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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

BIBLIOGRAFIA ADHD MARZO 2019

ADHD Atten Deficit Hyperact Disord. 2019.

RELATIONAL IMPAIRMENTS, SLUGGISH COGNITIVE TEMPO, AND SEVERE INATTENTION ARE ASSOCIATED WITH ELEVATED SELF-RATED DEPRESSIVE SYMPTOMS IN ADOLESCENTS WITH ADHD.

Ward AR, Sibley MH, Musser ED, et al.

This study examines how ADHD-related symptoms and impairments interact to predict depression symptoms in young adolescents with ADHD. A sample of 342 adolescents (71% male, mean age = 13 years old) with DSM-IV-TR diagnosed ADHD completed baseline clinical assessments upon entry to a psychosocial treatment study for ADHD. Ratings of ADHD and sluggish cognitive tempo (SCT) symptoms, and social and academic impairment were obtained from parents, while ratings of depressive symptoms and conflict with parents were obtained from youth. Among adolescents with ADHD, elevated depressive symptoms were associated with higher SCT symptom severity, lower hyperactive/impulsive (HI) symptom severity, higher social impairments, higher conflict with parents, and lower academic problems. Interaction effects indicated that clinically significant depressive symptoms were most likely to occur when high levels of parent' youth conflict were present along with high inattentive (IN) symptoms, high SCT, and/or low HI. Among children and adolescents with ADHD, depression prevention efforts might target IN/SCT symptom management, as well as improving interpersonal relationships with parents and peers. Future work is needed to verify these findings longitudinally

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ADHD Atten Deficit Hyperact Disord. 2019.

ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND FUTURE EXPECTATIONS IN RUSSIAN ADOLESCENTS.

Stickley A, Koposov R, Kamio Y, et al.

In recent years, there has been an increasing focus on the role of future expectations the extent to which a future outcome is deemed likely in the health and well-being of adolescents, with research linking future expectations to outcomes such as an increased likelihood of engaging in risky health behaviors. As yet, however, there has been no research on future expectations and attention deficit/hyperactivity disorder (ADHD) in adolescence. To address this research gap, the current study examined the association between ADHD symptoms/possible ADHD status and future expectations in a school-based sample of adolescents. Data were analyzed from 537 Russian adolescents (aged 12-17) with teacher-reported ADHD symptoms and self-reported future expectations. Logistic regression analysis was used to examine associations. In fully adjusted analyses, inattention symptoms/possible ADHD inattentive status was associated with lower future educational expectations, while a possible ADHD hyperactivity status was associated with increased odds for negative future expectations relating to work, family and succeeding in what is most important. The findings of this study suggest that greater ADHD symptoms/possible ADHD status in adolescence may be linked to an increased risk for negative future expectations across a variety of different life domains

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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.

Anaesthesia. 2019 Jan;74:57-63.

THE ASSOCIATION BETWEEN ATTENTION DEFICIT HYPERACTIVITY DISORDER AND GENERAL ANAESTHESIA - A NARRATIVE REVIEW.

Xu L, Hu Y, Huang L, et al.

Attention deficit hyperactivity disorder is a chronic neurodevelopmental disorder, manifesting primarily as attention deficit, hyperactivity and impulsive behaviour. General anaesthetics can be neurotoxic, affecting neuronal differentiation and synaptogenesis, which can lead to abnormalities of cognition, learning and behaviour. We hypothesise that exposure of the immature brain to general anaesthetics predisposes to the development of attention deficit hyperactivity disorder. In this review, we summarise clinical and animal studies that relate attention deficit hyperactivity disorder to general anaesthesia, by actions on neural molecular mechanisms and neural networks. We also describe potential therapeutic approaches to modulate these effects

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Ann Gen Psychiatry. 2019;18.

THE RELATIONSHIP BETWEEN SMARTPHONE ADDICTION AND SYMPTOMS OF DEPRESSION, ANXIETY, AND ATTENTION-DEFICIT/HYPERACTIVITY IN SOUTH KOREAN ADOLESCENTS.

Kim S-G, Park J, Kim H-T, et al.

Background: Excessive smartphone use has been associated with numerous psychiatric disorders. This study aimed to investigate the prevalence of smartphone addiction and its association with depression, anxiety, and attention-deficit hyperactivity disorder (ADHD) symptoms in a large sample of Korean adolescents.

Methods: A total of 4512 (2034 males and 2478 females) middle- and high-school students in South Korea were included in this study. Subjects were asked to complete a self-reported questionnaire, including measures of the Korean Smartphone Addiction Scale (SAS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Conners-Wells' Adolescent Self-Report Scale (CASS). Smartphone addiction and non-addiction groups were defined using SAS score of 42 as a cut-off. The data were analyzed using multivariate logistic regression analyses.

Results: 338 subjects (7.5%) were categorized to the addiction group. Total SAS score was positively correlated with total CASS score, BDI score, BAI score, female sex, smoking, and alcohol use. Using multivariate logistic regression analyses, the odds ratio of ADHD group compared to the non-ADHD group for smartphone addiction was 6.43, the highest among all variables (95% CI 4.60-9.00).

Conclusions: Our findings indicate that ADHD may be a significant risk factor for developing smartphone addiction. The neurobiological substrates subserving smartphone addiction may provide insights on to both shared and discrete mechanisms with other brain-based disorders

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Ann Gen Psychiatry. 2019;18.

GUANFACINE MONOTHERAPY FOR ADHD/ASD COMORBID WITH TOURETTE SYNDROME: A CASE REPORT.

Okazaki K, Yamamuro K, Iida J, et al.

Background: Patients with attention deficit/hyperactivity disorder (ADHD) often experience comorbid conditions, such as autism spectrum disorder (ASD) and Tourette syndrome (TS). Although pharmacotherapies are effective for treating ADHD, they are likely to elicit a variety of adverse effects. It is, thus, important to select an effective and well-tolerated pharmacotherapeutic treatment for patients with ADHD/ASD comorbid with TS.

Case presentation: We report the case of a 10-year-old boy with ADHD/ASD comorbid with TS who was treated with guanfacine (GUAN). He experienced several side effects of atomoxetine (ATX) and methylphenidate (MPH) before being treated with GUAN. In the presented case, symptoms of ADHD as well as tic symptoms were improved by treatment with GUAN.

Conclusion: GUAN might be effective and well tolerated in the treatment of patients with ADHD/ASD comorbid with TS who experience side effects of ATX and MPH

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Arch Clin Neuropsychol. 2019 Feb;34:89-95.

FACTOR STRUCTURE OF THE WECHSLER INTELLIGENCE SCALE FOR CHILDREN-FOURTH EDITION SPANISH IN A CLINICAL SAMPLE.

Nuñez A, Zink DN, Barchard KA, et al.

[Correction Notice: An Erratum for this article was reported in Vol 34(1) of Archives of Clinical Neuropsychology (see record [rid]2019-11787-012[/rid]). In the original article, two of the labels in Figure 1 were displayed in reverse order. The corrected figure has been included in the final version and is also shown in the erratum for reference.]

Objective: The Wechsler Intelligence Scale for Children-Fourth Edition Spanish (WISC-IV Spanish) is a translation and adaptation of the WISC-IV that is often used in neuropsychological evaluation of children and adolescents with acquired or developmental brain disorders. However, there is limited information on the factor structure of the WISC-IV Spanish when used with clinical populations. To address the potential effects of language and culture on the validity of the WISC-IV Spanish factor structure, this study examined the construct validity of the WISV-IV Spanish scores using confirmatory factor analysis in a clinical sample of Hispanic children with Attention-Deficit/Hyperactivity Disorder (ADHD).

Method: Participants included 148 children whose primary language was Spanish, who had a primary diagnosis of ADHD, and who had been administered the WISC-IV Spanish as part of a clinical evaluation (mean age = 10.6 years; SD = 2.7). Confirmatory factor analyses were performed to evaluate if the WISC-IV Spanish was best explained by a 1-, 2-, 3-, 4-, or 5-factor model based on the Cattell-Horn-Carroll theory.

Results: A 4-factor model composed of verbal comprehension, perceptual reasoning, working memory, and processing speed factors provided the best fit for the data (comparative fit index = .95; root mean square error of approximation = .06).

Conclusions: Findings for children with ADHD and LD support interpretation of WISC-IV Spanish Index scores based on the 4-factor model identified in Spanish- and English-speaking normative samples. Additional research with understudied clinical populations is warranted to address gaps in cross-cultural research

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Asian J Psychiatry. 2019;41:20-22.

PARTICIPATING FROM HOMES AND OFFICES: PROOF-OF-CONCEPT STUDY OF MULTI-POINT VIDEOCONFERENCING TO DELIVER GROUP PARENT TRAINING INTERVENTION FOR ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER.

Shah R, Chakrabarti S, Sharma A, et al.

To find technology-based solution to logistical difficulties in conducting group parent training for ADHD, this pilot study evaluated feasibility and acceptability of multi-point videoconferencing, wherein parents participated from homes or offices. Ten 90-minute weekly sessions were delivered using online videoconferencing platform. Most parents found videoconferencing quite useful, convenient, satisfactory and acceptable; and reported improved self-competency. Compared to face-to-face consultations, they perceived videoconferencing as more cost and time-saving. Clinicians faced occasional problems with internet connectivity at spoke end and audio-video lag. Post-intervention improvement was noted in VADPRS scores. Overall, multi-point video-conferencing for delivering group interventions for ADHD is feasible and acceptable

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Assessment. 2019 Jan;26:99-110.

HOW CONSISTENT IS SLUGGISH COGNITIVE TEMPO ACROSS OCCASIONS, SOURCES, AND SETTINGS? EVIDENCE FROM LATENT STATE TRAIT MODELING.

Preszler J, Burns GL, Litson K, et al.

Research has yet to determine how much of the variance in sluggish cognitive tempo (SCT) symptom ratings is consistent across occasions, sources, and settings versus specific to occasion, source, and setting. Our first objective was to determine the amount of variance in SCT ratings that was consistent (trait consistency) across three occasions of measurement over 12 months versus specific to the occasion (occasion-specificity) with ratings by mothers, fathers, primary teachers, and secondary teachers of 811 Spanish children. Our second objective was then to determine the convergent validity for trait consistency and occasion-specificity variance components within and across settings. SCT ratings reflected mostly trait consistency for mothers, fathers, and primary teachers (less so for secondary teachers) with the convergent validity for trait consistency also being strong for mothers with fathers and for primary teachers with secondary teachers. Across home and school, however, convergent validity for trait consistency was low and even lower for occasion-specificity. SCT appears to be more trait-like rather than state-like, with similar levels of trait consistency across occasions and convergent validity within settings as attention-deficit/hyperactivity disorder (ADHD) symptoms in a prior study. However, SCT symptoms had slightly weaker convergent validity for trait consistency across settings relative to ADHD symptoms

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Assessment. 2019 Mar;26:305-14.

REEXAMINING ADHD-RELATED SELF-REPORTING PROBLEMS USING POLYNOMIAL REGRESSION.

Sibley MH, Campez M, Raiker JS.

Individuals with attention deficit hyperactivity disorder (ADHD) underreport symptoms compared with informants and objective measures. This study applied enhanced statistical methodology (polynomial regression) to the study of ADHD self-reporting to clarify what contributes to symptom underreporting by adolescents with ADHD (N = 107; ages = 11-15 years). Polynomial regression models were conducted to test competing hypotheses about the nature of self-reporting problems. Traditional difference score models were nested within polynomial regression models to examine how modeling strategy influences results. Sixty-six percent of the sample substantially underreported symptoms compared with parents and 23.6% denied all symptoms. Polynomial regression models provided no evidence that the size of the discrepancy between parent and adolescent symptom reports possessed meaningful linear associations with any of the hypothesized predictors. Nested models indicated that the difference score approach led to very poor model fit and increased risk for Type I errors when examining underreporting among youth with ADHD. This finding suggests that past evaluations using a difference score approach should be replicated using polynomial regression to ensure that significant effects do not represent statistical artifact

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Autism. 2019.

