive (ADHD-I) subtypes and their associations with ADHD symptoms. We studied the task-free functional magnetic resonance imaging (fMRI) data of 58 boys with ADHD and 28 demographically matched healthy controls. We measured within- and between-network connectivity of both low-level (sensorimotor) and high-level (cognitive) large-scale intrinsic connectivity networks and network modularity. We found that children with ADHD-C but not those with ADHD-I exhibited hyper-connectivity within the anterior default mode network (DMN) compared with controls. Additionally, children with ADHD-C had higher inter-network FC between the left executive control (ECN) and the salience (SN) networks, between subcortical and visual networks, and between the DMN and left auditory networks than controls, while children with ADHD-I did not show differences compared with controls. Similarly, children with ADHD-C but not ADHD-I showed lower network modularity compared with controls. Importantly, these observed abnormal inter-network connectivity and network modularity metrics were associated with Child Behavioral Checklist (CBCL) attention-deficit/hyperactivity problems and internalizing problems in children with ADHD. This study revealed relatively greater loss of brain functional

network segregation in childhood ADHD combined subtype compared to the inattentive subtype, suggesting differential large-scale functional brain network topology phenotype underlying childhood ADHD heterogeneity

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Neuropsychiatr Enfance Adolesc. 2018;66:13-21.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH OR WITHOUT ASSOCIATED DISORDERS: EVIDENCE FOR DIFFERENCES IN ATTENTIONAL AND EXECUTIVE PROCESSES.

Puyjarinet F.

Background: Children with attention-deficit hyperactivity disorder (ADHD) manifest deficits in attentional and executive domains. Yet, although ADHD is often associated with other neurodevelopmental syndromes such as developmental dyslexia (DD) and developmental coordination disorder (DCD), very few studies exploring the impact of these associated disorders on cognitive abilities of children with ADHD are available. Whether and how these comorbid disorders may influence attentional and executive abilities among ADHD patients remained to be explored.

Aim of the study: The goal of the current study was to compare the attentional and executive profiles of ADHD children with and without one or two often-associated comorbid neurodevelopmental disorders: DD, and DCD. Participants and method: One hundred and sixty-one children (mean age: 8.9 years) were classified into four groups: children with ADHD in isolation (n = 61), children with ADHD and associated DD (n = 36), children with ADHD and associated DCD (n = 27), and children with the three associated disorders (ADHD-DCD-DD, n = 37). For assessing attentional and executive skills, we used the Test of Everyday Attention for Children (TEA-Ch).

Results: We observed differences between the groups among the majority of attentional and executive measures: selective visual attention, auditive attention, divided attention, inhibition, and sustained attention.

Conclusion: These results show that children with ADHD manifest different cognitive performances depending on the presence of associated DD and/or DCD. Most of attentional executive domains are negatively impacted by DD and/or DCD. These findings concur with the current theoretical point of view whereby neurodevelopmental disorders partially share etiological and clinical factors. Our results also matter in the way professionals can understand how neurodevelopmental disorders influence each other, and how specific therapeutic projects could be built taking into consideration often-associated disorders in ADHD

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Neuropsychopharmacology. 2018;43:2548-55.

INCREASED RISK OF DISEASES OF THE BASAL GANGLIA AND CEREBELLUM IN PATIENTS WITH A HISTORY OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Curtin K, Fleckenstein AE, Keeshin BR, et al.

Attention-deficit/hyperactivity disorder (ADHD) is marked by an ongoing pattern of inattention and/or hyperactivity and involves dysregulated dopaminergic pathways. Dopaminergic agents (i.e., amphetamine and methylphenidate) are thus prescribed to treat ADHD. As little is known regarding long-term consequences of either ADHD or its treatment, the objective of this study was to determine if either alters the risk of diseases of the basal ganglia and cerebellum, including ParkinsonΓÇÖs disease. Statewide medical records from 1996 to 2016 were retrieved from the Utah Population Database to conduct a retrospective cohort study. Participants included ADHD patients (International Classification of Diseases, 9th revision (ICD-9) diagnosis codes 314.0ΓÇô314.2, 314.8, 314.9) and 5:1 random sex-matched and age-matched subjects with no ADHD diagnosis history. Both patients and non-ADHD subjects met the following eligibility criteria: (1) no prior diagnosis of ParkinsonΓÇÖs disease, secondary parkinsonism, basal ganglia disease, or essential tremor (ICD-9 codes 332.0, 332.1, 333.0, 333.1), (2) born in 1950 or later and age ΓëÑ20 years at last follow-up, and (3) no history of substance abuse (illicit drugs or alcohol). Outcomes were measured as time to diagnosis of diseases of the basal ganglia and cerebellum, death, or study-end. A Cox model incorporating a competing risk of death was used to provide hazard ratio estimates. Patients with ADHD (N = 31,769) had a 2.4-fold increased risk of basal ganglia and cerebellum diseases (95% confidence interval

(CI): 2.0 3.0; P < 0.0001) compared with 158,790 non-ADHD persons, after controlling for sex and age and adjusting for tobacco use and psychotic conditions. In 4960 ADHD patients prescribed psychostimulants, risk of basal ganglia and cerebellum diseases between ages 21 and 49 years was especially pronounced, at 8.6-fold (95% CI: 4.8 15.6; P < 0001). The association of ADHD patients prescribed psychostimulants with higher risk of diseases of the basal ganglia and cerebellum may reflect a more severe ADHD phenotype rather than a direct association between prescribed stimulant use and basal ganglia or cerebellum disorders. Future studies to assess and stratify patient risk so as to inform treatment are warranted

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Pediatr Emerg Care. 2018 Nov;34:e217-e218.

EFFECT OF BIPERIDEN TREATMENT IN ACUTE OROFACIAL AND EXTREMITY DYSKINESIA WITH METHYLPHENIDATE THERAPY.

Arslan EA, Arslan E, Kilinc A, et al.

Methylphenidate is a stimulant drug commonly prescribed to individuals with attention-deficit/hyperactivity disorder. The suggested underlying mechanism of acute dyskinesias is dopaminergic transmission increase. We describe a 9-year-old boy with a diagnosis of attention-deficit/hyperactivity disorder admitted to emergency clinic with primarily orofacial and extremity dyskinesia after administration of a first dose of 18 mg OROS (osmotic [controlled] release oral) methylphenidate (Concerta). OROS methylphenidate was discontinued, and the patient's symptoms resolved within 20 minutes after injection of biperiden by intravenous route (0.04 mg/kg). We wish to emphasize that acute orofacial dyskinesia and extremity dyskinesia can be observed during methylphenidate therapy and that biperiden can be successfully used in the treatment of this unpleasant condition. To the best of our knowledge, this is the first report of the use of biperiden therapy in this condition. This case report highlights the importance for physicians of awareness of dyskinesia as a potential adverse effect of methylphenidate therapy and indicates benefit of biperiden therapy

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Pharmacotherapy. 2018.

IMPACT OF CENTRAL NERVOUS SYSTEM STIMULANT MEDICATION USE ON GROWTH IN PEDIATRIC POPULATIONS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A REVIEW.

Troksa K, Kovacich N, Moro M, et al.

Central nervous system stimulants are a commonly used first-line treatment option for attention-deficit/hyperactivity disorder (ADHD). Stimulants are generally well tolerated, with anorexia and insomnia the most common adverse effects. However, there are some concerns with long-term use of stimulants, such as potential growth delay. Historically, data regarding this long-term adverse effect have been conflicting. In this article, we review the newer data surrounding the effects of central nervous system stimulants on growth parameters in children with ADHD. We conducted a literature search of the PubMed database; only articles using ADHD criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, were included to ensure the most up-to-date review of literature. Nine articles were identified for relevance and quality and are discussed in this review, describing clinical observations of height and weight of adolescent or pediatric patients receiving stimulant medications for ADHD therapy. In summary, this review points toward potential associations between duration of treatment and higher doses of stimulants with decreased weight and body mass index. Furthermore, this review demonstrates that evidence is still conflicting regarding the relationship between stimulant use and significant height decreases. Future studies with higher quality of evidence are needed to observe this potential adverse effect of stimulants in children and adolescents

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PLoS ONE. 2018;13.

ADHD SYMPTOMS AND LEARNING BEHAVIORS IN CHILDREN WITH ASD WITHOUT INTELLECTUAL DISABILITY. A MEDIATION ANALYSIS OF EXECUTIVE FUNCTIONS.

Rosello B, Berenguer C, Baixauli I, et al.

In spite of its importance for education, the relationship between learning behaviors (LB), attention deficit hyperactivity disorder symptoms (ADHD) and executive functioning (EF) in children with autism spectrum disorder (ASD) has hardly been explored. The first objective of the present study was to compare children with ASD without intellectual disability and children with typical development (TD) on ADHD symptoms and learning behaviors: Motivation/ competence, attitude toward learning, persistence on the task, and strategy/flexibility. The second objective was to analyze the mediator role of behavioral regulation and metacognition components of EF between ADHD symptoms and learning behaviors in children with ASD. Participants were 89 children between 7 and 11 years old, 52 with ASD and 37 with TD, matched on age and intelligence. Their teachers filled out questionnaires assessing executive functioning as well as learning behaviors. Parents and teachers reported on inattention and hyperactivity/impulsivity behaviors. Compared to children with TD, children with ASD presented significantly more ADHD symptoms and poorer learning behaviors. In addition, there were significant mediation effects of the behavioral regulation index (BRI) and metacognition index (MI) of EF, indicating that both are part of the route through which ADHD symptoms impact to learning behaviors of children with ASD

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PLoS ONE. 2018;13.

GENETIC ASSOCIATION STUDY OF DYSLEXIA AND ADHD CANDIDATE GENES IN A SPANISH COHORT: IMPLICATIONS OF COMORBID SAMPLES.

Sánchez-Morán M, Hernández JA, Duñabeitia JA, et al.

Dyslexia and attention deficit hyperactivity disorder (ADHD) are two complex neuro-behaviorally disorders that co-occur more often than expected, so that reading disability has been linked to inattention symptoms. We examined 4 SNPs located on genes previously associated to dyslexia (KIAA0319, DCDC2, DYX1C1 and FOXP2) and 3 SNPs within genes related to ADHD (COMT, MAOA and DBH) in a cohort of Spanish children (N = 2078) that met the criteria of having one, both or none of these disorders (dyslexia and ADHD). We used a case-control approach comparing different groups of samples based on each individual diagnosis. In addition, we also performed a quantitative trait analysis with psychometric measures on the general population (N = 3357). The results indicated that the significance values for some markers change depending on the phenotypic groups compared and/or when considering pair-wise marker interactions. Furthermore, our quantitative trait study showed significant genetic associations with specific cognitive processes. These outcomes advocate the importance of establishing rigorous and homogeneous criteria for the diagnosis of cognitive disorders, as well as the relevance of considering cognitive endophenotypes

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Prax Kinderpsychol Kinderpsychiatr. 2018 Sep;67:510-28.

PERSONALITY ASSESSMENT AS CONTRIBUTION TO DIAGNOSTIC DIFFERENTIATION BETWEEN ADHD AND RAD IN MIDDLE CHILDHOOD.

Meier SA, Zimmermann P.

Early and prolonged social and emotional deprivation can result in symptoms of both ADHD and attachment disorder (RAD). The present study compares children between 7 and 13 years of age diagnosed with either ADHD or RAD, regarding their disorder specific behavior by using the Conners Rating Scale, a RAD screening scale, the overall psychopathology in the CASCAP-D, and the childrenâ€™s personality using the California Child-Q-sort (CCQ). The RAD group showed an increased overall psychopathology score and both increased ADHD and RAD symptomatology. In addition, they also were characterized as lower in self-regulatory personality characteristics (e. g. ego-resiliency). The results suggest that children with a RAD diagnosis do not show two comorbid disorders (RAD plus ADHD) but are characterized by an even more intense deficit of self-regulation in social and emotional contexts, compared to the children of the pure ADHD

group. This should be considered in diagnosis and treatment. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

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Psychiatry and Clinical Psychopharmacology. 2018.

THE EFFECTS OF THE TRIPLE P-POSITIVE PARENTING PROGRAMME ON PARENTING, FAMILY FUNCTIONING AND SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER. A RANDOMIZED CONTROLLED TRIAL.

Yusuf Ö, Gonka Ö, Peckanlar AA.

OBJECTIVES: This is the first study to evaluate the efficacy of parent training in attention-deficit/hyperactivity disorder (ADHD) in Turkey. The aim of this study was to evaluate the effectiveness of the positive parenting programme (Triple P) on ADHD symptoms, functionality, severity of disease, and behavioural and emotional problems of children. An additional aim was to evaluate the potential effects of Triple P on parental attitudes and family functioning of children with ADHD.

METHODS: The study was a randomized controlled study. A total of 48 subjects aged between 7 and 12 years, who were diagnosed as ADHD by Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Life-time Kiddie (K-SADS-PL). Following randomization into two equal groups, mothers of the first group participated to Group Triple-P Programme while the second group was receiving no treatment. The two groups were compared right before and after the intervention on rates of ADHD symptoms, emotional, behavioural variables, family functioning and parental attitudes.

RESULTS: When we compared the results before and after the implementation of Triple P in the intervention group, there was a statistically significant increase in CGAS scores, and a statistically significant decrease in CGI scores. There was a statistically significant decrease subscale scores of SDQ; and total score of the DuPaul Questionnaire; a statistically significant decrease in problem solving, communication, roles in family, affective sensitivity, behaviour controlling, and general functioning subscale scores in FAD; a statistically significant decrease of parenting attitude, hostility, and rejecting attitude, and authoritarian attitude subscale scores; and a statistically significant increase in democratic attitude subscale scores of PARI.

CONCLUSION: The results of our study suggest that Triple P could be useful in the treatment of children with ADHD, but further studies about Triple P on children with ADHD are needed

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Psychiatry Clin Neurosci. 2018 Nov;72:836-48.

IDENTIFICATION OF NEUROPHYSIOLOGICAL BIOTYPES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Barth B, Mayer-Carius K, Strehl U, et al.

AIM: Findings on neurophysiological alterations in attention deficit hyperactivity disorder (ADHD) have been proposed to underlie ADHD symptoms, with different etiological pathways for different patient biotypes. We aimed at determining whether neurophysiological deviations confirm distinct neurophysiological profiles in ADHD, thus providing direct evidence for the endophenotype concept.

METHODS: Neurophysiological biotypes were investigated in 87 adult patients with ADHD using cluster analysis. Parameters fed into the analysis comprised both hemodynamic and electrophysiological data. To validate results, the independent variables of the clusters were compared with healthy controls.

RESULTS: Cluster analysis yielded three neurophysiologically based ADHD biotypes showing: (i) above-average functioning in attention allocation; (ii) difficulties in attention allocation and inhibitory control but elevated frontal activation during a working memory task; and (iii) functional impairments in state regulation.

CONCLUSION: Classifying patients with ADHD into neurophysiological biotypes sheds light on etiological pathways, with implications for diagnostics and (individualized) treatment options

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Psychiatry Res. 2018;270:780-85.

COMORBIDITY OF ATTENTION DEFICIT HYPERACTIVITY DISORDER AND GENERALIZED ANXIETY DISORDER IN CHILDREN AND ADOLESCENTS.

Melegari MG, Bruni O, Sacco R, et al.

The aim of the study is to explore the impact of Generalized Anxiety Disorder (GAD) comorbidity in children with Attention Deficit Hyperactivity Disorder (ADHD). Six hundred children with ADHD (mean age = 9.12 years), recruited from 2013 to 2017, participated in the study. A total of 96 (16%) children with ADHD displayed a comorbidity with GAD. ADHD + GAD were compared to 504 ADHD children without GAD in terms of cognitive and psychiatric profile, ADHD subtype and family psychiatric history. The ADHD + GAD, predominantly represented from ADHD combined (72.6%), displayed higher psychiatry comorbidity, in particular with depressive disorders, and were associated with higher rates of maternal depression, of ADHD in fathers, and bipolar disorders in second degree relatives. Moreover, younger preschool-primary school age children with ADHD + GAD showed significant higher frequency of depressive disorders versus younger preschool-primary children with ADHD without GAD. ADHD + GAD comorbidity represents a more complex clinical condition compared to ADHD without GAD, characterized by the higher frequency of multiple comorbidities and by a psychiatric family with higher rates of mood and disruptive disorders

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Psychiatry Res. 2018 Nov;269:585-92.

TESTING THE EXACERBATION AND ATTENUATION HYPOTHESES OF THE ROLE OF ANXIETY IN THE RELATION BETWEEN ADHD AND REACTIVE/PROACTIVE AGGRESSION: A 10-YEAR LONGITUDINAL STUDY.

Murray AL, Booth T, Obsuth I, et al.

Both anxiety and aggression commonly co-occur with ADHD symptoms. Two competing hypotheses describing the role of anxiety in aggression associated with ADHD symptoms have previously been advanced. The exacerbation hypothesis proposes that the presence of anxiety increases the risk of aggression in the context of ADHD symptoms. The attenuation hypothesis proposes that the presence of anxiety protects against aggression in the context of ADHD symptoms. We tested these hypotheses using moderated cross-lagged panel models in the Zurich project on social development from childhood to adulthood (z-proso) sample using both self-report (3 waves) and informant-report (8 waves) data spanning ages 7-17. We found evidence that anxiety protects against both reactive and proactive aggression; however, the effect was direct: there was no evidence for anxiety moderating the strength of ADHD symptom-aggression links. Results suggest that anxiety likely plays an important role in inhibiting aggression but does not interact with ADHD symptoms in the manner predicted by either the exacerbation or attenuation hypothesis

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Psychol Assess. 2018 Nov.

SLEEPY, SLUGGISH, WORRIED, OR DOWN? THE DISTINCTION BETWEEN SELF-REPORTED SLUGGISH COGNITIVE TEMPO, DAYTIME SLEEPINESS, AND INTERNALIZING SYMPTOMS IN YOUTH WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Smith ZR, Eadeh HM, Breaux RP, et al.

Sluggish cognitive tempo (SCT) consists of symptoms of slowness, sluggishness, daydreaming, and low motivation. SCT has been linked to attention-deficit/hyperactivity disorder (ADHD), internalizing symptoms, and daytime sleepiness. Although there is clear evidence that SCT and ADHD symptoms are distinct constructs, the distinction between SCT, anxiety/depression, and daytime sleepiness is less clear. Prior research has largely relied upon parent-report to evaluate potential overlap between SCT, sleep, and anxiety/depression, despite best practice suggesting that self-report should be used to assess internalizing symptoms. The present study used adolescent self-report to evaluate whether SCT was distinct from daytime sleepiness, anxiety, and depression. Participants were 285 middle school students comprehensively diagnosed with ADHD. Ten confirmatory factor analyses were conducted: four 1-factor models, three 2-factor models, one 3-factor model, one 4-factor model, and a higher order model. Results showed that SCT was

indeed distinct from all tested constructs, with the four-factor model including self-report of SCT, anxiety, depression, and daytime sleepiness meeting adequate model fit criteria. All models including SCT as its own factor had improved model fit over models with SCT in a combined factor with another construct. Implications for the assessment and treatment of SCT are discussed

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Res Dev Disabil. 2018;83:260-69.

CHILDREN WITH AUTISM AND ATTENTION DEFICIT HYPERACTIVITY DISORDER. RELATIONSHIPS BETWEEN SYMPTOMS AND EXECUTIVE FUNCTION, THEORY OF MIND, AND BEHAVIORAL PROBLEMS.

Berenguer C, Rosell+¦ B, Colomer C, et al.

Background: The underlying mechanisms of comorbidity between autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are still unknown. Executive function (EF) deficits and theory of mind (ToM) have been the most investigated cognitive processes.

Aims: This study proposed to analyze EF, ToM and behavioral problems in children with ASD + ADHD, ADHD, ASD and typical development (TD). The relationship between ADHD and ASD symptoms with EF, ToM and behavioral problems in children with ASD + ADHD was also explored.

Methods and procedures: Participants were 124 children between 7 and 11 years old (22 ASD + ADHD, 35 ADHD, 30 ASD, and 37 TD), matched on age and IQ. Teachers evaluated EF, and parents assessed ToM skills and behavioral problems through Strengths and Difficulties Questionnaire (SDQ).

Outcomes and results: Children with ASD + ADHD and ADHD showed impairments in EF whereas the difficulties in ToM skills of ASD + ADHD group were similar to ASD group. Inattention symptoms were significantly associated with EF metacognitive deficits and ToM difficulties in ASD + ADHD, while ASD symptoms were associated with total score in behavioral problems.

Conclusions and implications: These findings show the complex difficulties of children with both ASD and ADHD and support the need to take these difficulties into account when designing the treatments

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Rev Colomb Psiquiatr. 2018.

REVERSIBLE ALOPECIA SECONDARY TO OROS METHYLPHENIDATE.

Nez-Garces M, Sínchez-Gayango A, et al.

Introduction: Attention deficit hyperactivity disorder has a prevalence of 1-4% of the Spanish school population. Its treatment consists of giving amphetamine derivatives and, recently, non-stimulant drugs, without finding any differences in efficacy in the studies performed.

Clinical case: A 7-year-old girl was referred from neurology due to learning delay and behaviour disorders. Diagnosed as likely ADHD, treatment was started with immediate release methylphenidate, and later with an osmotic release oral system (OROS) methylphenidate. When alopecia areata appeared, this treatment was withdrawn. After the re-introduction of modified release methylphenidate 30:70, symptom control was achieved without the appearance of alopecia.

Discussion: There is a published history of two cases of alopecia areata with OROS methylphenidate that resolved after increasing the dose of the drug without clearly knowing the reason for this event. There is no consensus on the priority use of the immediate release formula or the OROS methylphenidate

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Ricerca e Pratica. 2018;34:198-214.

ADHD IN DEVELOPMENTAL AGE: COMORBIDITY AND TREATMENT OUTCOMES AIM.

Travellini S, Trabattoni S, Molteni M, et al.

To assess the prevalence rates of neuropsychiatrie comorbidities in children and adolescents with and without ADHD, and compare the effectiveness of treatment in relation to comorbidity. Methods. Clinical data on 378 suspected patients (86% M, 5-17 yr), entered in the Lombardy Region's ADHD Registry in the period 2011-2017 by regional reference center "Medea" of Bosisio Parini (LC), are analyzed to identify: prevalence

rates, comparison between prescribed and performed treatments, improvement rates and effectiveness of the treatment in relation to the different therapeutic approaches. Results. 70% (213/306) of first ADHD diagnosis and never treated patients has one (or more) comorbidity: learning disorders (LD) (48%), sleep disturbances (21%), anxiety disorders (16%), intellectual disability (17%), oppositional defiant disorder (12%), language disorders (12%), autism spectrum disorders (10%). Comorbidity is a risk factor for symptom severity (GCI-S Z5). One year after diagnosis, 51% of the population has improved (CGI-I <3). Overall, multi-modal treatment is the most effective for ADHD with other comorbid disorders (Effect Size - ES 0.50) and specifically for ADHD with: LD (ES 0.71), sleep disorders (ES 0.87), anxiety disorders (ES 0.86). Similar efficacy is achieved by child/parent training for ADHD with sleep disorders (ES 0.53) and ADHD with anxiety disorders (ES 0.88). Conclusions. Comorbidity in ADHD is the rule, not the exception. The regional ADHD Registry is a unique tool to agree and share actions for the appropriate management of diagnosis and treatment of ADHD. The results achieved through the application in clinical practice of shared operational lines are highlighted

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Sleep. 2018;41.

NEUROCOGNITIVE AND BEHAVIORAL SIGNIFICANCE OF PERIODIC LIMB MOVEMENTS DURING SLEEP IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Frye SS, Fernandez-Mendoza J, Calhoun SL, et al.

Study Objectives The purpose of this study is to examine the association of abnormal periodic limb movements during sleep (PLMS) with neurocognitive and behavioral outcomes in adolescents with attention-deficit/hyperactivity disorder (ADHD) from the general population.

Methods Four hundred twenty-one adolescents (17.0 -¦ 2.3 years, 53.9% male) from the Penn State Child Cohort, a random general population sample, underwent 9 hr polysomnography, clinical history, physical examination, neurocognitive evaluation, and completed the Child or Adult Behavioral Checklist (C/ABCL). The presence of ADHD was ascertained by parent- or self-report of receiving a diagnosis of ADHD. PLMS were defined as a PLM index (PLMI) of 5 events per hour of sleep.

Results Adolescents with ADHD (n = 98) had a significantly higher PLMI (5.4 -¦ 7.3) and prevalence of PLMS (35%) when compared with controls (3.4 -¦ 5.6, p = 0.006 and 21%, p = 0.004). Significant interactions between ADHD and PLMS showed that adolescents with both disorders (n = 35) were characterized by deficits in control interference, as measured by Stroop test, and elevated internalizing behaviors, as measured by C/ABCL. ADHD severity and externalizing behaviors were elevated in a dose-response manner across ADHD-alone (n = 63) and ADHD + PLMS groups. The association of ADHD with other neurocognitive functions did not vary as a function of PLMS.

Conclusions PLMS are significantly more frequent in adolescents with ADHD. Importantly, adolescents with both disorders not only have worse neurobehavioral functioning than adolescents with ADHD-alone but specifically presented with executive deficits and anxiety symptoms. These data suggest that PLMS may be a marker of more severe underlying neurobiological deficits in adolescents with ADHD and comorbid internalizing problems

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Therapeutic Drug Monitoring. 2018;40:435-42.

INTERINDIVIDUAL AND INTRAINDIVIDUAL VARIATION OF METHYLPHENIDATE CONCENTRATIONS IN SERUM AND SALIVA OF PATIENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Preiskorn J, Studer S, Rauh R, et al.

Background: Therapeutic drug monitoring is becoming increasingly important in psychiatric therapy, especially in children. However, for several reasons, it cannot yet be implemented as a daily routine in clinical or outpatient settings. To evaluate new, noninvasive procedures, blood and saliva (oral fluid) samples were collected from patients with attention-deficit/hyperactivity disorder (ADHD) who were also being administered methylphenidate (MPH). The study's main purposes were to correlate MPH concentrations in serum and saliva between subjects and to analyze intraindividual variation of serum concentration.

Methods: Thirty-six patients with ADHD (27 children and 9 adults) on MPH medication were included for drug analysis. MPH and its major metabolite ritalinic acid were quantified using liquid chromatographyΓÇôtandem mass spectrometry measurements. The following correlations were investigated: (1) between drug concentrations in serum and saliva, and (2) between pH value and saliva to serum concentration ratio. Furthermore, the mean intraindividual MPH-concentration fluctuation in saliva under constant frame conditions was analyzed.
Results: After quantification, MPH concentrations were approximately 5 times higher in the saliva than in the serum, whereas the concentrations of ritalinic acid were much lower in saliva. We found significant correlations between concentrations of MPH in serum and saliva (r = 0.51, P, 0.05). Saliva MPH measures, compared with serum, were pH-dependent (r = 20.56, P, 0.01). Daily coefficient of variance of saliva concentration in children taking constant medication was 27.3% (11% 42%), whereas the coefficient of variance for the ratio of saliva to serum was 122% (2% 2060%).
Conclusions: Our data indicate that the interindividual variation in saliva to serum concentrations is rather high, whereas the intraindividual variation is fairly low, as already shown in the literature for repeated citalopram serum measurements. Saliva may well serve as an alternative matrix for therapeutic drug monitoring of MPH in patients with ADHD, especially for follow-up examinations. Future research should focus on analyzing the relationship between drug levels in saliva and clinical effects as well as on understanding the mechanisms that generate saliva drug concentrations. These are essential steps before potential clinical use

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World Journal of Pediatrics. 2018.
EFFECT OF VITAMIN D TREATMENT IN CHILDREN WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER.
Dehbokri N, Noorazar G, Ghaffari A, et al .
Background: In this research the symptom improvement of attention-deficit hyperactivity disorder (ADHD) of children was assessed by oral vitamin D administration in Tabriz, Iran.
Methods: In this double-blind, randomized clinical trials, 96 children (2-18 years) were enrolled to placebo and vitamin D groups. Children took vitamin D pearl (50,000-áIU/week) or placebo for 6-áweeks. Children, who had the change in methylphenidate dosage and received any anticonvulsants and corticosteroids were excluded from the research. ADHD symptoms were diagnosed by Conners parent rating scale (CPRS) test at baseline and after intervention. ADHD Conners divided into inattention (IA), hyperactivity/impulsivity (H/I) and combination type (C) subscales. Vitamin D serum level was assessed at baseline and after 8-áweeks in both groups.
Results: The differences between CPRS and its subscales were not significant at baseline (P > 0.05). The Conners IA score was decreased in vitamin D group (P < 0.05; adjusted with age and baseline values). ADHD Conners and all subscale scores reduced remarkably after intervention in patients with insufficient level of vitamin D compared to placebo (P < 0.05).
Conclusions: Oral vitamin D improved ADHD symptoms with a particular effect on inattention symptoms. In addition, symptoms related to all subscales were improved remarkably in patients with insufficient level of vitamin D. Vitamin D treatment in children with ADHD could be considered due to the expand benefit of vitamin D in body

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Z Psych Psychol Psychother. 2018;66:219-31.
ESCALATE-AN ADAPTIVE TREATMENT APPROACH FOR ADOLESCENTS AND ADULTS WITH ADHD.
Zinnow T, Banaschewski T, Fallgatter AJ, et al.
In the treatment of adult ADHD, both pharmacological interventions and psychosocial treatments have been shown to be effective. However, in day-to-day clinical routine, treatment is less influenced by the outcomes of clinical trials than by treatment guidelines and require-ments of national institutions (Federal Joint Committee). The main aspect of these regulations is the requirement that a step-by-step approach, starting with low-threshold interventions, is most appropriate for treatment in adult ADHD patients. Unfortunately,

almost all clinical studies investigate the effects of individual therapeutic strategies. The tiered supply model does not seem to have been sufficiently validated yet. This is exactly where the ESCAlate study described below would like to start. ESCAlate is a randomized, controlled trial. 279 patients between the ages of 16.00 and 45,11 years will be enrolled in the treatment program, which is divided into several sections. In a first stage of treatment, patients are randomized into three groups: Individualized Psychoeducation (PE), Self-Helped Telephone Assisted Self-Help (TASH), or Waiting Control Group. All patients in the waiting group receive treatment with TASH after a waiting period of three months. In the second part of the treatment, patients are divided into the three groups full responders, partial responders and non-responders according to the severity of their persistent symptoms. Patients classified as full-responders receive behavioral-oriented coaching. Partial responders also receive this coaching, whereby in this group patients can be randomized to an additionally neurofeedback training (NF). Non-responders receive pharmacological treatment with methylphenidate and can be randomized to the additionally neurofeedbacktraining. ESCAlate is characterized by a relatively naturalistic sampling composition, as it does away with highly specific inclusion and exclusion criteria in order to obtain a patient sample that reflects the patients' daily routine in the practices. The effectiveness of an evidence-based intervention with graded treatment is assessed by primary (reduction in the severity of ADHD symptoms) and secondary outcomes (functional outcomes such as quality of life, anger management, increase in psychosocial well-being). Therapeutic response / non-response predictors are evaluated at each step of the intervention. In addition, any gender differences can be investigated

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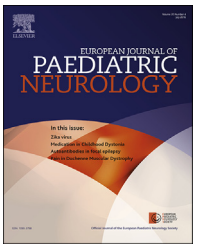

Review article

A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder

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ABSTRACT

Objectives: The aim of this systematic review was to examine the incidence and prevalence of comorbidity between Cerebral Palsy (CP), Autism spectrum disorders (ASDs) and Attention-Deficit/Hyperactivity Disorder (ADHD).

Methods: We searched for articles indexed in PubMed, EBSCOhost, Scopus, Web of Science and other potentially relevant internet sources using a combination of expressions including "cerebral palsy" AND "autism" OR "ASD" OR "pervasive development disorder" AND "Attention Deficit Hyperactivity Disorder" OR "ADHD".

Results: We identified 2542 studies on CP and ASD and 998 studies on CP and ADHD. After screening titles and abstracts and removing duplicated studies, 47 full papers (CP and ASD n = 28; CP and ADHD n = 19) were downloaded and screened for eligibility. Twenty-eight (CP and ASD n = 16; CP and ADHD n = 12) studies were identified in the peer-review literature. Based on this systematic review, ASD and ADHD seem to be more common in people with CP than in the general population, yet the gold standard methods for diagnosing ASD or ADHD are not suitable for children with motor problems.

Conclusions: Assessing the occurrence of ASD and ADHD would improve the significant cost of healthcare, therapies, and overall daily living for families with children affected by CP. However, psychometric studies are needed in the future to promote development of measures suitable for individuals with CP. In addition, this review highlights the paucity of peer-reviewed studies investigating the occurrence of ASD and ADHD in children with different CP subtypes or functional abilities, and there are still some open questions about pathogenic mechanisms common to CP, ASD and ADHD.