FAMILIAL CONFOUNDING ON THE ABILITY TO READ MINDS: A CO-TWIN CONTROL STUDY.

Isaksson J, Taylor MJ, Lundin K, et al.

Alterations in social cognition are hypothesized to underlie social communication challenges in autism spectrum disorder. However, the etiologic underpinnings driving this association, as well as the impact of other psychiatric conditions on the association, remain unclear. Using a co-twin control design, we examined n = 308 twins (mean age = 16.63; 46% females) with autism spectrum disorder, attention-deficit/hyperactivity disorder, affective disorders, or typical development using the Reading the Mind in the Eyes Test to operationalize social cognition ability. Clinical diagnosis of autism spectrum disorder, as well as the extent of quantitative autistic traits, as measured by parental reports using the Social Responsiveness Scale-2, predicted fewer expected responses on the Reading the Mind in the Eyes Test across the pairs. The association remained when adjusting for other diagnoses and IQ. In addition, male sex, lower age, and lower IQ predicted poorer performance on the Reading the Mind in the Eyes Test. The associations between autism

and social cognition ability were lost within pairs in both the full sample and the monozygotic subsample. We conclude that the association between autism and social cognition across the sample highlights the importance of social cognition alterations in autism spectrum disorder when compared with other conditions. The attenuation of the association in the within-pair models indicate familial confounding, such as genes and shared environment, influencing both autism and social cognition

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Behav Processes. 2019 Jan;158:155-62.

AN EXPERIMENTAL PARADIGM EXAMINING THE INFLUENCE OF FRUSTRATION ON RISK-TAKING BEHAVIOR.

Loya JM, McCauley KL, Chronis-Tuscano A, et al.

The present study examined the impact of frustration on risk-taking in college students with low and high ADHD symptomatology (L-ADHD and H-ADHD). Participants completed the Balloon Analogue Risk Task (BART) following induced frustration from a mood manipulation task (experimental session) and following no mood manipulation (control session). A manipulation check revealed a significant three-way interaction where the H-ADHD group reported higher frustration levels compared to the L-ADHD group, particularly in response to the frustration induction in the experimental condition. Primary results revealed that the L-ADHD group exploded significantly fewer balloons in the experimental condition compared to the control condition; there was a nonsignificant difference of balloon explosions across conditions for the H-ADHD group. The study provides initial laboratory-based support for the impact of frustration on the risk behavior of those with low and high levels of ADHD, with potential implications for future studies and ultimately for intervention

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Child Neuropsychol. 2019;25:528-47.

DELAY DISCOUNTING OF MONETARY GAINS AND LOSSES IN ADOLESCENTS WITH ADHD: CONTRIBUTION OF DELAY AVERSION TO CHOICE.

Mies GW, De WE, Wiersema JR, et al.

Adolescents with attention-deficit/hyperactivity disorder (ADHD) are known to have stronger preferences for smaller immediate rewards over larger delayed rewards in delay discounting tasks than their peers, which has been argued to reflect delay aversion. Here, participants performed a delay discounting task with gains and losses. In this latter condition, participants were asked whether they were willing to wait in order to lose less money. Following the core assumption of the delay aversion model that individuals with ADHD have a general aversion to delay, one would predict adolescents with ADHD to avoid waiting in both conditions. Adolescents (12-17 years) with ADHD (n = 29) and controls (n = 28) made choices between smaller immediate and larger delayed gains, and between larger immediate and smaller delayed losses. All delays (5-25 s) and gains/losses (2-10 cents) were experienced. In addition to an area under the curve approach, a mixed-model analysis was conducted to disentangle the contributions of delay duration and immediate gain/delayed loss amount to choice. The ADHD group chose the immediate option more often than controls in the gain condition, but not in the loss condition. The contribution of delay duration to immediate choices was stronger for the ADHD group than the control group in the gain condition only. In addition, the ADHD group scored higher on self-reported delay aversion, and delay aversion was associated with delay sensitivity in the gain condition, but not in the loss condition. In sum, we found no clear evidence for a general aversion to delay in adolescents with ADHD

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Clin Pharmacol Ther. 2019;105:S87-S88.

THE IMPACT OF CARBOXYLESTERASE 1 VARIANTS ON METHYLPHENIDATE DOSE AND ADVERSE EFFECTS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Brown JT, Monaghan Beery NK, Regal R, et al.

Background: Among children 6-17 years of age in the United States, attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder. Methylphenidate (MPH) is the most commonly

prescribed stimulant to treat ADHD, as well as the most commonly dispensed medication to adolescents. MPH is metabolized to an inactive metabolite predominantly through carboxylesterase 1 (CES1). The primary objective of this study was to analyze the effect of CES1 single nucleotide polymorphisms (SNPs) or insertion deletion polymorphisms (INDELs) on the frequency of adverse effects with MPH.
Methods: This was a retrospective, pharmacogenetic descriptive/associative study in children 6-17 years of age with a diagnosis of ADHD and prescribed MPH for at least 3 months. A total of 172 participants were enrolled in the study, with 170 completing all study procedures. Clinical data was extracted from electronic medical records. Saliva samples for gene sequencing were acquired after permission/assent were obtained. DNA was extracted via Oragene-Discover OGR-500 Kits. The CES1 gene was enriched via a custom LAPCR reaction and then sequenced on an Illumina MiSeq. Genetic and clinical data were analyzed using Fisher's exact test.
Results: 690 SNPs and INDELs were identified within CES1. The most significant association was between ss12587849 and change in medication ($P < 0.0001$). rs71374102 was significantly associated with a decrease in dose ($P = 0.01$). Several variants were significantly associated ($P < 0.01$) with decreased appetite, growth suppression, and stomach aches.
Conclusion: CES1 exhibits considerable genetic heterogeneity, where several SNPs are significantly associated with adverse effects and changes in medication/dose in children prescribed methylphenidate

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CNS Spectr. 2018;23:103.

EFFICACY OF DASOTRALINE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER IN A LABORATORY CLASSROOM SETTING.

Goldman R, Childress A, Wigal SB, et al.

Objectives: Once-daily dosing with dasotraline, a novel dopamine and norepinephrine reuptakeinhibitor, achieves stable plasma concentrations over24 hours. This phase 3 study evaluated the efficacy andsafety of dasotraline in children with attention deficithyperactivity disorder (ADHD) throughout the day, in alaboratory classroom setting (NCT02734693).
METHODS: Children (6-12 years) meeting DSM-5 criteriafor ADHD were randomized to 2 weeks of dasotraline orplacebo (dosed daily at home at approximately 8 PM).Following an abbreviated practice day, laboratory classroom evaluations took place at baseline and on Day 15.The primary endpoint was mean change from baseline atDay 15 in ADHD symptoms, as measured by theSwanson, Kotkin, Agler, M-Flynn, and Pelham Combined Score (SKAMP-CS), obtained from the average of 7assessments collected across the 12-hour laboratoryclassroom day (12-24 hours post-dose). Secondary endpoints included SKAMP scores obtained throughout theday at individual timepoints from 8 AM through 8 PM (12-24 hours post-dose), and measures of safety andtolerability.
RESULTS: The ITT population comprised 112 patients.Mean age was 9.5 years, 68.8% were male; 92%completed the study. Dasotraline 4 mg/day significantlyimproved mean SKAMP-CS versus placebo ($p < 0.0001$, effect size 0.85) with significant effects persistingthroughout the day. Mean SKAMP subscores improvedsignificantly versus placebo (Attention $p < 0.0001$, effectsize 0.81; Deportment $p < 0.001$, effect size 0.70).Treatment-emergent adverse events were generally mildor moderate in severity; most frequent (with dasotraline4 mg/day; placebo) included: insomnia (19.6%; 3.6%, allterms combined), decreased appetite (10.7%; 3.6%),headache (10.7%; 8.9%), affect lability (8.9%; 7.1%),irritability (5.4%; 3.6%), postural orthostatic tachycardia syndrome (5.4%; 0%), and perceptual disturbances(5.4%; 0%).
CONCLUSIONS: In this 2-week, randomizeduble-blind,laboratory classroom study in children with ADHD,once-daily dasotraline significantly improved ADHDsymptoms (including deportment and attention),compared with placebo, and demonstrated sustainedefficacyup to 24 hours post-dose. The most commonadverse events were insomnia, decreased appetite, andheadache

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CNS Spectr. 2018;23:82.

CONSISTENT EFFICACY OF DR/ER-MPH ON EARLY MORNING FUNCTIONING IN CHILDREN WITH ADHD: ANALYSIS OF BSFQ ITEM RATINGS FROM A PIVOTAL PHASE 3 TRIAL.

Wilens TE, Pliszka SR, Arnold VK, et al.

Objective: In a phase 3 trial of children withattention-deficit/hyperactivity disorder (ADHD), DR/ERMPH (formerly HLD200), a delayed-release and extendedrelease methylphenidate, improved ADHD symptoms andreduced at-home early morning and late afternoon/evening functional impairment versus placebo. Thevalidated Before School Functioning Questionnaire(BSFQ), a key secondary endpoint, was used to measureearly morning functional (EMF) impairment. This posthoc analysis evaluated the effect of DR/ER-MPH versusplacebo on individual BSFQ item scores from baseline.

METHOD: Data were analyzed from a pivotal, randomized,double-blind, multicenter, placebo-controlled, parallelgroup, phase 3 trial of DR/ER-MPH in children (6-12years) withADHD (NCT02520388). Using the 20-itemBSFQ, investigators evaluated EMF impairment by scoring each item on a severity scale of 0 to 3, with 0 denoting"no impairment" and 3 denoting "severe impairment".For post hoc analyses, treatment comparisons betweenDR/ER-MPH and placebo at endpoint were determinedby using least squares mean changes from baseline onindividual BSFQ items score derived from an analysis ofcovariance (ANCOVA) model with treatment as the maineffect, and study center and baseline score as covariates.

RESULTS: Of 163 children enrolled across 22 sites, 161 wereincluded in the intent-to-treat population (DR/ER-MPH,n = 81; placebo, n = 80) and 138 completed the study. Themean DR/ER-MPH dose achieved after 3 weeks oftreatment was 68.1 mg. Following 3 weeks of treatment,DR/ER-MPH significantly reduced mean BSFQ item scoresfrombaseline on 18 out of 20 items versus placebo($P < 0.001$ in 8 items [listening, following directions, attention, forgetfulness, talkativeness, silliness, time awareness, getting to school]; $P < 0.01$ in 7 items [overallorganization, being quiet, distraction, interrupt/blurt out,breakfast, hygiene, independence]; $P < 0.05$ in 3 items[procrastination, hyperactivity, awaiting turn]). Only "dressing" and "misplacing/losing items" showed no significantbetween-group differences ($P = 0.171$ and $P = 0.175$,respectively). Distributions of the severity ratings for eachitem will be presented. No serious TEAEs were reported;TEAEs were consistent with methylphenidate.

CONCLUSIONS: Post hoc analyses revealed that DR/ERMPH significantly reduced 18 out of 20 individual BSFQitem scores versus placebo in children with ADHD.These findings are worth further exploration

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CNS Spectr. 2018;23:80-81.

EFFECT OF DR/ER-MPH ON EARLY MORNING AND LATE AFTERNOON/EVENING FUNCTIONING IN CHILDREN WITH ADHD: ANALYSIS OF PREMB-R ITEMS FROM A PHASE 3 TRIAL.

Pliszka SR, Arnold VK, Marraffino A, et al.

Objective: In a phase 3 trial of children withADHD, DR/ER-MPH (formerly HLD200), a delayedrelease and extended-release methylphenidate, improvedADHD symptoms and reduced at-home early morningand late afternoon/evening functional impairmentsversus placebo, as measured by the validated ParentRating of Evening andMorning Behaviors-Revised,Morning (PREMB-R AM) and Evening (PREMB-R PM)subscales. This post hoc analysis evaluated the effect ofDR/ER-MPH versus placebo onindividual PREMB-RAM/PM item scores.