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1. Introduction

Cerebral Palsy (CP) is a group of lifelong neurological disorders and a major cause of childhood disability. According to previous population-based studies from countries around the world, prevalence estimates for CP range from 1.5 to more than 4 per 1000 live births or children of a defined age range.[1–3]

The Executive Committee on the Definition and Classification of Cerebral Palsy delineated the definition of this disorder with the intent of providing a common conceptualization of this clinical entity for use by a broad international audience.[4] CP was defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[4] The prevailing trend in clinical practice is to classify CP by functional independence in terms of gross motor function, fine motor function, and communication abilities through the Gross Motor Function Classification System (GMFCS),[5] the Manual Abilities Classification System (MACS),[6] and the Communication Function Classification System (CFCS).[7] These measures were designed to better delineate the functional profile of children with CP by focusing on activity and participation levels.[8]

Motor disorders in CP are often associated with disturbances of sensation, perception, cognition, communication, behavior, and epilepsy.[1,9] In addition, a recent systematic review and meta-analysis showed increased risk rates for emotional lability, irritability, impulsiveness and behavioral problems in people with CP.[10] All these conditions are a wide range of common disorders that may be associated with other Neurodevelopmental Disorders (NDDs) such as Attention Deficit/Hyperactivity Disorder (ADHD), Autism Spectrum disorder (ASD), Learning Disabilities (LD), Intellectual Disability (ID), Speech and Language Delay, Developmental Delay (DD), and Developmental Coordination Disorder (DCD).[11,12] Indeed, comorbidity with other NDDs could directly or indirectly influence habilitation and rehabilitation of children or adults with CP. For this reason, it is very important to establish the impact of comorbidities in CP patients in order to promote their adjustment and participation as well as subjective and relational well-being. Currently, there is an unambiguous link between CP and other NDDs.[13] Based on previous studies, the same genetic risk factors could underlie different pathological phenotypes.[13,14] Yet, similar phenotypes could have different genetic risk factors.[13,15] Therefore, many NDDs – rather than being distinct conditions – may be part of a continuum of clinical expression. As suggested by Zwaigenbaum, injury-related processes versus genetically influenced developmental processes in the comorbidity between CP and other NDDs remain an interesting and challenging question.[16] Further studies on comorbid conditions are needed to increase our understanding of the complexity of CP.

Recently, the National Institute for Health and Care Excellence (NICE) Guideline on diagnosing, assessing and managing CP[17] underlined the importance of investigating the prevalence of ASD and ADHD in children and young people with CP. According to the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5), the diagnosis of ASD relies on persisting deficits of social communication and interaction and restricted and repetitive behaviors, interests, activities, while ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity interfering with functioning or development.[18] ASD and ADHD are common NDDs in the pediatric population with a prevalence of 1% and 5%, respectively.[18] Recent studies on epidemiological, clinical, neuroimaging and biological risk factors showed high rates of comorbidity and support several overlapping traits between ASD and ADHD.[19–21] Furthermore, given the link between mental and physical health, detection and

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management of specific comorbid diagnoses such as ASD and ADHD could improve planning for service and treatment of people with CP. The main aim of this systematic review was to explore the relationship between CP, ASD and ADHD and to investigate how these disorders overlap. This review starts with a discussion of the incidence and prevalence of CP and ASD and then presents research findings focusing on the incidence and prevalence of CP and ADHD.

2. Methods

2.1. Study selection and data collection

PRISMA guidelines were followed.[22] The search strategy included research databases such as PubMed, Scopus, Web of Science, EBSCOhost and other potentially relevant internet sources such as Google®. All database searches were performed on January 6th, 2018 using a combination of the following free-text terms: "cerebral palsy" AND "autism" OR "ASD" OR "pervasive development disorder" AND "Attention Deficit Hyperactivity Disorder" OR "ADHD".

After this initial literature search, each single study title and abstract was screened by the first author. All references with duplicate data were excluded. Based on eligibility criteria, two reviewers (FC and RS) independently screened an abstract of available citations to identify potentially eligible studies. The full text of all potentially relevant studies was subsequently retrieved and further examined for eligibility. All references included in the papers identified as relevant from the database search were also examined for possible inclusion in this review. Data were extracted independently by two authors (FC and RS) and disagreements were resolved by negotiation with a third author (AT). Agreement as to whether or not the study met the inclusion criteria was 100%.

2.2. Eligibility criteria

All the studies included in this review met the following five criteria: They 1) investigated the prevalence of ASD in CP or vice versa; 2) investigated the prevalence of ADHD in CP or vice versa; 3) enrolled children, adolescents and young adults (18–35 years); 4) were published in English; and 5) were published in peer-reviewed journals. No restrictions were placed on the date of publication. Review articles and single clinical reports were excluded.

2.3. Data extraction

Studies meeting the inclusion criteria were summarized in terms of: I) type of study; II) number of participants (sample size); III) diagnosis-related groups; III) country of data collection; IV) participants' age; V) diagnostic criteria and assessment tools; VI) rates of comorbidity.

3. Results

We identified 2542 studies on CP and ASD (PubMed n = 817, Scopus n = 840, Web of Science n = 738, EBSCOhost n = 120, and other sources n = 27) and 998 studies on CP and ADHD (PubMed n = 425, Scopus n = 265, Web of Science n = 184, EBSCOhost n = 108, and other sources n = 17). The screening phase involved the examination of titles and abstracts of all identified studies. 2411 studies (CP and ASD n = 1639; CP and ADHD n = 772) were excluded as they were not deemed suitable. After adjusting for duplicates, 533 studies on CP and ASD and 135 studies on CP and ADHD were screened to identify potentially eligible studies. 47 studies (CP and ASD n = 28; CP and ADHD n = 19) were selected for the eligibility phase. Out of these, 12 studies on CP and ASD and 7 studies on CP and ADHD were excluded as they did not provide sufficient data on ASD or ADHD in children or young people with CP. Following this, 16 empirical studies on CP and ASD and 12 empirical studies on CP and ADHD fully met the previously stipulated eligibility criteria for inclusion in the systematic review process. The PRISMA flow diagram (Fig. 1) provides more detailed information on the study selection process.

3.1. Study characteristics

The main methodological features and general characteristics of all reviewed studies are summarized in Tables 1 and 2.

3.2. Countries of data collection

Studies on the co-occurrence of CP and ASD were conducted in the United Kingdom (n = 4), Sweden (n = 7); Turkey (n = 2); Finland (n = 1); United States of America (n = 3), Iceland (n = 1) and France (n = 1).

Studies on the co-occurrence of CP and ADHD were carried out in the United States of America (n = 3), United Kingdom (n = 1); Israel (n = 3); England (n = 1), Sweden (n = 1), Northern Ireland (n = 1), France (n = 1), Ireland, Italy (n = 1), Denmark (n = 2), Iceland (n = 1), Canada (n = 1), and Norway (n = 1).

3.3. Characteristics of participants

The reviewed studies included 5050 participants with a primary diagnosis of CP or ASD, and none of them included participants with a primary diagnosis of ADHD. Studies focusing on ASD in children or young people with CP involved 2770 children or young people (age range: 0–19 years) with CP, of whom 240 (8.7%) met the criteria for ASD. Studies focusing on the co-occurrence of CP in populations with ASD or Pervasive Developmental Disorders (PDDs) involved 485 children or adolescents (age range: 2–18 years) with ASD, 23 (4.7%) of whom met the criteria for CP.

Studies evaluating the co-occurrence of CP and ADHD involved 1795 children or adolescents (age range: 1.8–20 years) with CP, 399 (22%) of whom met the criteria for ADHD.

3.4. Diagnostic criteria and assessment tools

NDDs can potentially be assessed both categorically and dimensionally. We found a multiplicity of assessment tools for ASD or ADHD in children and young people with CP. Thirteen studies used a categorical approach based on the DSM (n = 12) or the International Classification of Diseases (ICD; n = 2) to define ASD (n = 10) or ADHD (n = 4). One of these

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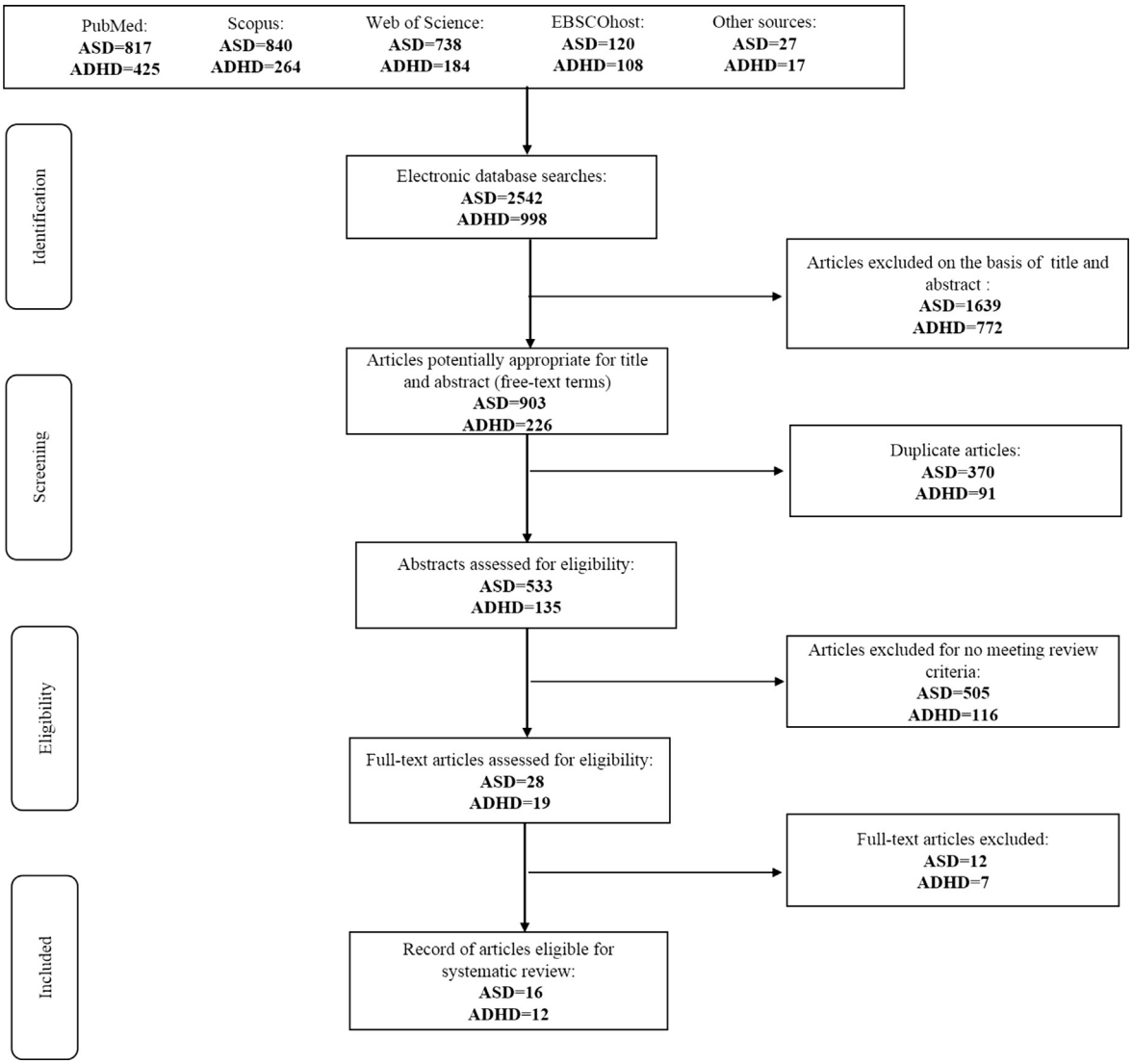

Fig. 1 – The PRISMA flow diagram provides more detailed information regarding the selection process of studies.

studies used both DSM and ICD. The gold standards for the diagnosis of ASD were used in five studies, four of which used the Autism Diagnostic Interview – Revised (ADI-R)[23] and one used the Autism Diagnostic Observation Schedule (ADOS).[24] Eight studies used a dimensional approach to the diagnosis of ASD. The Autism Behavior Checklist (ABC)[25] was used in five studies, the Childhood Autism Rating Scale (CARS)[26] was used in three studies and the Strength and Difficulties Questionnaire (SDQ),[27] the Social Communication Questionnaire (SCQ),[28] and the Questionnaire measures of psychiatric caseness[29] were used in three studies separately.

Six studies used a dimensional approach to the diagnosis of ADHD. The Conners' Rating Scale (CRS)[30] was used in three studies, the SDQ was used in two studies, and the Child Behavior Checklist (CBCL)[31] and the Teacher's Report Form (TRF)[32] were used in one study. The Behavior Problem Index (BPI),[33] the Rutter questionnaires,[34] the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)[35] and the Test of Everyday Attention for Children (TEA-Ch)[36] were used in four studies separately.

The functional levels measured by GMFCS were provided in eight studies (CP and ASD n = 4; CP and ADHD n = 4), while only one study measured fine motor function in children with CP by MACS.

3.5. *Comorbidity of CP and ASD*

Sixteen studies were eligible for inclusion. The literature review revealed two groups of studies on the co-occurrence of CP and ASD. The first group comprises twelve studies focusing on ASD in children or young people with CP. In 1996, Goodman & Graham found that 4 (3%) out of 149 hemiplegic children had ASD and suggested that this rate was ten times higher than in the general population.[29] One hundred seventy-seven children were screened for autistic-type symptoms by Nordin and Gillberg and ASD was found in 4 (10.5%) of the 38 children with CP.[37] Of these, two children had an autistic disorder, one had an autistic-like condition and one had PDD-NOS. Ek et al. recruited 29 Swedish children diagnosed with blindness due to bilateral retinopathy of prematurity (ROP) stage 5 (i.e. total

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Table 1 – Summary of the epidemiologic evidence on CP and ASD.

Authors	Year of publication	Type of study	Number of participants (N)	Diagnosis-related groups	Country	Age	Diagnostic criteria and assessment tools	Prevalence of ASD or CP n (%)
Goodman and Graham	1996	cross-sectional	149	CP	UK	6–10 years	Questionnaire measures of psychiatric caseness	4 (3%)
Nordin & Gillberg	1996	epidemiological	38	CP	Sweden	school-age	ABC, CARS, DSM-III-R	4 (10.5%)
Fombonne et al.	1997	epidemiological	174	Autism	UK	6–16 years	ADI-R	5 (2.9%)
Ek et al.	1998	population-based	27	Autistic Disorder + blindness	Sweden	7–17 years	CARS, DSM-IV	8 (29.6%)
Chakrabarti & Fombonne	2001	cross-sectional	97	PDD	UK	2.5–6.5 years	ADI-R	2 (2%)
Steffenburg & Gillberg	2003	population-based	37	CP	Sweden	8–16 years	ABC, CARS, ADI, DSM-III-R	6 (16.2%)
Kielinen et al.	2004	population-based study	187	Autistic Disorder	Turkey	4–18 years	DSM-IV	8 (4.3%)
Lindquist et al.	2006	population-based study	18	CP + hydrocephalus	Sweden	5–12 years	CARS	6 (33%)
Mukaddes et al.	2007	case–control	30	CP + visually impaired	Turkey	7–18 years	ABC, CARS, DSM-IV	10 (33%)
Carlsson et al.	2008	population-based study	34	CP + epilepsy	Sweden	8–12 years	SDQ	5 (14%)
Kilincaslan & Mukaddes	2008	case–control	126	CP	Finland	3–18 years	ABC, CARS, DSM-IV	19 (15%)
Himmelmann and Uvebrand	2011	population-based	186	CP	Sweden	4–8 years	DSM-IV, GMFCS	9 (4.8%)
Kirby et al.	2011	population-based	476	CP	USA	8 year	GMFCS, DSM-IV-TR	39 (8.2%)
Christensen et al.	2013	population-based	451	CP	USA	9 year	GMFCS, DSM-IV-TR	31 (6.9)
Delobel-ayoub et al.	2017	population-based	1225	CP	Iceland, Sweden, France, UK	0–19 years	ICD-10-R; GMFCS	107 (8.7%)
Hirschberger et al.	2018	multicenter, prospective cohort follow-up	93	CP	USA	10 years	SCQ, ADI-R, ADOS-2	8 (20%)

Cerebral Palsy (CP), Autism spectrum disorders (ASD), Pervasive Development Disorder (PDD), Autism Behavior Checklist (ABC), childhood Autism Rating Scale (CARS), diagnostic and statistical manual of mental disorders (DSM), Autism Diagnostic Interview (ADI), Strength and Difficulties Questionnaire(SDQ), Autism Diagnostic Observation Schedule-2 (ADOS-2), Social Communication Questionnaire (SCQ), Gross Motor Function Classification System (GMFCS), International Classification of Diseases (ICD).

Table 2 – Summary of the epidemiologic evidence on CP and ADHD.

Authors	Year of publication	Type of study	Number of participants (N)	Diagnosis-related groups	Country	AGE	Diagnostic criteria and assessment tools	Prevalence of ADHD or CP n (%)
McDermott et al.	1996	population-based	47	CP	USA	4–17 years	Behavior Problem Index	12 (25.5%)
Goodman	1998	prospective	328	hemiplegia	UK	2.5–4.9 years	CTRS; Rutter questionnaires	–
Gross-Tsur et al.	2002	prospective, double-blind, placebo controlled, crossover	116	CP + ADHD	Israel	3.9–20.0 years	CRS; DSM-IV	29 (33%)
Schenker et al.	2005	cross-sectional study	148	CP	Israel	6.1–13.6 years	GMFCS	28 (19%)
Symons et al.	2007	double-blind, placebo-controlled, randomized, single-case	3	CP + ADHD	USA	8–11 years	DSM-IV	3 (100%)
Parkes et al.	2008	crosssectional multi-centre survey	818	CP	England, Sweden, Northern Ireland, France, Ireland, Denmark, Italy	8–12 years	SDQ	253 (31%)
Bottcher et al.	2009	population-based	33	CP	Denmark	9.11–13.6 years	TEA-Ch	–
Sigurdardottir et al.	2010	case–control	36	CP	Iceland	4–6 years	CBCL, TRF	3 (6%)
Shank et al.	2010	case–control	33	CP	USA	8–16 years	CPRS-R, GMFCS	–
Brossard-Racine et al.	2011	cross-sectional	76	CP	Canada	6–12 years	SDQ	23 (30.3%)
Bjorgaas et al.	2012	population-based	67	CP	Norway	8–12 years	ICD-10, GMFCS, Kiddie-SADS, DSM-IV, MACS	28 (18%)
Gabis et al.	2015	Population-based	90	CP	Israel	1.8–15.4 years	GMFCS	20 (22.5%)

Cerebral palsy (CP), attention-deficit/hyperactivity disorder (ADHD), Gross Motor Function Classification System (GMFCS), Child Behavior Checklist (CBCL), Teacher's Report Form(TRF), Conners' Rating Scale (CRS), Conners Parent Rating Scales – Revised (CPRS-R), Strengths and Difficulties Questionnaire (SDQ), Test of Everyday Attention for Children (TEA-Ch), Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), diagnostic and statistical manual of mental disorders (DSM), Conners teacher rating-scale (CTRS), Manual Abilities Classification System (MACS).

retinal detachment). 15 children (8 boys, 7 girls) had an autistic disorder, however only 8 children (29.6%) met two of the DSM-IV criteria for this disorder.[38] Steffenburg et al. examined 98 children with active epilepsy and learning disability and reported that 6 (16.2%) children with concurrent CP had a diagnosis of ASD.[39] A population-based study comprised 67 children with hydrocephalus, 18 of whom with CP.[40] Among children with additional impairments in the form of CP, 6 (33%) subjects out of 18 had autism. This was significantly more common than in the 3 children with autism among the 49 (6%) without these additional impairments. Carlsson et al. described and compared behavioral problems in a group of children with CP, with and without epilepsy.[41] Five out of the 34 children (14%) enrolled had autism, all in the epilepsy group, suggesting that behavioral problems (incl. autism) are common in CP, and this is even more so when epilepsy is present. In 2009, Kilincaslan & Mukaddes assessed the prevalence of autistic disorder and PDD-NOS in a group of 126 children with CP, with 19 (15%) children diagnosed with autism (11% autistic disorder and 4% PDD-NOS).[42] PDD was more common in children with tetraplegic, mixed, and hemiplegic CP as well as in children with epilepsy, learning disability, and low level of speech. In a functional neuroimaging study, Himmelmann & Uvebrant found that nine out of 186 children with CP had a diagnosis of autism or ASD (n = 3 with an intelligence quotient in the lower normal range, n = 1 with a mild learning disability, and n = 5 with a severe learning disability). In children diagnosed with autism, the authors found periventricular white-matter lesions in 3 subjects, cortical/subcortical and basal ganglia lesions in 2 subjects, a malformation in one child, and normal imaging in three subjects.[43] The Autism and Developmental Disabilities Monitoring (ADDM) Network published two studies to monitor CP prevalence in different USA regions and evaluate sociodemographic correlates and characteristics of children with CP. Based on these two reports, it is possible to estimate the rates of comorbid ASD in children with CP. In Kirby et al.'s study, 39 (8.2%) out of 476 children with CP were diagnosed with ASD.[44] They found that ASD co-occurred in 24 (6.2%) children with spastic subtype, 7 (6.4%) of whom with unilateral subtype and 17 (6.2%) with bilateral subtype, and in 4 (14.8%) children with non-spastic subtype as well as 11 (17.7%) children with other subtypes (spastic-ataxic, spastic-dyskinetic, and cerebral palsy not otherwise specified). The authors concluded that comorbid ASD was present in approximately 8% of children with CP across all sites. They also found that, as walking ability decreased, the proportion of children with a comorbid ASD also declined – from 12.9% among children who walked independently to 3.4% among those with limited or no walking ability. In the second report of the ADDM Network, Christensen et al. found that 31 (6.9%) of the 451 children with CP were diagnosed with ASD.[45] ASD co-occurred in 21 (6%) children with spastic subtype, 7 (5.5%) of whom with unilateral subtype and 14 (6.3%) with bilateral subtype, and in 7 children (18.4%) with non-spastic subtype and 3 children (4.7%) with mixed/not otherwise specified subtype (the authors included: spastic-ataxic, spastic-dyskinetic, and cerebral palsy not otherwise specified).[45] Recently, Delobel-Ayoub et al. evaluated the prevalence of comorbid ASD among children with CP and described their characteristics.[46] A total of 1225 children with CP were included in the study, 107 (8.7%) of whom had an associated diagnosis of ASD. 6.4% of children with CP without intellectual disability presented with comorbid ASD, a proportion obviously higher than in the general population. The authors concluded that children with CP appear to be at greater risk of ASD than the general population, independently of their intellectual level. A recent study by Hirschberger et al. investigated the prevalence of neurodevelopmental impairments in children aged 10 who were born extremely preterm.[47] A total of 93 out of 849 children (11%) had CP, 8 (20%) of whom presented with comorbid ASD. At age ten years, children who had been diagnosed with CP at age two years had a +1.71 risk of having ASD compared with children without CP.

The second group comprises four studies focusing on comorbid CP in populations with autistic disorder or PDDs. In an epidemiological survey on 325,347 children including 174 subjects diagnosed with autism, Forbonne et al. found a 2.9% rate for CP among children with autism, suggesting that the rate of CP in children with autism was higher than the population rate but twice as low as that in the comparison group (children without autism suffered from a range of different medical and developmental problems as well as intellectual deficits).[48] Subsequently, in a group of 97 children, Chakrabarti & Fombonne found two females (2%) with CP diagnosed with PPD and autism, respectively.[49] A population-based study by Kielinen et al. investigated associated medical disorders and disabilities in 187 children with autistic disorder.[50] The rate of CP –4.3% (eight subjects out of 187)– is almost 10 times the population rate of 5.7 per 1000 in northern Finland (von Wendt et al., 1985b). In addition, this study reported comorbid ASD in 4 (2.1%) children with diplegia, 2 (1.1%) with triplegia and 2 (1.1%) with tetraplegia. Finally, a case–control study compared 227 children with visual impairments and 30 children with visual impairments plus ASD.[51] Mukaddes et al. found that the two groups differed significantly in terms of CP (13% vs. 33%), concluding that subjects with blindness plus autism have a greater neurological impairment such as intellectual level and cerebral palsy.

Full details of these studies are shown in Table 1.

3.6. *Comorbidity of CP and ADHD*

We found twelve studies evaluating the comorbidity between CP and ADHD. Our review of the literature revealed three groups of studies on the co-occurrence of ADHD and CP.

The first group of studies investigated the prevalence of ADHD symptoms in CP populations. In a population-based research, McDermott el al. measured behavioral problems in children with CP in a non-clinical setting.[52] They reported that 12 (25.5%) children with CP out of a group of 47 children presented with hyperactive problems including concentration difficulty, forgetfulness, and impulsive behavior. Motor and cognitive or behavioral problems were examined in 148 children with CP.[53] The most frequently co-occurring neuropsychiatric impairments were ADHD (19%) and learning disorders (46%). To describe psychological symptoms in children with CP aged 8–12-years, Parkes et al. conducted a cross-sectional multi-centre survey[54] using a dimensional approach to evaluate emotional and behavioral problems. The authors used

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the parent form of the SDQ and found that approximately 31% of children with CP (N = 818) showed hyperactivity disorders. Sigurdardottir et al. assessed emotional and behavioral problems in 33 pre-school children with congenital CP by the CBCL.[55] Two of these children presented with ADHD. In children with CP, attention problems and withdrawal were the most problematic symptoms both at home and at preschool. In a cross-sectional study, Brossard-Racine et al. explored behavioral problems in school-aged children with CP (N = 76) and identified modifiable factors associated with problematic behavior.[56] Hyperactivity-inattention problems affected 30.3% of them. In this group, 18 children (23.7%) fell in the hyperactivity abnormal range and 5 (6.6%) in the hyperactivity borderline range. Furthermore, the authors suggested that the presence of hyperactivity problems in children with CP is predictive of later peer-related problems. Recently, in a population-based study, Bjorgaas et al. assessed the rate of psychiatric disorders using a diagnostic interview.[57] Among the 56 children identified with GMFCS level I–IV, 32 subjects (57%) met the criteria for a child psychiatric disorder. Specifically, 28 children met the criteria for ADHD/ADD. These children had a GMFCS level III–IV and a MACS level III–V. In another study, Gabis et al. investigated the association between functional level and mental comorbidity in a large cohort of children with CP[58] by stratifying a sample of 90 children by GMFCS level and CP subtype. ADHD was prevalent in 22.5% of the children. Among children with ADHD, three (50%) children were categorized into GMFCS Level I, 3 children (30%) into GMFCS Level II, 4 children (33%) into GMFCS Level III, 7 children (44%) into GMFCS Level IV, and 6 children (14%) into GMFCS Level V. In addition, ADHD was found to co-occur in 11 (12.9) children with quadriplegia, 4 (4.8%) children with hemiplegia, 3 (3.5%) children with athetoid CP, and 4 (4.8%) children with spastic diplegia.

Studies in the second group evaluated the effect of methylphenidate on ADHD in children with CP. Goodman found that hyperactivity was particularly predictive of continuing psychiatric problems in school-age children (N = 240) with hemiplegia[59] and suggested that use of stimulants could prevent the emergence of other psychiatric problems. Two studies explored the use of methylphenidate for ADHD in children with CP. In a prospective, cross-over, double-blind study, Gross-Tsur et al. treated twenty-nine patients with CP and ADHD (33% on 116 subjects) with methylphenidate or placebo, each for 4 weeks.[60] The effect of methylphenidate on attentional skills were evaluated using parent and teacher reports. The study showed the efficacy of methylphenidate in children with dual diagnosis of CP and ADHD, at least in the short term. Symons et al. evaluated methylphenidate administration in 3 school-aged children with CP and comorbid ADHD symptoms and found that low-dose vs. high-dose methylphenidate resulted in clinically significant reductions in directly observed stereotyped and disruptive behavior.[61]

Studies belonging to the third group assume that children with CP present with impairments in attention and executive function similar to ADHD children. Bottcher et al. tested attention and executive functions with standardized neuropsychological measures in a group of children with unilateral (n = 15) or bilateral (n = 18) spastic CP, highlighting that children with CP had particular difficulties on measures of sustained and divided attention, while no significant differences on attention tasks were found between participants with unilateral and bilateral spastic CP.[62] Shank et al. hypothesized that children with CP and control peers would show positive correlations between visual inspection time (IT) task duration thresholds and parent/guardian ratings of ADHD symptom severity.[63] Children with CP exhibited significantly slower IT, with more symptoms of inattention and hyperactivity than the control group. However, while correlations between IT durations and reported ADHD symptoms were significant in the control group, no such finding were observed in the CP group.

Studies included in this section are summarized in Table 2.

4. Discussion

The purpose of this systematic review was to establish the incidence and prevalence of comorbid NDDs in the CP population. According to the NICE Guideline on diagnosing, assessing and managing CP (Shaunak & Kelly, 2017), we focused on ASD and ADHD, as these NDDs are interrelated and may share pathological mechanisms and clinical features.[19,20,64,65]

The ASD prevalence estimates in CP vary widely from 2% to 30%. This may in part be due to the variety of the populations studied. We found a higher prevalence of ASD (from 29% to 33%) in studies where CP was associated with other medical conditions such as visual impairment, retinopathy of prematurity, and hydrocephalus, which suggests that these additional medical conditions increased the risk of ASD. Studies focusing on comorbid CP in populations with ASD revealed a prevalence from 2.9% to 4.3%. Similarly, the prevalence of ASD in populations with CP varies from approximately 3%–16%, suggesting a higher frequency of ASD in children with CP compared with the estimated prevalence (ca. 1.5%–2%) in the ASD population.[66] Regarding the comorbidity between CP and ADHD, we found that ADHD prevalence in CP ranged from 19% to 35%. A recent meta-analysis on ADHD prevalence in children up to 18 years of age found an overall pooled estimate of 7.2%.[67] These findings suggest that ADHD seems to be more common in children with CP than in the general population.

Taken together, the studies discussed in this review point out that children and young people with CP are clearly at increased risk of ASD and ADHD. However, differences in prevalence rates between studies could be due to the different diagnostic tools used. Traditionally, the question of whether ASD and ADHD are best classified using categorical or dimensional approaches is a contentious one and has profound implications for clinical practice and scientific enquiry alike. Both categorical and dimensional solutions appear to be valuable and this varies according to the disorder considered.[68] However, many neurodevelopmental conditions are better described as dimensional rather than categorical disorders.[69] This has been suggested for both ASD and ADHD, as dimensional approaches can be used to identify discrete subgroups of individuals within each disorder. Thus, in the current review, we reported the empirical literature into studies taking a categorical and dimensional

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approach to evaluate the comorbidity between CP and ASD or ADHD.

Although diagnostic procedures for ASD have improved, diagnosing this disorder in children with CP remains a complex issue. Probably the gold standards for diagnosis such as the ADOS and ADI-R are not suitable for some children with CP. Assessing communication impairments in CP is difficult owing to common oral-motor disorders.[42] Besides, diagnostic measures for ASD include complex motor tasks that are not suitable to the motor skills of children with CP. Most studies relied on DSM or ICD criteria for the diagnosis of ASD, whereas only three studies used DSM criteria for ADHD diagnosis. Most studies used a dimensional approach to evaluate attention or behavioral problems associated with ADHD. Some studies employed the revised CRS-R, which is considered the gold standard for assessing ADHD, others evaluated ADHD symptoms using tools tapping emotional and behavioral aspects such as the SDQ or CBCL. Compared with the DSM- or ICD-based categorical approach, these dimensional tools tend to generate higher prevalence rates for ADHD.[70] It should be noted that the SDQ and the CBCL are not diagnostic measures for ADHD but only reflect parental or teachers' perceptions of a child's specific disruptive behaviors. Parent and teacher reports on a screening questionnaire cannot replace clinical validation of a diagnosis. Furthermore, these dimensional tests (CRS-R, SDQ, and CBCL) include a significant number of questions irrelevant to the level of motor activity and behavior of children or adults with CP. Therefore, there are still diagnostic challenges to overcome in order to successfully implement a screening approach for other NDDs in people with CP. Early identification of ASD or ADHD symptoms through a dimensional approach in children with CP could help clinicians improve management decisions and lead to targeted treatment and therefore better outcomes. In addition, our review highlights the paucity of published studies on the occurrence of ASD and ADHD in children with different CP subtypes or functional abilities. Only two studies reported that ASD was more frequent in children with non-spastic CP, particularly hypotonic CP.[44,45] No studies report the prevalence of ASD based on functional levels measured by GMFCS, CFCS and MACS. Regarding the comorbidity between CP and ADHD, only two recent studies evaluated the prevalence of ADHD symptoms in children with CP based on GMFCS functional levels: One study reported ADHD symptoms, and comorbid ADHD was found to be more frequent in children with quadriplegia.[58] The other study reported a prevalence of ADHD in children with GMFCS level III–IV and MACS level III–V, while no differences in ADHD symptom prevalence were found in children with different CP subtypes.[57] This would be a fruitful area for further research, in order to establish whether occurrence of other NDDs in CP varies according to CP subtypes or functional abilities. In fact, the precise quantification of comorbidity between ASD or ADHD in children or young people with CP could help determine the effectiveness of medical and physical therapeutic interventions.