METHOD: Data were analyzed from a pivotal, randomized, double-blind, multicenter, placebo-controlled, parallel group, phase 3 trial of DR/ER-MPH in children (6-12years) with ADHD (NCT02520388). Using the 3-itemPREMB-R AM and 8-item PREMB-R PM, both key secondary endpoints, investigators evaluated early morning and late afternoon/evening functional impairment by scoring each item on a severity scale from 0 (none) to 3 (alot). For post hoc analyses, treatment comparisons between DR/ER-MPH and placebo at endpoint were determined by using least squares mean changes from baseline on individual PREMB-R AM/PM items score derived from an analysis of covariance (ANCOVA) model with treatment as the main effect, and study center and baseline score as covariates.

RESULTS: Of 163 children enrolled across 22 sites, 161were included in the intent-to-treat population (DR/ERMPH, n = 81; placebo, n = 80) and 138 completed the study. The mean DR/ER-MPH dose achieved after3 weeks of treatment was 68.1 mg. Following 3 weeks of treatment, DR/ER-MPH significantly reduced mean individual item scores from baseline versus placebo on all PREMB-R AM items (all P=0.002; "getting

out of bed", "getting ready", and "arguing or struggling in the morning"). Additionally, DR/ER-MPH significantly reduced mean individual item scores from baseline on 5 out of 8 PREMB-R PM items (P < 0.01 in 2 items["sitting through dinner" and "playing quietly"] and P < 0.05 in 3 items ["inattentive/distractible", "transitioning between activities", and "settling down/getting ready for bed"]). There was a trend towards a reduction on 2 other items of the PREMB-R PM (P < 0.09). Distributions of the ratings for each item will be presented. No serious TEAEs were reported; TEAE s were consistent with methylphenidate.
CONCLUSIONS: Post hoc analyses revealed that DR/ERMPH significantly reduced all PREMB-R AM item scores, including "getting out of bed", and many PREMB-R PMitems, including "getting ready for bed" in children with ADHD. These findings are worth further exploration

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CNS Spectr. 2018;23:81.

EFFECT OF DR/ER-MPH ON CAREGIVER-REPORTED ADHD SYMPTOM IMPROVEMENT IN CHILDREN WITH ADHD AND CAREGIVER STRAIN: RESULTS FROM A PHASE 3 TRIAL.

Pliszka SR, Arnold VK, Marraffino A, et al.

Objective: Evening-dosed DR/ER-MPH (formerly HLD200), a delayed-release and extended-release methylphenidate, was designed to provide efficacy up on awakening and through the evening. The objective was to evaluate whether treatment with DR/ER-MPH in children with attention-deficit/hyperactivity disorder(ADHD): (1) improves caregiver-rated ADHD symptoms, and (2) reduces caregiver strain, versus placebo.
METHOD: Caregiver-rated ADHD symptoms (Conners' Global Index-Parent [CGI-P]) and caregiver strain(Caregiver Strain Questionnaire [CGSQ]) were assessed as secondary endpoints following 3 weeks of treatment in a randomize duble-blind, multicenter, placebo-controlled, parallel-group, phase 3 trial of DR/ER-MPH in children (6-12 years) with ADHD (NCT02520388).Using the 10-item CGI-P, parents rated their child's ADHD symptoms on a 4-point scale (0 = never/seldom;3 = very often/frequently). Caregivers also rated the impact of caring for a child with emotional and behavioral challenges on the 21-item CGSQ (5-pointscale: 1 = not at all; 5 = very much). A reduction on individual item and total scores for both measures indicated an improvement.
RESULTS: Of 163 children enrolled across 22 sites, 161 were included in the intent-to-treat population (DR/ER-MPH,n = 81; placebo, n = 80) and 138 completed the study. The mean DR/ER-MPH dose after 3 weeks of treatment was68.1 mg. Mean CGI-P scores at baseline and CGSQ scores at screening (ie, before washout of prior ADHD therapy) were comparable for both DR/ER-MPH (CGI-P: 22.8,CGSQ: 54.5) and placebo (CGI-P: 21.8; CGSQ: 54.9)groups. After 3 weeks of treatment, caregivers of children on DR/ER-MPH reported significant reductions in CGI-P scores versus those on placebo (least-squares [LS] mean:12.3 vs 17.4; P < 0.001). Additionally, there was a significant reduction in CGSQ scores after 3 weeks oftreatment with DR/ER-MPH versus placebo (LS mean:41.2 vs 49.1; P < 0.001). Post hoc analyses on the effect of DR/ER-MPH versus placebo on individual items of CGI-Pand CGSQ, and the two subscales of CGI-P will be presented. No serious TEAEs were reported and all TEAEswere consistent with those of MPH.CONCLUSIONS: Caregivers reported significant improvements in their child's ADHD symptoms and these improvements coincided with reductions in care giverstrain after 3 weeks of treatment on evening-dosed DR/ER-MPH versus placebo

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CNS Spectr. 2018;23:102-03.

DASOTRALINE IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER: RESULTS OF A RANDOMIZEDUBLE-BLIND, PLACEBO-CONTROLLED STUDY.

Goldman R, Adler L, Spencer T, et al.

Objectives: Once-daily dosing with dasotraline, a novel dopamine and norepinephrine reuptake inhibitor, achieves stable plasma concentrations over 24 hours with once-daily dosing. This study evaluated dasotraline in children aged 6-12 years(NCT02428088).

METHODS: Patients were randomized 1:1:1 to 6 weeks of once-daily, fixed-dose dasotraline 2 or 4 mg/day, or placebo. The primary efficacy endpoint was change from baseline(CFB) at Week 6 in ADHD Rating Scale Version IV-Home Version (ADHD RS-IV HV) total score, using a mixed model for repeated measures (MMRM) in the intent-to-treat (ITT)population. Secondary endpoints included Clinical Global Impression-Severity (CGI-S) score and safety endpoints.
RESULTS: The mean age of 342 randomized patients was9.1 [SD: 1.9] years; 66.7% were male. Overall, 79% of patients completed the study. In the ITT population (N = 336), ADHD RS-IV HV total score improved significantly with dasotraline 4 mg/day vs placebo (least squares [LS] mean [SE] CFB at Week 6:-17.53 [-¦ 1.31]vs-11.36 [-¦ 1.29], respectively, p < 0.001; effect size[ES]: 0.48). Inattentiveness and hyperactivity/impulsivity subscale scores significantly improved with 4 mg/day vs placebo at Week 6 (p = 0.001, p = 0.003, respectively). Improvement in CGI-S score was statistically significant with dasotraline 4 mg/day vs placebo (LS mean [SE] CFB at Week 6:-1.39 [-¦ 0.12] vs-1.04 [-¦ 0.12], respectively, p = 0.040; ES: 0.29). No significant improvement was observed on the ADHD RS-IV HV total score and the CGI-S score for dasotraline 2 mg/day vs placebo. The most frequent treatment-emergent AEs (=5% and higher than placebo) were (2 mg/day; 4 mg/day; placebo):insomnia (15.3%; 21.7%; 4.3%, all terms combined),decreased appetite (12.6%; 21.7%; 5.2%), weight loss(5.4%; 8.7%; 0%), irritability (3.6%; 7.0%; 6.0%), nasopharyngitis (0.9%; 5.2%; 0.9%), and nausea (0%;5.2%; 2.6%).
CONCLUSIONS: Compared with placebo, dasotraline4 mg/day significantly improved ADHD symptoms in children, as assessed by ADHD RS-IV HV total score and inattentiveness and hyperactivity/impulsivity subscale scores. Dasotraline was generally well tolerated; most common AEs were insomnia, decreased appetite, weight loss and irritability

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Dev Med Child Neurol. 2019 Feb;61:174-80.

ATTENTION TO FACES IN SOCIAL CONTEXT IN CHILDREN WITH NEUROFIBROMATOSIS TYPE 1.

Lewis AK, Porter MA, Williams TA, et al.

AIM: To examine visual attention to faces within social scenes in children with neurofibromatosis type 1 (NF1) and typically developing peers.
METHOD: Using eye-tracking technology we investigated the time taken to fixate on a face and the percentage of time spent attending to faces relative to the rest of the screen within social scenes in 24 children with NF1 (17 females, seven males; mean age 10y 4mo [SD 1y 9mo]). Results were compared with those of 24 age-matched typically developing controls (11 females, 13 males; mean age 10y 3mo [SD 2y]).
RESULTS: There was no significant between-group differences in time taken to initially fixate on a face (p=0.617); however, children with NF1 spent less time attending to faces within scenes than controls (p=0.048). Decreased attention to faces was associated with elevated autism traits in children with NF1.
INTERPRETATION: Children with NF1 spend less time attending to faces than typically developing children when presented in social scenes. Our findings contribute to a growing body of literature suggesting that abnormal face processing is a key aspect of the social-cognitive phenotype of NF1 and appears to be related to autism spectrum disorder traits. Clinicians should consider the impact of reduced attention to faces when designing and implementing treatment programmes for social dysfunction in this population.
WHAT THIS PAPER ADDS: Children with neurofibromatosis type 1 (NF1) demonstrated atypical gaze behaviour when attending to faces. NF1 gaze behaviour was characterized by normal initial fixation on faces but shorter face dwell time. Decreased attention to faces was associated with elevated autism traits in the sample with NF1

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Dev Cognitive Neurosci. 2019;36.

PUBERTAL INFLUENCES ON NEURAL ACTIVATION DURING RISKY DECISION-MAKING IN YOUTH WITH ADHD AND DISRUPTIVE BEHAVIOR DISORDERS.

Dir AL, Hummer TA, Aalsma MC, et al.

Objective: Risk-taking during adolescence is a leading cause of mortality; Neuroscience research examining pubertal effects on decision-making is needed to better inform interventions, particularly among youth with attention-deficit/hyperactivity (ADHD) and disruptive behavior disorders (DBD), who are particularly prone to risky decision-making. We examined effects of pubertal development on risky decision-making and neural activation during decision-making among youth with ADHD/DBDs.

Method: Forty-six 11-12-year-olds (29.4% girls; 54.9% white; Tanner M(SD) = 2.08(1.32)) who met DSM-5 criteria for ADHD/DBD completed the Balloon Analog Risk Task (BART) during fMRI scanning. We examined effects of Tanner stage, sex, and age on risky decision-making (mean wager at which individuals stopped balloon inflation) and neural activation in the middle frontal gyrus and the ventral striatum during the choice and outcome phases of decision-making.

Results: Those in earlier pubertal stages made riskier decisions during the BART compared to those in later Tanner stages (β=-0.62, p = .02). Later pubertal stage was associated with greater activation in the left middle frontal gyrus (β=0.61, p = .03) during the choice phase and in the right ventral striatum in response to rewards (β=0.59, p = .03).

Conclusion: Youth with ADHD/DBD in later stages of puberty, regardless of age, show greater ventral striatal activation in response to rewards

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Dev Med Child Neurol. 2018;60:95-96.

MOTOR CORTEX PHYSIOLOGY OF MOVEMENT PREPARATION IN ADHD CHILDREN.

Epperson M, Horn P, Wu S, et al.

Background and Objective(s): Executive function difficulties commonly cause impairment in children with traumatic brain injury, cerebral palsy, and in many neurodevelopmental conditions. While evaluation of cognitive and behavioral symptoms poses some methodological challenges, the motor system may manifest parallel difficulties which are more amenable to quantification. Based on characteristic difficulties in response inhibition related to executive dysfunction, as well as data in healthy adults showing that the motor cortex becomes increasingly disinhibited during movement preparation, we developed a child-friendly task which would allow for concurrent assessment of response inhibition and measurement of motor physiology during movement preparation. In order to establish the feasibility and characteristics of this experimental paradigm, we tested it in an age-matched cohort of children with ADHD and Healthy Controls ages 8-12 years. We hypothesized that motor cortex physiology during movement preparation would be less regular and less inhibited in children with ADHD.

Study Design: Cross Sectional Case - Control study. Study Participants & Setting: 82 right-handed children, (45 ADHD: mean age 10.41 years, 31 males; 37 HC: mean age of 10.31 years, 24 males) were recruited through community advertisement.