Some studies indicate some overlap of cognitive deficits between ADHD and CP.[62,63] Attention and executive functions seem to be more commonly affected in children with CP or ADHD than typically developing children. Improving attention and executive functions such as working memory may be beneficial for both patients and their families, reduce the need for special education and improve social and daily life functioning.[71] Nevertheless, there is a lack of evidence-based knowledge regarding cognitive function and the effects of cognitive interventions in CP.

The studies included in our review also addressed the effects of stimulant therapy in children with CP and ADHD. Methylphenidate showed to be beneficial in ADHD, even when associated with other neurologic disorders such as intellectual disabilities, fragile X syndrome, autism spectrum disorder, and epilepsy.[60] However, pharmacological treatments targeting ADHD symptoms in CP have received little attention. Two studies reported that methylphenidate is effective in children with dual diagnosis of CP and ADHD[60,61] and emphasized that low-dose (0.3 mg/kg/dose) methylphenidate was associated with clinical significant reductions of ADHD symptoms in children with CP, at least in the short term. However, caution is recommended as findings cannot be generalized given the small sample size.

5. Conclusion and future directions

Based on our systematic review, people with CP are clearly at increased risk of other NDDs such as ASD or ADHD. The complexity of the CP condition is a challenge when diagnosing ASD or ADHD. Children with CP should specifically be screened for both these conditions; however, future psychometric studies are needed to promote the development of measures suitable for individuals with CP, particularly when sensory impairments and motor deficits limit use of gestures such as pointing, that may complicate differential diagnosis. Measures tapping ASD or ADHD symptoms need to be valid, reliable, sensitive, and able to detect change over time, and they also need to be appropriate for use in CP. Characteristics associated to ASD or ADHD such as social communication, attention, executive function and behavior problems may be overlooked or thought of as being part of the disorder. Therefore, ASD or ADHD may go undiagnosed in individuals with CP. In order to avoid this risk, health care professionals need to be more informed and knowledgeable about the symptoms of ASD or ADHD. Assessing the presence of these conditions would improve the significant cost of healthcare, therapies, and overall daily live for families with children affected by CP. A comorbidity between NDD and a disabling condition such as CP could be either a pathology, an impairment, a functional limitation, or an additional disability. Further studies are needed to ensure that appropriate services are in place to provide parents and carers with information on the diagnosis and management of CP and that this information is tailored to their individual needs and learning styles.

Unfortunately, no attempts were made to understand the common pathogenic mechanisms linking CP, ASD and ADHD. One may argue that the brain lesion itself causes an increased prevalence of ASD and ADHD in CP people, pointing to a direct brain behavior link, and it would be reasonable to assume that CP may be a risk factor for other NDDs. Thus, a possible hypothesis could be that the CP-related brain damage or malformation could affect the same brain areas involved in the etiopathogenetic mechanisms of ASD or ADHD. However, it is well known that CP may occur in the absence of clear and

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definitive lesions on the current neuroimaging techniques.[72] So far, it would be reasonable to assume that a neural connectivity impairment rather than a localized deficit is involved in the pathophysiological process of NDDs. This could also apply to CP individuals, in whom aberrant brain connectivity was demonstrated not only at the injury's site, but also in the normally-appearing perilesional cortex.[73] In addition, the associations between excessive risks of a wide range of ASD and ADHD in the CP population reveal the presence of unmeasured shared causes. Such shared causes may be of genetic or environmental nature, or a combination of the two factors. However, genetic risk factors for CP and other neurodevelopmental conditions present with considerable heterogeneity and complexity. Researchers have demonstrated a number of quite heterogeneous genetic variants and have documented causal relationships between different NDDs through advanced methods.[74–76] These findings corroborate the hypothesis of a common underlying disturbance for comorbid CP, ASD and ADHD. Further research is needed to determine the extent of genetic or neuroimaging overlap between individuals with CP and ASD and ADHD.

In conclusion, improved characterization of behavioral phenomenology and comorbidity complexes might be taken as starting point for the development of emerging methods of brain imaging and genetics, and ultimately lead to the development of optimized treatment approaches to ease the burden of children and young people with CP and their caregivers who struggle daily with these devastating conditions.

Conflict of Interest

I confirm that there is no financial or others conflict of interest that may be related to the authors.

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AFFECTIVE TEMPERAMENT IN PATIENTS WITH PERSISTENT ADHD AND SUBSTANCE USE DISORDER (COCAINE).

Caloro M, de RP, et al.

INTRODUCTION: Attention Deficit Hyperactivity Disorder (ADHD) is characterized by hyperactivity, memory disturbances, distractibility, impulsivity and/ or attention deficit. Although sideways thinking has its onset and maximum expression during childhood, it commonly occurs in adolescence and adulthood. In adolescence, in fact, there is a high risk of trauma and accidents, inability to follow the rules, learning difficulties, reckless behaviour, conduct disorders, and alcohol and substance abuse. ADHD is accompanied in 80% by psychiatric comorbidity, like Substance Use Disorder (SUD) and Bipolar Disorder (BD), which in turn negatively impact quality of life.

METHODS: We selected 128 consecutive outpatients referring to the psychiatric clinic of the Sant'Andrea Hospital, U.O.C. of Psychiatry at Sapienza University, Rome, and at the Va.R.Co. (Regional Evaluation for Cocaine) of the Rome RM1 Dependency Service (SerD) during the span of 12 months. We divided patients into three groups, i.e., patients with SUD (n = 66), with ADHD (n = 31), and comorbid SUD + ADHD (n = 31). Clinical data were collected through a semistructured interview. To evaluate persistent ADHD in adulthood, patients completed the Adult ADHD Self- Scale Report (ASRS-v1.1) and clinicians conducted the DIVA 2.0 semi-structured interview. To evaluate temperament we used the Italian TEMPS-A self-rated questionnaire.

RESULTS: Age at first substance use was significantly lower in the SUD + ADHD group compared to SUD alone, while the weekly use frequency was similar. As regards ASRS, we observed significant differences in the two diagnostic groups; in fact, in the SUD + ADHD, the mean values were higher than in the ADHD group. Moreover, the prevalent diagnosis was ADHD persistent in adult age of the combined inattention/motor-verbal hyperactivityimpulsivity subtype in the SUD + ADHD, while in the ADHD alone group, the inattentive subtype prevailed. In SUD-only patients, the most represented temperament was dysthymic, in the SUD + ADHD group hyperthymic, finally in the ADHD-only group, the most represented temperament was anxious.

CONCLUSIONS: Most adults with ADHD have another associated psychiatric disorder, which can mask ADHD; comorbidity in turn influences the clinical picture, severity, natural history, prognosis, and treatment of the disorder. SUD and mood disorders are the conditions with which ADHD is most frequently associated. SUD is widespread in the general population, and a significant proportion of people with SUD show symptoms of ADHD. In our case series, almost 30% of patients diagnosed with cocaine use had a history of ADHD since childhood and presented ADHD symptoms at the time of evaluation. Our data appear to agree with the observation that the association between SUD and ADHD would favour earlier onset of substance use. The relationship between adult ADHD and SUD is likely to be mediated by affective temperament, which would contribute to mood fluctuations and impulsive behaviours with substances abuse

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The Decrease in Human Endogenous Retrovirus-H Activity Runs in Parallel with Improvement in ADHD Symptoms in Patients Undergoing Methylphenidate Therapy

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Abstract: Increasing scientific evidence demonstrated the deregulation of human endogenous retroviruses (HERVs) expression in complex diseases, such as cancer, autoimmune, psychiatric, and neurological disorders. The dynamic regulation of HERV activity and their responsiveness to a variety of environmental stimuli designate HERVs as genetic elements that could be modulated by drugs. Methylphenidate (MPH) is widely used in the treatment of attention deficit hyperactivity disorder (ADHD). The aim of this study was to evaluate the time course of human endogenous retrovirus H (HERV-H) expression in peripheral blood mononuclear cells (PBMCs) with respect to clinical response in ADHD patients undergoing MPH therapy. A fast reduction in HERV-H activity in ADHD patients undergoing MPH therapy was observed in parallel with an improvement in clinical symptoms. Moreover, when PBMCs from drug-naïve patients were cultured in vitro, HERV-H expression increased, while no changes in the expression levels were found in ADHD patients undergoing therapy. This suggests that MPH could affect the HERV-H activity and supports the hypothesis that high expression levels of HERV-H could be considered a distinctive trait of ADHD patients.

Keywords: HERVs; HERV-H; ADHD; methylphenidate; neurodevelopmental disorders; environmental stimuli

1. Introduction

Endogenous retroviruses are genetic elements present in the genomes of all vertebrates, including humans [1,2]. They are residual of ancestral infections of germ cells by exogenous viruses, which have been integrated as proviruses into the host genome and transmitted to subsequent generations in a Mendelian fashion [3–5].

During evolution, human endogenous retroviruses (HERVs) amplified and spread throughout the entire genome by repeated events of retrotransposition and/or reinfection [6]. Their integration into the genome alters the structure and/or the function of neighboring genes [7]. Currently, about 8% of the human genome consists of endogenous retroviral sequences [8]. Many cellular mechanisms have evolved to restrict HERVs' intracellular ability to replicate and to express mRNAs and proteins, including deletion and recombination events, epigenetic mechanisms such as DNA methylation and chromatin remodeling, post-transcriptional processing, and RNA interference [9,10]. However, at least some members of the HERV groups are still transcriptionally active in a tissue-specific manner [11,12], maintaining open reading frames (ORFs) that potentially code for viral proteins [13].

HERVs have been mainly taken into account for their role in the molecular evolution of genomes [14]. However, in the last decades, several studies have underlined their involvement in the etiopathogenesis of complex diseases, such as cancer [15,16], autoimmune diseases [17], type 1 diabetes [18], and neurological and psychiatric disorders [19].

Peculiarly, numerous endogenous/exogenous factors lead to the activation of HERVs, including hormones [20], cytokines [21], cytotoxic chemicals/drugs [22,23], and interactions with microorganisms [24,25].

In addition, HERV expression can be modified by different types of drugs, such as DNA methyltransferase and histone deacetylase inhibitors [26,27], antiretroviral drugs [28–30], and neuroleptics and/or antidepressants (valproic acid, haloperidol, risperidone, clozapine) [22]. In agreement, in an earlier study using a murine model of autism we showed that valproic acid activates endogenous retroviruses expression in blood and brain tissue [31].

Among several HERV groups, copies of HERV-H have been found distributed throughout the entire human genome [32], with the majority of HERV-H elements showing large deletions in the *pol* region, lack of the entire *env* region, and rare full-length copies with intact ORFs [33]. The presence of HERV-H insertional polymorphisms in human genome supports the idea that this group is still active [34], contributing to pluripotency in human embryonic stem cells harboring binding sites of pluripotency transcription factors, such as NANOG, OCT4, and SOX2 [35]. Expression of several HERV groups, including HERV-H, has also been demonstrated in different types of cancer [36]. In patients with active multiple sclerosis, antibody reactivity towards HERV-H env and high expression of HERV-H env epitopes on B cells and monocytes have been found [37]. Among neurodevelopmental disorders, an increased transcriptional activity of HERV-H sequences has been found in patients with autism spectrum disorders (ASD) [38,39] and attention deficit hyperactivity disorder (ADHD) [40].

With an estimated prevalence of 5% in children and 2.5% in adults in the United States, ADHD is one of the most common neurodevelopmental disorders, which leads to persistent inattention, hyperactivity, and impulsivity [41]. Among a wide variety of pharmacological options available in ADHD treatment, the stimulant drug methylphenidate (MPH) is the most frequently prescribed in the treatment of children. It is believed that MPH increases the concentration of catecholamines, including dopamine and norepinephrine, in the synaptic cleft by blocking their reuptake [42,43]. MPH is thought to predominantly affect the dopaminergic system, and its action consists of blocking the reverse dopamine transporter (DAT) [44]. Magnetic resonance studies and/or positron emission tomography and genetic studies using molecular techniques have revealed that the ADHD neurobiological substratum consists of a dopaminergic system dysfunction and an alteration of cerebral networks involving the frontostriatal system [45–48]. Moreover, it has been shown that the attentional processes and the ability to inhibit impulsive responses are mediated by catecholaminergic neurotransmitters, such as dopamine and noradrenaline [49,50].

Several studies have shown that MPH is able to improve the core symptoms of ADHD [51,52], and the efficacy of pharmacological treatment has been demonstrated by improvements in a variety of social settings [53]. In our previous work, we described a high transcriptional activity of HERV-H in peripheral blood mononuclear cells (PBMCs) from 30 drug-naïve ADHD children compared to healthy controls, that correlated positively with the core symptoms of the disorder, suggesting HERV-H as a

possible new molecular signature of the disease [40]. More recently, we demonstrated a significant reduction in HERV-H expression associated with improvement in ADHD symptoms in a 16-year-old ADHD patient after six months of MPH therapy [54]. On this basis, the aim of this study was to evaluate the time course of HERV-H expression with respect to clinical response in ADHD patients undergoing MPH therapy. For this purpose, HERV-H expression was analyzed in fresh- and in-vitro-stimulated PBMCs from drug-naïve ADHD patients after 1, 8, and 24 weeks of therapy.

2. Results

In order to evaluate the time course of HERV-H expression during MPH therapy, the transcriptional activity was evaluated in fresh PBMCs from drug-naïve ADHD patients (grey box plot in Figure 1) after 1, 8, and 24 weeks of MPH therapy (green box plots).

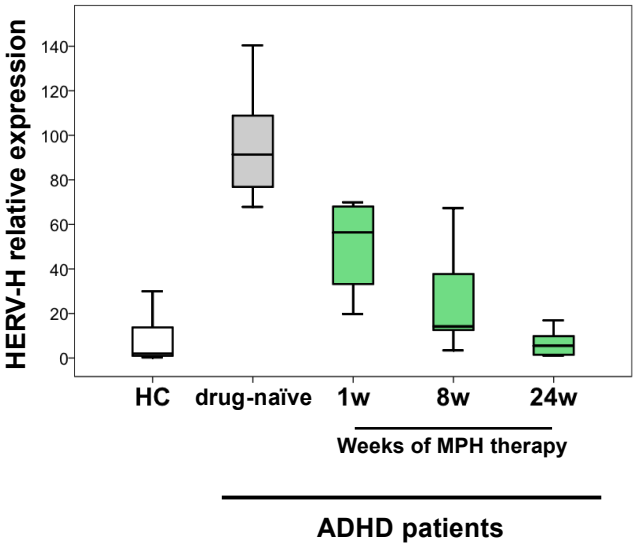

Figure 1. HERV-H expression in peripheral blood mononuclear cells (PBMCs) from attention deficit hyperactivity disorder (ADHD) patients at different times of methylphenidate (MPH) therapy. HERV-H relative expression was evaluated in fresh PBMCs from seven drug-naïve ADHD patients (grey box plot) and after 1, 8, and 24 weeks of MPH therapy (green box plots) and compared to that obtained in fresh PBMCs from 12 healthy controls (HC), age- and sex-matched (white box plot).

The transcriptional levels evaluated by real-time RT-PCR were compared to those in fresh PBMCs from age- and sex-matched healthy controls (HC) (white box plot). Before therapy, relative HERV-H expression was significantly higher in PBMCs from ADHD patients compared to HC ($p < 0.001$). As early as the first week of treatment, HERV-H relative expression significantly decreased ($p = 0.012$), and a further reduction was observed after eight weeks ($p = 0.001$) and 24 weeks ($p = 0.001$) of therapy. Notably, after 24 weeks of MPH therapy, HERV-H levels were comparable to those found in PBMCs from HC ($p = 0.659$).

The intensity and frequency of the core symptoms of ADHD were assessed with the long version of the Conners' Parents Rating Scale-Revised questionnaire (CPRS-R). The CPRS-R was conducted at eight and 24 weeks after MPH treatment as any clinical response cannot be detected before that time [55,56]. Four clinical variables were considered: the Conners' parent oppositional (CP-O), the Conners' parent inattention (CP-I), the parent hyperactivity/impulsivity (CP-H), and the Conners' parent ADHD-Index (CP-AI).

In Figure 2, panel A represents the mean values ± standard deviations (SD) of the scores recorded before and during the MPH therapy.

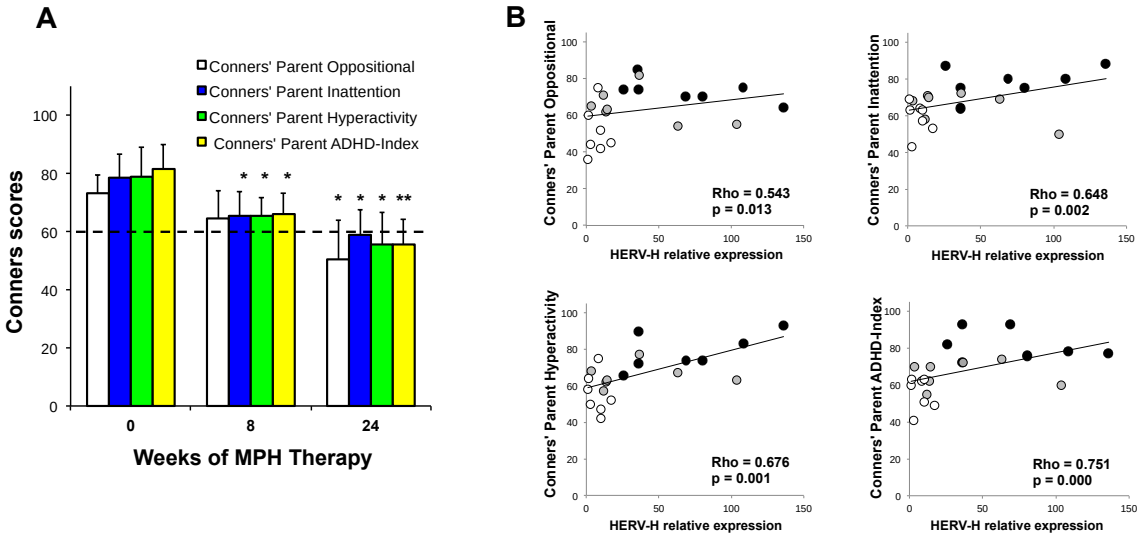

Figure 2. Clinical variables from Conners' Parents Rating Scale-Revised (CPRS-R) and human endogenous retrovirus H (HERV-H) expression. (**A**) Mean values ± standard deviations (SD) of the four clinical variables (Conners' parent oppositional, Conners' parent inattention, Conners' parent hyperactivity/impulsivity, and Conners' parent ADHD-Index) in seven ADHD patients before the beginning of MPH therapy and after eight and 24 weeks. The dashed line represents the cut-off score. Single asterisk (*) indicates p values < 0.05 and double (**) indicates p values < 0.001. (**B**) HERV-H relative expression evaluated by real-time RT-PCR analysis plotted against the clinical variables. The patients are represented according to the time points by different colors: black for patients at the beginning of therapy, grey for patients analyzed after eight weeks of therapy, and white for patients after 24 weeks of therapy. Rho and p values for Spearman correlation analysis are shown.

A general trend of reduction for all the scores was observed in response to therapy. In particular, when compared to the scores values before therapy, a statistically significant decrease in the CP-I ($p = 0.028$), CP-H ($p = 0.044$), and CP-AI ($p = 0.006$) scores was observed after eight weeks of therapy. After 24 weeks of therapy, a significant decrease in the CP-I ($p = 0.001$), CP-H ($p = 0.001$), CP-O ($p = 0.002$) and a highly significant decrease in CP-AI ($p < 0.001$) was achieved.

As the decreasing trend observed in Conners' scores (Figure 2, panel A) paralleled with HERV-H expression during therapy (Figure 1), to assess this association, we performed a Spearman correlation analysis between the expression of HERV-H and the values for the different clinical scores. The statistical analysis demonstrated a positive correlation between HERV-H relative expression and all the scores values (Figure 2, panel B): in particular CP-O (rho 0.543, $p = 0.013$), CP-I (rho 0.648, $p = 0.002$), CP-H (0.676, $p = 0.001$) and CP-AI (rho 0.751, $p < 0.001$), in ADHD patients before and during treatment.

Finally, in order to consider cell responsiveness to the in vitro stimulation with IL-2 and PHA, HERV-H transcriptional activity was assessed in cultured PBMCs from ADHD patients. To this purpose, HERV-H relative expression was evaluated by real-time RT-PCR in fresh PBMCs (T0) and after 72 h of culture in absence (not stimulated, NS) or in presence of IL-2 and PHA (stimulated, ST) before and during MPH therapy. The HERV-H relative expression was also evaluated in PBMCs from HC maintained in the same culture conditions. In PBMCs from drug-naïve ADHD patients, HERV-H expression was significantly higher after 72 h of culture in both the conditions, i.e., in presence or not of IL-2/PHA, with respect to fresh PBMCs ($p \leq 0.004$) (Figure 3, grey box plots). Conversely, when PBMCs from ADHD patients in therapy were cultured in vitro, no differences in HERV-H expression were found, either in presence or not of IL-2/PHA, at all the observation times (1, 8, and 24 weeks) after the beginning of therapy (Figure 3, green box plots). Likewise, the PBMCs from HC did not show any changes in HERV-H expression when maintained in culture (Figure 3, white box plots).

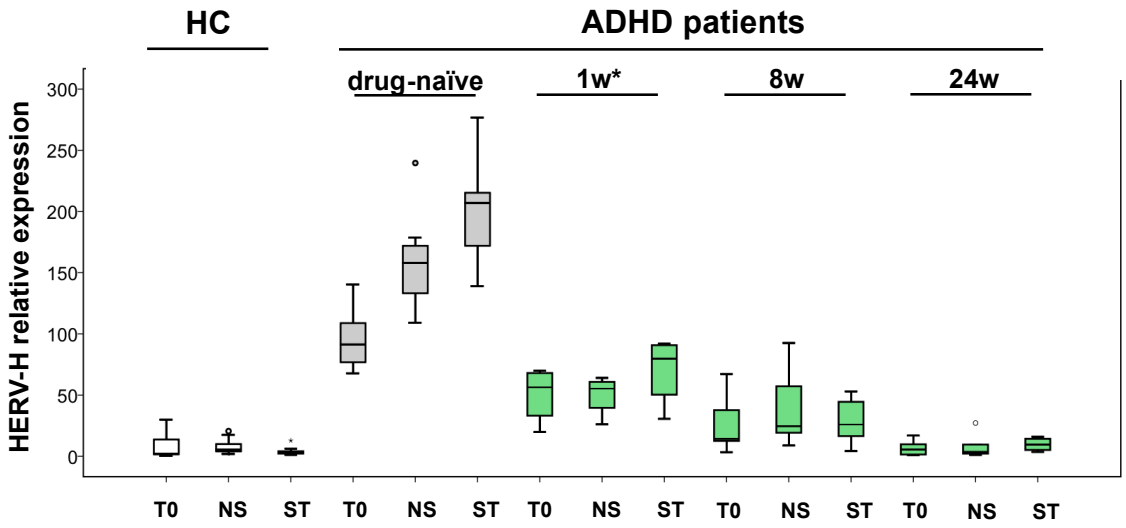

Figure 3. HERV-H expression in PBMCs from ADHD patients after in vitro culture. The relative expression of HERV-H was evaluated in fresh PBMCs (T0) and after 72 h in culture in absence (not stimulated, NS) or in presence of IL-2 and PHA (stimulated, ST). The levels were measured in seven drug-naïve ADHD patients (grey box plots) and during MPH therapy (green box plots) at 1, 8, and 24 weeks. The results were compared to those obtained in PBMCs from 12 healthy controls (HC) (white box plots), maintained in the same culture conditions (* weeks of therapy).

3. Discussion

Scientific reports support the involvement of HERV genetic elements in many complex human diseases, including neurological and psychiatric disorders [19]. Evidence of an association between HERV expression and neurodevelopmental diseases had also emerged from our previous published studies in which we demonstrated an increase in HERV-H transcriptional activity in PBMCs from ASD [38,39] and drug-naïve ADHD patients [40] compared to healthy controls, suggesting that HERVs could play a role in the etiology of these complex diseases. Moreover, HERV-H transcriptional activity correlated with inattention and hyperactivity symptoms in ADHD patients [40]. Interestingly, we had also described the reduction in HERV-H expression and the significant improvement in ADHD symptoms in PBMCs from an ADHD patient after 24 weeks of MPH treatment [54]. In agreement with our previous findings, the present study showed that the HERV-H expression was higher in drug-naïve ADHD patients compared to HC and was significantly reduced after 24 weeks of MPH treatment. These data further support our hypothesis that the transcriptional activation of this specific retroviral element might represent a molecular signature of the disorder.

Herein, we analyzed the time-course of HERV-H transcriptional activity in PBMCs from ADHD patients after 1, 8, and 24 weeks of MPH therapy, demonstrating that the expression of HERV-H significantly decreased after only one week. Interestingly, at this time of observation, no significant improvement of clinical symptoms by MPH treatment can be achieved [55,56]. Subsequent to the fast downregulation of HERV-H expression, a further decreasing trend was confirmed throughout the 24 weeks of therapy. Notably, at the endpoint of observation, HERV-H expression in treated ADHD patients reached levels comparable to those found in HC. The improvement of the clinical signs, as evidenced by the reduction in the CPRS-R scores during MPH treatment, proceeded in parallel with the decrease in HERV-H expression, and the statistical analysis demonstrated the correlation between the CPRS-R scores and HERV-H expression levels. All these data support the hypothesis that the deregulation of HERV-H expression is closely associated with the disorder.

Treatment with neuroleptics and/or antidepressants induces epigenetic modifications influencing gene expression [22,57,58]. By exploring the mechanism of action of MPH, the modulation of the expression of several genes has been demonstrated in animal models as well as in ADHD patients. In the striatum of MPH-treated rats, more than 700 genes were found upregulated [59]. These genes are involved

in migration of immature neural/glial cells and/or growth of novel axons, active axonal myelination, upregulation of mature processes, and more enduring enhancement of neurobehavioral plasticity [59]. Recently, long non-coding RNAs (lncRNAs) signature in the prefrontal cortex of MPH-exposed rats was identified [60] and among the lncRNAs modulated by MPH, the MRAK081997 positively correlated with the dihydrofolatereductase gene, which may be involved in axon regeneration in rodents through DNA methylation [61]. Finally, a microarray analysis of patient-derived lymphoblastoid cells revealed that several genes were regulated by MPH treatment [62].

The responsiveness to environmental triggers designates HERVs as genetic elements that could be modulated by MPH treatment. Our thought is supported by evidence that HERV activity is modulated in response to a variety of environmental stimuli, including epigenetic drugs [63]. On the other hand, the HERV sequences spread in the genome may regulate the expression of neighboring genes [7,64]. Particularly, HERV-H, acting as promoter enhancer of nearby genes and functioning as lncRNAs, plays an important role in the pluripotency of human cells [35], and the aberrant HERV-H expression in embryonic stem cells and induced pluripotent stem cells determines the differentiation-defective phenotype in neural lineage [65–67]. We recently demonstrated in a valproic acid-induced mouse model of ASD that high expression of different murine ERVs and inflammatory mediators was related to autistic-like traits. Notably, we showed that the high levels of ERVs expression identified in brain were also revealed in blood tissue from the same mice, supporting the view that altered ERVs expression in the blood could be a reliable biomarker for brain atypical development [31].

Finally, herein we reported an increase in HERV-H expression in response to culture or stimulation in vitro (with IL-2 and PHA) of PBMCs from drug-naïve ADHD patients, which was in line with our previous findings in ASD patients [38]. Intriguingly, this intrinsic predisposition to express HERV-H, observed in PBMCs of drug-naïve patients, was lost early after MPH therapy, suggesting that the drug could directly or indirectly influence HERV-H activity. In addition, no changes in expression levels of HERV-H were observed in PBMCs from HC after culture or stimulation in vitro, supporting the hypothesis that the predisposition to express HERV-H could be considered as a distinctive trait of drug-naïve ADHD patients.

Although the present study provides preliminary data, we have highlighted for the first time the fast decrease in HERV-H activity after only one week of MPH treatment and how the further activity reduction runs in parallel with improvement in symptoms in ADHD patients undergoing therapy. MPH is the most frequently used drug in ADHD treatment, showing several favorable effects on symptoms; however, its use is associated with serious and nonserious adverse events, both in children and adolescents, with about 30% of patients not responding to the therapy [68–70]. In this context, it may be important to identify patients who are most susceptible to adverse events or are nonresponders in order to select patients to whom MPH treatment could exert major benefits. Future well-designed prospective studies will greatly help to candidate HERV-H as a predictive marker of the response to MPH therapy.

4. Materials and Methods

4.1. Participants

The study included 7 drug-naive ADHD patients, all males and aged between 7 and 17 years (median age 13) with IQ > 80, recruited among those attending the Child Neurology and Psychiatry Unit of "Tor Vergata" University Hospital of Rome (Table 1).

Table 1. Demographic information of individuals included in the study.

	ADHD Patients (n = 7)	Healthy Controls (n = 12)	p Value
Gender	males	males	1
Median age (range) years	13 (7–17)	11 (7–17)	0.249

The patients were compared to 12 healthy controls (HC) of the same sex, aged between 7 and 17 years (median age 11), attending the outpatient facilities of the same hospital for routine control visits. None of them had a history of neurological or psychiatric disorders, learning disability, or infectious diseases.

All participants were of Caucasian origin without significant economic, social, and cultural differences.

At the time of onset of the study, no participants were taking medication known to affect the central nervous system.

The study was carried out following the rules of the Declaration of Helsinki of 1975 (revised in 2008); the University Hospital of "Tor Vergata" Ethics Committee approved the study, and all examinations were performed after receiving written informed consent of the parents.

4.2. Clinical Assessment

The diagnosis of ADHD was based on clinical assessment, observations of children, and interviews with parents and children, which were carried out by an experienced child psychiatrist. To make the diagnosis of ADHD, the long version of the Conners' Parents Rating Scale-Revised (CPRS-R) was used, including four clinical variables: the Conners' parent oppositional (CP-O), the Conners' parent inattention (CP-I), the Conner' parent hyperactivity/impulsivity (CP-H), and the Conners' parent ADHD-Index (CP-AI) [71]. The CPRS-R was also conducted after eight and 24 weeks of MPH treatment, to evaluate the clinical response. The interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) was used to exclude other psychiatric comorbidities in the ADHD group [72].

4.3. Pharmacological Intervention

The planned treating schedule required the administration of MPH at the dose of 0.3 mg/kg/die for 1 week to subsequently reach the entire dose (0.5 ÷ 0.8 mg/kg/die). The immediate release formulation was used during the MPH titration phase. Once the absence of adverse effects was tested, the patients were treated with modified-release MPH because it allows once-daily dosing and therefore guarantees better compliance with the drug's intake.

4.4. Samples Preparation and RT-PCR Analysis

PBMCs were separated by density gradient centrifugation (Lympholyte-H, Merck Darmstadt, Germany) from both ADHD patients and healthy controls. PBMCs were collected immediately after separation (fresh PBMCs) or cultured in RPMI 1640 medium (Merck, Darmstadt, Germany) supplemented with 12% fetal bovine serum (Life Technologies, Carlsbad, CA, USA), 2 mM glutamine (Merck, Darmstadt, Germany), 50 U/mL penicillin, 50 U/mL streptomycin (Merck, Darmstadt, Germany) at 37 °C under 5% CO2, without any stimulation (condition termed "not stimulated", NS) or in presence of human recombinant interleukin-2 (IL-2), 20 U/mL (Chiron corporation, Emeryville, CA, USA) and T-lymphocyte-specific mitogen phytohemagglutinin (PHA), 2 µg/mL (Merck, Darmstadt, Germany) (condition called "stimulated", ST).

HERV-H activity was evaluated both in fresh and cultured PBMCs of drug-naïve patients and after 1, 8, and 24 weeks of MPH therapy. The expression levels of the *env* sequence from HERV-H were quantitatively assessed by real-time RT-PCR, as previously described [38]. Briefly, 250 ng of DNase-treated RNA from PBMCs of ADHD patients and HC subjects were reverse-transcribed and amplified using primers specific for HERV-H and the housekeeping gene glucoronidase beta (*GUSB*) using SYBR Green chemistry. Each experiment was completed with a melting curve analysis to confirm the specificity of amplification and the relative expression was calculated as $2^{-[\Delta Ct(sample) - \Delta Ct(calibrator)]}$, where Δ Ct(sample) = [Ct(HERV-H *env*) − Ct(*GUSB*)],and Δ Ct(calibrator) was the mean of ΔCT of data obtained from fresh PBMCs of HC individuals. Real-time RT-PCR results were represented by box plots.