Materials/Methods: Children were seated in a comfortable chair and trained in a response inhibition task we designed involving a race car, with a 3:1 ratio of Go to Stop-Signal tasks. During 80 trials, Transcranial Magnetic Stimulation (TMS, Magstim Bistim, Morrisville, NC) single and 3 m sec inhibitory paired pulses evoked motor potentials in the first dorsal interosseous muscle at precise times. Using a repeated measures regression, the trajectory of pre-movement time and motor cortex excitability was modeled using linear, reciprocal, and quadratic functions.

Results: Children were able to learn the task and perform it during TMS. As expected, motor cortex inhibition diminished closer to time of movement (both linear and reciprocal models p<0.0001). In children with ADHD, baseline measures were disinhibited, and the time trajectory of motor cortex disinhibition was shallower than in HC (model interaction terms, reciprocal p=0.032; linear p=0.051). This time trajectory did not correlate with independent clinical ratings of symptom severity.

Conclusions/Significance: Combining precise functional motor tasks with measurement of motor cortex physiology using TMS appears feasible in children with behavioral disorders. This technique, or modifications

of it, may hold promise for developing quantitative, brain-based biomarkers for motor and behavioral dysfunction in a variety of childhood developmental or rehabilitative settings

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Dev Neuropsychol. 2019 Jan;44:50-70.

TIME REPRODUCTION DEFICITS AT YOUNG ADULT FOLLOW-UP IN CHILDHOOD ADHD: THE ROLE OF PERSISTENCE OF DISORDER AND EXECUTIVE FUNCTIONING.

Barkley RA, Fischer M.

No studies have examined if time reproduction deficits exist in children with attention deficit hyperactivity disorder (ADHD) by adulthood. We followed 131 ADHD and 71 community control (CC) cases for 20+ years to young adulthood at which time they were given a time reproduction task. The ADHD group made smaller time reproductions and showed greater variability of errors at the longer durations compared to CC cases, whether ADHD was still present or not at follow-up. Nonverbal working memory and design fluency tests were related to timing errors while anxiety and depression were not. Childhood ADHD is associated with timing deficits at adult follow-up

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Emot Behav Difficulties. 2019.

ADOLESCENT EXPERIENCES OF LIVING WITH A DIAGNOSIS OF ADHD: A SYSTEMATIC REVIEW AND THEMATIC SYNTHESIS.

Eccleston L, Williams J, Knowles S, et al.

Seeking young people's perspectives is integral to delivering effective mental health care. This systematic review aimed to synthesis e the qualitative research exploring the life experiences of young people diagnosed with ADHD. Four electronic databases (CINAHL, MEDLINE, PsycInfo and SCOPUS) were searched in February 2017 for peer-reviewed, qualitative English language studies exploring the perspectives of adolescents formally diagnosed with ADHD. Eleven studies were included and appraised for methodological quality and a thematic synthesis was undertaken. ParticipantsΓÇÖ stories highlighted both positives and challenges within five analytical themes: Differing perspectives of the problem, Societal pressures, Sense of self, Feelings about medication, and Maturational shift from passive to active. The findings suggested that interpersonal conflict, stigma, and invalidation have a negative psychological impact upon young people's self-esteem and identity. Support strategies are needed to maximise adolescents resilience, autonomy and abilities

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Environ Res. 2019;135-56.

ASSOCIATION BETWEEN AMBIENT GASEOUS AND PARTICULATE AIR POLLUTANTS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN; A SYSTEMATIC REVIEW.

Aghaei M, Janjani H, Yousefian F, et al.

ADHD is a common neurodevelopmental disorder highly attributed to genetics, but the combination of other social and environmental determinants, as well as potential gene-environment interactions, can also be responsible. This paper aims to review relevant literature published up to April 2018 for determining whether air pollution caused by ambient gaseous (NO2, SO2, PCDD/Fs, Benzene) and particulate matters (PM10, PM2.5, PM7, PAH, BC/EC) as an environmental risk factor is associated with increased risk of ADHD in children. Relevant literature was identified through electronic searches of PubMed, Embase, Web of Science, Scopus database and gray literature. A total of 872 articles were initially identified 28 of which meeting the defined inclusion criteria were included. The methodological quality of the included articles was evaluated using the modified Critical Appraisal Skills Programs (CASP) and confounding variables, exposure and outcome measurement were assessed. The results of this systematic review revealed that there is more evidence on the detrimental effects of EC, BC, and PM on ADHD compared to PAH. Among gaseous air pollutants, association was found between SO2 and urinary level of t,t-MA (trans, trans-muconic acid) as a

proxy-biomarker of NO2 exposure, not merely benzene. However few studies related to NO2 (0.46%) found detrimental effects. Overall, the number of studies reporting an association between air pollution and increased risk of ADHD is relatively higher compared to the number of studies reporting no association. However, the findings of the studies provided limited evidence to support the idea that exposure to air pollution may be linked to increased risk of ADHD. Well-designed and harmonized studies considering standard methods for individual exposure assessment, critical windows of susceptibility, and appropriate tools for outcome measurement, can improve the quality of epidemiological studies and strengthen the evidence. Since ADHD with its long-term consequences can impose large costs to communities and impact the children performance, determination of the risk factors in children and particularly the role of the environment as priorities for research should be considered

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Epidemiology. 2019 Jan;30:130-44.

MATERNAL THYROID FUNCTION DURING PREGNANCY OR NEONATAL THYROID FUNCTION AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Drover SSM, Villanger GD, Aase H, et al.

BACKGROUND: Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children, yet its etiology is poorly understood. Early thyroid hormone disruption may contribute to the development of ADHD. Disrupted maternal thyroid hormone function has been associated with adverse neurodevelopmental outcomes in children. Among newborns, early-treated congenital hypothyroidism has been consistently associated with later cognitive deficits.

METHODS: We systematically reviewed literature on the association between maternal or neonatal thyroid hormones and ADHD diagnosis or symptoms. We searched Embase, Pubmed, Cinahl, PsycInfo, ERIC, Medline, Scopus, and Web of Science for articles published or available ahead of print as of April 2018.

RESULTS: We identified 28 eligible articles: 16 studies of maternal thyroid hormones, seven studies of early-treated congenital hypothyroidism, and five studies of neonatal thyroid hormones. The studies provide moderate evidence for an association between maternal thyroid hormone levels and offspring ADHD, some evidence for an association between early-treated congenital hypothyroidism and ADHD, and little evidence for an association between neonatal thyroid hormone levels and later ADHD.

CONCLUSIONS: The reviewed articles suggest an association between maternal thyroid function and ADHD, and possibly between early-treated congenital hypothyroidism and ADHD. Study limitations, however, weaken the conclusions in our systematic review, underlining the need for more research. Importantly, there was much variation in the measurement of thyroid hormone function and of ADHD symptoms. Recommendations for future research include using population-based designs, attending to measurement issues for thyroid hormones and ADHD, considering biologically relevant covariates (e.g., iodine intake), and assessing nonlinear dose-responses

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Epilepsy Behav. 2019;94:29-34.

PARENT-REPORTED SYMPTOMS OF ADHD IN YOUNG PEOPLE WITH EPILEPSY BEFORE AND TWO YEARS AFTER EPILEPSY SURGERY.

Reilly C, Hallb+Â+Âk T, Viggedal G, et al.

The aim was to compare parent-reported symptoms of attention-deficit/hyperactivity disorder (ADHD) before (baseline) and two years after pediatric epilepsy surgery (follow-up). The parents of 107 children who underwent epilepsy surgery completed surveys including the Conners 10-item scale at baseline and follow-up. Changes in scores between baseline and follow-up were compared using paired sample t-test. Factors associated with changes in scores were analyzed using linear regression. Features of ADHD were significantly reduced at follow-up ($p < 0.001$). Items with the greatest reduction were items focusing on core aspects of the diagnostic criteria for ADHD. Fewer children were in the at-risk range for ADHD on the Conners 10-item scale at follow-up but this did not reach statistical significance (49% vs. 43%; $p = 0.481$). Factors independently significantly associated with improvement in ADHD symptoms on multivariable analysis were

higher baseline scores (p < 0.001), seizure-free status (p = 0.029), and right-sided surgery (p = 0.031). Children who undergo epilepsy surgery have a high rate of ADHD symptoms. Parent-rated symptoms of ADHD improved at 2-year follow-up after epilepsy surgery. All children undergoing epilepsy surgery should undergo assessment for ADHD at baseline and follow-up

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Eur Child Adolesc Psychiatry. 2019 Feb;28:155-64.

DOES METHYLPHENIDATE IMPROVE ACADEMIC PERFORMANCE? A SYSTEMATIC REVIEW AND META-ANALYSIS.

Kortekaas-Rijlaarsdam AF, Luman M, Sonuga-Barke E, et al.

Academic improvement is amongst the most common treatment targets when prescribing stimulants to children with ADHD. Previous reviews on stimulant-related academic improvements are inconclusive and focus on task engagement. Recent literature suggests outcome-domain-specific medication effects that are larger for productivity than for accuracy. The aims of this study are quantifying methylphenidate effects on academic productivity and accuracy for math, reading, spelling; exploring the mediating or moderating effects of symptom improvements, demographic-, design- and disorder-related variables. PubMed, EMBASE, ERIC and PsycINFO were searched for articles reporting methylphenidate effects on academic productivity and accuracy. Thirty-four studies met entry criteria. Methylphenidate improved math productivity (7.8% increase, p < .001); math accuracy (3.0% increase, p = .001); increased reading speed (SMD .47, p < .001) but not reading accuracy. None of the mediators or moderators tested affected methylphenidate efficacy. Academic improvements were small compared to symptom improvements; qualitative changes limited to math. Clinicians should take this discrepancy into account when prescribing medication for ADHD

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Eur Child Adolesc Psychiatry. 2019 Feb;28:165-75.

EFFICACY OF INDIVIDUALIZED SOCIAL COMPETENCE TRAINING FOR CHILDREN WITH OPPOSITIONAL DEFIANT DISORDERS/CONDUCT DISORDERS: A RANDOMIZED CONTROLLED TRIAL WITH AN ACTIVE CONTROL GROUP.

Goertz-Dorten A, Benesch C, Berk-Pawlitzek E, et al.

Patient-focused cognitive-behavioral therapy in children with aggressive behavior, which uses group-based social skills training, has resulted in significant reductions in behavioral problems, with effect sizes in the small-to-medium range. However, effects of individually delivered treatments and effects on aggressive behavior and comorbid conditions rated from different perspectives, child functional impairment, child quality of life, parent-child relationship, and parental psychopathology have rarely been assessed. In a randomized controlled trial, 91 boys aged 6-12 years with a diagnosis of oppositional defiant disorder/conduct disorder and peer-related aggression were randomized to receive individually delivered social competence training (Treatment Program for Children with Aggressive Behavior, THAV) or to an active control involving group play that included techniques to activate resources and the opportunity to train prosocial interactions in groups (PLAY). Outcome measures were rated by parents, teachers, or clinicians. Mostly moderate treatment effects for THAV compared to PLAY were found in parent ratings and/or clinician ratings on aggressive behavior, comorbid symptoms, psychosocial impairment, quality of life, parental stress, and negative expressed emotions. In teacher ratings, significant effects were found for ADHD symptoms and prosocial behavior only. THAV is a specifically effective intervention for boys aged 6-12 years with oppositional defiant disorder/conduct disorder and peer-related aggressive behavior as rated by parents and clinicians

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Eur Child Adolesc Psychiatry. 2019 Jan;28:145-46.

METHODOLOGICAL CONCERNS WITH NETWORK META-ANALYSIS ON DRUGS FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Faltinsen EG, Storebo OJ, Gluud C.

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Eur J Med Genet. 2019 Mar;62:204-09.

NRXN1 DELETION SYNDROME; PHENOTYPIC AND PENETRANCE DATA FROM 34 FAMILIES.

Al SM, Forman EB, Fitzgerald JE, et al.