4.5. Statistical Analysis

The Mann–Whitney test was used to compare HERV-H relative expression between ADHD and HC groups, within ADHD patients at different times of therapy, and in all the conditions analyzed. The ANOVA analysis of variance and post-hoc Bonferroni tests were used to determine changes in Conners' parent scores (CP-O, CP-I, CP-H, and CP-AI) during the treatment. To determine any correlation between HERV-H relative expression and core symptoms (or scores value), the Spearman's rho correlation coefficient was calculated. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) software version 23.0 (SPSS Inc., Chicago, IL, USA). Statistical significant comparisons were considered when $p < 0.050$.

5. Conclusions

Growing evidence supports the role of HERVs in the onset and/or progression of several complex diseases, such as cancer, autoimmunity, neurological, and psychiatric disorders. Spatial and temporal fine-tuning mechanisms regulate HERV expression, and numerous endogenous/exogenous factors influence their activity, as the main common feature of HERVs is the responsiveness to environmental stimuli. Several drugs seem to affect HERV expression, candidating HERVs as predictive markers for the response to therapy, especially for those disorders where none of the available clinical parameters can discriminate a non-response as a priori or an early response after the beginning of therapy.

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The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders

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ABSTRACT

Objective: The aim of our study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are responders and non-responders to long-term treatment with Atomoxetine at baseline and after 6 and 12 months of treatment. Patients with attention deficit hyperactivity disorder (ADHD) received atomoxetine titrated, over 7 days, from 0.5 to 1.2 mg/kg/day. QEEG and Swanson, Nolan, and Pelham–IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy.

Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked ear-lobes. Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values.

Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values.

Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity that interferes with functioning or development and causes impairment in multiple settings: home, school and work. Population surveys suggest that in most cultures ADHD occurs in about 5% of children (Szatmari, 1992.) In general ADHD is more frequent in males than females, with an approximate 2:1 ratio in children. Its course is chronic in 30–50% of the affected children (American Psychiatry Association, DSM-V, 2013).

Extensive neuroimaging studies (QEEG, VARETA, ERPs, PET, fMRI) have demonstrated that during the execution of cognitive tasks, children with ADHD show a pattern of hypoactivation of the prefrontal lobes and of the striatal regions (di Michele et al., 2005; Lou et al., 1984, 1989; Rubia et al., 1999, 2001, 2011; Hastings and Barkley, 1978; Klorman, 1992; Taylor, 1986). Neuropsychological studies have also shown the impairment of several executive functions (sustained, focused and divided attention, working memory, response inhibition, time perception, flexibility, programming and delayed reward response). These executive functions are located in the frontal and prefrontal lobes and in particular in the dorso-lateral prefrontal cortex (Barkley, 1977a, 1997b; Barkley et al., 1992; Goodyear and Hynd, 1992). Neuropharmacological studies both in humans and animals have demonstrated that these executive functions are mediated by noradrenergic and dopaminergic neurotransmitters, adding more evidence of a probable deficit of these circuits in ADHD (Arnsten and Li, 2005; Hunt et al., 1988; Rapaport and Zametkin, 1988; Shaywitz

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and Shaywitz, 1984; Shaywitz et al., 1983; Zametkin and Rapoport, 1986). Furthermore, Castellanos et al. (1994, 1996) have shown that in ADHD adults there is an evident reduction of the volume of some cerebral areas, including the right prefrontal areas, the nucleus caudatus, the globus pallidus and the cerebellum. It has been suggested that ADHD children show a maturational lag in the development of these cortical regions and their interconnections (Barry et al., 2003, 2009b). This maturational lag has been associated with elevated slow wave activity and deficiencies of fast wave. Elevated high amplitude theta with deficiencies of beta activity was associated with hypoarousal and excess beta activity was tentatively interpreted as hyperarousal. This profile has been found primarily in children with the combined type of ADHD (Chabot et al., 1999; Clarke et al., 2001d). All these studies used very restrictive ADHD inclusion criteria, with children with comorbidities being excluded (Clarke et al., 1998, 2001a, 2001c, 2001d). However, in line with recent works that links arousal abnormalities with global alpha activity (Barry et al., 2009b), the hyperarousal hypothesis as the underlying CNS abnormality was not confirmed (Clarke et al., 2011). On the other hand, Jaworska et al. (2013) examining QEEG relationships between anger and non-angry adults with ADHD noted increased beta 1 associated with anger and it was interpreted as modest resting cortical hyperarousal.

Recent evidence indicates that quantitative Electroencephalogram (QEEG) is a powerful tool in pharmaco-EEG applications. The identification of treatment responsive QEEG subtypes have been described in depression (Leuchter et al., 2009a, 2009b), obsessive compulsive disorder (Prichep et al., 1993; Hansen et al., 2003) and schizophrenia (John et al., 2007), suggesting that understanding of the underlying neurophysiology of the patient can contribute significantly to treatment optimization. QEEG has been shown to distinguish between ADHD responders (R) and non-responders (NR) to stimulant medication with sensitivity levels that fell between 68.7% and 81% with response to stimulants related to ADHD subtypes based upon QEEG profile differences (di Michele et al., 2005; Ogrim et al., 2014). Barry et al. (2007, 2009a) investigated the effects of a single dose of a selective inhibitor of norepinephrine transporters (SNRI), atomoxetine (ATX), on the electroencephalogram (EEG) and performance of children with ADHD. After 1 h ATX produced significant global increases in absolute and relative beta, with several topographic changes in other bands. This was accompanied by a significant reduction in omission errors on a Continuous Performance Task. The authors concluded that SNRIs can produce substantial normalization of the ADHD QEEG profile, together with behavioural performance improvements.

It has been previously shown that atomoxetine increased extracellular concentrations of norepinephrine (NE) and dopamine (DA) in prefrontal cortex (Viggiano et al., 2004). Furthermore, chronic administration of atomoxetine for 21 days also increased NA and DA, but not 5-HT, levels in the prefrontal cortex. Acute and chronic atomoxetine increased the expression of c-Fos, a neuronal activity marker in the prefrontal cortex, but not in the striatum. These results suggest that acute and chronic administration of ATX selectively activate the prefrontal catecholamine systems in mice (Koda et al., 2010).

At the moment, in Italy, the drugs available and currently being used for the pharmacotherapy of ADHD are: methylphenidate (MPH) and atomoxetine. We are not aware of studies that measured the effect on the QEEG of long-term treatment of ATX in children with ADHD. In the light of personalized medicine and in order to reduce this gap, the aim of this study is to examine whether QEEG subtypes are related to treatment response to Atomoxetine in ADHD. We hypothesize: 1. at baseline both R and NR will have QEEG absolute power findings consistent with those reported in the literature to include increased power in delta, theta or alpha especially in frontal and anterior temporal regions (Chabot et al., 2001; Barry et al., 2003, 2009b); 2. absolute power increases at baseline will be greater in NR than in R especially in the delta and theta frequency bands; 3. increased absolute power findings in R will decrease as a function of treatment with atomoxetine, whereas, increased absolute power in NR will not change as a function of treatment with atomoxetine; 4. QEEG source localization using VARETA will reveal more widespread abnormal findings in NR than R when compared to the normal population of children; and 5. after 12 months of treatment with atomoxetine the R will show decreased abnormal activity, whereas, NR will remain at baseline levels.

2. Material and methods

This study was conducted by recruiting consecutive patients from the ADHD Centre of the Child and Adolescent Neuropsychiatry Department of Rho hospital. The following protocol was approved by the Ethical Committee of the hospital.

2.1. Clinical protocol

2.1.1. Inclusion criteria

Patients between 6 and 16 years of age were included in the study if they met all of the following criteria: patients met DSM-IV diagnostic criteria for ADHD (any subtype), scored at least 1.5 standard deviations above the age norm for their diagnostic subtype using published norms for the Swanson, Nolan, and Pelham–IV Questionnaire (SNAP-IV) (Swanson, 1992) subscale scores, and scored above one of the given cut-offs (T-score > 55) of the Conners subscale based on age and gender (Conners, 1997). Laboratory results, including serum chemistries, hematology, and urine analysis, showed no clinically significant abnormalities. An ECG was performed to exclude cardiac diseases at the baseline/screening visit.

2.1.2. Exclusion criteria

Patients were excluded from the study if they met any of the following criteria: presence of documented psychiatric disorders of the parents, weight <20 kg at baseline visit, a documented history of Bipolar type I or II disorder, history of psychosis or pervasive developmental disorder, seizure disorder, head injury with loss of consciousness or concussion, migraine, neurological/systemic medical disease (e.g.: lupus, diabetes) or with history of stroke or arterious-venus malformation or brain surgery. Comorbid non-psychotic psychiatric disorders (not more than two) were not an exclusion criteria but were documented. Functional comorbidities such as visual or auditory processing problems were not an exclusion criteria, but were documented with above IQ testing. Additional exclusion criteria were: serious suicidal risk as assessed by the investigator, history of alcohol or drug abuse within the past 3 months or currently using alcohol or drugs, current or past history of hypertension, narrow angle (Angle-Closure) glaucoma, uncontrolled hyperthyroidism or hypothyroidism, use of monoamine oxidase inhibitors, pregnant, breastfeeding young women and sexually active who do not use a medically acceptable method of contraception.

2.2. Phase 1 protocol

The study consisted of two phases. During phase 1 the screening and assessment were conducted according to the following protocol. Family history was obtained by clinical interviewing one or both parents. The patients were diagnosed as children or adolescents with ADHD according to the DSM-IV. At the first visit, after explaining to the patient and the parent/caretaker the purpose and the procedures of the study, informed consent was obtained from both parents, adolescents and children. Adequate time to consider the information was provided. In the assessment phase the following information was obtained: demographics, medical and psychiatric history, previous and concomitant medications, physical and neurological examination, laboratory samples, Electrocardiogram (ECG), QEEG, Amsterdam Neuropsychological Test (ANT, de Sonneville, 2014) a battery to test executive functions

and attention, SNAP-IV ADHD scale revised (SNAP IV - Swanson, 1992; Gaub and Carlson, 1997), Conners' rating scale-R for teachers (CTRS-S - Conners, 1997), Clinical Global Impressions–ADHD-Severity (CGI-ADHD-S, Guy, 1976). Children Depression Rating Scale, derived from the Hamilton Rating Scale for Depression (HAM-D), Paediatric Anxiety Rating Scale (PARS) were used to exclude mood and anxiety disorders. All patients were free of any medications according to the following guidelines for medications washouts: patients who were taking any medication that had a half-life >24 h had a washout equal to a minimum of 5 half-lives of the parent compound and any active metabolite of the parent compound prior to the second visit; patients who were taking any health food supplements that in the investigator's opinion had a central nervous system activity (for example, melatonin) had a washout equal to a minimum of 5 half-lives of that supplement prior to the second visit. If the half-life of the supplement was unknown, then the patients had a 28-day washout; no patient used monoamine oxidase inhibitors (MAOIs) during the 2 weeks (14 days) prior the first visit.

2.3. Phase 2 protocol

The second phase consisted of follow-up visits after the beginning of atomoxetine therapy, conducted at 3, 6 and 12 months. The tests administered in every subsequent visit were the SNAP-VI ADHD scale, CTRS-S, CGI, ANT and QEEG. We report only the QEEG and the SNAP results for brevity.

2.4. Atomoxetine treatment

The atomoxetine drug was titrated, in 7 days, from 0.5 mg/kg/day (dose ranging from 0.5 to 0.8 mg/kg/day) to the target dose of 1.2 mg/kg/day (range from 0.8 to 1.2 mg/kg/day). The total daily dose was administered once daily in the morning. If patients while taking atomoxetine at the target dose developed intolerable side effects, but were gaining a therapeutic benefit regarding their ADHD symptoms, the investigator administered atomoxetine in 2 divided doses (in the morning and in the evening). The dosing regimen was chosen on the basis of the research literature (Weiss et al., 2005; Kelsey et al., 2004; Michelson et al., 2002).

Safety assessment was monitored throughout the study by a qualified physician who reviewed every patient's safety data with the patient and/or parent at each visit. Adverse events were collected by open-ended discussion at all visits. Subject compliance was assessed at each visit by direct questioning. Patients were asked to return both used (including empty) and unused bottles distributed on the previous visit. No concomitant medications were present during ATX treatment.

2.5. Neurophysiologic assessment

2.5.1. EEG data acquisition

Twenty minutes of eyes closed resting EEG were recorded from 19 electrodes, using Electro-caps which place the sensors in accordance with the International 10/20 Electrode Placement System, referenced to linked earlobes. A differential eye channel (diagonally placed above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were below 5000 Ω. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points). All EEG data was collected on the same digital system compatible with the demands of the protocol in order to achieve amplifier equivalence. A standard calibration system was provided with the digital EEG machine. Data were sampled at a rate of 256 Hz with 12 bit resolution. In order to avoid drowsiness during EEG recordings and to have similar conditions throughout the different sessions, all the patients were recorded in the morning, instructed to keep their eyes closed and stay awake. Patients were monitored with a closed circuit television system, throughout EEG recording. EEG was recorded before therapy (baseline) and after 3, 6 and 12 months of therapy.

2.6. EEG data analysis

The raw EEG data were visually edited by trained EEG technologists, to identify and eliminate biological (e.g., muscle movement, EMG) and non-biological (e.g., electrical noise in the room) artifacts. This was augmented by a computerized artifact detection algorithm. Two minutes artifact-free data, collected from the beginning of the EEG recording were then submitted to frequency analysis (FFT) and features log transformed to obtain Gaussianity (John et al., 1980; Gasser et al., 1982). Absolute power values for each electrode position and for the delta (1.2–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25.0 Hz), frequency bands are reported in this paper. All absolute power values were Z-transformed relative to the difference between normative values and the values obtained from each individual child (John et al., 1983, 1988). Significant test re-test reliability for these measures has been demonstrated (John et al., 1983; Kondacs and Szabo, 1999).

2.7. QEEG source analysis

Two minutes of artifact-free EEG was also submitted for computation of source localization using Variable Resolution Electrical Tomography (VARETA) (Bosch-Bayard et al., 2001). With this method, very narrow band (VNB) spectra were computed using FFT with bins 0.39 Hz wide from 1.5–20 Hz, for every electrode derivation. Abnormalities in these data were identified using Z-spectra computed relative to normative values. The scalp electrode positions were placed in spatial distribution with a probabilistic MRI Brain Atlas (Evans et al., 1994). The mathematically most probable underlying sources of QEEG abnormalities recorded on the scalp were then superimposed upon MRI slices from that Atlas, and the values computed for each frequency in every voxel were encoded using a color palette with hues proportional to the standard- or Z-scores of deviations from expected normative values. The significance levels of the images take into consideration the large number of measurements made, using the correction introduced by Worsley et al. (1995). The anatomical accuracy of the functional QEEG source localization obtained by VARETA and other QEEG-based source localization methods has been repeatedly confirmed by co-registration with other brain imaging modalities e.g. functional magnetic resonance, fMRI (Mulert et al., 2004), positron emission tomography, PET (Zumsteg et al., 2005; Bolwig et al., 2007), and computerized tomography (Prichep et al., 2001).

2.8. Subjects

After screening and assessment, 61 children and adolescents, 52 male (85.25%) and 9 female (14.75%), 7–16 years of age (mean age 10.36 s.d. 2.85) with ADHD with or without co-morbidities, who meet DSM-IV criteria for ADHD, agreed to participate in the experiment. 41 (69.49%) belonged to ADHD combined type, 16 (27.12%) to the inattentive type and 2 (3.39%) to the hyperactive-impulsive type. The subjects were of normal intelligence with a total IQ of 101.09 s.d. 14.29, verbal IQ 101.27 s.d. 15.66, and performance IQ 99.17 s.d. 13.5 (WISC-III). Table 1 reports the presence of comorbidities of the total sample.

A total of 37 patients (60.6%), mean age 10.29 (s.d. 2.30) continued therapy for 6 and 12 months (33 M and 4 F). Of these 37 patients, 27 subjects belonged to ADHD_Combined type, 9 subjects to ADHD_inattentive type and 1 subject to ADHD_hyperactive type. 24 subjects (39.4%) discontinued ATX: 8 for side effects (tachyarrhythmia, increased blood pressure, syncope, allergic reaction, increased irritability) of which 2 were switched to MPH; 7 dropped out for low compliance of parents.; 8 for absence of positive outcome (2 subjects were switched to MPH); and 1 for “early” positive outcome.

Table 1
Reports the presence of comorbidities and percentage in the total sample of children with ADHD.

Comorbidity	Patients	%
Oppositional Defiant Disorder	23	37.70%
Specific learning disorder	15	24.59%
Anxiety disorder	4	6.56%
Conduct disorder	2	3.28%
Language disorder	2	3.28%
Generalized learning disorder	1	1.64%
Conduct disorder + anxiety disorder	1	1.64%
Language disorder + anxiety disorder	1	1.64%
Tics	1	1.64%
None	11	18.03%
Total	61	100.00%

2.9. Statistical analysis

Preliminary statistical analyses were conducted on those 37 patients for whom data was available 6 months after the initiation of therapy. These subjects were classified as responders (R), non-responders (NR) or partial responders (PR) based upon an increase/decrease of SNAP Z scores values between baseline and each of the time points (treatment). Subjects with a 30% increase or greater in SNAP scores were classified as responders. Subjects with a decrease of 30% or more in SNAP scores were called Non-Responders. All others were classified as partial responders. Age, SNAP-Inattentive, SNAP-Hyperactivity, SNAP-Combined and SNAP-Oppositional scores for R, NR, and PR patients at baseline, 3, 6 and 12 months were submitted to two way analysis of variance (ANOVA) with levels corresponding to response type (R, NR, and PR) and time (baseline, 3, 6, 12 months). In order to reduce the number of statistical comparisons and to simplify the QEEG findings all reported analyses included only the R and NR patient groups. The only QEEG variables used to compare responders and non-responders were Z-score absolute power from 19 monopolar regions for the delta, theta, alpha, and beta frequency bands. Separate ANOVAs were conducted for the differences between responders and non-responders for each electrode location and each frequency band. The $p < 0.005$ criteria were used to determine statistical significance in order to account for the use of multiple ANOVAs (19 electrodes by 4 frequency bands). The QEEG results are displayed as a set of maps color coded by the F values corresponding to the differences between the 2 groups.

The same type of analysis was conducted within each group only for R and NR, between BL and 3 months between BL and 6 months, BL and 12 months, separately. The results are displayed as a set of maps color coded by the F value of the significance of the differences between the 2 groups.

3. Results

3.1. Atomoxetine

Atomoxetine had a positive effect on 21 subjects (55.6%), of which 11 (27.8%) were classified as responders and 10 (27.8%) as partial responders. 16 subjects, (44.4%) were defined as non-responders according to the criteria defined above. Table 2 shows the distribution of the comorbidities of children with ADHD divided in R, PR and NR. As seen in the group of NR there is a higher rate of Oppositional Defiant Disorder (ODD) compared to the other 2 groups. The other more frequent comorbidity, specific learning disorder was nearly equally distributed in all the 3 groups.

3.2. Demographic and SNAP scores

The ages of the R, NR, and PR groups did not differ from one another ($F = 1.1$, $p = 0.34$). Changes in SNAP scores varied as a function of treatment interval across the R, NR, and PR groups (Table 3). At baseline there were no significant differences between the three groups for any SNAP score. Children in the NR group showed no changes for any SNAP score across treatment intervals. Children in the PR group showed decreased inattention scores after 3, 6, and 12 months of treatment although hyperactivity, combined, and oppositional SNAP scores remained at baseline levels across the 12 months of treatment. Children classified as responders showed decreased SNAP inattention, hyperactivity, combined, and oppositional SNAP scores after 3 months and these changes remained present after 6 and 12 months of treatment.

Table 2
Shows the distribution of the comorbidities of the 37 children with ADHD divided in responders (R), partial responders (PR) and non-responders (NR) for whom data was available after the third month of therapy.

Comorbidity	R	PR	NR
Oppositive Defiant Disorder	3	4	8
Specific learning disorder	4	3	2
Anxiety disorder	1	–	2
Conduct disorder	–	–	1
Language disorder	1	–	–
Generalized learning disorder	–	–	1
Conduct disorder + anxiety disorder	–	–	–
Language disorder + anxiety disorder	1	–	–
Tics + Oppositive Defiant Disorder	1	–	–
None	–	3	2
Total	11	10	16

3.3. QEEG

Fig. 1 presents color coded head maps of Z-absolute power (compared to database of normal children) separately for the R and NR groups at baseline, 6 months, and 12 months following treatment. At baseline responders showed increased frontal/anterior temporal alpha and elevated frontal/anterior temporal delta and theta in comparison to the normal population. Non-responders showed increased power across all frequency bands that were greatest in anterior and central regions. Across the 12 month treatment interval these increased absolute power values decreased in the responders (moved towards normal values), whereas, across these same time intervals the increased absolute power levels remained constant for the non-responders. Fig. 2 shows color coded head maps of the significance of the difference between R and NR children at each electrode location and each frequency band at baseline, 6 months and 12 months after treatment. It should

Table 3
Reports the Anova results at baseline (BL), 6 and 12 months for non-responders and responders of the SNAP-Combined (SNAP-C), SNAP-Hyperactivity (SNAP-H), SNAP-Inattention (SNAP-I) and SNAP-Opposition (SNAP-O) scores, respectively.

	Non-responders		Responders			
	Mean	SD	Mean	SD	F-value	p-Value
SNAP-C						
BL	2.17	0.74	2.51	1.2	0.64	0.43
6 months	2.46	0.54	1.21	0.76	17.9	0.0003
12 months	2.32	1.02	1.20	1.1	3.41	0.08
SNAP-H						
BL	2.15	0.90	2.19	1.5	0.01	0.94
6 months	2.55	0.75	1.04	0.8	22.1	0.0001
12 months	2.10	1.2	0.71	0.9	6.8	0.02
SNAP-I						
BL	2.05	0.40	2.54	1.0	1.4	0.25
6 months	2.50	0.50	1.20	0.8	6.9	0.01
12 months	2.21	0.99	1.51	1.3	1.9	0.32
SNAP-O						
BL	1.56	0.43	1.42	0.54	0.35	0.56
6 months	1.52	0.37	1.07	0.37	7.7	0.01
12 months	2.10	0.29	0.99	0.41	25.0	0.0001

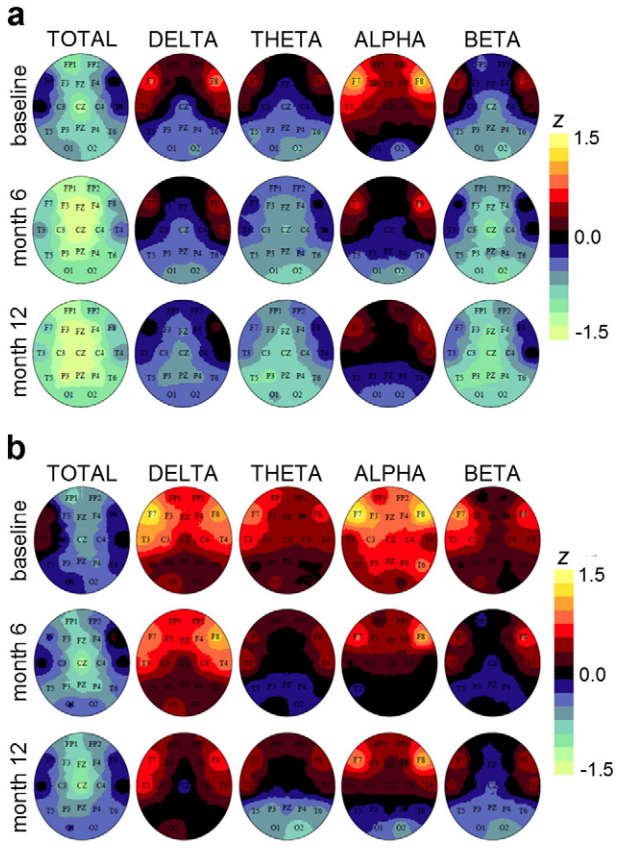

Fig. 1. Shows the average Z-score maps of absolute power for the delta, theta, alpha, and beta frequency bands of the responders and non-responders at baseline, 6 months and 12 months. Z-scores are relative to the normal population with statistical significance at the $p < 0.01$ level equal to a Z-score of 1.96/Square root of N.

be noted that at baseline significant R vs. NR differences involved mainly posterior regions but that by 6 and 12 months were generalized across all locations. Fig. 3 shows color coded head maps of the significance of the difference between baseline and 6 and 12 months after treatment separately for responders and non-responders. Responders showed significant decreases in power for all frequency bands at 6 and 12 months that was greatest in anterior, central, and temporal regions (regions where baseline abnormal findings were present) with no changes in posterior regions. Non-responders showed no changes in

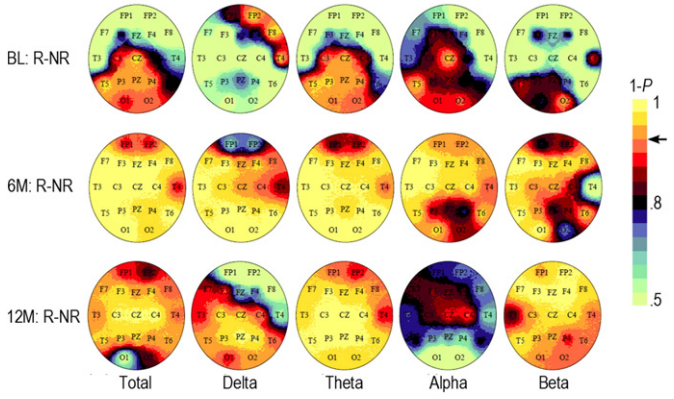

Fig. 2. Shows color coded head maps of the significance of absolute power difference between responders and non-responders at baseline (BL), 6 months (6 M) and 12 months (12 M). The black arrow indicates significance at the $p < 0.005$ level.

absolute power levels after 6 and 12 months of treatment compared to baseline values. Thus, treatment with ATX reduced the frontal QEEG abnormality present in the responders and had no effect upon the QEEG of the non-responders.

3.4. VARETA

Fig. 4a presents VARETA images for the responders at an average single Hertz frequency band of 11.7 Hz, the frequency band with the highest average Z-score relative to the normal population (1.5 to 30 Hz in 0.39 Hz steps). The responders at baseline showed increased activation relative to the normal population in the right middle, superior, and inferior temporal gyrus, in the right insular, in the pre and post central gyrus, in the supramarginal gyrus, in the mid frontal gyrus, in the posterior cingulate region, in the angular gyrus, in the medial frontal gyrus, and the superior parietal lobule. Fig. 4b shows the same VARETA images 12 months after treatment. Abnormal activation has decreased dramatically with significant findings seen only in the lateral, medial, and fronto-orbital gyrus, in the medial frontal gyrus, and the anterior cingulate region. Fig. 5a presents VARETA images at BL for the NR's at 15.2 Hz the frequency value with the greatest average increased Z-score relative to the normal population. Increased activity can be seen in right medial, inferior, and superior temporal gyrus, in the pre and post central gyrus, in the left inferior frontal gyrus, the supramarginal gyrus, in the left medial frontal gyrus, and in the angular gyrus. Decreased activation is present in the latero-medial fronto-orbital gyrus, superior and medial frontal gyrus the anterior cingulate region, the occipito-temporal gyrus and the cerebellum. Fig. 5b shows the same VARETA images 12 months after treatment. It can be seen that increased activity remains present in all areas that showed abnormal activation at baseline. The reduced activation is still present in the occipito-temporal gyrus and the cerebellum.

4. Discussion

In our study Atomoxetine had a positive effect on 21 subjects (55.6%), of which 11 (27.8%) were classified as responders and 10 (27.8%) showed a partial remission of ADHD symptoms (Partial Responders). Responders showed remission of all SNAP symptoms, whereas, the partial responders only showed a decrease in SNAP inattention. These results are in agreement with previous studies reporting that the effect size for atomoxetine treatment in ADHD patients ranges from 0.63 to 0.71 and the response to atomoxetine treatment ranges from 59.5% to 69% while remission ranges from 27% to 28.6% (Weiss et al., 2005; Kelsey et al., 2004; Michelson et al., 2002). 16 subjects, (44.4%) were defined as non-responders with SNAP-C, SNAP-I, and SNAP-O scores increasing and SNAP-I scores remaining at baseline levels.

An expanding literature has demonstrated a relationship between baseline profiles of quantitative Electroencephalogram (QEEG) or differences between baseline, retest profiles and ultimate clinical/treatment outcome (Prichep et al., 1993; Hansen et al., 2003; Pizzagalli et al., 2001; Leuchter et al., 2009a, 2009b). Saletu et al. (2002, 2005) suggested a “key and lock” model where the medication of choice is that which causes changes in brain electrical activity which is opposite to abnormalities seen in the baseline QEEG. Suffin and Emory (1995) conducted a prospective, randomized, multiply blinded, controlled pilot study to test clinical efficacy of the QEEG model, and found that pretreatment QEEG data predicted medication response with high accuracy in treatment resistant child and adolescent depression. In our sample responders to ATX had baseline QEEG alpha excess localized to frontal and anterior temporal regions and these abnormal findings decreased after 6 and 12 months of treatment. Non-responders showed QEEG abnormalities across all frequency bands and across frontal and central regions. These QEEG

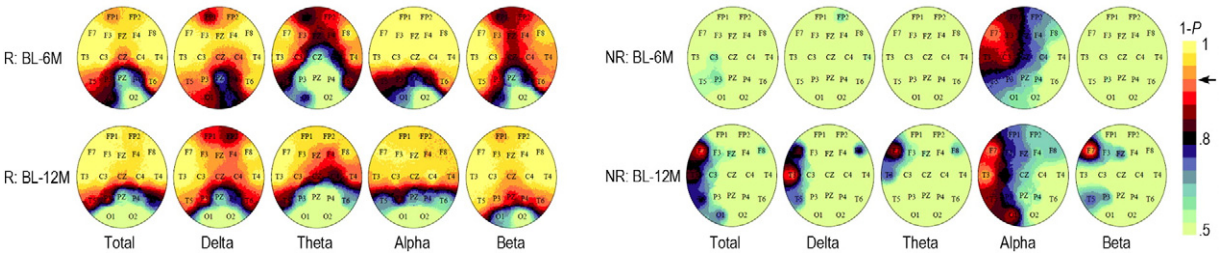

Fig. 3. Shows color coded head maps of the significance of absolute power difference between baseline (BL) and 6 months and 12 months after treatment separately for responders (left panel) and non-responders (right panel). The black arrow indicates significance at the $p < 0.005$ level.

abnormal findings remained constant after 6 and 12 months of treatment.

Many independent laboratories have reported that there are at least 5 different neurophysiological clusters (subtypes) that describe ADHD children. Furthermore, it has been demonstrated that each neurophysiological subtype shows abnormalities in all frequency bands, in terms of absolute, relative power and coherence in prefrontal and frontal areas and there may be a relationship between QEEG subtypes and treatment response. The QEEG profiles shown by the responders and non-responders in this study are consistent with those reported to characterize QEEG subtypes of children with ADHD (Clarke et al., 1998, 2001a, 2001b, 2001c, 2001d, 2002a, 2003a, 2006a; Barry et al., 2003, 2009a; Chabot and Serfontein, 1996; Chabot et al., 1996, 1999, 2001). As described above the responders and non-responders may represent two different QEEG subtypes of ADHD.

QEEG has been shown to have sensitivity and specificity levels varying from 90% to 98% in discriminating normal subjects from those with ADHD and ADHD children from LD children (di Michele et al., 2005; Monastra et al., 1999, 2001; Monastra, 2005). QEEG was also proved useful in the management of treatment response to stimulant medication. A number of studies have investigated changes in the EEG due to stimulant medications with the majority of studies finding that the stimulants result in some normalization of the EEG. Swartwood et al. (1998) and Lubar et al. (1999) failed to find changes in EEG power due to stimulant medication but Chabot et al. (1999) found that 56.9% of a group of children with ADHD showed normalization of the EEG after the administration of a stimulant, while 33.8% remained unchanged and 9.3% showed an increase in EEG abnormality. Loo et al. (1999) found that after the administration of methylphenidate, good responders had decreased theta and alpha but increased beta activity in the frontal regions, while poor responders showed the opposite EEG changes. Clarke et al. (2002b, 2003a, 2003b, 2007) found that stimulant medications resulted in normalization of the EEG with a reduction in theta activity and an increase in beta activity. These results were interpreted as indicating that stimulants acted at a cortical level by increasing arousal although complete normalization was not found in the entire sample.