The spectrum of phenotypes associated with heterozygous deletions of neurexin-1 (NRXN1) is diverse and includes: autism spectrum disorder, attention deficit hyperactivity disorder, intellectual disability, seizures, schizophrenia, mood disorders and congenital malformations. Reduced penetrance and variable expressivity of deletions in this gene remain a challenge for genetic counselling. We clinically reviewed 67 NRXN1 deletions from 34 families to document the phenotype and determine odds ratio. Thirty-four pro bands (5 adults, 29 children (<16 years)) were initially identified from a cohort clinically referred for array CGH. A further 33 NRXN1 deletions (16 with established phenotype) from the families were identified following cascade screening. Speech and language delay was a consistent clinical presentation. Pedigree analysis of the inherited group revealed numerous untested relatives with a history of mental health and developmental issues, most notably in the NRXN1beta isoform patients. Our study highlights the complex nature of the NRXN1 phenotype in this population

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Eur J Med Genet. 2019 Jan;62:55-60.

DE NOVO LOSS-OF-FUNCTION VARIANTS OF ASH1L ARE ASSOCIATED WITH AN EMERGENT NEURODEVELOPMENTAL DISORDER.

Shen W, Krautscheid P, Rutz AM, et al.

De novo variants of ASH1L, which encodes a histone methyltransferase, have been reported in a few patients with intellectual disability and autistic features. Here, we identified a novel de novo frame-shift variant, c.2422_2423delAAinsT which predicts p.(Lys808TyrfsTer40), in ASH1L in a patient with multiple congenital anomalies (MCA), fine motor developmental delay, learning difficulties, attention deficit hyperactivity disorder, sleep apnea, and scoliosis. This frame-shift variant is expected to result in loss-of-function. Our report provides further evidence to support loss-of-function alterations of ASH1L as causative for an emergent neurodevelopmental syndrome characterized by MCA, intellectual disability, and behavioral problems, and further delineates this genetic disorder

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Eur Psychiatry. 2019 Jan;55:116-21.

PSYCHIATRIC DISORDERS AND AUTISM IN YOUNG CHILDREN WITH 22Q11.2 DELETION SYNDROME COMPARED TO CHILDREN WITH IDIOPATHIC AUTISM.

Serur Y, Sofrin FD, Daon K, et al.

BACKGROUND: The 22q11.2 deletion syndrome (22q11DS) is a neurogenetic condition characterized by high rates of psychiatric disorders. To our knowledge, this is the first study to assess psychiatric disorders in young children with 22q11DS using a structured psychiatric diagnostic interview, and one of few studies to use the complete gold standard diagnostic evaluation to examine the prevalence of autism spectrum disorder (ASD) in young children with 22q11DS and compare it to a matched control group with iASD.

METHODS: We identified the psychiatric disorders and autistic phenotype of young children with 22q11DS (age 3-8 years) and compared them with those of age and sex-matched children with idiopathic autism (iASD). We used the gold standard psychiatric and ASD assessments including the Autism Diagnostic Interview-Revised (ADI-R), the Autism Diagnostic Observation Schedule (ADOS) and a clinical examination by a child psychiatrist.

RESULTS: Eighty-four percent of the children with 22q11DS had at least one psychiatric disorder, including anxiety disorders and ADHD, and 16% met strict criteria for ASD. Children with 22q11DS and ASD symptoms had less severe overall ASD symptoms than those with iASD. Children with 22q11DS, regardless of ASD diagnosis, were characterized by repetitive restricted behaviors.
CONCLUSIONS: Our results highlight the need to screen for psychiatric disorders in 22q11DS and treat them already in preschool years

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Eur Child Adolesc Psychiatry. 2019.

EARLY MOTOR SIGNS OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A SYSTEMATIC REVIEW.

Athanasiadou A, Buitelaar JK, Brovedani P, et al.

ADHD is a common neurodevelopmental disorder with onset of symptoms typically in early childhood. First signs of the disorder, including language delay, motor delay and temperament characteristics, may be evident as early as infancy. The present review describes published evidence about early motor signs of either children with later symptoms of ADHD or a later diagnosis of the disorder. Nine published cohort studies were included after a systematic search of related terms in PubMed and PsycInfo databases. Study eligibility criteria included: (1) report on early motor function or any motor-related signs; (2) the presence of a participantsΓÇÖ assessment by/at 12-ámonths of age; (3) report of a later presence of ADHD symptoms. The limited number of reports included suggests an association between mild early neurological markers and later developmental coordination disorder and motor overflow movements. Unfortunately, due to their small sample sizes and focus on group reports rather than individuals, they have limited power to find strong associations. Early motor indicators of ADHD, if present, appear to be non-specific, and therefore not yet useful in clinical screening. Spontaneous motility seems to be a promising measure for early ADHD detection, although further studies with large cohorts are recommended to determine its clinical role in children at risk for ADHD

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Eur Child Adolesc Psychiatry. 2019.

DEVELOPMENTAL TRAJECTORIES OF MOTOR SKILLS DURING THE PRESCHOOL PERIOD.

Peyre H, Albaret J-M, Bernard JY, et al.

Children with developmental coordination disorder also manifest difficulties in non-motor domains (attentional, emotional, behavioral and socialization skills). Longitudinal studies can help disentangle the complex relationships between the development of motor skills and other cognitive domains. This study aims to examine the contribution of early cognitive factors to changes in motor skills during the preschool period. Children (N = 1144) from the EDEN mother-child cohort were assessed for motor skills with the Copy Design task (NEPSY battery) and the parent-rated Ages and Stages Questionnaire (fine and gross motor skills scores) at ages 3 and 5-6 years. At 3 years, language skills were evaluated using tests from the NEPSY and ELOLA batteries. Emotional problems, conduct problems, inattention and hyperactivity symptoms, peer relationships and pro-social behavior were assessed with the Strengths and Difficulties Questionnaire (SDQ) also at 3 years. Linear and logistic regression models were performed to examine whether positive and negative changes in motor skills between 3 and 5-6 years are associated with specific cognitive skills at 3 years, while adjusting for a broad range of pre- and postnatal environmental factors. In the linear regression model, the SDQ Inattention symptoms score at 3 years was associated with negative changes in motor skills (standardized $\beta = -0.09$, SD = 0.03, p value = 0.007) and language skills at 3 years were associated with positive changes in motor skills (standardized $\beta = 0.05$, SD = 0.02, p value = 0.041) during the preschool period. In logistic regression models, the SDQ Inattention symptoms score at 3 years was associated with a higher likelihood of a declining trajectory of motor skills (OR [95% CI] = 1.37 [1.02-1.84]). A higher language skills score at 3 years was associated with an increased likelihood of a resilient trajectory (1.67 [1.17-2.39]).

This study provides a better understanding of the natural history of developmental coordination delays by identifying cognitive factors that predict changes in motor skills between the ages of 3 and 5-6 years

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Eur Child Adolesc Psychiatry. 2019.

CRITICAL COMMENTS ON THE ARTICLE "INCREASED RISK OF DEVELOPING PSYCHIATRIC DISORDERS IN CHILDREN WITH ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD) RECEIVING SENSORY INTEGRATION THERAPY: A POPULATION-BASED COHORT STUDY".

Lai H-Y, Hu C-C, Kuo N-C, et al.

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Eur Child Adolesc Psychiatry. 2019.

CHILDHOOD METHYLPHENIDATE ADHERENCE AS A PREDICTOR OF ANTIDEPRESSANTS USE DURING ADOLESCENCE.

Madjar N, Shlosberg D, Leventer-Roberts M, et al.

Methylphenidate (MPH) is a common and effective treatment for attention deficit hyperactivity disorder (ADHD), but little is known about the relationship between early childhood intake of MPH and onset of antidepressant treatment during adolescence. The study aimed to examine whether adherence to MPH during early childhood predicts the initiation of antidepressants during adolescence. This is a 12-year historical prospective nationwide cohort study of children enrolled in an integrated care system who were first prescribed MPH between the ages of 6 and 8-áyears (N = 6830). We tested for an association between their adherence to MPH during early childhood (as indicated by medication possession ratio from MPH onset through the age of twelve) and the likelihood of being prescribed any antidepressant during adolescence (age 13ΓÇô18). As all country citizens are covered by mandatory health insurance, and full services are provided by one of the four integrated care systems, data regarding patientsΓÇÖ diagnoses, prescriptions, and medical purchases are well documented. Logistic regression analysis indicated that those with higher adherence to MPH had a 50% higher risk (95% CI 1.16ΓÇô1.93) of receiving antidepressants during adolescence when controlling for other comorbid psychiatric conditions and parental use of antidepressants. In this large-scale longitudinal study, MPH adherence during early childhood emerged as a predictor for antidepressant treatment during adolescence, which may reflect increased emotional and behavioral dysregulation in this group. The highly adherent patients are at higher risk and should be clinically monitored more closely, particularly into adolescence

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Eur Child Adolesc Psychiatry. 2019.

BODY DISSATISFACTION AND WEIGHT CONTROL BEHAVIOUR IN CHILDREN WITH ADHD: A POPULATION-BASED STUDY.

Bisset M, Rinehart N, Sciberras E.

Although attention-deficit/hyperactivity disorder (ADHD) is associated with eating disorders (EDs), it is unclear when ED risk emerges in children with ADHD. We compared differences in body dissatisfaction and weight control behaviour in children with/without ADHD aged 12-13 years concurrently, and when aged 8-9 and 10-11 years, to determine when risk emerges. We also examined differences by ADHD medication status at each age. This study uses waves 1-5 from the Longitudinal Study of Australian Children (n = 2323-2972). ADHD (7.7%) was defined at age 12-13 years by both parent- and teacher-reported SDQ Hyperactivity-Inattention scores > 90th percentile, parent-reported ADHD diagnosis and/or ADHD medication treatment. Children reported body dissatisfaction and weight control behaviour at 8-9, 10-11 and 12-13 years. Children with ADHD had greater odds of body dissatisfaction at ages 8-9 and 12-13 years. Comorbidities drove this relationship at 8-9 but not at 12-13 years [adjusted odds ratio (AOR): 1.6; 95 % CI 1.1-2.4; p = 0.01]. At 12-13 years, children with ADHD had greater odds of both trying to lose and gain weight, regardless of BMI status. Comorbidities drove the risk of trying to lose weight in ADHD but not of trying to gain weight (AOR 2.3; 95% CI 1.1-4.6; p = 0.03), which is likely accounted for by ADHD medication treatment.

ADHD moderately increases body dissatisfaction risk in children aged 8-9 and 12-13 years. Clinicians should monitor this and weight control behaviour throughout mid-late childhood, particularly in children with comorbid conditions and those taking ADHD medication, to reduce the likelihood of later ED onset

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Eur Child Adolesc Psychiatry. 2019.

MENTAL HEALTH PROBLEMS AND SCHOOL PERFORMANCE IN FIRST GRADERS: RESULTS OF THE PROSPECTIVE COHORT STUDY IKIDS.

Gräf C, Hoffmann I, Diefenbach C, et al.

We aimed to estimate unbiased effects of mental health problems (MHPs) on school performance in first graders, with an emphasis on rigorous adjustment for potential confounders. A population-based prospective cohort study was performed in the area of Mainz-Bingen (Germany). In 2015, all preschoolers were approached, and the presence and type of MHP (externalising/internalising) and other physical chronic health conditions were identified by the preschool health examination and study-specific questionnaires. At the end of the first grade, school performance (reading, writing, numeracy, and science) was assessed by the class teacher and rated on a four-item scale ranging from - 8 to + 8. Of 3683 children approached, 2003 (54%) were enrolled. School performance was available for 1462 children (51% boys, mean age 7.3 years). Of these, 41% had signs of at least one MHP. Compared to children without indications of mental and physical chronic health conditions, children with MHPs had lower school performance scores [adjusted mean difference - 0.98, 95% CI (- 1.35; - 0.61); P < 0.001]. Regarding the type of MHP, externalising MHPs were associated with poor school performance [adjusted mean difference - 1.44, 95% CI (- 1.83; - 1.05); P < 0.001], while internalising MHPs were not. Children with hyperactivity inattention problems were most affected [adjusted mean difference - 1.96, 95% CI (- 2.36; - 1.56); P < 0.001]. Externalising MHPs and in particular hyperactivity inattention problems may already affect school performance in early primary school. Identification of children with externalising MHPs prior to school entry may help to prevent impaired academic achievement in affected children

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Eur Child Adolesc Psychiatry. 2019.