However, the effects of non-stimulants on the EEG of children with ADHD have not been widely investigated. Clarke et al. (2006b, 2008) examined the EEG characteristics of responders to imipramine hydrochloride (Tofranil®) treatment. The authors reported that the responders to Tofranil© had significantly more absolute and relative theta with deficiencies of relative alpha across all sites compared to controls. Leuchter et al. (2014) used the theta cordance index in predicting atomoxetine treatment response in adult ADHD. Left temporo-parietal cordance in the theta frequency band after one week of treatment was associated with ADHD symptom improvement and quality of life measured at 12 weeks in atomoxetine-treated subjects, but not in those treated with placebo. In the scientific literature there is only one study that investigated the acute treatment effect of 20 mg of atomoxetine in children and adolescents with ADHD (Barry et al., 2007, 2009a). The EEG was recorded after 1 h of ATX administration. Acute atomoxetine administration produced a significant decrease of posterior absolute theta and an increase of absolute beta (especially in right and midline anterior regions). Relative delta was increased, particularly in central regions, and relative beta was globally increased. There were no significant medication effects on absolute alpha activity. However, this study has minimal implications on the long term effects of ATX on QEEG changes. In the present study ATX lead to a normalization of the QEEG's of the responders but had no effect upon the QEEG's of the non-responders.

Our study confirms that children with ADHD at baseline show QEEG abnormalities as reported in the literature and adds new data about the chronic effects of ATX on the QEEG of ADHD children. The effects of therapy are clearly visible at 6 months when R is compared with NR. Differences between R and NR were seen at baseline: the R show greater activity in the right prefrontal and frontal regions compared to the NR in the delta band. Theta activity is greater in the NR in the left temporal and parietal areas. The NR had greater alpha absolute power in central and left temporo-parietal and occipital regions bilaterally. Absolute power in the beta band especially in the posterior regions is higher in

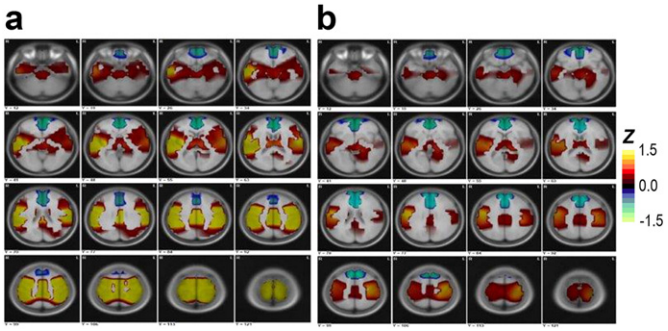

Fig. 4. a: Presents VARETA images at baseline for the responders at an average single Hertz frequency band of 11.7 Hz, the frequency band with the highest average Z-score relative to the normal population. b: Shows the same VARETA images 12 months after treatment.

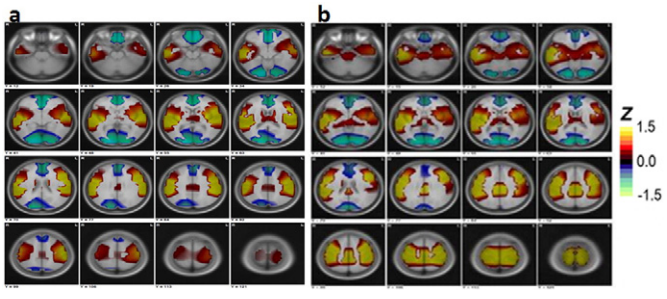

Fig. 5. a: Presents VARETA images at baseline for the non-responders at an average single Hertz frequency band of 15.2 Hz, the frequency range with the greatest average increased Z-score relative to the normal population. b: Shows the same VARETA images 12 months after treatment.

the NR. At 12 months of therapy the R show a normalization of absolute power in all frequency bands while the NR maintain the excess of activity in all frequency bands except the alpha band. The differences between R and NR at 12 months were highly significant especially in the delta band posteriorly, the theta band centrally and the beta band anteriorly.

VARETA source localization proved useful in the current study by indicating the cortical structures which show abnormal function in ADHD children. In a recent paper (Chabot et al., 2015) it was noted that groups of ADHD children and autistic children could be sub-typed based upon the mean frequency bands showing the greatest deviation from normal population. VARETA images calculated at these different frequency values showed consistent anatomical differences from normal that were similar across each subtype of autism and ADHD but that differences persisted between the autistic and ADHD at all frequency levels. ATX responders showed increased activation in right middle, superior, and inferior temporal gyrus, in the right insula, in the pre and post central gyrus, in the supramarginal gyrus, in the mid frontal gyrus, in the posterior cingulate region, in the angular gyrus, in the medial frontal gyrus, and the superior parietal lobe. This increased activation decreased after 6 and 12 months of ATX. Non-responders to ATX showed increased activation in right medial, inferior, and superior temporal gyrus, in the pre and post central gyrus, in the left inferior frontal gyrus, the supramarginal gyrus, in the left medial frontal gyrus, and in the angular gyrus with this increased activation remaining constant despite 12 months of treatment with ATZ. The reduced activation remained the same in the occipito-temporal gyrus and the cerebellum. Similar findings have been reported with different techniques supporting the evidence that these cerebral areas are involved in the pathophysiology of ADHD (Barkley, 2006).

The analysis of sources localization shows that at baseline the brain regions that show an excess of beta activity are the same in R and in NR. This might suggest that subjects with ADHD_C both R and NR share the same structural organization, but what distinguishes the R from NR is the functional organization as it appears by absolute power spectra. The NR continued to have an excess of beta activity and an excess of delta and theta activity.

One of the possible factors of the lack of response to ATX could be the presence of a greater number of ADHD subjects with Oppositional Defiant Disorders (ODD). Recently Chiarenza et al. (2014) reported that subjects with ADHD_C + ODD show abnormal EEG activity in the right anterior cingulate, in the right lateral and medial orbito frontal gyrus, in the alpha and beta bands in comparison to a group of subjects with ADHD_C.

Cortese et al. (2012) recently performed a comprehensive meta-analysis of 55 task-based functional MRI studies of attention deficit hyperactivity disorder. In children, hypoactivation in ADHD relative to comparison subjects was observed mostly in systems involved in executive function (fronto-parietal network) and attention (ventral attentional network). The authors provide evidence that ADHD is a result of dysfunction in multiple neuronal systems involved in higher-level cognitive functions and in sensorimotor processes, including the visual system and the default network. Our VARETA source localization method applied to QEEG, even if recorded with eyes closed and in quiet state, fully confirms these observations and contributes to the understanding of ADHD pathophysiology. It should be noted that the interpretation of VARETA has some pros/cons: it is statistically more robust, diminishes the effect of outliers and increases the chances of regions to become biomarkers. However if the region is big and few voxels are significant, the average can mask those significant voxels activities.

To date there are no studies that demonstrate a clear relationship between clinical profile of subjects with ADHD at “baseline” and response to treatment. Further, a limitation of most studies which have investigated the efficacy of stimulants or SNRI is that response measurements involve subjective teacher and parent ratings (Efron et al., 1997, 2002; Elia et al., 1991) and/or continuous performance tests (CPT) (Efron et al., 1997) without including objective and physiological measurements. Therefore, the questions related to aetiology, pathophysiology, diagnosis and therapy that ADHD imposes remain unresolved. There is a need for more precise and objective formulation of the diagnosis of ADHD, leading the way to more optimal treatment and increase the diagnostic sensitivity to ADHD. Increased understanding of neurophysiological profiles of children with ADHD could offer a refined definition of the pathology and a proper selection of subjects that may take some advantages from treatment optimization selection.

4.1. Study limitation

It should be remembered that the ATX selective inhibition of norepinephrine transporters action mechanism is still largely unknown. Therefore further studies are needed to draw a consistent action profile. Another limitation regards the use of multiple comparisons in analyzing the QEEG absolute power variables. Despite setting the significance level at 0.005 the changes observed in the different EEG frequency bands must be taken with caution although if significance was set at $p < 0.001$ the result interpretation would not change. Caution should also be used due to the relatively small number of responders and non-responders present in this study. Further large N studies should be conducted in order to build discriminative functions that may predict treatment response to ATX.

With these assumptions in mind, the results cannot be considered definitive and further research is necessary to confirm the observed significant differences on the QEEG of ADHD children between responders and non-responders after one year of ATX treatment.

5. Conclusions

We conclude that ADHD children with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased activity in the beta band coupled with increased alpha band power, seems to be related to non-responders and stopping atomoxetine should be considered, especially if there is persistence of elevated alpha and beta and an increase of theta after 3 months of treatment. VARETA showed more widespread abnormality in non-responders than responders. R showed abnormal findings localized to frontal and temporal regions whereas in NR abnormal findings also included more posterior regions.

To our knowledge, this study represents the first tentative attempt to detect objective variables of QEEG of patients with ADHD obtained after one year treatment with ATX. These variables could be used as a predictive index of treatment response to ATX. Waiting for further research to confirm the validity of these results, the prolonged observation of the QEEG variables should be considered as reference point of a certain consistency.

Disclosure

Giuseppe Augusto Chiarenza, Robert Chabot, Robert Isenhart, Luciano Montaldi, Marco Paolo Chiarenza, Maria Grazia Lo Torto, and Leslie S. Prichep within 3 years to the time of data collection had not any institutional or commercial relationship with pharmaceutical companies that might pose a conflict of interest.

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Comorbidity of Attention Deficit Hyperactivity Disorder and Generalized Anxiety Disorder in children and adolescents

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ABSTRACT

The aim of the study is to explore the impact of Generalized Anxiety Disorder (GAD) comorbidity in children with Attention Deficit Hyperactivity Disorder (ADHD).

Six hundred children with ADHD (mean age = 9.12 years), recruited from 2013 to 2017, participated in the study. A total of 96 (16%) children with ADHD displayed a comorbidity with GAD. ADHD + GAD were compared to 504 ADHD children without GAD in terms of cognitive and psychiatric profile, ADHD subtype and family psychiatric history.

The ADHD + GAD, predominantly represented from ADHD combined (72.6%), displayed higher psychiatry comorbidity, in particular with depressive disorders, and were associated with higher rates of maternal depression, of ADHD in fathers, and bipolar disorders in second degree relatives. Moreover, younger preschool-primary school age children with ADHD + GAD showed significant higher frequency of depressive disorders versus younger preschool-primary children with ADHD without GAD.

ADHD + GAD comorbidity represents a more complex clinical condition compared to ADHD without GAD, characterized by the higher frequency of multiple comorbidities and by a psychiatric family with higher rates of mood and disruptive disorders.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder that carries a significantly increased risk for comorbidity with a wide range of psychiatric disorders. In particular, children with ADHD are reported to display more disruptive, anxiety or depression symptoms than either typically development children or children with other neurodevelopmental disorders (Brown, 2000; Jensen et al., 1993; Yoshimasu et al., 2012).

Within a developmental approach, the comorbidity between two or more disorders is widely recognised to modify the nature of the clinical picture, the developmental trajectories and the outputs (Caye et al., 2016; Jensen and Steinhausen, 2015; Newcorn et al., 2004). The detection of a comorbidity in children with ADHD may therefore shed light on the phenotypical variations of the heterogeneous ADHD population and consequently might explain the changes in the behavioral patterns from childhood through to adolescence. Several reports exist on the comorbidity between depression (DD), oppositional defiant disorder (ODD), conduct disorder (CD) and tics, but few studies have addressed the comorbidity between ADHD and specific anxiety disorders (Cuffe et al., 2015; Jensen and Steinhausen, 2015).

Although some studies considered ADHD and anxiety disorders as mutually exclusive (Weiss et al., 2011), high rates of comorbidity between the two disorders have been registered in developmental age (de la Barra el al., 2013; Jensen, 2001;Yüce et al., 2013). According to prevalence reported in the literature, 13–51% of children with ADHD have a comorbidity with an anxiety disorder (Biederman et al., 1991; Jensen, 2001; Mitchison and Njardvik, 2015; Shea et al., 2018; Tannock, 2000; Xia et al., 2015). By contrast, only 15–30% of children with any anxiety disorder showed to have a comorbidity with ADHD (Bowen et al., 2008; Tannock, 2000). ADHD may have a comorbidity with multiple anxiety disorders; Wilens et al., (2002) found that 28% of preschool children with ADHD and 33% of school children with ADHD had two or more anxiety disorders.

Their co-occurrence is reported be strongly related to the ADHD subtypes; in a multimodal treatment study of ADHD (MTA) 33–39% of

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children with the ADHD combined subtype (ADHD-C) were also found to have one anxiety disorder (March et al., 2000; Newcorn et al., 2001). Elia et al. (2008) reported that ADHD-C is the subtype most frequently associated with any anxiety disorder (57.3%) followed by the ADHD inattentive subtype (ADHD-I) (32.7%) and the ADHD hyperactive subtype (ADHD-H) (8.2%) The prevalence rates also vary according to gender and age. Some studies have reported that 17% of girls and 21% of boys with ADHD between 4–11 years of age had at least one anxiety or mood disorder (Szatmari et al., 1989), though these rates increase to 24% for boys and 50% for girls during adolescence (Munir et al., 1987). More recent studies have also highlighted gender differences though results are somewhat conflicting: Yüce et al. (2013) reported that depression and anxiety disorders in ADHD children were more common in girls, whereas Mitchison and Njardvik (2015) reported a significantly higher prevalence of anxiety symptoms in boys than in girls.

Moreover longitudinal studies on children and adolescents provided a strong evidence that ADHD might be considered as a risk factor for the development of an anxiety disorder (Tai et al., 2013; Weiss et al., 2011). In particular the findings showed that children with ADHD with respect to controls, displayed an earlier age of onset of anxiety disorders (Tai et al., 2013) and higher levels of lifetime anxiety disorders (Biederman et al., 2010; March et al., 2000).

Concerning their specific influences is reported that anxiety in ADHD may alter the expression of the ADHD phenotype, reducting impulsivity and self-esteem and increasing the level of inattention when compared with children with ADHD without anxiety (Brown, 2000; Bussing et al., 2000; Epstein et al., 1997; Gordon et al., 1990; Manassis et al., 2007; Pliskza, 1998, 2000; Tannock, 2000). On the other hand, attention deficits might induce anxiety (Weiss et al., 2011). Since intrusive worries and hypervigilance to threat cues associated with anxiety, often manifest as symptoms of inattention (Jarrett and Ollendick, 2008), some researchers believe that the nature of the association between ADHD and anxiety disorders, particularly Generalized Anxiety Disorder (GAD) and social anxiety, may be attributed to attention problems, rather than to hyperactivity/impulsivity (Bowen et al., 2008).

Studies on this topic published in the literature have certain limitations: most of them considered the comorbidity by combined multiple anxiety disorders, which obscures specific relations between each anxiety disorder and ADHD; some studies were based on ADHD samples that were small and/or with markedly different age ranges; most of the data are derived from studies that were designed to assess the prevalence of psychiatric disorders that are comorbid with ADHD but did not evaluate the clinical characteristics the define the comorbid profile; lastly, although Generalized Anxiety Disorder (GAD) is the most frequent comorbid anxiety disorder with ADHD, it is paradoxically the anxiety disorder less studied.

The aim of our study, conducted on a large sample of children with ADHD, was to describe the clinical profile of children with ADHD and GAD comorbidity (ADHD + GAD), and to evaluate the role that subtypes of ADHD, psychiatric comorbidities and familiar psychiatric history play in explaining the co-occurrence of ADHD + GAD. Moreover, we analyzed the psychopathological characteristics of children ADHD with and without GAD, in two age range (preschool-primary school vs. secondary school).

2. Method

2.1. Participants

Six hundred Caucasian children with a clinical diagnosis of ADHD (522 males, 87%, mean age: 9.07 years, SD ± 2.52; 78 females, 13%, mean age: 9.44 years, SD ± 2.97; range: 4–17 years) recruited from a larger sample of outpatients Center for ADHD in Rome from 2013 to 2017, participated to study (Table 1). The Center for ADHD is a specialized structure for diagnosis and pharmacological treatment for ADHD children to which several Mental Health Services, sent children showing ADHD symptoms, for an accurate diagnostic assessment and decisions of pharmacological treatment. From 2013 to 2017 the Center followed 656 ADHD children with or without other comorbidities. Fifty-six children with an IQ <70, and/or with comorbid medical and neurological conditions, or with other anxiety disorders associated with or without GAD, have been excluded from the study. At the time of recruitment all children were drug-naïve.

For the purposes of our study the sample was divided into two groups: ADHD children that presented a comorbidity with GAD (ADHD + GAD) and ADHD without GAD but with other psychiatric comorbidities (ADHDnoGAD).

2.2. Measures

Both the children and parents of the samples (ADHD + GAD and ADHDnoGAD) participated in three clinical sessions to reconstruct the child's lifetime and medical history and to assess familial psychiatric symptoms (only first and second-degree relatives were included). The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997) was conducted by the same experienced child psychiatrist (MD) on the children with ADHD and their parents to make a primary diagnosis, to detect any concurrent comorbidity and to characterize the clinical profile of the sample.

The K-SADS-PL is a semistructured diagnostic interview constructed for assessing current and past episodes of psychopathology during childhood and adolescence according to DSM-IV criteria (Kaufmann et al. 1997).

The diagnostic assessment included also a medical history, neurological and physical examinations and EEG. The Wechsler Intelligence Scale for Children III (WISC III), Italian version (Orsini and Picone, 2006) was used to estimate the intelligence quotient (IQ).

In addition, the parents and school teachers of all the children with ADHD were asked to fill out the ADHD-Rating Scale (ADHD-RS) (DuPaul et al., 1998) adapted for the Italian population (Marzocchi and Cornoldi, 2000). The participants' parents signed a statement of informed written consent according to the privacy policy.

2.3. Procedure

Two groups were selected according to the presence/absence of a comorbidity with GAD. We evaluated the possible presence of other psychiatric disorders in both the ADHD + GAD and ADHD without GAD (ADHDnoGAD) groups: a) depressive disorders (DD) including combined major depressive disorder and dysthymia; b) Disruptive Mood Dysregulation Disorders c) bipolar disorders I and II, bipolar disorder NOS; *d)* oppositional-defiance disorder (ODD) and e) conduct disorders (CD). These disorders were diagnosed according to DSM-5 (American Psychiatric Association, 2013).

We have excluded other comorbidities (Obsessive-Compulsive Disorders, learning disabilities etc.), putting the focus on the principal psychiatric disorders; the evaluation of these comordib disorders will be analyzed in future studies.

Lastly, we divided the ADHD sample into two age range: a) younger preschool-primary school age children with ADHD (4–10 years, $N = 441$; 73.5%); b) older secondary school-age children with ADHD (11–17 years, $N = 159$; 26.5%) to evaluate the eventual differences in the psychiatric comorbidity in relation with age.

The psychiatric family history of 1st degree relatives has been collected through careful direct anamnestic psychiatric interview administered to both parents by an expert child psychiatrist, to define the presence/absence of DSM5 symptoms of each disorder reported in the study (ADHD, Depressive Disorders, Anxiety Disorders and Bipolar Disorders). Regarding 2nd-degree relatives, the psychiatric history was carried out with parents of children and we included those reported to

Table 1
Characteristics of the study variables.

		ADHD + GAD *n* 96 (16%) *n (%)*	ADHDnoGAD *n* 504(84%) *n (%)*	χ^2	*P*
Gender	Boys	84 (87.5)	438 (86.9)	0.025	NS
	Girls	12 (12.5)	66 (13.1)		
Age	4–10 years	66 (68.8)	375 (74.4)	1.324	NS
	11–17 years	30 (31.2)	129 (25.6)		
ADHD subtypes*	Inattentive	22 (23.2)	151 (31.2)	12.591	**0.002**
	Hyperactive-Impulsive	4 (4.2)	69 (14.3)		
	Combined	69 (72.6)	264 (54.5)		
		Mean (SD)	*Mean (SD)*	*t*	*p*
IQ	Total	90.40 (25.25)	95.22 (25.44)	1.583	NS
	Verbal	85.96 (34.08)	97.82 (58.24)	1.759	NS
	Performance	91.64 (21.56)	93.42 (25.64)	0.580	NS

Note. *Missing 21 subtypes data.

have a psychiatric certification.

2.4. Statistical analyses

ADHD + GAD and ADHDnoGAD were compared using a series of chi square tests (χ^2) or Fisher exact tests, as appropriate, for categorical variables (gender, ADHD subtypes, other comorbidities, psychiatric familiar disorders) and independent sample *t*-test for continuous variables (age, IQ). Data are reported as frequencies (%) or mean ± S.D.; statistical significance is set at a nominal two-tail $p < .05$. Statistical analyses were performed using SPSS software release 24.0 (SPSS Inc., Chicago, IL).

3. Results

A total of 96 children with ADHD (16%) (mean age:9.38 ± 2.35 years; 84 males: 87.5%) displayed a GAD comorbidity (ADHD + GAD) vs. 504 ADHD without any anxiety disorder but with possible other psychiatric comorbidities (84%) (mean age:9.07 ± 2.62 years; 438 males: 86.9%). The two groups did not differ for age ($t = -1.082$; df = 598; $p = .28$) and gender, χ^2 (1) = 0.025, $p = .87$).

The ADHD + GAD group is mostly represented by ADHD combined (ADHD-C: 72.6%; inattentive ADHD-I: 23.2%; hyperactive-impulsive ADHD-H: 4.2%) compared to ADHDnoGAD (ADHD-C: 54.5%; ADHD-I: 31.2%; ADHD-H: 14.3%). In particular, ADHD + GAD showed significantly higher frequencies in ADHD-C and lower frequencies in ADHD-H (Table 1).

The two groups differed for the frequency of psychiatric disease in the family history (33.3% vs. 21.1% of ADHDnoGAD (Table 2). More specifically, ADHD + GAD showed a higher frequency for maternal depression (8.3% vs 2.4%), father with ADHD (5.2% vs. 1.4%) and relatives with bipolar disorders (BD) (5.2% vs. 1.6%).

A comorbidity with almost another psychiatric disorder was found in 58.3% of children with ADHD + GAD vs. 42.9% of ADHDnoGAD. More precisely 37.5% of ADHD + GAD showed a comorbidity with another disorder and 20.8% with two or more disorders vs. 27.6% and 15.3%, respectively, of ADHDnoGAD (Table 2).

The ADHD + GAD group vs. ADHDnoGAD showed a significant higher frequency of comorbidity with DD. No significant difference were found for ODD, CD, DMDD, BD (Table 2).

Chi-square test between two groups, within each range of age, showed that younger ADHD + GAD had higher comorbidity with DD psychiatric disorder compared to the younger ADHDnoGAD. No significant differences were found for comorbidity and psychiatric disorders between the two older ADHD groups (Table 3). Chi-square test conducted separately within each group across two ranges of age, revealed that the older ADHDnoGAD children reported significant higher frequencies of depressive disorders, $\chi^2(1) = 14.476$, $p < .01$, and conduct disorder, $\chi^2(1) = 7.854$, $p < .01$ compared to younger ADHDnoGAD children. No significant difference was found between younger and older ADHD + GAD children (Table 4).

Table 2
Psychiatric family history and psychiatric comorbidities.

Variables		ADHD + GAD *n* 96 (%)	ADHDnoGAD *n* 504 (%)	χ^2	*p*
Psychiatric family history	0	64 (66.7)	398 (79)	7.969	**0.019**
	1	25 (26.0)	90 (17.9)		
	2	7(7.3)	16 (3.2)		
Mother depression		8 (8.3)	12 (2.4)		**0.008***
Mother anxiety		6 (6.3)	13(2.6)		NS*
Mother ADHD		0 (0.0)	2 (0.4)		NS*
Mother bipolar disorder		0 (0.0)	4 (0.8)		NS *
Father depression		1 (1.0)	9 (1.8)		NS *
Father anxiety		2 (2.1)	7 (1.4)		NS *
Father ADHD		5 (5.2)	7 (1.4)		**0.030***
Father bipolar disorder		2 (2.1)	8 (1.6)		NS *
Siblings with ADHD		4 (4.2)	28 (5.6)	0.308	NS
Depression in 2° relatives		7 (7.3)	23 (4.6)		NS *
Bipolar disorder in 2° relatives		5 (5.2)	8 (1.6)		**0.042***
Comorbidities with psychiatric disorders	0	40 (41.7)	288 (57.1)	8.477	**0.037**
	1	36 (37.5)	139 (27.6)		
	2	15 (15.6)	51 (10.1)		
	3	5 (5.2)	26 (5.2)		
Depressive disorders		17 (17.7)	53 (10.5)	4.048	**0.044**
Bipolar disorders		9 (9.4)	35 (6.9)	0.701	NS
Disruptive Mood Dysregulation Disorders		8 (8.3)	20 (4)		NS*
Oppositional Defiant disorder		40 (41.7)	168 (33.3)	2.473	NS
Conduct Disorder		6 (6.2)	41 (8.1)	0.397	NS

Note. *Calculated by Fisher's exact test.

4. Discussion

Our results on 600 ADHD patients showed that 16% of them had a comorbidity with GAD, consistent with previous studies reporting a prevalence ranging from 12.8% (Souza et al., 2005) to 15.2% (Elia et al., 2008), with a stronger occurrence in males. The percentage of females (13%) in our sample was lower than that reported in the North-American population of children with ADHD, but similar to those found in European studies (Buitelaar et al., 2006). Independently from gender, this study showed that GAD represents one of the most commonly anxiety disorders in comorbidity with ADHD in childhood and adolescence and studies in adulthood confirmed that patients with GAD were more likely than adults with social phobia to have a childhood history of ADHD (Safren et al., 2001).

Table 3
Descriptive statistics for ADHD + GAD and ADHDnoGAD within each age group.

		Younger (4–10 years)				Older (11–17 years)			
		ADHD + GAD *n* (%)	ADHDnoGAD *n* (%)	χ^2	*p*	ADHD + GAD *n* (%)	ADHDnoGAD *n* (%)	χ^2	*P*
Gender	Boys	54 (81.8)	328 (87.5)	1.54	NS	30 (100.0)	110 (85.3)	5.018	**0.025**
	Girls	12 (18.2)	47 (12.5)			0 (0.0)	19 (14.7)		
ADHD subtypes	Inattentive	16 (24.6)	98 (27.1)	5.97	0 **0.05**	6 (20.0)	53 (43.1)	9.04	**0.011**
	Hyperactive-Impulsive	4 (6.2)	61 (16.9)			0 (0.0)	8 (6.5)		
	Combined	45 (69.2)	202 (56.0)			24 (80.0)	62 (50.4)		
Comorbidity with psychiatric disorders	0	26 (39.4)	221 (58.9)	10.40	**0.015**	14 (46.7)	67 (51.9)	1.879	NS
	1	25 (37.9)	107 (28.5)			11 (36.7)	32 (24.8)		
	2	12 (18.2)	33 (8.8)			3 (10.0)	18 (14.0)		
	3	3 (4.5)	14 (3.7)			2 (6.7)	12 (9.3)		
Depressive disorders		13 (19.7)	28 (7.5)	9.95	**0 0.002**	4 (13.3)	25(19.4)	0.597	NS
Disruptive Mood Dysregulation Disorders		6 (9.1.)	16 (4.3)		NS*	2 (6.7)	4 (3.1)		NS*
Bipolar Disorders		7 (10.6)	23 (6.1)		NS*	2 (7.1)	12 (9.3.)		NS*
Oppositional Defiance Disorder		27 (40.9)	124 (33.1)	1.533	NS	13 (43.3)	44 (34.1)	0.901	NS
Conduct Disorder		4 (6.1)	23 (6.1)		NS*	2 (6.7)	18 (14)		NS*

Note. *Calculated by Fisher's exact test.

Table 4
Descriptive statistics for younger vs. older children within each group.

	ADHD + GAD younger *n* (%)	older *n* (%)	χ^2	*p*	ADHDnoGAD younger *n* (%)	older *n* (%)	χ^2	*P*
Depressive disorders	13 (19.7)	4 (13.3)		NS*	28 (7.5)	25(19.4	14.476	**0.000**
Disruptive Mood Dysregulation Disorders	6 (9.1.)	2 (6.7)		NS*	16 (4.3)	4 (3.1)		NS.*
Bipolar Disorders	7 (10.6)	2(7.1		NS*	23 (6.1)	12 (9.3.)	.377	NS
Oppositional Defiance Disorder	27 (40.9)	13 (43.3)	0.050	.823	124 (33.1)	44 (34.1)	0.47	NS
Conduct Disorder	4 (6.1)	2 (6.7)		NS*	23 (6.1)	18 (14)	7.854	**0.005**

Note. *Calculated by Fisher's exact test.

Children ADHD + GAD were prevalently represented from ADHD-C subtype, in agreement with the meta-analytic work of Willcutt et al. (2012), which showed that children and adolescents with ADHD-C were 6.5 times more likely to meet criteria for comorbid GAD compared to healthy controls. Differently, the ADHD-I subtype is reported to have a more specific relationship with social anxiety disorder (Koyuncu et al., 2015a; Koyuncu et al., 2015b). Both GAD and ADHD present some degree of overlap in the symptom criteria, including difficulties with inattention, problems concentrating, restlessness (American Psychiatric Association, 2013) that can explain higher presence of ADHD-C vs. other two subtypes. However, our findings are not comparable with other studies on patients with anxiety as primary disorder (Koyuncu et al., 2016; March et al., 2000; Michelini et al., 2015), stating that the association between anxiety (included generalised anxiety) and ADHD could be entirely attributed to attention problems. In our study we cannot infer that the association between ADHD and anxiety is linked to attentional problems since the design of the study was based on the presence/absence of the disorders and not on the specific symptoms.

4.1. Psychiatric family history and comorbidity in ADHD + GAD children

Literature reported specific links between ADHD-anxiety comorbidity and psychiatric family history; while relatives of children with ADHD had markedly higher risk to have ADHD themselves, relatives of children with ADHD and anxiety had a threefold risk to present anxiety disorders (Tannok, 2000).

The relatives of 1st or 2nd degree of our ADHD + GAD children showed a significant higher frequency of psychiatric disorders; among them, higher rates of depression of mothers, ADHD of fathers and bipolar symptoms in relatives of 2nd degree were reported when compared to ADHDnoGAD.

In agreement with the Breslau et al. (1987), we did not find significant higher rates of anxiety symptoms in the family history, although anxiety maternal values approached to statistical significance ($p = .060$). Some studies reported a high prevalence of symptoms of anxiety and depression in mothers of children with ADHD (Segenreich et al., 2009). On the other hand, about a third of children of mothers with current major depressive episode were at high risk for disruptive behavior and anxiety disorders. (Pilowsky et al., 2006). A recent study reported that offspring of depressed and anxious patients were at very high risk of a mood and/or anxiety disorder, mainly GAD (Havinga et al., 2017). Since the strong association between maternal depression and offspring with ADHD or anxiety disorders, a shared etiology can account for the higher frequency of this familiar psychiatric condition in the ADHD + GAD group.

Similarly, there is consistent evidence that children of parents with BD are vulnerable to a wide range of individual and comorbid behavioral and emotional conditions including ADHD, anxiety, depression, and higher rates of BD compared to the general population (Birmaher et al., 2011; Duffy et al., 2013). Our data suggest that also higher rates of BD in relatives of second-degree differentiated ADHD + GAD from ADHDnoGAD children. Generational studies including second-degree relatives should be warranted to better define genetic and environmental factors and mechanisms that play in comorbidity in children with ADHD.

ADHD + GAD children showed also an increased comorbidity with one or more other psychiatric disorders; in particular, with DD. GAD and DD present a high co-occurrence for the overlapping of some symptoms (i.e., insomnia; fatigue; difficulty in concentrating, etc.), shared genetic risk factors (Hettema, 2008; Kendler et al., 1995) and a strong cross-predictivity each other as reported in longitudinal studies (Copeland et al., 2009). Since the presence of DD represented a risk factor for the co-occurrence of GAD in ADHD children, our findings support the hypothesis of Trosper et al. (2012), that a shared factor of "negative affectivity", might explain the higher co-presence of

depressive disorders in this group. On the other hand, GAD in ADHD children might increase and exacerbate the presence of depressive behaviours, as reported in a previous study on GAD comorbidity in children with ODD (Drabick et al., 2010). Altogether, our data are consistent with the study of Xia et al. (2015) that reported a strong relation between self-reported anxiety and depressive symptoms in children with ADHD and self-reported ratings of corresponding symptoms in their parents, overall mothers.

The results did not show a significant prevalence of ODD in ADHD + GAD compared to ADHDnoGAD and are in disagreement with Humphreys et al. (2012) reporting that comorbid anxiety in ADHD may strengthen the association of ADHD and ODD/CD, particularly in the combined subtype. It is known that ADHD and GAD disorders show a great comorbidity with ODD (Dougherty et al., 2013), but the few studies that concerned the co-occurrence ADHD + GAD + ODD reported contrasting results. In a community-based sample, Angold et al. (1999) found that, controlling for ADHD, the odds ratio for the co-occurrence of ODD and anxiety (included GAD) was reduced, suggesting that the comorbidity between ODD and anxiety disorders may be an artefact of their joint association with ADHD. Other studies on clinic-based sample, highlighted that the comorbidity of ODD and GAD was not better accounted for by their joint co-occurrence with ADHD (Garland and Garland, 2001; Drabick et al., 2008).

Further studies carried out by distinct ODD DSM-5 dimensions (irritable,headstrong and hurtful) (Stingaris and Goodman, 2009) could help to better clarify this controversial topic.

4.2. Comorbidity in younger and older ADHD + GAD children

Interesting results were found when associated psychiatric comorbidity was studied within each group across range of age. In ADHD + GAD we did not find variations in frequency of comorbid psychiatric disorders between younger and older children. On the contrary, older ADHDnoGAD children showed a significant increased presence of DD and CD vs. younger ADHDnoGAD children. Again, younger ADHD + GAD children showed significant higher frequency of comorbidity with DD, compared to younger ADHDnoGAD.

Longitudinal studies are required to evaluate if the lack of variation in rates of psychiatric comorbidities between younger and older ADHD + GAD children is due to stability of multi-comorbid clinical pattern along developmental lifetime. Moreover, cross-sectional with more narrow range of age and longitudinal studies could explain if higher frequency of DD in younger ADHD + GAD vs. ADHDnoGAD children, represent an early onset of comorbidity among these three disorders.

5. Conclusions

Our results allow us to assume that co-occurrence ADHD + GAD is a different clinical profile than ADHDnoGAD that outlines as a complex condition characterized by a higher prevalence of multiple comorbidities and by a higher frequency of mood familiar disorders other than ADHD. The present study has some limitations that must be acknowledged. The first limitation is that we did not consider the severity of the two disorders. The second one, we have excluded other comorbidities (as Obsessive-Compulsive Disorders, learning disabilities etc.), putting the focus on the principal psychiatric disorders. The third one concerns the fact that family psychiatric history in parents of ADHD was evaluated through an anamnestic psychiatric interview on symptoms criteria of disorders considered, but no specific structured interviews has been used. This methodological procedure doesn't exclude the risk that psychiatric disorders frequencies in parents could have been underestimated.

Similarly, another weakness of the study is that family psychiatric history regarding 2nd-degree relatives was collected by an psychiatric interview to primary caretakers, without using a structured screen (Family History screen; Weissman et al., 2000) as reported in other studies (Rende et al., 2007). Nevertheless, we evaluated those who had the psychiatric certification reported by parents.

However, to our knowledge, this is the first study that defines the clinical profile and familiar psychopathology in children with ADHD + GAD and the study has been performed on a consistent sample of ADHD children with no pharmacological treatment before diagnosis. This may give us a better clinical detection, given that treatment and medication may to affect the course and modify some characteristics of both disorders.

Although further cross-sectional and longitudinal studies should be necessary to clarify the link among these disorders, and verify their developmental trajectories in developmental age, this study outlines a well-defined ADHD + GAD psychopathological and familiar profile and offers clinical documentation for comparative studies with other anxiety disorders in comorbidity with ADHD.

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Declaration of conflict of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.10.078.

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ADHD in età evolutiva: comorbilità ed esiti di trattamento

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ABSTRACT

ADHD in developmental age: comorbidity and treatment outcomes

▶ **Aim.** *To assess the prevalence rates of neuropsychiatric comorbidities in children and adolescents with and without ADHD, and compare the effectiveness of treatment in relation to comorbidity.*

▶ **Methods.** *Clinical data on 378 suspected patients (86% M, 5-17 yr), entered in the Lombardy Region's ADHD Registry in the period 2011-2017 by regional reference center "Medea" of Bosisio Parini (LC), are analyzed to identify: prevalence rates, comparison between prescribed and performed treatments, improvement rates and effectiveness of the treatment in relation to the different therapeutic approaches.*

▶ **Results.** *70% (213/306) of first ADHD diagnosis and never treated patients has one (or more) comorbidity: learning disorders (LD) (48%), sleep disturbances (21%), anxiety disorders (16%), intellectual disability (17%), oppositional defiant disorder (12%), language disorders (12%), autism spectrum disorders (10%). Comorbidity is a risk factor for symptom severity (GGI-S ≥5). One year after diagnosis, 51% of the population has improved (CGI-I <3). Overall, multi-modal treatment is the most effective for ADHD with other comorbid disorders (Effect Size - ES 0.50) and specifically for ADHD with: LD (ES 0.71), sleep disorders (ES 0.87), anxiety disorders (ES 0.86). Similar efficacy is achieved by child/parent training for ADHD with sleep disorders (ES 0.53) and ADHD with anxiety disorders (ES 0.88).*

▶ **Conclusions.** *Comorbidity in ADHD is the rule, not the exception. The regional ADHD Registry is a unique tool to agree and share actions for the appropriate management of diagnosis and treatment of ADHD. The results achieved through the application in clinical practice of shared operational lines are highlighted.*

▶ **Key words.** *ADHD | comorbidity | prevalence | treatment | effectiveness | disease registry.*

RIASSUNTO

▶ **Obiettivo.** Valutare gli indici di prevalenza delle comorbilità neuropsichiatriche in bambini e adolescenti con e senza ADHD, e valutare l'efficacia del trattamento in relazione alle comorbilità.

▶ **Metodi.** I dati clinici di 378 soggetti (86% M, 5-17 anni), primi casi, nel Registro ADHD lombardo presso il Centro ADHD "Medea" di Bosisio Parini (LC) nel periodo 2011-2017 sono stati analizzati per identificare: indici di prevalenza, confronto fra

trattamenti prescritti ed eseguiti, indici di miglioramento ed efficacia del trattamento in relazione ai diversi approcci terapeutici.

▶ **Risultati.** Il 70% (213/306) dei bambini con ADHD alla prima diagnosi e mai trattati presentava una (o più) comorbilità: disturbi dell'apprendimento (48%), disturbi del sonno (21%), disturbi d'ansia (16%), disabilità intellettiva (17%), disturbo oppositivo provocatorio (12%), disturbi del linguaggio (12%), disturbi dello spettro autistico (10%). La presenza di comorbilità è risultata essere un fattore di rischio per la gravità sintomatologica (GGI-S ≥5). A un anno dalla diagnosi il 51% della popolazione è migliorato (CGI-I <3). Il trattamento combinato risulta essere il più efficace per ADHD in comorbilità (Effect Size – ES 0.50), in particolare in presenza di disturbi specifici dell'apprendimento (ES 0.71), disturbi del sonno (ES 0,87), disturbi d'ansia (ES 0,86). Efficacia simile è raggiunta dal *child/parent training* per ADHD con disturbi del sonno (ES 0,53) e ADHD con disturbi d'ansia (ES 0,88).

▶ **Conclusioni.** La comorbilità nell'ADHD è una condizione che interessa la maggioranza dei casi. I risultati raggiunti con l'applicazione nella pratica clinica di percorsi assistenziali condivisi nella rete del Progetto regionale indica un fruttuoso approccio da mantenere e implementare nel tempo.

▶ **Parole chiave.** ADHD | comorbilità | prevalenza | trattamento | efficacia | registro.

INTRODUZIONE

L'Attention Deficit/Hyperactivity Disorder (ADHD) è un disturbo con esordio in età evolutiva e persistenza anche in età adulta, caratterizzato dai sintomi *core* di disattenzione, iperattività e impulsività, con significativo impatto nei contesti di vita del soggetto.[1]

Dalla pubblicazione del DSM-5[2], l'ADHD è concettualizzato come disturbo del neurosviluppo.

Questo gruppo di disturbi è caratterizzato da persistenza relativamente stabile nel tempo, prevalenza maschile, multi-fattorialità eziologica, alta eterogeneità di caratteristiche cliniche, frequente sovrapposizione sintomatologica e comorbilità.[1]

PREVALENZA

Gli indici di prevalenza dell'ADHD possono variare in relazione a diversi fattori con valori compresi tra il 5,29 e il 7,2% della popolazione generale[2]. Pur essendo un disturbo che può essere presente lungo tutto il corso di vita, con una prevalenza in età adulta stimata tra 1,2 e 7,3%[3]. La prevalenza appare stabile nel tempo[4], sebbene caratterizzata da ampia variabilità a seconda del contesto geografico preso in considerazione. Gli studi condotti in Italia riportano prevalenze comprese tra 0,4 e il 3,6%[5], con relativo consenso fissato a 1%[6]. Le variazioni possono essere imputabili a differenze territoriali, culturali e metodologiche nel processo diagnostico[4].

COMORBILITÀ

Alla definizione del profilo di funzionamento di bambini e adolescenti con ADHD spesso concorrono altri disturbi, con la consapevolezza condivisa che la comorbilità rappresenti la regola, anziché l'eccezione[7]. La prevalenza generale di disturbi psicopatologici in associazione ad ADHD in

bambini e adolescenti varia da 40% a 80% a seconda del campione, della metodologia adottata. In modo non esaustivo, è possibile osservare ADHD in comorbilità con: Disturbo Oppositivo Provocatorio (DOP) (30-50%)[8], Disturbo della Condotta (DC) (10-20%), disturbi d'ansia (25-42%), disturbi dell'umore (25-75%), disturbo bipolare (20%), tic (4-14%), disturbi dello spettro autistico (Autism Spectrum Disorder – ASD) (10-19%), Disturbi Specifici dell'Apprendimento (DSA) (15-45%), alterazioni o disturbi del sonno (2-70%)[7].

In letteratura, la comorbilità con disturbi internalizzanti ed esternalizzanti nell'ADHD è descritta come un fattore di vulnerabilità per esiti più sfavorevoli sul funzionamento del bambino a lungo termine e nell'immediato, soprattutto sulla qualità delle relazioni con i pari e sulla qualità della vita familiare rispetto ai bambini con ADHD senza comorbilità[9]. La condizione ADHD con DOP e/o DC è ampiamente studiata in letteratura e sembra riservare traiettorie di aumentato rischio per uso di sostanze, condanne per reati, tasso di mortalità più elevato in età adolescenziale e adulta[10]. Attribuendo una diagnosi di ADHD, è quindi necessario che i clinici tengano in considerazione le possibili condizioni psicopatologiche in associazione, che concorrono alla definizione della tipologia di intervento necessario e agli esiti di trattamento.

TRATTAMENTO

Nella prospettiva di offrire una gestione ottimale, la presa in carico di soggetti con ADHD necessita di un approccio multimodale, che combini interventi psicologici con il bambino, i genitori e la scuola e terapie farmacologiche, così come condiviso dalle linee guida nazionali[11] e internazionali[12]. Le linee guida condividono il presupposto che ogni intervento sia costruito attorno al soggetto, sulla base dei bisogni specifici individuali, all'età, alla gravità dei sintomi, alle comorbilità, alle caratteristiche dei contesti familiare e sociale. Nonostante l'ADHD e, in particolare, l'ADHD con comorbilità siano situazioni diffusamente studiate in letteratura, rimangono temi aperti in merito alla diagnosi e all'intervento per l'ADHD in associazione con altri disturbi. Ancora pochi studi sono stati condotti con un approccio multidimensionale, osservando l'intero ventaglio di possibili comorbilità neuropsichiatriche e analizzando i risultati secondo la tipologia di trattamento ricevuto. Questo contributo si propone di valutare gli indici di prevalenza delle comorbilità neuropsichiatriche e i risultati del trattamento in bambini e adolescenti con ADHD, attraverso quattro livelli di analisi: indici di prevalenza, confronto tra trattamenti prescritti ed eseguiti, indici di miglioramento ed efficacia del trattamento in relazione ai diversi approcci terapeutici.

METODO

In questo studio sono state analizzate le informazioni cliniche di bambini e adolescenti di età compresa tra 5 e 17 anni, afferenti da giugno 2011 fino a ottobre 2017 al Centro ADHD del Polo di Neuropsichiatria dell'Infanzia e dell'Adolescenza (NPIA) dell'IRCCS Istituto Eugenio Medea di Bosisio Parini (LC), alla prima valutazione presso il Servizio Sanitario

Nazionale e senza precedente trattamento effettuato, seguiti per 12 ± 6 mesi in base al loro profilo di comorbilità. I dati utilizzati sono stati raccolti nel Registro regionale per l'ADHD, replicando un precedente studio multicentro che aveva analizzato i dati provenienti da tutti i 18 Centri regionali[7].

Per la valutazione degli esiti clinici sono stati considerati gli indici di miglioramento del soggetto e di efficacia del trattamento misurati rispettivamente attraverso le scale CGI-Improvement e CGI-Severity (cambiamento pre-post trattamento, media della variazione).

Sono state calcolate le dimensioni dell'effect size (ES) per ciascun gruppo di trattamento rispetto a una condizione di controllo, rappresentata dai soggetti che non hanno ricevuto alcun trattamento. Una modalità condivisa per interpretare le dimensioni dell'effect size considera un ES di 0,2 come "piccolo", 0,5 come "medio"e uno di 0,8 o più come "grande".

IL REGISTRO PER L'ADHD IN LOMBARDIA

A differenza del Registro italiano ADHD istituito nel 2007, al quale accedono solo i soggetti in trattamento farmacologico[13], dal giugno 2011 in Lombardia è attivo il Registro regionale ADHD, che monitora ogni bambino o adolescente che accede ai Centri di riferimento del ADHD per il sospettato o segnalato ADHD[14,15]. Il Registro regionale ADHD rappresenta quindi uno strumento unico e distintivo nel contesto europeo e internazionale per assicurare l'appropriatezza delle cure e la sicurezza dei farmaci utilizzati per il trattamento dei bambini con ADHD.

In merito alla diagnosi, tra gli obiettivi principali ci sono la definizione e il mantenimento di un percorso di valutazione diagnostica evidence-based, condiviso e applicato per tutti i bambini e adolescenti di età compresa tra i 5 e 17 anni che accedono a uno dei 18 Centri di riferimento per il sospetto di presenza di ADHD. Dopo la diagnosi, il protocollo condiviso prevede visite di follow-up da effettuare a intervalli periodici: a 3 e 6 mesi e successivamente ogni 6 mesi. I pazienti in trattamento con metilfenidato (MPH), inoltre, devono essere monitorati a distanza di 1 settimana e 1 mese dall'inizio della terapia (dopo 1 mese se in trattamento con atomoxetina – ATX).

Tutti i dati raccolti relativi alla valutazione diagnostica e ai follow-up sono analizzati mensilmente dal Laboratorio per la Salute Materno-Infantile dell'Istituto di Ricerche Farmacologiche Mario Negri IRCCS.

ORGANIZZAZIONE DEL CENTRO REGIONALE ADHD "MEDEA" DI BOSISIO PARINI (LC)

Il Centro ADHD "Medea" di Bosisio Parini effettua diagnosi e percorsi terapeutici per soggetti ADHD secondo le modalità condivise nel Progetto regionale. La diagnosi avviene all'interno dei percorsi del Polo di NPIA, o nel reparto di degenza. Al momento dell'accesso al Centro, ai genitori del minore viene chiesto di firmare il consenso per l'inserimento dei dati nel registro ADHD. Al termine del percorso diagnostico, le diverse tipologie di intervento sono prescritte in relazione alla gravità della sintomatologia, codificata con la CGI-S, e al funzionamento del bambino, all'eventuale comorbilità e alle risorse famigliari e ambientali. La condizione strutturale di

Centro sovra-territoriale, cui accedono famiglie provenienti da altre province e regioni, rende indispensabile per la frequenza dei percorsi di training il requisito di facile raggiungibilità del Centro da parte della famiglia. Nel dettaglio, sono previsti trattamenti di Parent Training (PT) e Child Training (CT) cognitivo-comportamentale, empowerment genitoriale cognitivo-comportamentale, counselling genitoriale, trattamento farmacologico.

ANALISI DEI DATI

L'analisi dei dati è stata effettuata utilizzando il software SAS (versione 9.2). Sono state riassunte le statistiche descrittive e usati i test Kruskal-Wallis o Chi-quadrato per determinare le differenze nelle caratteristiche della popolazione e tra i gruppi di soggetti. Le differenze statisticamente significative sono state valutate a un livello α di 0,05. Sono state applicate analisi di regressione logistica con selezione *stepwise* e livello di significatività di 0,05 per identificare in primo luogo i fattori di rischio associati all'ADHD e, successivamente, i fattori di rischio associati alla comorbilità, prendendo in considerazione come variabili indipendenti le caratteristiche socio-demografiche e anamnestiche, i sottotipi di ADHD, la gravità dei sintomi (solo per la seconda fase di analisi). Per valutare l'efficacia del trattamento, sono stati calcolati i residui standardizzati[16] e la dimensione dell'effetto *d* di Cohen[17]. Un residuo standardizzato è la differenza tra i valori osservati e quelli attesi per un singolo gruppo di trattamento: maggiore è il residuo, maggiore è il contributo del gruppo all'ampiezza del valore Chi-quadro ottenuto.

RISULTATI

Indici di prevalenza

Sono stati considerati i dati relativi a 378 soggetti (326 M, 86%; 52 F, 14%; età min 5 anni - max 17; età media 8,9 anni) presentati per sospetto ADHD, nel Centro di riferimento di Bosisiso Parini (LC) nel periodo 2011-2017 (figura 1). Al termine della valutazione, 306 soggetti (81%) hanno soddisfatto i criteri diagnostici per la presenza di ADHD (264 M, 86%; 42 F, 14%). La maggior parte dei soggetti ADHD (N=203, 66%) presentava un sottotipo combinato (ADHD-C), mentre 63 (21%) di tipo inattentivo (ADHD-I) e 40 (13%) di tipo iperattivo/impulsivo (ADHD-H). Nei soggetti ADHD, le comorbilità tendono a essere più frequenti in modo statisticamente significativo ($p < 0,01$) tra quelli con un punteggio di CGI-S uguale o maggiore di 5 (OR 2,09, IC 95% 1,15-3,82); nessuna relazione significativa è stata osservata tra sottotipo e comorbilità (ADHD tipo C: OR 1,43, IC 95% 0,79-2,58; ADHD tipo H: OR 1,00, IC 95% 0,45-2,21; ADHD tipo I: OR 0,68, IC 0,35-1,32).

La storia di ritardo nello sviluppo del linguaggio mostra un'associazione statisticamente significativa ($p<0,05$) con la presenza di ADHD in generale e nello specifico in comorbilità con altri disturbi. Gli indicatori legati al parto (basso peso alla nascita o nascita pre-termine <37 settimane) mostrano associazione statisticamente significativa ($p < 0,01$) con un esito del percorso di valutazione con altra diagnosi (tabella I).

Figura 1. **Diagramma di flusso di selezione della popolazione.**

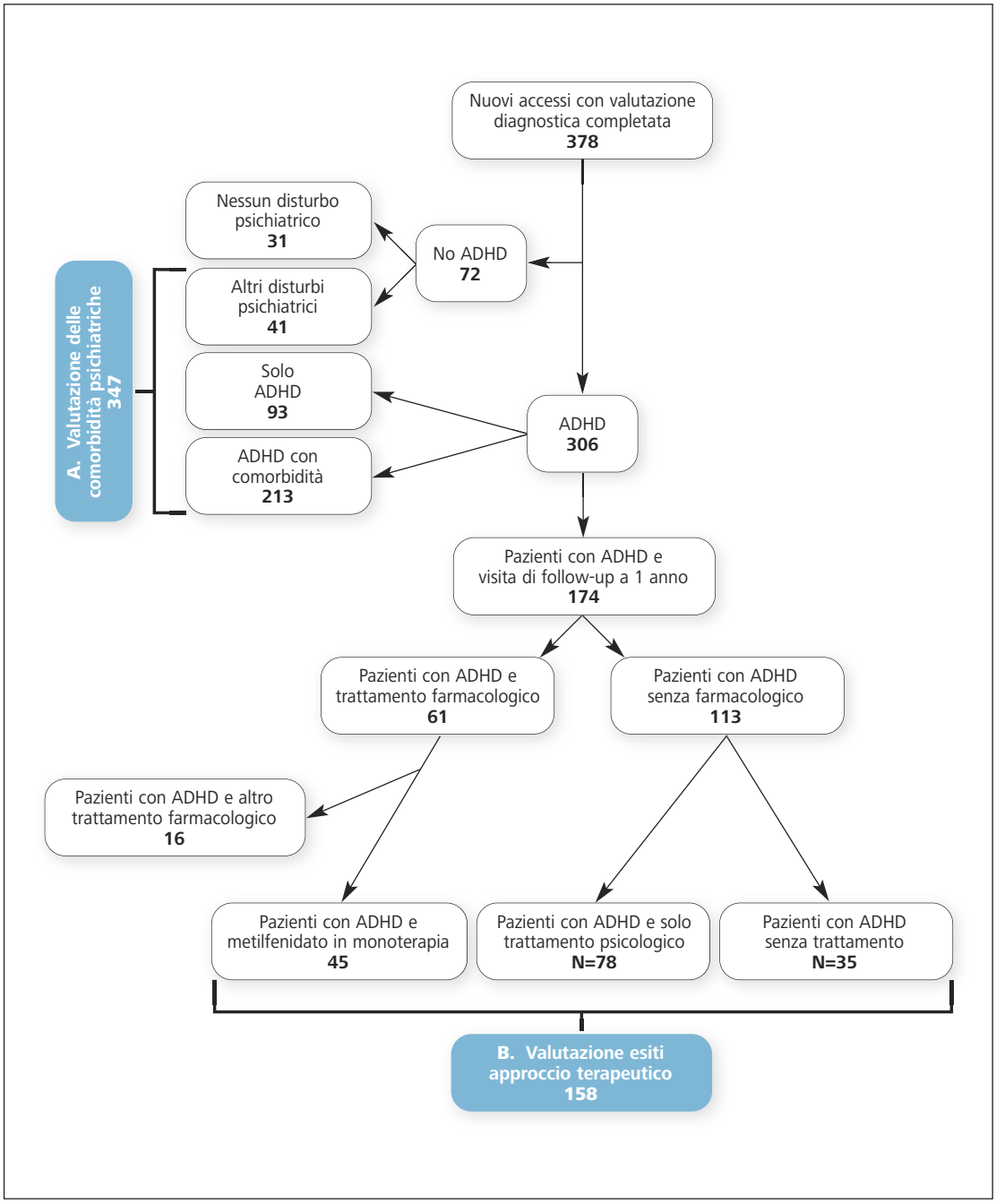

Tabella I. Caratteristiche socio-demografiche e anamnestiche dei pazienti selezionati.

Caratteristiche	ADHD (N=306)			NO ADHD (N=72)			Totale N=213 n (%)	p[1]
	Solo ADHD N=93 n (%)	ADHD con comorbilità N=213 n (%)	ADHD Totale N=306 n (%)	Nessun disturbo N=31 n (%)	Altri disturbi N=41 n (%)	No ADHD Totale N=72 n (%)		
Età alla diagnosi: media (DS) mediana	8,5 (2,3) 8	9,0 (2,3) 9	8,9 (2,3) 9	9,1 (2,7) 9	9,2 (1,9) 9	9,2 (2,3) 9	8,9 (2,3) 9	0,0973
12-17 anni	11 (12)	30 (14)	41 (13)	5 (16)	4 (10)	9 (13)	50 (13)	0,8497
Maschi	77 (83)	187 (88)	264 (86)	30 (97)	32 (78)	62 (86)	326 (86)	0,9695
Figlio unico	36 (39)	56 (26)	92 (30)	10 (32)	8 (20)	18 (25)	110 (29)	0,2683
Nato all'estero	2 (2)	13 (6)	15 (5)	—	—	—	15 (4)	0,0694
Adottivo	3 (3)	11 (5)	14 (5)	—	2 (5)	2 (3)	16 (4)	0,5699
Bocciato	2 (2)	12 (6)	14 (5)	—	1 (2)	1 (1)	15 (4)	0,2640
Insegnante sostegno	3 (3)	38 (18)	41 (13)	—	5 (12)	5 (7)	46 (12)	0,2472
Occupazione genitori	51 (55)	104 (49)	155 (51)	16 (52)	21 (51)	37 (51)	192 (51)	0,9847
ADHD in famiglia	5 (5)	18 (8)	23 (8)	2 (6)	2 (5)	4 (6)	27 (7)	0,6135
Parto cesareo	18 (21)	45 (24)	63 (23)	6 (21)	10 (26)	16 (24)	79 (23)	0,8184
Inappropriatezza parto[2]	7 (8)	21 (11)	28 (10)	9 (31)	7 (18)	16 (24)	44 (13)	0,0042*
Allattamento[3]	28 (74)	57 (75)	85 (75)	5 (56)	9 (56)	14 (56)	99 (71)	0,0659
Ritardo motorio	3 (3)	14 (7)	17 (6)	1 (3)	1 (3)	2 (3)	19 (6)	0,3334
Ritardo linguistico	17 (19)	63 (33)	80 (28)	3 (10)	7 (18)	10 (14)	90 (26)	0,0304*

1. test χ^2_{MH} per variabili categoriche, test di Kruskall-Wallis per variabili continue; **2.** pre-termine (<37 sett.), oppure sottopeso (<2500 gr); **3.** ≥3 mesi.

Tra i 347 soggetti che al termine della valutazione hanno soddisfatto i criteri per almeno un disturbo, 123 (35%) soggetti hanno ricevuto una diagnosi singola, mentre 224 (65%) soggetti presentano due (N=142, 41%) o più di due disturbi (N=82, 24%) in compresenza. Tra tutti i 306 soggetti diagnosticati come ADHD, solo 93 (30%) presentano il disturbo isolato, mentre 213 (70%) presentano ADHD una o più comorbilità psichiatriche, in particolare 132 (43%) in associazione a un solo altro disturbo mentre 81 (26%) hanno almeno tre disturbi in comorbilità. Nei soggetti con ADHD, DSA (48%), disturbi del sonno (21%), disturbi d'ansia (16%), ritardo mentale (17%), disturbi del linguaggio (12%), DOP (12%) e ASD (10%) sono le comorbilità più frequenti. La frequenza di disturbi del sonno (21 vs 7%; p <0,05) è significativamente più alta nei soggetti ADHD rispetto ai soggetti con altre diagnosi.

La presenza di disturbi del sonno si configura come fattore di rischio significativo (associazione moderata) per la presenza di ADHD. La variabile "Disturbi d'ansia" presenta un'associazione moderata di rischio per "Disturbi del sonno" (tabella II).

Tabella II. **Fattori di rischio[1] per disturbi psichiatrici più frequenti.**

Disturbi psichiatrici	Fattori di rischio	OR	IC 95%	p
Disturbi dell'apprendimento	Disturbi del sonno	0,35	(0,14 – 0,86)	0,0214
	Disturbi d'ansia	0,26	(0,11 – 0,65)	0,0039
	Ritardo mentale	0,01	(0,00 – 0,09)	<0,0001
	Disturbi del linguaggio	0,13	(0,04 – 0,41)	0,0005
	Autismo	0,07	(0,02 – 0,21)	<0,0001
	Disturbo oppositivo provocatorio	0,07	(0,02 – 0,25)	<0,0001
	Tic	0,06	(0,02 – 0,26)	0,0001
	Disturbi dell'umore	0,08	(0,01 – 0,48)	0,0058
Disturbi del sonno	Disturbi d'ansia	2,28	(1,03 – 5,02)	0,0418
Disturbi d'ansia	—			
Ritardo mentale	Ritardo linguistico	3,18	(1,29 – 7,80)	0,0117
	Disturbi dell'apprendimento	0,02	(0,00 – 0,19)	0,0003
	Disturbi d'ansia	0,08	(0,01 – 0,65)	0,0179
	Autismo	0,25	(0,07 – 0,99)	0,0487
Disturbi del linguaggio	Ritardo motorio	3,78	(1,10 – 12,96)	0,0344
	Ritardo linguistico	3,04	(1,27 – 7,28)	0,0127
Autismo	Disturbi dell'apprendimento	0,25	(0,09 – 0,70)	0,0083
Disturbo oppositivo provocatorio	Sostegno scolastico	5,54	(2,11 – 14,56)	0,0005
	Parto cesareo	2,96	(1,15 – 7,64)	0,0247
	Disturbi dell'apprendimento	0,02	(0,06 – 0,63)	0,0059
Tic	Disturbi dell'apprendimento	0,25	(0,07 – 0,89)	0,0324
Disturbi dell'umore	Maschi	0,14	(0,03 – 0,60)	0,0081
Disturbi della condotta	—			
Disturbi della coordinazione motoria	—			
ADHD	Disturbi del sonno	3,43	(1,00 – 11,75)	0,0499

1.per ciascun disturbo psichiatrico è stato calcolato un modello di regressione logistica *stepwise* con le variabili sociodemgrafiche e cliniche, e con tutte le comorbilità psichiatriche (compreso ADHD).

Approcci terapeutici

I dati riguardanti la valutazione e l'esito degli approcci terapeutici sono stati analizzati solo per i pazienti con ADHD in carico al Centro regionale che avessero completato il follow-up in un periodo di 12±6 mesi previsto dalla procedura condivisa tra i Centri. Tra i pazienti sottoposti a trattamento farmacologico, con o senza intervento psicologico associato, sono stati considerati solo quelli trattati con MPH (n=45, 74%), escludendo coloro i quali avessero ricevuto altre tipologie di farmaco o in politerapia (n=16), al fine di garantire una valutazione omogenea dell'outcome del trattamento.

Sono stati confrontati i dati relativi ai diversi trattamenti prescritti al momento della diagnosi e quelli effettivamente ricevuti durante l'anno successivo alla diagnosi per 158 soggetti con ADHD con e senza altre comorbilità (tabella III). Le percentuali di terapie psicologiche erogate sono inferiori rispetto a

Tabella III. Trattamento prescritto alla diagnosi e trattamento effettuato entro la visita di follow-up nei pazienti con ADHD e visita di follow-up a 1 anno.

Trattamento[1]	Solo ADHD (N=53)		ADHD con comorbilità (N=105)		ADHD totale (N=158)	
	Prescritto n (%)	Effettuato n (%)	Prescritto n (%)	Effettuato n (%)	Prescritto n (%)	Effettuato n (%)
A	13 (25)	7 (13)	21 (20)	8 (8)	34 (22)	15 (9)
C	—	—	—	3 (3)	—	3 (2)
F	1 (2)	7 (13)	6 (6)	20 (19)	7 (4)	27 (17)
N	—	13 (25)	—	22 (21)	—	35 (22)
T	31 (58)	24 (45)	56 (53)	36 (34)	87 (55)	60 (38)
X	8 (15)	2 (4)	22 (21)	16 (15)	30 (19)	18 (11)

1. Trattamento prescritto alla diagnosi: ai pazienti a cui non è stato prescritto niente alla diagnosi è stato assegnato d'ufficio il trattamento C (*Counselling*) – Nel caso del Centro di Bosisio Parini non si è verificato per nessun paziente.
Trattamento effettuato entro la visita di *follow-up*: A = Almeno un altro trattamento psicologico (esclusi *training* e *counselling*); C = Solo *counselling;* F = Solo Metilfenidato; N = Nessun trattamento; T = *Training* (almeno uno tra CT, PT, TT); X = Combinato (metilfenidato e almeno un trattamento psicologico qualsiasi).

quanto prescritto alla diagnosi in entrambi i gruppi di ADHD con e senza comorbilità; almeno uno tra parent o child *training* è effettuato per il gruppo ADHD senza comorbilità (45%) rispetto a quello con comorbilità (34%). La stessa tendenza di riduzione tra prescrizione ed erogazione è osservabile per le indicazioni di intervento combinato (MPH e almeno un trattamento psicologico), tanto per i soggetti con ADHD senza comorbilità (da 15% prescritto a 4% erogato), quanto per i soggetti ADHD con comorbilità (da 21 a 15%).

Rispetto alla prescrizione di trattamento "solo farmacologico" al momento della diagnosi, sono maggiori le percentuali di soggetti che al follow-up hanno ricevuto solo MPH come trattamento: ADHD senza comorbilità (da 2 a 13%), ADHD con comorbilità (da 6 a 19%). A nessun soggetto al momento della diagnosi è stata data indicazione di "nessun trattamento", ma all'osservazione in follow-up 1 soggetto su 4 (25%) con ADHD senza comorbilità e circa 1 su 5 in comorbilità (21%) non hanno ricevuto alcun intervento terapeutico.

Le percentuali relative ai trattamenti prescritti e ricevuti in pazienti con ADHD in associazione alle comorbilità più frequenti nel campione osservato mostrano tendenze simili. Solo per le indicazioni di "trattamento combinato" per soggetti ADHD+DSA, di "intervento psicologico" per ADHD+ Disturbi d'ansia e di "training" per ADHD+ASD, si rileva esatta corrispondenza di prescrizione ed effettiva erogazione di trattamento; tuttavia, la percentuale di soggetti ADHD+ASD è la più elevata tra i gruppi di ADHD con specifica comorbilità che non ricevono alcun trattamento (tabella IV).

Indici di miglioramento

La valutazione degli esiti clinici è stata effettuata con la Scala CGI-Improvement. Nel gruppo ADHD totale (N = 158), 32 (20%) soggetti hanno mostrato un miglioramento elevato e 49 (31%) un miglioramento apprezzabile, mentre 65 (41%) non hanno mostrato alcun cambiamento cli-

Tabella IV. Trattamento prescritto alla diagnosi e trattamento effettuato entro la visita di follow-up nei pazienti con ADHD e visita di follow-up a 1 anno, per tipo di comorbilità.