DOES MATERNAL SOMATIC ANXIETY IN PREGNANCY PREDISPOSE CHILDREN TO HYPERACTIVITY?

Bolea-Alamañac B, Davies SJC, Evans J, et al.

The objective of this study is to explore the association between maternal somatic anxiety in pregnancy and hyperactivity symptoms and ADHD diagnosis in children. Data from the Avon Longitudinal Study of Parents and Children cohort were used to examine the association between somatic anxiety symptoms in pregnancy measured with five items of the Crown-Crisp Experiential Index, ADHD diagnosis in children at 7.5 and 15 years (obtained with the Development and Well-Being Assessment-DAWBA) and hyperactivity at 4 and 16 years (measured with the Strengths and Difficulties Questionnaire hyperactivity subscale-SDQ). Maternal somatic anxiety was associated with ADHD diagnosis at age 7.5 [crude OR = 1.87 (95% CI = 1.21-2.91)], adjusted model [OR = 1.57 (95% CI = 0.99-2.48)]. There was no evidence of association with ADHD at 15: crude OR = 2.27 (95% CI = 0.90-5.71), adjusted OR = 1.65 (95% CI = 0.63-4.35). An association was found at 4 and 16 with the SDQ hyperactivity subscale: crude OR at 4: 1.70 (95% CI =1.37-2.11), adjusted OR = 1.34 (95% CI = 1.07-1.69); crude OR at 16: 1.95 (95% CI = 1.47-2.58), adjusted OR = 1.62 (95% CI = 1.21-2.17). Thus, there was evidence for an association between maternal somatic anxiety in pregnancy and increased hyperactivity symptoms (SDQ) at 4 and 16. There was no association with ADHD diagnosis

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Eur Child Adolesc Psychiatry. 2019.

IRRITABILITY IN ADHD: ASSOCIATION WITH LATER DEPRESSION SYMPTOMS.

Eyre O, Riglin L, Leibenluft E, et al.

Attention-deficit/hyperactivity disorder (ADHD) and depression commonly co-occur. Identifying children with ADHD at risk for later depression may allow early intervention and prevention. Irritability is one possible mechanism linking these two disorders. It is common in ADHD and associated with later depression in the general population. Cross-sectional studies suggest an association between irritability and depression in ADHD, but longitudinal research is limited. This study followed up a clinical ADHD sample longitudinally to examine: (1) the association between childhood irritability and later depression symptoms, and (2) whether irritability persistence is important in this association. At baseline, parents (n = 696) completed semi-structured interviews about their child (mean age = 10.9), providing information on child psychopathology, including irritability. A subsample (n = 249) was followed up after a mean of 5.4-áyears. Parent-completed Mood and Feelings Questionnaires provided information on depressive symptoms at follow-up. Parent-rated structured diagnostic interviews provided information on ADHD diagnosis and irritability at follow-up. Regression analyses examined associations between (i) baseline irritability and depression symptoms at follow-up, and (ii) persistent (vs. remitted) irritability and depression symptoms at follow-up. Analyses controlled for age, gender, depression symptoms, anxiety, ADHD symptoms, and ADHD medication at baseline. Baseline irritability was associated with depression symptoms at follow-up, but the association attenuated after controlling for anxiety and ADHD symptoms. Persistent irritability was associated with depression symptoms at follow-up, after including all covariates. Children with ADHD with persistent irritability are at elevated risk of developing depression symptoms. They may be a target for early intervention and prevention of depression

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Europ J Spec Needs Educ. 2019.

FOREIGN LANGUAGE LEARNING FOR CHILDREN WITH ADHD: EVIDENCE FROM A TECHNOLOGY-ENHANCED LEARNING ENVIRONMENT.

Liontou T.

The need to give equal access to education and make the learning process fruitful for every student, regardless of his/her individual abilities, has resulted in an increased focus of attention by modern educators who have explored the impact of different teaching practices on students with Learning Differences (LDs). However, there is still lack of empirical evidence as regards the most efficient English as a Foreign Language (EFL) teaching methodology and pertinent material for students with such differences. This paper reports on a one-year study that aimed at investigating the development of young Attention Deficit Hyperactivity Disorder (ADHD) learners reading competence within a Technology-Enhanced Learning Environment (TELE). A total of ten EFL students aged 9 to 12-áyears old participated in the research, all of which were officially diagnosed with ADHD syndrome. The study concludes by presenting explicit teaching and testing accommodations that could be adopted from primary to tertiary one. As such, the included suggestions aspire to yield practical guidance and insight to EFL instructors, material developers and curricula designers from primary to tertiary education in reference to specific computer-based features embedded in reading comprehension activities that might prove helpful to ADHD learners throughout their lives

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Europ J Spec Needs Educ. 2019.

THE ADVANTAGES OF AN ADHD CLASSIFICATION FROM THE PERSPECTIVE OF TEACHERS.

Wienen AW, Sluiter MN, Thoutenhoofd E, et al.

In Western countries, the number of ADHD diagnoses and medical treatments of children has risen spectacularly over the last decennia, as has the amount of criticism about this trend. Various studies have shown that children receiving an ADHD classification often follow from initial signals that were raised in a school context. Hence, it becomes important to investigate precisely what advantages attach to ADHD classification in educational practice. In this qualitative study, 30 teachers were interviewed about their

experiences and views of ADHD. The results suggest that a small number of interviewees sees no advantages to ADHD classification: the classification does not practically help them as teachers, they are familiar with the drawbacks of ADHD classification, and they take issue with the idea of labelling children. The greater number of interviewees, however, suggest ambivalence about ADHD classification: they are aware of its drawbacks while experiencing mainly advantages. According to the interviewees, ADHD classification explains undesirable behaviours and disappointing academic achievement. Classification thereby removes blame from pupils, parents and teachers, and so can be a starting point for productive agreement and collaboration. We will discuss the implications of these findings in the light of the concept of reification, child-centred problematisation and the development of more inclusive education

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Eur Neuropsychopharmacol. 2019;29:S757-S758.

HERITABILITY OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER ACROSS THE LIFESPAN.

Brikell I, Kuja-Halkola R, Larsson H.

Attention-Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder affecting around 5-10% of children and 2.5-5% of adults worldwide. Research addressing the heritability of ADHD have yielded inconsistent findings, with studies in children suggesting higher heritability (75-90%) compared to studies in adults (30-50%) (Brikell, Kuja-Halkola, and Larsson 2015). To review the role of rater effects on the observed differences in heritability between children and adults, and to address the role of genetic and environmental influences on stability and change of ADHD over the life-span, we conducted a literature review of cross-sectional and longitudinal studies addressing the heritability of ADHD across ages, or in adulthood. We identified quantitative genetic studies published up until May 2017 by searching the NCBI's PubMed database using a combination of the keywords heritability, attention-deficit hyperactivity disorder, attention problems, ADHD, adult, genetic, self-report, twin, longitudinal and family studies. Based on the reviewed cross-sectional studies, the heritability of self-rated ADHD symptoms in adults ranged between 30%-44% and the heritability of self-rated symptoms in adolescent between 34%-54%. Cross-sectional studies including multiple informants showed that heritability estimates based on ratings from different informants (i.e., self-ratings and different parents/teachers rating each twin in a pair) consistently yield lower heritability estimates compared to studies based on ratings from a single informant. This effect appears to be independent of age. One study using cross-informant data in adults (combined parent and self-ratings) and two studies using register based clinical diagnoses in twin and family data reported the heritability of ADHD in adults to be 70-80%. The reviewed longitudinal twin studies suggest that stability in ADHD is largely due to genetic factors. In addition, longitudinal studies also provide evidence that new genetic effects for ADHD come online at different developmental stages and that these genetic factors are partly independent of those contributing to baseline symptoms. We identified one study assessing late-onset adult ADHD, which reported the heritability of both self-reported and co-informant (mother or co-twin) reported clinically relevant ADHD at age 18 to be around 35%. Together, the reviewed cross-sectional studies suggest that the reported lower heritability of ADHD in adults is likely to be at least partly explained by the switch from relying one rater (parent/teacher) in childhood, to relying on self-ratings (where each twin rates themselves) of ADHD symptoms in adulthood. When rater effects are addressed using cross-informant data or clinical diagnoses, the heritability of ADHD in adulthood appears to be comparable to the heritability of ADHD in childhood. Longitudinal studies show evidence for the role of genetic factors in both the stability and change in ADHD across ages. Emerging evidence suggest that the genes implicated in the onset of childhood ADHD are in part distinct from those associated with the developmental course of ADHD. Such findings raise new questions as to whether the heterogeneity in heritability estimates of ADHD across ages may be related to differential developmental trajectories of ADHD

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Eur Neuropsychopharmacol. 2019;29:S753-S754.

ASSOCIATIONS BETWEEN GENETIC RISK FOR PSYCHIATRIC DISORDERS AND CHILDHOOD NEURODEVELOPMENT: INVESTIGATING POLYGENIC RISK SCORES FOR PSYCHIATRIC DISORDERS AND TRAITS IN GENERAL POPULATION SAMPLES.

Riglin L, Collishaw S, Thapar AK, et al.

Most psychiatric disorders are thought to have their origins at least in part in childhood, even if early manifestations of liability are quite different from the later full-blown clinical picture. This work aims to identify traits relevant to risk for psychiatric disorders early in development by investigating which neurodevelopmental domains are associated with psychiatric disorder risk alleles during childhood. Findings will be presented testing the hypothesis that psychiatric disorder risk alleles, as measured by polygenic risk scores, affect normative, dimensional childhood characteristics in the general population. Specifically, this work investigates associations between polygenic risk scores for schizophrenia, bipolar disorder, major depressive disorder and Attention Deficit Hyperactivity Disorder and primarily pre-pubertal neurodevelopmental traits using longitudinal general population samples

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Eur Neuropsychopharmacol. 2019;29:S758-S759.

META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES ON ADULT ATTENTION-DEFICIT AND HYPERACTIVITY DISORDER.

Ribasòs M, Rovira P, Soler M, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is among the most heritable psychiatric disorders. Given that around 65% of children diagnosed in childhood continue to suffer from ADHD during adulthood, we aim to identify the genetic influence on the stability of ADHD symptoms that may contribute to discern between ADHD subjects with and without symptomatic persistence using the genomic data from the International Multi-centre persistent ADHD CollaboraTion (IMpACT). In an attempt to unravel novel genes underlying persistent ADHD, we conducted a meta-analysis of genome-wide association studies (GWAS) for adult ADHD in a total sample of 5,981 cases and 15,180 controls from IMpACT. None of the findings exceeded the genome-wide threshold for significance (P<5e-08). Top hits included genes previously associated with learning, memory deficits, impaired long-term potentiation, bipolar disorder, suicidality or autism. The SNP heritability for adult ADHD was estimated as h2=0.15 (S.E.=0.03), which is in line with previous estimates in children. We also found evidence for a strong overlap in genetic risk variants between adult and children ADHD (rg = 0.92 (SE = 0.22); P-value=3.74e-05), supporting a shared genetic background. These data suggest that common genetic variation is involved in the etiology of the persistent form of the disorder and that many risk loci exert shared effects on ADHD through lifespan. Follow-up studies of children with ADHD may allow us to discern between individuals with and without symptomatic remission and will provide more insights into the genetic influence on the stability of ADHD symptoms

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Eur Neuropsychopharmacol. 2019;29:S994-S995.

CAPICE: CHILDHOOD AND ADOLESCENCE PSYCHOPATHOLOGY: UNRAVELLING THE COMPLEX ETIOLOGY BY A LARGE INTERDISCIPLINARY COLLABORATION IN EUROPE.

Middeldorp CM, Drevets W, Jarvelin M-R, et al.