Trattamento[1]	Disturbi dell'apprendimento (N=50)		Disturbi del sonno (N=26)		Disturbi d'ansia (N=16)		Autismo (N=11)	
	Prescritto n (%)	Effettuato n (%)	Prescritto n (%)	Effettuato n (%)	Prescritto n (%)	Effettuato n (%)	Prescritto n (%)	Effettuato n (%)
A	11 (22)	4 (8)	4 (15)	1 (4)	3 (19)	3 (19)	6 (55)	1 (9)
C	—	2 (4)	—	—	—	1 (6)	—	—
F	1 (2)	7 (14)	1 (4)	7 (27)	—	1 (6)	1 (9)	4 (36)
N	—	10 (20)	—	5 (23)	—	3 (19)	—	4 (36)
T	28 (56)	17 (34)	13 (50)	9 (35)	10 (63)	5 (31)	2 (18)	2 (18)
X	10 (20)	10 (20)	8 (31)	4 (15)	3 (19)	3 (19)	2 (18)	—

1. Trattamento prescritto alla diagnosi: ai pazienti a cui non è stato prescritto niente alla diagnosi è stato assegnato d'ufficio il trattamento C (*Counselling*) – Nel caso del Centro di Bosisio Parini non si è verificato per nessun paziente. Trattamento effettuato entro la visita di *follow-up*: A = Almeno un altro trattamento psicologico (esclusi *training* e *counselling*); C = Solo *counselling;* F = Solo Metilfenidato; N = Nessun trattamento; T = *Training* (almeno uno tra CT, PT, TT); X = Combinato (metilfenidato e almeno un trattamento psicologico qualsiasi).

nico significativo e 12 (8%) sono peggiorati. Percentuali simili sono rilevate sia nel sottogruppo ADHD senza comorbilità che nel sottogruppo ADHD con comorbilità; nel gruppo ADHD senza comorbilità è superiore la percentuale di soggetti "migliorati" rispetto al totale, nel gruppo ADHD con comorbilità è maggiore la percentuale di "molto migliorati" rispetto al gruppo ADHD totale.

I gruppi con comorbilità ADHD + Disturbi del sonno e ADHD + ASD hanno riportato percentuali più elevate di soggetti peggiorati, 12 e 9% rispettivamente; per il gruppo ADHD + ASD è più alta anche la percentuale di soggetti migliorati (36%).

Nei soggetti con ADHD + ASD coloro i quali avevano ricevuto trattamento "solo MPH" avevano significative maggiori probabilità di miglioramento se confrontati con le altre tipologie di trattamento. Nello stesso gruppo, è statisticamente significativa la relazione tra "nessun trattamento" e la minor possibilità di miglioramento. Inoltre, è stato valutato se una sintomatologia più grave in fase di diagnosi (con riferimento a CGI-S <5 vs ≥5) potesse agire come moderatore per il tasso di miglioramento: nessuna differenza significativa è stata osservata nelle frequenze di miglioramento per tutti i gruppi di trattamento (p>0,05).

Efficacia del trattamento

Nel campione ADHD totale, si osserva un ES piccolo (0,24) per il trattamento "solo MPH", mentre un ES medio (0,50) per il trattamento combinato (farmacologico e psicologico). Confrontando i gruppi ADHD senza comorbilità e ADHD con comorbilità, il trattamento "solo MPH" ha mostrato un ES medio (0,71) per i pazienti con solo ADHD e un ES minore (0,13) per l'ADHD con comorbilità. Il trattamento combinato (farmacologico e psicologico) mostra un ES medio (0,50) sia per gli ADHD senza comorbilità, sia per gli ADHD con comorbilità. Altri trattamenti hanno mostrato valori di ES inferiori per questi gruppi (tabella V).

Tabella V. Esito dei trattamenti dei pazienti con ADHD e visita di follow-up a 1 anno rispetto al gruppo senza trattamento.

Trattamento[1]	Solo ADHD (N=53)				ADHD con comorbilità (N=105)				ADHD totale (N=158)			
		Punteggio CGIS				Punteggio CGIS				Punteggio CGIS		
	N	Base media (DS)	FUP media (DS)	ES[2]	N	Base media (DS)	FUP media (DS)	ES[2]	N	Base media (DS)	FUP media (DS)	ES[2]
A	7	4,1 (0,9)	4,0 (0,8)	0,00	8	3,6 (0,5)	3,6 (0,5)	-0,46	15	3,9 (0,7)	3,8 (0,7)	-0,27
C	—	—	—	—	3	4,0 (-)	4,3 (0,6)	-0,86	3	4,0 (-)	4,3 (0,6)	-0,86
F	7	4,4 (0,8)	3,7 (0,8)	0,71	20	5,1 (0,5)	4,7 (0,8)	0,13	27	4,9 (0,6)	4,4 (0,9)	0,24
T	24	4,0 (0,6)	3,8 (0,6)	0,13	36	4,1 (0,5)	3,9 (0,6)	-0,14	60	4,1 (0,5)	3,9 (0,6)	-0,14
X	2	5,0 (—)	4,5 (0,7)	0,50	16	4,9 (0,6)	4,2 (0,8)	0,50	18	4,9 (0,5)	4,2 (0,8)	0,50
N	13	3,8 (0,9)	3,7 (0,9)	(rif.)	22	4,0 (0,7)	3,7 (0,8)	(rif.)	35	4,0 (3,7)	3,7 (0,8)	(rif.)

1. Trattamento effettuato entro la visita di follow-up: A = Almeno un altro trattamento psicologico (esclusi *training* e *counselling*).
C = Solo *counselling*. F = Metilfenidato. N = Nessun trattamento. T = *Training* (almeno uno tra CT, PT, TT) X = Combinato (Metilfenidato e almeno un trattamento psicologico qualsiasi).
2. *Effect size* di Cohen, calcolato con la formula: $ES = \frac{[\mu(CGIS\ V1) - \mu(CGIS\ V2)]_{\text{trattati}} - [\mu(CGIS\ V1) - \mu(CGIS\ V2)]_{\text{non trattati}}}{\left(\frac{[\sigma(CGIS\ V2)]_{\text{trattati}} + [\sigma(CGIS\ V2)]_{\text{non trattati}}}{2}\right)}$

Le analisi per gruppi di ADHD con comorbilità più frequenti (DSA, disturbi del sonno, disturbi d'ansia, ASD) mostrano un ES medio (0,71) del trattamento combinato per soggetti con ADHD + DSA, gruppo per il quale tutte le altre tipologie di trattamento hanno ES negativo. Per ADHD + disturbi del sonno si ottengono ampiezze di ES medio (0,53) per i training con genitore o bambino (PT e/o CT) e grande (0,87) per trattamento combinato. Nel gruppo ADHD + Disturbi d'ansia i soggetti che hanno ricevuto trattamento "solo MPH" mostrano ES molto grande (3,33), mentre i soggetti che hanno ricevuto trattamento combinato o training PT/CT mostrano un ES grande (0,86 e 0,88 rispettivamente). Per il gruppo ADHD + ASD non sono osservabili ES positivi (tabella VI).

DISCUSSIONE

Indici di prevalenza

Nel campione considerato, la maggior parte (70%) dei soggetti alla prima diagnosi di ADHD aveva in comorbilità uno o più disturbi, in largo accordo con quanto indicato da studi precedenti[8] e con i dati provenienti dal registro ADHD lombardo[7]. Si è osservato che per 2 bambini e adolescenti su 3 alla diagnosi di ADHD è associato almeno un altro disturbo psicopatologico, dato in accorso con quanto riportato in letteratura sulla rarità dell'ADHD "puro", anche nella popolazione generale[18]. Il sottotipo più rappresentato nel campione è il combinato (ADHD-C, 66%), sia per ADHD senza comorbilità (61%) che per ADHD associato ad altri disturbi (69%), sebbene per la maggior probabilità di osservare disturbi comorbidi in questo sottotipo non è statisticamente significativa, come invece riscontrato nello studio multi-centrico precedente[7]. C'è invece una significativa probabilità di riscontrare un numero superiore di comorbilità nei soggetti ADHD con profilo di maggior gravità sintomatologica (CGI-S ≥5) al momento della diagnosi. Inoltre, c'è maggior pro-

Tabella VI. Esito dei trattamenti dei pazienti con ADHD e visita di follow-up a 1 anno rispetto al gruppo senza trattamento.

	Disturbi dell'apprendimento (N=50)				Disturbi del sonno (N=26)			
		Punteggio CGIS				Punteggio CGIS		
Trattamento effettuato[1]	N	Base media (DS)	FUP media (DS)	ES[2]	N	Base media (DS)	FUP media (DS)	ES[2])
A	4	3,8 (0,5)	3,8 (0,5)	-0,46	1	3,0 (-)	3,0 (-)	0,00
C	2	4,0 (-)	4,5 (0,7)	-1,07	—	—	—	—
F	7	4,7 (0,5)	4,6 (0,5)	-0,31	7	5,1 (0,7)	5,0 (1,2)	0,10
T	17	4,2 (0,4)	4,0 (0,5)	-0,15	9	4,1 (0,6)	3,7 (0,7)	0,53
X	10	5,1 (0,3)	4,2 (0,9)	0,71	4	4,8 (1,3)	3,8 (1,5)	0,87
N	10	4,1 (0,6)	3,8 (0,8)	(rif.)	5	3,8 (0,8)	3,8 (0,8)	(rif.)

	Disturbi d'ansia (N=16)				Autismo (N=11)			
		Punteggio CGIS				Punteggio CGIS		
Trattamento effettuato[1]	N	Base media (DS)	FUP media (DS)	ES[2]	N	Base media (DS)	FUP media (DS)	ES[2])
A	3	3,3 (0,6)	3,0 (-)	1,00	1	3,0 (-)	4,0 (-)	-3,00
C	1	4,0 (-)	4,0 (-)	0,00	—	—	—	—
F	1	5,0 (-)	4,0 (-)	3,33	4	5,3 (0,5)	5,0 (0,8)	-0,22
T	5	4,4 (0,5)	3,8 (0,8)	0,86	2	4,0 (-)	4,0 (-)	-1,00
X	3	4,7 (1,5)	4,0 (1,0)	0,88	—	—	—	—
N	3	3,7 (0,6)	3,7 (0,6)	(rif.)	4	4,8 (0,5)	4,3 (1,0)	(rif.)

1. Trattamento effettuato entro la visita di follow-up: A = Almeno un altro trattamento psicologico (esclusi *training* e *counselling*); C = Solo *counselling*; F = Metilfenidato; N = Nessun trattamento; T = *Training* (almeno uno tra CT, PT, TT); X = Combinato (Metilfenidato e almeno un trattamento psicologico qualsiasi).
2. Effect size di Cohen, calcolato con la formula: $ES = \frac{[\mu(CGIS\ V1) - \mu(CGIS\ V2)]_{trattati} - [\mu(CGIS\ V1) - \mu(CGIS\ V2)]_{non\ tratta}}{\left(\frac{[\sigma(CGIS\ V2)]_{trattati} + [\sigma(CGIS\ V2)]_{non\ trattati}}{2}\right)}$

babilità di comorbidità di 2 o più disturbi per soggetti con ADHD rispetto a soggetti con diagnosi di altri disturbi psichiatrici (70 e 26%, rispettivamente). Le comorbilità più frequentemente rilevate nel campione sono state: DSA, disturbi del sonno, disturbi d'ansia, ritardo mentale, disturbi del linguaggio, DOP e ASD, con indici di prevalenza leggermente diversi rispetto ad altri studi8, ma mostrano coerenza con i dati dello studio multi-centrico originale[7].

La frequenza di ADHD+DOP nel presente studio e in quello multi-centrico è inferiore a quanto riportato in letteratura (12 vs 15-75%)[8], con una prevalenza maggiore negli studi di popolazione (61%) rispetto a studi di campioni clinici (39%)[19]. La differenza può essere letta facendo riferimento al peculiare contesto italiano, per il quale studi precedenti[20] hanno osservato una percentuale inferiore di disturbi esternalizzanti (1,2%) in età evolutiva rispetto a quelli stimati in altri Paesi.

La frequenza di ADHD+ASD rilevata nel campione del Centro Medea (10%) è in linea con quanto riportato in letteratura, con indicazioni di 1 bambino ADHD su 8 (13%) con comorbilità ADHD + ASD[21].

Nel campione del Centro Medea la comorbilità più frequentemente rilevata è ADHD+DSA (48%). In accordo con quanto descritto in letteratura[21].

Nonostante non ci sia ancora chiarezza sui fattori eziopatogenetici nella assai frequente associazione dei due disturbi del neurosviluppo, nella revisione del 2011 Sexton e colleghi descrivono le caratteristiche comuni di ADHD e DSA (es. deficit di attenzione e inibizione della risposta, velocità di elaborazione e memoria di lavoro), delineando due ipotesi: un "modello a deficit multiplo", che postula che fattori genetici e neuropsicologici comuni aumentino la vulnerabilità a entrambi i disturbi, ma anche la possibilità che possano esistere percorsi di sviluppo separati per ADHD+DSA, rispetto all'ADHD o al DSA isolati[21].

Bambini o adolescenti con disturbi del sonno presentano un significativo fattore di rischio per ADHD, nel campione analizzato; contemporaneamente, si è osservata una significativa associazione tra i disturbi d'ansia come fattore di rischio per i disturbi del sonno. L'associazione tra ADHD e disturbi del sonno è ampiamente documentata[22], ma sono ancora poco chiare le relazioni tra i due disturbi ed eventuali funzioni intermedie di altri fattori. La mediazione dei disturbi d'ansia in comorbilità con l'ADHD sembra poter essere rilevante nel facilitare la presenza e il mantenimento di disturbi e disregolazioni del sonno. Nel dettaglio, l'ansia è associata ad aumentata probabilità di svegliarsi durante la notte, avere sonno irrequieto, aver paura di dormire nel buio, lamentarsi di difficoltà ad addormentarsi e andare in bagno durante la notte e a una diminuita probabilità di addormentarsi facilmente o di andare a letto volentieri.

Tra le caratteristiche socio-demografiche e anamnestiche, la storia di ritardo nello sviluppo del linguaggio è significativamente associata a maggior rischio di comorbilità. In età evolutiva, un ritardo di linguaggio è un fattore di rischio per un successivo Disturbo Specifico del Linguaggio (DSL) e per numerosi altri disturbi e spesso si presenta in co-occorrenza con sintomatologia ADHD già nei bambini pre-scolari[23]. Sembra che lo sviluppo del linguaggio in soggetti ADHD possa essere caratterizzato da difficoltà di organizzazione e monitoraggio della narrazione, riconducibili a deficit a carico delle funzioni esecutive. Inoltre, confrontando bambini con ADHD senza comorbilità e con ADHD e compresenti difficoltà linguistiche, i secondi mostrano peggiori prestazioni di memoria a breve termine, rievocazione di sequenze verbali e testi. Nei bambini ADHD che presentano anche difficoltà di linguaggio sembrano inoltre evidenziabili screzi a carico delle competenze pragmatiche, probabilmente correlati ai sintomi core di impulsività[24], che ricadono anche sulle competenze sociali[25].

Approcci terapeutici

Complessivamente si è osservato la diminuzione del numero di trattamenti psicologici effettuati rispetto a quanto prescritto alla chiusura del percorso psicodiagnostico. Questa tendenza riguarda sia i soggetti con ADHD senza comorbilità sia gli ADHD con comorbilità, senza differenze tra le diverse tipologie di intervento psicologico disponibile (CT/PT o altri interventi). Fa eccezione una ridotta percentuale (3%) di ADHD con comorbilità, ai quali è stato erogato un intervento di counselling, pur non essendo stato inizialmente prescritto. Alla maggior parte dei bambini e adolescenti con ADHD in fase di comunicazione della diagnosi è stato pre-

scritto un trattamento "training", con percentuali di effettiva realizzazione inferiori per gli ADHD con comorbilità. A pochi ADHD viene prescritto come primo intervento "solo farmaco", ma all'effettivo è il trattamento che vede almeno triplicata la sua attuazione nell'anno di presa in carico considerato. Il trattamento "Combinato" ha scarso tasso di realizzazione effettiva per gli ADHD senza comorbilità, mentre riesce a essere più frequentemente erogato ai soggetti ADHD con comorbilità. Queste tendenze si osservano anche nelle principali comorbilità rilevate (DSA, disturbi del sonno, disturbi d'ansia, ASD), con eccezione dei gruppi ADHD+DSA e ADHD+disturbo d'ansia, per i quali c'è più consistenza tra prescrizione ed erogazione del trattamento combinato. Per gli ADHD con comorbilità c'è comunque una minor frequenza di "nessun trattamento" erogato entro l'anno rispetto agli ADHD senza comorbilità: probabilmente maggior complessità del profilo comporta una priorità di erogazione di intervento all'interno dell'organizzazione del servizio. È infatti clinicamente ragionevole che i soggetti con maggior comorbilità e maggior compromissione siano considerati una priorità per l'intervento presentino una maggiore corrispondenza tra i trattamenti prescritti e quelli ricevuti.

In fase di prescrizione i dati appaiono coerenti con le indicazioni delle Linee Guida, ma nell'attuazione gli interventi sembrano risentire delle note e diffuse difficoltà relative all'organizzazione dei Servizi. Anche sul territorio italiano, come nel resto del mondo, solo un numero limitato di bambini e adolescenti con bisogni di salute mentale ha accesso alle cure. In particolare, l'accesso ai servizi sembra avvenire solo in 1 caso ogni 4 per i bambini con un disturbo neuropsichiatrico[25]. Le liste di attesa per la diagnosi e il trattamento rappresentano un problema importante da risolvere nella pratica clinica e potrebbero essere una possibile spiegazione della differenza riscontrata tra i trattamenti prescritti e quelli ricevuti. Infine, è importante ricordare che non tutti i fattori clinici e ambientali che potrebbero concorrere alla definizione delle strategie terapeutiche sono stati considerati in questo studio. Le analisi hanno infatti considerato solo l'anno direttamente successivo alla diagnosi e il campione non è sufficientemente esteso da poter garantire la corretta analisi di un numero più elevato di variabili.

Indici di miglioramento

Oltre la metà dei soggetti con ADHD, con e senza comorbilità, ha mostrato scostamenti in direzione positiva al follow-up ("migliorato" e "molto migliorato"); solo una percentuale minore presentava un peggioramento del quadro sintomatologico. In relazione alle diverse tipologie di trattamento erogato, non si è osservata differenza significativa degli indici di miglioramento in relazione al profilo di ADHD senza comorbilità o con comorbilità. Significativo appare invece il miglioramento con trattamento farmacologico per i soggetti ADHD+ASD, ma questo dato andrebbe valutato con cautela per l'esigua numerosità del campione.

Gli indici di miglioramento non sembrano essere correlati alla gravità clinica al momento della diagnosi. Questo potrebbe significare che sono state compiute scelte terapeutiche appropriate e ben differenziate in base ai diversi livelli di gravità alla diagnosi.

Efficacia del trattamento

Nel campione totale ADHD, l'intervento combinato è la modalità di trattamento con maggior ES, seguito dall'intervento "solo MPH", al confronto con il gruppo soggetti che non hanno ricevuto trattamento. Lo stesso andamento è delineato prendendo in considerazione il gruppo ADHD con comorbilità nel suo complesso. Per il gruppo ADHD senza comorbilità, invece, è più ampio l'effetto del trattamento "solo MPH", seguito da quello combinato e, con ampiezza minore, dall'intervento di training (CT/PT). I dati ottenuti sono in accordo con i principali risultati di uno degli studi di riferimento sull'efficacia dei trattamenti per l'ADHD[26], secondo il quale il trattamento combinato non avrebbe offerto per i sintomi *core* nell'ADHD vantaggi significativamente maggiori rispetto alla sola terapia farmacologica, ma potrebbe aver contribuito a migliori esiti generali sul funzionamento. Aggiornamenti successivi dello stesso studio[27] hanno mostrato una scarsa tenuta nel tempo dei miglioramenti del gruppo di trattamento solo farmacologico, rispetto al combinato. Pertanto, i risultati orientano alla conferma di indicazione di intervento combinato per l'intervento nell'ADHD.

Tra i gruppi di ADHD con comorbilità specifica, per gli ADHD+DSA è risultato maggiormente efficace l'intervento combinato. In questa tipologia di profilo di comorbilità sembrano infatti concorrere al buon esito dell'intervento tanto gli effetti derivanti dall'uso del MPH, quanto quelli del training cognitivo-comportamentale. La terapia farmacologica in soggetti ADHD+DSA migliora sul piano del comportamento i sintomi di impulsività e iperattività, così come la capacità di attenzione e il rendimento scolastico. Il farmaco andrebbe comunque associato a interventi psico-educativi, comportamentali e neuropsicologici adattati alle peculiari caratteristiche e difficoltà dei bambini e adolescenti con questo profilo di comorbilità.

In merito ai profili ADHD + disturbi del sonno, è minima l'ampiezza dell'effetto considerando il solo trattamento farmacologico. Al contrario, appare medio l'effetto del training (CT/PT), grande quello dell'intervento combinato. Nonostante siano noti i possibili effetti del MPH sulle prime fasi di addormentamento, rimangono comunque da approfondire le traiettorie a lungo termine, su cui sembrano avere influenza gravità sintomatologica, comorbilità e condizioni ambientali[28].

Sui soggetti ADHD+ansia si è osservato un effetto molto grande dato dalla terapia farmacologica da sola, cui concorre probabilmente una distorsione dovuta all'esiguità dei numeri. Effetti di grande ampiezza sono riscontrati per intervento solo psicologico, training (PT/CT) e trattamento combinato. Nonostante siano elementi da approfondire con campioni più ampi, gli indici di miglioramento e gli effect size nel campione analizzato sono comunque in linea con quanto riscontrato altrove.

CONCLUSIONI

Il lavoro presentato porta ulteriore contributo su come nell'ADHD la complessità sia condizione frequente. Questa informazione proveniente dalla ricerca e dalla pratica clinica comporta alcune conseguenze per i Servizi per la salute mentale, a partire dalla necessità per i clinici di tener

presente l'osservazione di possibili quadri di comorbilità associate mentre conducono la valutazione di sospetto ADHD.

Un livello di analisi successivo richiederebbe lo studio dell'esito clinico di ciascuna specifica comorbilità, dettagliando informazioni relative a tipologia e gravità dei sintomi, tipologia di intervento ricevuto, valutazione clinica nel tempo, con necessità di ampliamento del campione. Sarebbe infine utile monitorare la tenuta a lungo termine degli esiti di trattamento, prolungando il periodo di follow-up e valutare possibili integrazioni dei training (PT/CT) con elementi pensati in funzione delle specifiche comorbilità.

Nella prospettiva di una sempre maggior necessità di razionalizzazione della spesa pubblica e dei finanziamenti ai servizi per la salute, valutare e uniformare i protocolli di intervento sulla base di dati di esito consente di rendere più efficienti ed efficaci i servizi erogati dal SSN, offrendo alla cittadinanza la garanzia di interventi evidence-based[29].

In questa direzione, il Registro regionale per l'ADHD in Lombardia e le attività dei Gruppi di lavoro dei 18 Centri rappresentano un'esperienza unica nel panorama italiano. Il contributo maggiore è dato dalla costruzione concreta di buone pratiche calate nei servizi reali, a partire dalla condivisione della necessità di valutazioni accurate e complete, di protocolli uniformi e di definizione ed erogazione di percorsi di trattamento appropriati, modulati a partire dal profilo specifico del bambino. E, non da ultimo, dal valore aggiunto della misurazione e della verifica dei risultati ottenuti, che diventano punto di partenza per il proseguimento delle azioni di miglioramento. **R&P**

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"Il riconoscimento di un diritto è sempre un progresso"

In Italia, dove l'allineamento all'uso consolidato delle evidenze è in ritardo rispetto ad altre nazioni, cosi da penalizzare un uso appropriato dei farmaci, l'uso *off label* degli antipsicotici in età evolutiva è frequente.

In particolare, è frequente l'uso *off label* di aripiprazolo, litio, pimozide, risperidone, sebbene siano disponibili almeno 2 studi clinici di elevata qualità, controllati e randomizzati e siano farmaci contemplati nelle linee guida nazionali e internazionali, oltre che in revisioni sistematiche[1].

Per tali considerazioni e per lo stato di autorizzazione in UK e negli USA, in data 16 ottobre 2017 abbiamo fatto formale richiesta con relativa documentazione all'AIFA (Agenzia Italiana del Farmaco) che le specialità contenenti i 4 farmaci antipsicotici venissero inserite nell'elenco delle specialità medicinali erogabili a totale carico del SSN ai sensi della Legge 648/96 per le indicazioni documentate.

Nella seduta del 13-15 novembre 2018, la Commissione Tecnico Scientifica dell'AIFA ha espresso parere alle richieste presentate[2].
Con la sola eccezione del litio, per la quasi totalità delle richieste per aripiprazolo, pimozide e risperidone è stato espresso parere favorevole.

Tale provvedimento costituisce un riconoscimento formale per le terapie di provata efficacia in età evolutiva che rappresentano bisogni largamente inevasi, come l'autismo e la Sindrome di Tourette. Un provvedimento che favorisce l'accesso alle cure: diritto di ogni cittadino.

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1. Bonati M, Reale L, Clavenna A, Putignano D, Piovani D, Miglio D. Off label e diritto alle cure disponibili più appropriate. Il caso degli antipsicotici per i disturbi psichiatrici in età evolutiva. Ricerca&Pratica 2017; 33: 247-61.
2. www.aifa.gov.it/sites/ default/files/evento/Esiti_APA_ CTS_13-15_ novembre2018.pdf

Ancora su pubblicità non veritiera e ingannevole

Sul numero 201 di R&P (pag. 111-113) e su Politiche del Farmaco (http://politichedelfarmaco.it/) era riportata la segnalazione fatta al Ministero della Salute della "Pubblicità non veritiera e ingannevole" del prodotto Equazen®. Sul numero 202 di R&P (pag. 174) è stata riportata la risposta del Ministero che la documentazione era stata trasmessa all'Autorità Garante della Concorrenza e del Mercato. Di seguito la comunicazione dell'Autorità Garante che ne documenta l'archiviazione e la replica inviata. ***Red.***

Autorità Garante della Concorrenza e del Mercato

Rif. N. DS2174_15

Oggetto: istanza pervenuta il 4 ottobre 2018 (prot. N. 67850/2028).

Si comunica che l'Autorità, nella sua adunanza del 10 ottobre 2018, ha esamitano la fattispecie segnalata e ne ha deliberato l'archiviazione per manifesta infondatezza, ai sensi dell'art. 5, comma 1, lett. C), del *"Regolamento sulle procedure istruttorie in materia di pubblicità ingannevole e comparativa, pratiche commerciali scorrette, violazione dei diritti dei consumatori nei contratti, violazione del divieto di discriminazioni e clausole vessatorie"*, adottato dall'Autorità con delibera del 1 Aprile 2015.

L'Autorità, in particolare, ha ritenuto che nella fattispecie segnalata, reltiva alla comunicazione commerciale dell'integratore alimentare *Equazen*, destinata ai professionisti, risultino assenti gli elementi di fatto idonei a giustificare ulteriori accertamenti in quanto la dichiarazione sul miglioramento della capacità di lettura e delle funzioni cognitive nei bambini non risulta un vanto in sé, ma riferito e circoscritto agli esiti dello studio scientifico "Oxford – Durham Study" (*"uno studio… ha mostrato come l'assunzione regolare di un integratore alimentare a base di omega 3 e omega 6, in uno speciale rapporto, abbia nettamente migliorato la loro abilità di lettura e scrittura, rispoetto a pazienti trattati con il placebo"*).

Si evidenzia, infine, che il predetto Regolamento è reperibile sul sito istituzionale dell'Autorità, all'indirizzo internet *www.agcm.it*

IL DIRETTORE GENERALE
Giovanni Calabrò.

Preso atto dell'archiviazione "per manifesta infondatezza" vogliamo sottolineare "in particolare":

- la comunicazione commerciale non era "destinata ai professionisti" ma anche ai cittadini con materiale diversificato, come documentato nella segnalazione (allegati 1 e 2 della nostra segnalazione al Ministero della Salute);
- circa la dichiarazione *"uno studio … ha mostrato come l'assunzione regolare di un integratore alimentare a base di omega 3 e omega 6, in uno speciale rapporto, abbia nettamente migliorato le loro abilità di lettura e scrittura, rispetto a pazienti trattati con placebo"*, ma riferito e circoscritto agli esiti dello studio scientifico Oxford-Durham Study", questa fa riferimento ad uno studio del 2005 i cui risultati sono stati ridiscussi e anche confutati da studi successivi condotti anche dagli stessi autori del lavoro citato (come da noi sottolineato al punto 3 della segnalazione). Come riportato dalla dottoressa Ferri nel trasmettere la segnalazione, l'EFSA (parere EFSA- Q- 2014 – 00462) ha ritenuto sulla base degli studi disponibili che non vi fosse una dimostrazione di un nesso di tipo causa-effetto tra l'assunzione dell'integratore e il miglioramento della capacità di lettura;
- nella comunicazione commerciale destinata ai genitori (allegato 2 della segnalazione da noi inviata al Ministero della Salute) si lascia intendere che la carenza di nutrienti, tra cui gli acidi grassi polinsaturi, possa portare a *"iperattività, deficit di attenzione, difficoltà di relazione, disturbi della sfera emotiva e problemi dell'apprendimento". Inoltre, si afferma che "Diversi studi, condotti su bambini con questi disturbi, dimostrano come l'integrazione di questi acidi grassi … possa aiutare il bambino nelle attività quotidiane e scolastiche"* citando due soli riferimenti: l'Oxford-Durham study (di cui sopra) e lo studio di Barragan et al. [referenza 7 della segnalazione], che si caratterizza per i limiti metodologici. La valutazione dell'efficacia dell'integratore dovrebbe tenere conto dei risultati complessivi degli studi scientifici condotti, mentre la selezione di pochi studi favorevoli potrebbe sovrastimare i possibili benefici e fornire informazioni parziali, non generalizzabili e per il consumatore, che non ha le capacità di discernere, ingannevoli.

Infine, nel caso dell'integratore Equazen®, si potrebbe ravvisare la violazione di quanto previsto al comma 2 punto a dell'articolo 21 *del Codice del Consumo "2. È altresì considerata ingannevole una pratica commerciale che, nella fattispecie concreta, tenuto conto di tutte le caratteristiche e circostanze del caso, induce o è idonea ad indurre il consumatore medio ad assumere una decisione di natura commerciale che non avrebbe altrimenti preso e comporti: a) una qualsivoglia attività di commercializzazione del prodotto che ingenera confusione con i prodotti, i marchi…"*, dal momento che è in commercio in Italia un farmaco per il trattamento dell'ADHD contenente metilfenidato dal nome commerciale Equasym®.

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Terapia dell'avventura: principi, pratica, prospettive

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Pervenuto il 28 settembre 2018.

Riassunto. Gli alti tassi di disagio psicologico, disabilità e/o malattia cronica segnalati tra bambini, adolescenti e giovani adulti rappresentano uno stimolo recente allo sviluppo e alla valutazione di nuove iniziative. La terapia dell'avventura (TdA), realizzata attraverso la navigazione a vela o la permanenza in montagna, è una strategia efficace per aumentare il benessere dei beneficiari, implementando autostima, autonomia e abilità sociali. Viene qui descritto il modello "Nave Italia" e vengono discusse prospettive di sviluppo in un settore non ancora in grado di produrre ricerca e formazione di alta qualità, secondo i criteri stabiliti dalla tradizione medica.

Parole chiave. Disabilità, disagio psicologico, terapia dell'avventura.

Adventure therapy: principles, practice, perspectives.

Summary. The high rates of psychological distress, disability and/or chronic illness reported among children, adolescents and young adults, are a recent stimulus for the development and evaluation of new initiatives. Adventure therapy, realized through sailing navigation or stay in the mountains are effective strategies to raise the welfare of the beneficiaries, implementing self-esteem, autonomy and social skills. A "Nave Italia" model is described and prospects for development in a sector not yet capable to produce high quality research and training, according to traditional gold standard criteria by medical research, are discussed.

Key words. Adventure therapy, disability, psychological distress.