Background: The CAPICE project aims to 1) identify genetic variants associated with the occurrence and course of common childhood psychopathology including depression, anxiety and Attention Deficit Hyperactivity Disorder related traits, and establish the genetic overlap within childhood psychiatric disorders and with adult psychiatric disorders, 2) unravel the mechanisms underlying the associations between early lifestyle factors and childhood psychiatric disorders, 3) identify new drug targets, and 4) build a risk prediction model that identifies groups of children that are at highest risk to have persistent symptoms. This poster provides an overview of the plan to achieve these goals.

Methods: CAPICE is an international training network, funded by an EU Marie Curie grant, in which 12 PhD students will be trained in psychiatric genomics. This network will elaborate on the EArly Genetics and

Lifecourse Epidemiology (EAGLE) consortium. EAGLE is a well-established collaboration of many birth and adolescent population based (twin and family) cohorts, with unique longitudinal information on lifestyle, family environment, health, and emotional and behavioral problems. Phenotypic and genome-wide data are available for over 60,000 children, in addition to genome-wide data for over 20,000 mothers and epigenome-wide data for over 6,000 children. Analyses will include (but will not be limited to) twin analyses, genome-wide association meta-analyses, polygenic analyses, Mendelian randomization, and biological pathway analyses.
Results: We expect that the results will provide insight into the etiology of mental health symptoms in children and adolescents and shed light on possible targets for prevention and intervention (e.g. by drug target validation or by tailoring treatment based on the risk for persisting symptoms).
Discussion: It is well known that psychiatric symptoms in childhood be the precursor of many psychiatric disorders during adulthood. Longitudinal population based cohorts provide a good opportunity to show how genetic factors influence development over the ages. Since these disorders are the extreme end of the continuum, collaborations with case-control samples may strengthen the results

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Eur Neuropsychopharmacol. 2019;29:S811-S812.

TRANSLATING DISCOVERIES IN ADHD GENOMICS TO THE CLINIC

Doyle A, Martin J, Vuijk P, et al.

Background: A recent genome-wide association analysis has identified specific susceptibility variants and a substantial polygenic component for Attention-Deficit/Hyperactivity Disorder (ADHD). Given that emerging risk variants are unlikely to track precisely with conventional diagnoses, whether these discoveries will have utility in clinical settings for improved diagnostics and risk stratification requires further study. Our overall goal is to establish the relevance of emerging psychiatric genetics findings to youth clinical samples. In the current study, we aimed to 1) confirm the convergent validity of ADHD polygenic risk with ADHD-related phenotypes in youth presenting for neuropsychiatric evaluation; and 2) determine the extent to which ADHD polygenic risk associates with phenotypes beyond ADHD that putatively share its underlying liability and have implications for functional outcome.
Methods: Participants were 470 youth, ages 7 to 18, consecutively referred for neuropsychiatric evaluation and genotyped on the Illumina Infinium PsychArray Beadchip. Diagnoses made subsequent to study enrollment reflected a range of psychopathology and comorbidity. We determined the burden of ADHD-related common variants in these patients at different significance thresholds from the ADHD PGC-iPSYCH meta-analysis. We then associated this polygenic risk with clinical phenotypes. First, we conducted univariate analyses relating ADHD polygenic risks scores (PRSs) to ADHD diagnoses (none/borderline/full) and symptoms, cognition, and dimensional ratings of aggression and mania. Second, we stratified youth by low, medium, and high ADHD polygenic burden and used a mixed modeling approach to determine whether risk strata associated with distinct multivariate clinical profiles. Third, we determined phenotypically distinct latent classes in these and other youth (N~900) based on eight dimensional measures of psychopathology and examined whether the ADHD-PRS discriminated among them.
Results: The ADHD-PRS predicted the ADHD diagnosis at seven discovery sample thresholds after correction for potential confounds and multiple testing. The strongest association occurred at discovery sample p <.000001 [Wald +ù2(2) = 13.34, p=.0013], where an ADHD PRS score increase of 1.0 SD increased the relative risk of having ADHD versus not having ADHD 1.5-fold among youth with a range of diagnoses. Variation in ADHD risk also predicted cross-diagnostic variation in ADHD symptoms, aggression and working memory at multiple discovery sample thresholds. Here, the strongest associations explained 2.3 -3.0% of the trait variation. Youth with high ADHD polygenic burden also showed a distinct clinical profile [Wald +ù2 (2) = 8.15, p=.017], driven by greater severity on measures of inattention, hyperactivity, inhibition, aggression and anxiety. Finally, among the four latent classes of youth, the ADHD PRS distinguished the two classes with the greatest and least psychopathology severity (F(1,421) = 10.73, p=.0011). These groups exhibited significant differences on ADHD symptoms as well as other dimensions of emotional and behavioral dysregulation.
Discussion: In a multi-diagnostic clinical sample, ADHD polygenic risk showed convergent validity with ADHD phenotypes. Genotype- and phenotype-first analyses also indicated that ADHD polygenic burden

associates with traits reflecting cognition and behavioral and emotional dysregulation that extend beyond ADHD and that have implications for functional outcome

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Eur Neuropsychopharmacol. 2019;29:S955.

ANALYZING THE ROLE OF COMMON EXOMIC VARIANTS ON MODULATING ADHD BEHAVIORS USING A BEHAVIORAL DYNAMIC APPROACH.

Mokhtar S, Sengupta S, Grizenko N, et al.

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common behavioural disorder in school-aged children (3ΓÇô6%). ADHD is characterized by developmentally inappropriate levels of attention, motor hyperactivity/impulsivity, or both. ADHD is a multifactorial highly heritable disorder, but its genetic underpinnings remain very difficult to unravel. This is mainly due to its multilayered phenotypic presentations (combination of several cognitive, emotional and motor traits), multiple environmental determinants and its complex genetic architecture. Our research group has been dissecting these various dimensions through a pharmaco-behavioural genetic study of ADHD while systematically collecting highly relevant environmental factors.

Methods: This unbiased and systematic approach will be deployed in two phases. First, we are using 179 children diagnosed with ADHD aged between 6ΓÇô12 years and their parents to identify common exomic SNPs that are associated with ADHD or behavioural traits that are relevant for ADHD. This genotyping has already been completed through collaboration with the international ADHD genetic consortium. Preliminary results of this genotyping and its quality control indicate that there are over 20 000 eligible SNPs that can be analysed. In the second phase, 100 SNPs were selected according to a specific algorithm being developed (including criteria such as consistent association with ADHD across various behavioural relevant traits, functional relevance based on the role of the SNP in gene function or expression, the role of the gene in functional neural networks) to be replicated in an independent sample of over 500 patients and their parents which are currently available in our laboratory.

Results: Preliminary results of this genotyping and its quality control indicate that there are over 20,000 eligible SNPs that can be analysed. In the second phase, 100 SNPs were selected according to a specific algorithm being developed (including criteria such as consistent association with ADHD across various behavioural relevant traits, functional relevance based on the role of the SNP in gene function or expression, the role of the gene in functional neural networks).

Discussion: To our knowledge, this is the largest study attempting to unravel the genetic architecture of ADHD combining highly enriched behavioural dimensions of ADHD, pharmacological probes and a two-pronged whole exomic exploratory and a confirmatory steps. It is expected that this highly sophisticated approach will enable us to better understand the genetic of ADHD and its phenotypic variability

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Eur Neuropsychopharmacol. 2019;29:S889-S890.

SYNERGISTIC EFFECT OF COMT AND KIAA0319 GENES IN MODULATING ADHD BEHAVIOURS.

Fageera W, Sengupta S, Grizenko N, et al.

Background: ADHD and Learning Disorder (LD) are complex disorders with genetic and environmental determinants. Twenty to 30% of the children with ADHD have an associated LD. These problems usually persist into adolescence and are associated with chronic academic underachievement and failure to complete school. Hypothesis: Given the evidence for overlapping heritability between ADHD and LD, we hypothesize KIAA0319, a gene associated with LD, may interact with genes that have shown to be implicated in ADHD. As proof of concept, we have selected the COMT gene because of the well-documented role of its Val/Met polymorphism in modulating dopamine transmission in the frontal cortex. We also anticipated that the interaction between these two genes would be more evident in the school environment.

Methods: 400 children with ADHD (9-12 years old) were included in a double-blind placebo controlled study with methylphenidate. Teachers and parents were asked to evaluate the child's behavior at baseline, placebo, and MPH weeks using the appropriate version of Conners scale. The association between

genotypes and ADHD behaviors were tested using repeated measure ANOVA, the two genes were the between-subject factors and the behaviors under the three experimental conditions (EC), were the within-subject factor.
Results: A highly significant 3-way interaction (KIAA0319ΓüÄCOMTΓüÄEC) was revealed in two SNPs of the KIAA0319 gene (rs4504469 p= 0.006 and rs7766230 p= 0.004) only according to teachers. By stratifying the children according to their COMT genotypes, we found that within the Met/Met genotype group, there were no significant differences in Conner's-T scores at baseline and on Placebo. However, significantly different patterns of response to MPH between KIAA0319 genotype groups were observed.
Discussion: This is the first study identifying an interaction between a gene involved in LD and a gene implicated in ADHD. This might help to individualize treatments for children with comorbid ADHD and learning disorders

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Eur Neuropsychopharmacol. 2019;29:S1012.
EXAMINING ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) INATTENTION SYMPTOM AS ANTECEDENTS OF PSYCHOSIS RISK IN 22Q11.2 DELETION SYNDROME (22Q11.2DS).
Niarchou M, Vorstman J, Schneider M, et al.
Background: 22q11.2 Deletion Syndrome (22q11.2DS) is associated with high risk for developing schizophrenia in adulthood while Attention Deficit Hyperactivity Disorder (ADHD) constitutes the most frequent diagnosis in childhood. Individuals with 22q11.2DS show marked inattention symptoms. Interestingly, schizophrenia is also characterized by attentional deficits. This raises the question of whether childhood inattention is an antecedent of psychosis in 22q11.2DS. This is the first longitudinal study to examine whether childhood inattention is associated with the later emergence of Psychotic Experiences (PEs) and psychosis spectrum disorders in 22q11.2DS.
Methods: 294 individuals (mean age (SD):15.9(5.8)) completed assessments on psychotic symptoms and ADHD at two time points and did not report PEs at time 1(T1).
Results: Inattention symptoms and ADHD diagnosis at T1 were associated with PEs at T2 when adjusting for age, sex, IQ and assessment differences (Odds Ratio: 1.18, p=0.02). ADHD diagnosis at T1 was also associated with psychosis spectrum disorder at T2 (Odds Ratio: 4.8, p<0.001).
Discussion: This is the first study to examine the longitudinal associations between ADHD and psychosis in 22q11.2DS. Our findings support an important role of ADHD inattention symptoms in the development of psychosis in 22q11.2DS

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Eur Neuropsychopharmacol. 2019;29:S954-S955.
FIVE NOVEL LOCI ASSOCIATED WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER ARE REVEALED BY LEVERAGING POLYGENIC OVERLAP WITH EDUCATIONAL ATTAINMENT.
Shadrin A, Smeland O, Zayats T, et al.
Background: Attention-Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental condition that affects about 5% of children and adolescents worldwide. Despite its high heritability little is known about underlying genetic factors. Among other things ADHD is tightly associated with educational failure. However, potential genetic overlap between ADHD and educational attainment has not been examined in detail so far. Exploiting epidemiological similarity between ADHD and educational attainment we aimed to improve discovery of ADHD-associated genetic factors and investigated genetic overlap between these phenotypes.
Methods: We used ADHD data from the PGC (2064 trios, 896 cases, 2455 controls) and educational attainment data from the SSGAC (N=328917). To investigate polygenic overlap between ADHD and educational attainment we constructed fold-enrichment plots and conditional QQ plots in both directions: conditioning ADHD on educational attainment and vice versa. To explore the nature of the polygenic overlap and test a hypothesis that investigated traits correlate genetically we calculated correlations between z-scores of ADHD and educational attainment variants for nested strata of variants, representing subsets of SNPs with increasing significance of p-values in one of the traits. Additionally we supported this hypothesis

by estimating genetic correlation between ADHD and educational attainment using LD score regression. We applied condFDR/conjFDR method to identify specific loci associated with ADHD and loci associated with both ADHD and educational attainment simultaneously. Consistency of effect directions for top association signals detected in our condFDR/conjFDR analyses was tested in the independent GWAS of ADHD symptoms from EAGLE consortium (N=17666).
Results: Using condFDR/conjFDR method we identified five novel loci associated with ADHD, three of these being shared between ADHD and educational attainment. Leading variants for four of five identified regions are located in introns of protein coding genes: KDM4A, MEF2C, PINK1, RUNX1T1, while the remaining one is an intergenic SNP on chromosome 2 at 2p24. Four of five loci have opposite directions of effect in ADHD and educational attainment and consistent directions of effect in the independent GWAS of ADHD symptoms from the EAGLE consortium. A hypothesis of polygenic overlap between ADHD and educational attainment was supported by significant genetic correlation (rg=-0.403, p=7.90E-8), consistent pleiotropic enrichment in conditional QQ plots, >10-fold mutual enrichment of SNPs associated with both traits and growing negative correlation of association z-scores for the nested SNP strata with increasing significance in both phenotypes.
Discussion: We found five novel loci associated with ADHD and provided evidence for a shared genetic basis between ADHD and educational attainment, implicating three genetic loci in this overlap. Four of five identified loci showed consistent effects in the independent data set of ADHD symptoms, and inverse correlation with educational attainment. The latter is in line with prior epidemiological and genetic studies. We belive that altogether these findings provide new insights into the relationship between ADHD and educational attainment, suggesting shared molecular genetic mechanisms. Further research is required to clarify the biological effects of the identified genetic variants and how these may influence educational attainment and ADHD pathogenesis

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Eur Neuropsychopharmacol. 2019;29:S956.