Introduzione

Gli alti tassi di disagio familiare, sociale, psicologico o di vera e propria disabilità o malattia cronica segnalati tra bambini, adolescenti, giovani adulti e anziani rappresentano uno stimolo relativamente recente allo sviluppo e alla valutazione di nuove iniziative[1,2]. La terapia dell'avventura (TdA), realizzata attraverso la navigazione a vela[3,4] o il soggiorno in montagna[5], è una strategia efficace per elevare il benessere dei beneficiari, implementarne autostima, autonomia e capacità relazionali (*social skills*). La TdA offre, inoltre, innovativi strumenti di prevenzione, intervento precoce e trattamento per persone con problemi comportamentali, psicologici e psicosociali. Può attrarre giovani a rischio, meno sensibili ai tradizionali interventi psicoterapeutici ed essere utilizzata per persone con disabilità. La Tda, riportata in letteratura anche come Wilderness Adventure Therapy (WAT), è caratterizzata dalla scelta di luoghi in cui l'esposizione alla natura del paziente (mare, montagna) prevede contesti condizionati da tempo meteorologico e tipologia dei luoghi, tutti di particolare fascino naturalistico. Dati relativi all'efficacia della WAT sono stati pubblicati da Bowen et al.[6] e valutati sulla base del pre-programma, del post-programma e delle risposte di follow-up ai questionari self-report dei partecipanti. Tali dati indicano che pazienti ambulatoriali adolescenti con problemi di salute mentale, che hanno completato un intervento WAT di 10 settimane, mostrano una dimensione dell'effetto (*effect size*) media a breve termine positivo e statisticamente significativo (0,26), con miglioramenti moderati e statisticamente significativi nella resilienza psicologica e nell'autostima sociale. Gli effetti a breve termine si sono mantenuti entro gli intervalli di confidenza al 90%. I cambiamenti a breve termine sono stati mantenuti al follow-up di tre mesi, a eccezione del funzionamento della famiglia (riduzione significativa) e della pulsione al suicidio (miglioramento significativo). Vi è stata una riduzione statisticamente significativa della sintomatologia depressiva e miglioramenti significativi nel funzionamento comportamentale ed emotivo. Anche per bambini e adolescenti oncologici, un programma di TdA della durata di una settimana ha aumentato i livelli di attività fisica durante l'esperienza e 3 mesi dopo la fine del campo, sebbene gli effetti siano stati attenuati nel tempo[7]. I risultati sugli effetti psicologici della TdA su giovani sopravvissuti al cancro (età 18-39) sono stati pubblicati sulla base di un programma di 6 giorni, che includeva istruzione personale e supervisione su kayak, surf o arrampicata. Rispetto a un gruppo di controllo, i partecipanti al programma hanno migliorato l'immagine corporea, l'autocompassione e l'autostima, risolto problemi di depressione e alienazione. Chi ha partecipato a una seconda settimana non ha mostrato risultati migliori rispetto ai pazienti che hanno vissuto l'avventura di una sola settimana[8]. Adolescenti obesi con disturbo del comportamento alimentare inseriti in percorsi outdoor avventurosi hanno dimostrato una significativa perdita di peso nel tempo[9]. Altre osservazioni su vari tipi di intervento esperienziale outdoor, confermano l'efficacia di processi avventurosi, emotivamente significativi, costruiti in un contesto ludico

relazionale intenso, sullo stato di benessere fisico e mentale dei partecipanti, il che suggerisce che la WAT possa essere pianificata come vera e propria terapia in soggetti resi fragili da disabilità, disagio, malattia cronica o disturbo sociale.

La fondazione Tender to Nave Italia (TTNI) è una organizzazione non lucrativa di utilità sociale (ONLUS) che ha sviluppato programmi di TdA dal 2007, in modo originale, grazie all'inserimento di regole e gerarchie militari, sia sul mare sia in montagna, previo accordo con il Ministero della Difesa e lo Stato Maggiore della Marina Militare Italiana e dell'Esercito Italiano, Truppe alpine. Tale sviluppo ha coinvolto nei dieci anni 4263 persone tra beneficiari e operatori sociosanitari, medici, infermieri, educatori. Ciascun progetto di navigazione a vela sul brigantino Italia coinvolge da 16 a 22 persone e 22 militari della marina, per un totale di circa 45 persone per imbarco. Il numero di imbarchi è di 22 all'anno per un periodo di 22 settimane ogni anno. I progetti "dalla nave alla neve" si sviluppano in Val d'Aosta, presso il padiglione Loreti Beghé dell'Ostello di Arpy, donato dalla ONLUS Camici & Pigiami; coinvolgono 30 persone per gruppo e un numero di Alpini variabile da 3 a 9, in ragione della tipologia dei beneficiari. Il numero dei progetti in montagna varia da 11 a 20 all'anno suddivisi tra stagione estiva e invernale.

La presenza dei militari è elemento organico in ciascun progetto di TdA con obiettivi di incremento di autostima, autonomia e social skill, elementi indispensabili alla crescita percepita del benessere individuale[3]. La metodologia Nave Italia combina i principi chiave dell'inclusione con una terapia personalizzata basata su impegno, rispetto di regole e gerarchie, elaborazione condivisa delle emozioni suscitate dall'avventura. Ogni programma realizzato a vantaggio di ospedali, scuole, servizi sanitari pubblici e privati non profit viene valutato tramite una combinazione di misure psicologiche pre- e post-intervento e interviste con partecipanti, operatori, medici infermieri e insegnanti. I risultati sinora ottenuti[3,10,11] suggeriscono che gran parte dei bambini, adolescenti, giovani adulti e perfino anziani partecipanti hanno riportato miglioramenti significativi nel benessere psicologico e nello sviluppo delle abilità individuali, a prescindere dal grado di disagio o disabilità presente, e che alcuni di tali miglioramenti siano perdurati nel tempo.

Sebbene la TdA non sia una panacea, è noto che l'esposizione alla natura e le attività all'aperto migliorano la salute fisica e mentale almeno per alcuni sintomi, cause, pazienti e circostanze[12]. Attività outdoor emozionanti e avventurose sono particolarmente rilevanti per le componenti psicologiche della sindrome da malattia cronica, in particolare depressione e demenza, ma anche condizioni oncologiche o genetico metaboliche[13]. L'attività all'aria aperta svolge un ruolo rilevante, in quanto capace di produrre benefici aggiuntivi rispetto a quelli terapeutici o riabilitativi tradizionali, praticati nelle ASL o in strutture private. Le terapie all'aperto possono anche aiutare a superare alcuni tipi di dolore cronico e sono risultate preziose per tutte le età, dai bambini[14] agli anziani e per quelle persone con sintomi clinici sia minori sia gravi[3,4].

Tutto ciò potrebbe comportare una sostanziale riduzione dei costi tradizionalmente affrontati per tali tipi di malati, come dimostrato nella terapia del diabete di tipo 2[15] e nelle malattie mentali[5]. Ciononostante, le terapie all'aperto sono poco o per nulla offerte, anche nelle nazioni ricche e urbanizzate, dove sarebbero preziose. Esistono programmi di educazione all'avventura per le scuole, ma sono sporadici e in ottica di prevenzione, piuttosto che terapeutici[16]. Alcuni Paesi hanno sperimentato programmi di "prescrizione ecologica", ma troppo piccoli e brevi per essere efficaci[17]. Inoltre, alcuni programmi gestiti privatamente potrebbero avere più successo, ma sono mirati a settori specifici, non collegati alle cure sanitarie tradizionali[18], oltreché essere privi di una analisi scientifica dei dati ottenuti. A mia conoscenza, nessun programma odierno del Servizio Sanitario Nazionale prevede una prescrizione di terapie all'aperto per pazienti che si presentano dai loro medici con problemi di salute mentale, malattia cronica o disabilità.

Principi metodologici originali

La metodologia utilizzata tra il 2007 e il 2017, i cui dati sono stati pubblicati da Capurso e Borsci[3,10], è stata implementata come TdA (WAT) in fase sperimentale dal 2017 su alcuni dei gruppi partecipanti all'imbarco sulla nave o in montagna[11,19-23]. Essa si basa sui seguenti principi.

1. *Sicurezza*: il contesto avventuroso prevede il minimo dell'assistenza e il massimo del rischio in tutte le attività marinaresche o di montagna predisposte, onde ottenere emozioni forti, positive, di facile memorizzazione. Una garanzia d'incolumità personale è rigorosamente predisposta per ciascuna delle attività pianificate, in fase di preimbarco o precampo.
2. *Pregiudizio*: ogni pregiudizio rispetto al deficit sensoriale, motorio, comportamentale o cognitivo deve essere preventivamente valutato per ciascun individuo e rimosso, in modo che sia data la possibilità a ciascun partecipante di esprimere risorse inattese e non espresse. Le persone con più forti pregiudizi sono i familiari e gli educatori; devono essere spinti a esprimerli, onde identificare gli ostacoli da affrontare nel superamento degli stessi.
3. *Supporto*: un supporto personale e collettivo deve essere non solo educativo ma anche cognitivo ed emotivo. Le azioni sono: implementazione di tecniche come l'apprendimento cooperativo, l'action learning, il problem solving, l'attivazione di un ascolto psicologico individuale e di gruppo e simili. Ogni attività emozionante deve essere seguita da un de-briefing collegiale in cui ciascuno deve rispondere a voce o con disegni a tre domande: 1) descrivi cosa è successo; 2) identifica la tua emozione prevalente; 3) descrivi ciò che hai imparato.

4. *Ricerca*: le attività svolte sono oggetto di specifiche ricerche scientifiche intese a dimostrare l'efficacia dei processi propri della WAT. A tale scopo, vengono definiti gruppi omogenei e gruppi di controllo e identificate le dimensioni del campione necessarie a dimostrare, su base statistica, il miglioramento raggiunto da individui e gruppi, i cui dati preliminari sono stati recentemente comunicati. Una piattaforma telematica ad accesso differenziato consente una più rapida raccolta dati[19-23].

Ruolo della Marina Militare

Per chi vive un disagio o una disabilità, che lo rende instabile e dipendente, avere punti di riferimento, un insieme di regole fisse e immutabili è fondamentale. Nonostante i pochi giorni a bordo, s'impara a essere protagonisti dentro queste regole, capendo che senza di esse è come essere sospesi nel nulla. Nelle regole si è liberi, senza regole si è schiavi dell'imprevisto. Entro i limiti della regola si ha libertà di scelta, di azione, di crescita, di comportamento; senza quei confini l'agire e il pensare vagano confusamente, privi di certezze e tutele, dipendenti da una sregolatezza assistita. Senza regole stabilite cognitivamente, il debole non ha spazio. La struttura stessa della regola è insita nella natura (mare, vento, pioggia, onde), per questo sottrarsi è pericolosa illusione. Senza regole chiare e non mutevoli, stabilite in maniera vantaggiosa e gerarchicamente imposte, si accetterebbero dinamiche spontanee, che garantiscono vantaggi solo al più forte. Facilitare, attraverso regole e disciplina militare, la gestione del cambiamento cui si sottopone, per esempio, il sistema percettivo del ragazzo autistico (che subisce stimoli sensoriali anomali), aiuta chi percepisce il mondo in altra maniera, offrendo spunti di riferimento per nuove strategie efficaci di socializzazione e comunicazione. Stabilire parametri di riferimento certi aiuta a gestire gli stimoli esterni e le reazioni emotive che ne conseguono e di migliorare la propria capacità di fare e interagire[3,10,11].

Ruolo della navigazione

La vita di una persona resa fragile da disabilità o disagio è un continuo alternarsi di cose che cambiano (insegnanti, terapisti, medici, infermieri) e cose che restano immutate (casa, genitori, parenti). A ben vedere, tutto cambia sempre e continuamente, anche se nessuno ci fa caso: il passaggio dall'inspirare all'espirare è cambiamento, aprire e chiudere gli occhi è cambiamento, il susseguirsi delle immagini del pensiero è continuo cambiamento, le voci che arrivano e colorano la mente sono cambiamento. Ogni cambiamento può diventare ansiogeno, in rapporto alla disabilità che si vive. Inspirare, per esempio, per un asmatico cronico, può creare ansia; mangiare la pasta, per un diabetico, può porre interrogativi non risolti; una cattiva percezione del proprio corpo, per un oncologico, può generare vergogna e ansia da esposizione, ecc. Per chi va in carrozzella, cambiare strada non è difficile, è spesso letteralmente impossibile. Il ragazzo autistico può avere problemi seri se il cibo è fatto da cose che non hanno un colore o una gerarchia chiara e individuabile. Cambiamenti considerati piccoli, non sono percepiti allo stesso modo da tutti; la stessa definizione di "piccolo" è arbitraria. Una persona diversa, inserita in una comunità, esprime esigenze non condivise dagli altri, né riconosciute.

Chi sale a bordo di Nave Italia viene investito da un cambiamento radicale di luoghi, relazioni, regole, abitudini. Impara e capisce cose talmente lontane dalla propria esperienza e da qualunque logica precedente e percepibile, che la gestione emotiva dell'avventura, proposta come nuovo strumento di terapia, diventa dominante. La navigazione a vela permette di eliminare pregiudizi e barriere: chi credeva di non essere capace, s'accorge di poter fare. Chi non mangiava per un disturbo alimentare, diventa complice di una proibita spaghettata di mezzanotte (fuori dalle regole, eppure studiata come laboratorio *ad hoc* per adolescenti anoressiche).

Ruolo degli Alpini

Analogamente al ruolo svolto dall'equipaggio della Marina Militare, ufficiali e sottufficiali delle Truppe alpine dell'Esercito Italiano di stanza ad Aosta svolgono un ruolo di guida nei progetti WAT realizzati ad Arpy. Nonostante il loro numero ridotto rispetto a quello dell'equipaggio della MM, durante i campi vengono scanditi e rispettati tempi, gerarchie e regole. L'esperienza della montagna è improntata specialmente sulla "sfida" fisica, personale e di gruppo, attraverso la programmazione di attività diversificate (invernali ed estive) come sci di fondo e ciaspolata, arrampicata, rafting e trekking e sempre calibrate in base alle caratteristiche del gruppo. Nel 2018 il numero dei progetti è stato portato a 17, mentre era stato di 11 nel 2017. L'esperienza di questi primi 28 gruppi fornirà la base di un approfondimento metodologico per la pianificazione del prossimo triennio.

L'équipe TTNI e il ruolo del project manager

La gestione emotiva di un profondo e radicale cambiamento di luoghi, relazioni e percezioni emotive è uno degli strumenti potenti della navigazione su Nave Italia e dell'avventura in montagna. La sua gestione è sartoriale. Ogni tipo di fragilità, infatti, beneficia di laboratori esperienziali che fanno parte di un menu complesso a disposizione di tutta l'équipe di project manager (PM) TTNI. L'équipe TTNI è andata definendosi nel corso degli anni come una vera e propria "comunità di lavoro" in cui ciascun componente si forma per comunicare con gli altri in un'interazione continua ed è consapevole della necessità di un costante confronto. Le riunioni d'équipe, svolte setti-

manalmente, rappresentano un momento continuo, puntuale e strutturato di scambio, riflessione e messa a punto delle problematiche che permette la realizzazione e la riuscita dei progetti. Si tratta di un appuntamento professionale in cui il gruppo riunito mette in gioco le proprie competenze per arrivare alla soluzione dei continui problemi ed emergenze che si presentano durante lo svolgimento della stagione. Ogni progetto è pianificato, concordato, sviluppato nelle tre fasi del prima, del durante e del dopo l'imbarco, in modo che il cambiamento generi nell'utenza processi stabili di mutazione della stima in se stessi, della propria autonomia e delle proprie capacità di relazione sociale. L'équipe TTNI, e per essa il PM, è garanzia che ciascun progetto nato dal piano originale degli operatori dei vari enti, venga condotto in tale direzione e obbedisca ai principi metodologi qui descritti. Il PM ha, inoltre, un ruolo cruciale come *ponte* tra il mondo militare (MM e Alpini) e quello civile dei gruppi che partecipano, punto di riferimento per i militari nella gestione dei gruppi e facilitatore delle relazioni nelle diverse fasi di progetto.

Discussione

Il principale ostacolo alla prescrizione di terapie outdoor è culturale. Le terapie all'aria aperta, infatti, non sono percepite come servizio o prestazione medica né dai sanitari né dai beneficiari stessi o dalle loro famiglie. Anche se l'offerta fosse in parte o del tutto simile a una fisioterapia o psicoterapia tradizionale, ampiamente prescritte nelle ASL, le terapie all'aria aperta sono, nei fatti, concepite come complementari o riempitive del tempo libero e affidate a iniziative del volontariato sociale. Non sono insegnate né apprese nelle scuole di medicina né nelle specialità mediche e dunque non sono disponibili attraverso il percorso tradizionale che va dalla diagnosi medica alla prescrizione, per cui non rientrano in alcun DRG e non sono finanziate pubblicamente, se non per limitate eccezioni, come nel casi del diabete di tipo 2 nella ASL di Cesena o per la sclerosi multipla nell'Istituto Don Gnocchi di Roma[24]. Possono essere offerte, ma non dentro schemi di terapia bensì come riempitivi, da fornitori privati o del terzo settore, costretti ad adottare modelli allineati ad attività scout o similari[25]. Ci vogliono dunque tempo, cambiamenti istituzionali e informazioni tecniche basate su ricerche scientifiche affinché siano accettate come terapie propriamente dette e non come complementi di scarso rilievo o perfino riempitivi compassionevoli di un tempo libero, non raramente conformato a istituzionalizzazione e solitudine.

La conoscenza degli effetti terapeutici tra esposizione alla natura e salute, sia essa fisica sia mentale, è dunque in una fase preliminare di proof-of-concept. La ricerca necessaria perché da qui si passi a una prescrizione terapeutica diffusa deve pertanto chiarire le relazioni dose-durata-risposta, con criteri analoghi a quelli utilizzati nei clinical trial tradizionalmente organizzati per la sperimentazione farmaceutica. Una prima area di ricerca necessaria consiste nel differenziare:

a. i sintomi del paziente e i tratti della personalità/disabilità/cronicità;
b. le caratteristiche delle terapie outdoor somministrate, perché soddisfino particolari pazienti e condizioni.

Una seconda area di ricerca deve testare le leve sociali necessarie per convincere singoli pazienti, medici e operatori sociosanitari ad adottare e seguire corsi di terapie all'aperto, una volta prescritti.

La ricerca fino a oggi ha dimostrato che l'esposizione alla natura può fornire una vasta gamma di benefici per la salute fisica e mentale, correlati all'attenzione e alla cognizione, alla memoria, allo stress e all'ansia, al sonno, alla stabilità emotiva e al benessere autopercepito o alla qualità della vita e persino al miglioramento della funzionalità di organi (cardiopatie croniche e metabolismo, diabete, obesità)[16] e che ciò giova a persone affette da malattie largamente diffuse come appunto il diabete, la sclerosi multipla, i disturbi mentali, l'Alzheimer, il morbo di Parkinson, ecc.[18]. Al momento, tuttavia, non ci sono stati confronti sistematici, test incrociati delle diverse terapie realizzate all'aperto per diverse condizioni di salute mentale, né tantomeno nel disagio psicosociale o nella disabilità sensoriale o cognitiva. Gli individui differiscono notevolmente nelle loro capacità e interessi psicologici e fisici, per le diverse attività all'aperto. Alcune persone potrebbero non essere interessate a provare una terapia che li coinvolga all'aria aperta in contesti avventurosi. Altri pazienti o condizioni potrebbero non rispondere a queste terapie. Per quei pazienti e quelle condizioni che invece rispondono, diversi tipi e intensità di terapie all'aperto possono rivelarsi più efficaci per i diversi individui e le differenti condizioni di età, sesso, salute fisica e mentale. Indispensabile, pertanto, identificare e confrontare schemi variabili per durata, intensità, tipologia.

Considerare queste differenze in modo esplicito quando si stabiliscono dati su metodo, quantità, durata e risposta è stato compito dei primi dieci anni di esperienza di Nave Italia. Lo scopo è stato quello di generare un portafoglio, o menu, di terapie all'aria aperta che possono essere abbinate ai singoli pazienti o tipologie di disagio o disabilità. Quantificare la salute mentale di ogni individuo, così da misurare le sue risposte alle terapie all'aperto, richiede una serie di parametri. Possiamo differenziare i pazienti sulla base di sintomi, tratti della personalità o tipi, capacità e interessi. Questi sono analoghi a fattori come peso corporeo del paziente, allergie e sensibilità ai farmaci nell'uso di trattamenti farmaceutici e sono ugualmente importanti. Per fare solo un esempio, alcuni individui hanno personalità in cerca di sensazioni e nuovi stimoli emozionali e sensoriali, mentre altri ne rifuggono.

La ricerca sinora condotta ha incluso molti tipi e diverse intensità di esposizione alla natura, che van-

no dagli sport tradizionali a quelli avventurosi, che coinvolgono abilità, brivido e rischio. Possiamo differenziare terapie sulla base di: durata, ripetizione e frequenza; caratteristiche degli ambienti naturali interessati; attività del paziente, del processo inclusivo, del grado di esercizio fisico e grado di rischio potenziale; e componenti emotive, come brivido, paura o gioia[19-23].

Alcuni di questi corrispondono alla dose e al regime di trattamento in modo simile a quanto si fa nelle terapie farmacologiche, mentre altri sono analoghi ad attività riabilitative. I primi includono: la durata di ogni singolo periodo trascorso all'aperto; l'ora del giorno in cui si verifica; il numero di occasioni al giorno, settimana, mese o anno; la durata complessiva del regime di trattamento. Questi ultimi includono: le caratteristiche ecologiche, estetiche e sociali dell'ambiente naturale in cui si svolge l'attività all'aperto e il tipo e le caratteristiche dell'attività stessa. Le caratteristiche di attività riabilitative includono: esercizio fisico; forza e abilità; rischio ed emozione; interazioni sociali coinvolte; supporto pedagogico (istruttore) o processo autodidattico; attrezzature utilizzate e procedure di sicurezza seguite; ambientazione emotiva e conseguenze, percezione sociale dell'attività tra gli amici e le famiglie dei pazienti, i colleghi e il pubblico in generale, regole condivise, gerarchie militarmente definite.

Sono sempre necessari test diagnostici, domande e osservazioni per selezionare, progettare e prescrivere terapie specifiche all'aperto per i singoli pazienti. Poiché la ricerca internazionale, fino a oggi, non è ancora stata né sistematica né completa, è stato necessario un approccio di apprendimento adattativo. Questo è stato ritenuto accettabile, poiché i rischi sono bassi. Le terapie all'aperto comportano dosi variabili e per un periodo di trattamento scelto per la sua durata settimanale, ripetibili nello stesso anno (mare + montagna) o in anni successivi.

Prospettive

I regimi di trattamento basati sulla TdA possono essere facilmente regolati se vengono rilevati effetti avversi o se la dose si dimostra troppo piccola per essere efficace. Gli effetti terapeutici primari positivi delle terapie all'aperto possono essere rilevati, durante il corso della terapia, dai singoli pazienti e descritti ai medici che prescrivono. Questo contrasta con molti altri tipi di terapia, in cui il paziente può essere in grado di rilevare solo effetti collaterali negativi. Se un praticante prescrive un regime di terapia all'aperto che è troppo potente per un particolare paziente, analogo al superamento della tolleranza al farmaco, allora il paziente semplicemente non avrà la capacità fisica o mentale per eseguirlo. Man mano che più persone adottano terapie esterne organizzate, ben definite e regolate, ciò fornirà l'opportunità di condurre studi longitudinali su larga scala, valutando i risultati per individui con problemi diversi e precedenti condizioni di salute fisica e mentale. Ciò vale sia per i programmi organizzati sia per quelli autoadottati[25]. I partecipanti potrebbero fornire informazioni individuali a una banca dati centrale anonima, in cambio di informazioni comparative sulla loro posizione in una popolazione complessiva. Questo stabilirà gradualmente un set di dati per l'analisi multivariata, che permetterà di identificare i trattamenti più efficaci per i pazienti con sintomi e disabilità, disagio o tratti di personalità diversi. In tal senso, la disponibilità di raccolta e analisi di "big data" anche in ambito socio sanitario grazie ai social network, rappresenta una sostanziale novità con forti prospettive positive. In alternativa, le metaanalisi di set di dati pubblicati con studi più ristretti possono dare risultati simili. Nel frattempo, un'opzione è quella di creare un menu di terapie all'aperto basata su criteri di TdA già consolidati e condivisi tra i ricercatori, come base per la discussione tra paziente e professionista, per consentire una selezione ragionata sulle opzioni possibili. Ci sono, al riguardo, una serie di considerazioni da sottolineare.

La prima riguarda la sicurezza: cosa ci si può aspettare che il paziente faccia, senza mettersi a rischio? Per esempio, una persona con disabilità cognitiva potrebbe non essere in grado di navigare o affrontare sentieri all'aperto senza assistenza; una con depressione grave con pregressi episodi di tentato suicidio non dovrebbe affrontare percorsi che lo espongano al fascino del vuoto, ecc.

Secondo, quali sono abilità e capacità fisiche e mentali del paziente? Per esempio, una persona anziana, inadatta o in sovrappeso potrebbe non essere in grado di completare una escursione all'aperto, anche a bassa velocità in condizioni agevoli; un non vedente potrebbe avere difficoltà di orientamento in montagna; un autistico potrebbe manifestare disagio per il rumore di un motore durante la navigazione, ecc.

Terzo, quali sono le precedenti abilità del paziente? Per esempio, una persona potrebbe beneficiare prima di affrontare una TdA, di esperienze che sfruttino immagini fotografiche, animazioni, film, identificazione di piante o animali, la descrizione di una serie di attività ricreative, alcune delle quali fattibili indoor. Questa la ragione per la quale il modello TdA costruito col metodo Nave Italia prevede una fase strutturata di preimbarco[3,10].

In quarto luogo, che cosa sa e gode il paziente dell'avventura all'aperto? In particolare, preferisce la contemplazione passiva e l'osservazione o l'esercizio attivo?

Quinta considerazione riguarda la durata del beneficio acquisito, che deve essere valutato nel tempo e dunque prevedere un coinvolgimento post-Tda non solo individuale ma collettivo, dentro programmi specificamente disegnati per favorire la narrazione e il coinvolgimento di famiglia, scuola e servizi sociosanitari nei quali ciascuno è curato. Per questa ragione il modello Nave Italia prevede un programma post-TdA dedicato a comunicazione e valutazione condivisa dei risultati ottenuti dopo mesi dall'avventura[3,10,11].

Il menu non deve necessariamente fornire un abbinamento perfetto tra paziente e terapia, poiché le terapie esterne sono facilmente regolabili, con basso rischio di effetti avversi. Il fattore limitante non è né la diagnosi né la progettazione dettagliata, ma l'attuazione effettiva: persuadere medici, altri operatori, familiari e pazienti a iniziare e perseverare. Fornire alle persone informazioni sui benefici individuali è, apparentemente, inefficace, mentre strategie di maggior successo potrebbero essere quelle che confezionano terapie all'aperto come se fossero prodotti commerciali acquistabili. I pacchetti più efficaci includono più leve sociali che operano in parallelo. Due leve sono particolarmente potenti. La prima è relativa alla giustificazione sociale, per consentire alle persone di trascorrere tempo e spendere denaro per attività personali all'aperto, senza critiche da parte dei curanti, familiari o amici. La seconda riguarda il sostegno reciproco tra pari. La terza riguarda il beneficio emotivo immediato. Se i partecipanti si sentono più felici dopo aver trascorso tempo nella natura all'aperto in un contesto emozionale avventuroso e positivo, troveranno modi per farlo più spesso. E se hanno pagato in anticipo, anche con un contributo minimale, per un'esperienza o un programma, hanno meno probabilità di cancellare. Per esempio, i prodotti turistici commerciali come i safari soddisfano entrambi questi criteri. I prodotti offerti da alcune imprese contribuiscono anche direttamente al benessere delle comunità impoverite e alla conservazione delle specie vegetali e animali minacciate, aggiungendo la leva dell'altruismo sociale identificata in ricerche precedenti[11,25,26]. In contrasto con le passate iniziative di sanità pubblica che fanno affidamento su un'educazione non mirata, suggeriamo quindi che la progettazione e la prescrizione (o commercializzazione) di programmi terapeutici riferiti alla TdA e altamente mirati, possano rivelarsi più efficaci. In forma di slogan: "vendere, non dire", in termini sanitari, invece, prescrizione terapeutica, non riempitivo compassionevole, destrutturato e inefficace.

Il percorso scientifico, culturale e tecnologico dello scorso ventennio ha permesso di rendere croniche malattie un tempo incompatibili con la sopravvivenza. Bambini nati prematuramente, con esiti a carico del sistema nervoso centrale, bambini oncologici trapiantati, con esiti cronici a carico di vari organi e sistemi, ecc. rappresentano una popolazione crescente nei confronti della quale la Pediatria ha saputo fornire intensi e collaudati programmi di follow-up, prevenzione e intervento medico o chirurgico in ambito ospedaliero, mentre in rari casi si è tenuto conto di un'attività all'aperto né si è stati in grado di proporre programmi rispettosi di caratteristiche essenziali dell'infanzia e dell'adolescenza, tra le quali rilevano in modo evidente quelle dell'avventura in contesti naturali condivisi tra pari.

Altrettanto è avvenuto per le persone anziane, in cui l'età sempre più avanzata, grazie alla disponibilità di tecnologie e farmaci, ha permesso di cronicizzare malattie un tempo incompatibili con la sopravvivenza. Queste persone, destinate a un isolamento intrafamiliare progressivo o a una istituzionalizzazione presso strutture sanitarie dedicate, sono private della possibilità di qualunque tipo di emozione positiva all'aria aperta, perché nei fatti non esistono che sporadici tentativi realizzati per cardiopatici, pazienti affetti da sindrome di Alzheimer, morbo di Parkinson o altra patologia cronica caratteristica dell'anziano e limitati comunque a un volontariato con caritatevole buon senso e che opera al di fuori di consolidate basi scientifiche.

Considerazioni analoghe potrebbero essere fatte per condizioni che riguardano malattie croniche di giovani adulti, per esempio, i malati di sclerosi multipla o gli psicotici, per i quali non esistono proposte terapeutiche che prendano in considerazione la TdA o altra forma di contatto con la natura all'aria aperta, entro schemi di trattamento strutturato da logiche basate su dati di ricerca condivisi. Molto, dunque, resta da fare per portare la TdA all'attenzione della Medicina, dei suoi strumenti di ricerca e formazione, perché la TdA diventi a tutti gli effetti prescrizione terapeutica dal valore riconosciuto. Servono iniziative capaci di rendere visibile il tema e il suo più recente sviluppo, serve navigare su un mare nuovo di conoscenze, che hanno necessità di essere confermate su larghi numeri, servono investimenti e confronti tra i costi di una TdA strutturata e ciò che attualmente si spende per offrire trattamenti indoor, tendenti a isolare il paziente, rendendolo dipendente da contesti urbani.

Conclusioni

Il termine "terapia", nella sua forma usuale, porta uno stigma, soprattutto tra adolescenti e giovani adulti, perché implica il concetto di "malattia". Inoltre, la terapia tradizionale non fornisce i risultati desiderati per questa popolazione resa fragile da disagio o disabilità. Associare il termine "terapia" al termine "avventura" consente di rimuovere lo stigma. Ecco perché è stata creata una metodologia innovativa e diversificata per fornire una soluzione terapeutica più efficace per adolescenti e giovani adulti curati da enti non profit, ospedali o affidati a scuole e servizi territoriali, per i quali un ambiente naturale e avventuroso offre un'opportunità più autentica per creare cambiamenti comportamentali positivi e duraturi. La base del modello è fatta per portare ciascuno a raggiungere un obiettivo personale focalizzato sulla soluzione ai suoi problemi.

Il team costituito da militari e PM qui descritto ha sviluppato piani di trattamento che utilizzano strategie individualizzate, associate a terapia comportamentale cognitiva, terapia comportamentale dialettica, colloqui motivazionali, pensiero sociale, problem solving collaborativo e psicologia positiva. L'obiettivo è fornire una valutazione funzionale accurata e sviluppare competenze mirate nelle aree di funzionamento sociale, emotivo, comportamen-

tale ed esecutivo. La TdA integra forme tradizionali di terapia della parola con un approccio pratico ed esperienziale.

L'intero programma è intenzionalmente progettato per essere curativo e per fornire risultati significativi che si trasferiscano alla vita domestica. L'ambiente sulla nave o in montagna offre una varietà di componenti terapeutici che consentono agli operatori di sviluppare e attuare piani di trattamento individualizzati utilizzando nelle tre fasi del progetto strumenti di terapia individuale, terapia familiare, terapia di gruppo, test psicologici, gestione dei farmaci, dieta sana, modelli di sonno regolari, attività fisica regolare. Piuttosto che concentrarsi sui metodi tradizionali di trattamento dei problemi (rimediare ai deficit), che non portano necessariamente a una migliore salute mentale, la pianificazione progettuale dovrebbe concentrarsi sulla costruzione dei punti di forza di ciascun partecipante. Qualunque modello di TdA o WAT, purché basato sulla ricerca scientifica, deve concentrarsi sui fattori chiave associati alla qualità della vita, tra cui autostima, autonomia, consapevolezza emotiva, responsabilità collettiva e maggiori capacità di comunicazione. Un programma di trattamento dosato e diversificato per intensità e durata, affidabile capace di fornire risorse, raccogliere testimonianze e sviluppare ricerche, per assicurarsi di prendere decisioni basate sull'analisi di risultati, misurabili, anche a lungo termine, difficili da raggiungere altrimenti.

Conflitto di interessi: l'autore dichiara l'assenza di conflitto di interessi.

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