GENE-GENE INTERACTION BETWEEN COMT AND NET IN MODULATING AND BEHAVIOURS.

Fageera W, Sengupta SM, Grizenko N, et al.

Background Cortico-subcortical circuit dysfunction plays an important role in the manifestation of ADHD symptoms. Dopamine (DA) and Norepinephrine (NE) are major players in the fine regulation of these circuits. Both of these neurotransmitters are major players in maintaining alertness, increasing focus, sustaining thoughts, and facilitating many cognitive functions. Thus, perturbation of either NE, DA (or both) signaling could be implicated in the pathogenesis of ADHD.
Hypothesis: Given the dynamic nature of the brain neuromodulation, where any action on one system may reverberate in the other systems, we hypothesize that NE transporter gene could interact with a gene that is essential for the metabolism of DA (COMT Val108/158Met) on modulating ADHD behaviors.
Methods 481 children with ADHD (9–12 years old) were included in a 2-week double blind placebo controlled study with methylphenidate. Teachers and parents were asked to evaluate the child's behavior at baseline, placebo, and MPH weeks. Repeated measure ANOVA with between-subject factor of both genes and within-subject factor of experimental conditions (EC) was used.
Results A highly significant 3-way interaction (NET□COMT□EC) was revealed in three SNPs of the NET gene (rs41154 p= 0.002, rs187714 p= 0.001, and rs2242447 p= 0.006) according to the parents' evaluation. By stratifying the children according to their COMT genotypes, we observe that all children behave in a similar fashion at baseline but respond differently to placebo and MPH. In the Met/Met and Val/Val genotype groups, children who are carrying the AG genotype of rs41154, CT genotype of rs41154, and CT genotype of rs41154 tend to respond poorly compared to patients with the GG, CC, and CT genotypes respectively on placebo and MPH.
Discussion Taken together, the current results suggest the epistatic interaction between COMT and NET genetic polymorphisms on response to pharmacological probes. Suggesting that complex gene-by-gene interactions may be important.

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Eur Neuropsychopharmacol. 2019;29:S810-S811.

POLYGENIC RISK FOR ADHD IS ASSOCIATED WITH READING- AND SPELLING RELATED TRAITS BEYOND PLEIOTROPIC EFFECTS DUE TO EDUCATIONAL ATTAINMENT

Verhoef E, Demontis D, Burgess S, et al.

Background: Language impairments often co-occur with Attention Deficit and Hyperactivity Disorder (ADHD) symptoms. Twin studies suggest that this comorbidity is at least partially due to shared genetic factors. Here, we aim to study the association between polygenic ADHD risk and language abilities in the general population. Using multivariable regression analysis, we also investigate whether this link persists conditional on the polygenic effects for Educational Attainment (EA), a factor that is known to be correlated with both ADHD and Language-Related Abilities (LRAs).

Methods: Thirteen LRAs capturing comprehension, reasoning, reading, spelling, phonological awareness/memory and verbal IQ were studied in 7 to 13 year-old children from a UK birth cohort (ALSPAC; NΓëñ5,919; SNP-h2>0.25). ADHD summary statistics were obtained from the Psychiatric Genomics Consortium (PGC; cases:4,163; controls:12,040), the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH; cases:14,584; controls:22,492) and a combined sample thereof (PGC+iPSYCH; cases:20,183; controls:35,191). EA summary statistics excluding ALSPAC participants were obtained through the Social Science Genetic Association Consortium (N=326,041). Genetic overlap between ADHD and LRAs was assessed using polygenic scoring (PGS). Conditional associations of genetically-predicted ADHD and EA with LRAs were estimated using Mendelian Randomisation techniques. However, the current data allows us to interpret findings in terms of shared genetic liability only. Effect estimates for spelling, reading and overall LRAs were combined using random-effects meta-regression, weighted by phenotypic correlations.

Results: Across all three ADHD samples, we consistently observed an inverse association between ADHD risk increasing alleles and both reading (e.g. PGC+iPSYCH; P=4+ù10ΓÇô19; +¦=-0.11; max OLS-R2 =1.5%) and spelling (PGC+iPSYCH; P=4+ù10ΓÇô18; +¦=-0.11; max OLS-R2 =1.2%) performance, but not overall LRAs, using PGS. Conditional analyses on EA confirmed inverse associations between ADHD polygenic risk and reading using both robust (15 SNPs; P-threshold<5+ù10-8; +¦standardised=-0.48; P=0.002) and less robust instruments (~2690 SNPs; P-threshold<0.0015; +¦standardised=-0.06; P=1+ù10-6). For latter, representing a higher proportion of pleiotropic effects, there was also evidence for a positive genetic association of EA as captured by ADHD instruments on reading (P=4+ù10-8). Conditional EA and ADHD genetic effects were replicated using EA instruments, confirming the robustness of our findings and suggesting reciprocal pleiotropy. Similar results were observed for spelling performance.

Discussion: Polygenic risk for ADHD shares genetic liability with reading- and spelling-related traits due to both disorder specific genetic effects but also pleiotropic effects with EA

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Eur Neuropsychopharmacol. 2019;29:S835.

AN INHERITED DISTAL 16P11.2 DELETION DEMONSTRATES VARIABLE EXPRESSIVITY AND INCOMPLETE PENETRACE FOR PSYCHIATRIC ILLNESS AS WELL AS ASSOCIATION WITH RHIZOMELIC SHORTENING: A CASE REPORT.

Morris E, McGillivray B, Lehman A, et al.

Background: The most commonly reported 16p Copy Number Variant (CNV) - 16p11.2 deletion syndrome (16pDS) (~600 kb; 29.5 -30.1 Mb) has been robustly associated with schizophrenia (SZ), as well as Intellectual Disabilities (ID)/Developmental Delays (DD), congenital anomalies, dysmorphic features and obesity. Non-overlapping distal 16p11.2 deletions (~200 kb; 28.7 -28.9 Mb) are less commonly reported, but have a variable phenotype similar to that of 16pDS, including emerging data suggesting a psychiatric phenotype. We report here on a parent/child dyad who share a distal 16p11.2 deletion.

Methods: Patient 1 (index) was assessed (for indications including seizures, DD, and short limbs) at ages 2, 17, and 36, when she had clinical Chromosomal Microarray (CMA) (Affymetrix Cytoscan HD array, clinical thresholds: 200 kb (deletions), 400 kb (duplications), Chromosome Analysis suite (v2.0.0 195)). Fluorescence in Situ Hybridization (FISH) was used to confirm the deletion and determine origin.

Results: Patient 1 was born at term to non-consanguineous parents. A 46XX karyotype was confirmed at age 2 and 17 (testing indications: myoclonic seizures, DD, rhizomelic shortening of upper limbs). At age 17, she was also noted to have small hands (<3rd %ile) and feet (-3.5 SD), large posteriorly rotated ears (+3

SD), brachycephaly, high nasal bridge, and low posterior hairline. She had developed psychosis at 13, and received diagnoses of bipolar disorder type I, ADHD, possible ASD and ID. At 37, she is obese with impaired fasting glucose, and ongoing psychiatric symptoms. CMA revealed a 238Kb deletion at 16p11.2 (28 819 028 29 056 973; hg19)) confirmed by FISH as being paternally inherited. Patient 2 is the 69 year-old father of Patient 1. He completed high school despite difficulties, and is not obese but has diabetes mellitus type II. He has rhizomelic shortening of both upper limbs but no history of psychiatric illness.
Discussion: While distal 16p11.2 deletions have been shown to increase risk for schizophrenia, this report contributes to the emerging evidence that this CNV is also associated with broader psychiatric phenotypes, such as bipolar disorder. The father's milder cognitive and metabolic phenotype supports variable expressivity of distal 16p11.2 deletions, even when inherited; his negative psychiatric history reinforces the incomplete penetrance of this CNV for psychiatric disorders. This report also contributes to the generation of a more thorough clinical description of the phenotypic range of distal 16p11.2 deletion, which we suggest, includes rhizomelic limb shortening

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Eur Neuropsychopharmacol. 2019;29:S757.

GENETICS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER ACROSS THE LIFESPAN.

Haavik J, Faraone S, Franke B.

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed childhood-onset neuropsychiatric condition, with impairing symptoms persisting into adulthood in the majority of cases. ADHD-diagnosed children, adolescents and adults share similar clinical features, co-morbidities and failures in major life domains. These associated problems increase the burden of disease and, consequently, global impairment, resistance to treatment and costs of illness. As most genetic studies on ADHD so far have been focusing on its childhood form only, there is limited knowledge about the genetics of ADHD at different ages, in clinical subgroups and across comorbid conditions. This symposium will present recent advances in our understanding of the genetics of ADHD and its major comorbid conditions across the lifespan. Speakers will address ADHD traits from a dimensional perspective using quantitative measures from national twin registry data, as well as unpublished genome wide molecular genetic data collected from large international multi-center clinical samples at different age groups. In this integrated symposium hosted by the International Multi-center persistent ADHD Collaboration (IMpACT), we will first present an updated review on ADHD heritability across the lifespan (presentation 1). We will then present a new international genome-wide association study of the adult form of ADHD (presentation 2), address genetic aspects of ADHD co-morbidity with adult obesity (presentation 3), and finally explore genetic correlations between ADHD dimensions in childhood and neuropsychiatric phenotypes in adulthood (presentation 4). As we gather more knowledge about ADHD, it is becoming clear that a full understanding of the disorder requires research from a lifetime perspective, integrating data from adults and children, using clinical samples as well as population registry data. Combination of different research traditions into a joint symposium will aid the exchange of information and future development of this important field

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Eur Psychiatry. 2019;58:38-44.

DIRECT MEDICAL COSTS OF ADHD AND ITS COMORBID CONDITIONS ON BASIS OF A CLAIMS DATA ANALYSIS.

Libutzki B, Ludwig S, May M, et al.

Background: ADHD is a highly prevalent disease in childhood which often persists into adulthood, then co-occurring with common adult conditions. Especially for adult ADHD, little is known about the costs of ADHD and the additional costs of comorbid conditions.
Aims: To determine medical costs of ADHD and costs of comorbidities (mood, anxiety and substance use disorders, obesity), including their co-occurrence rates, stratified by age and gender. Method: Claims data from a German Statutory Health Insurance database with approximately four million member-records per year were analysed. A total of 25,300 prevalent ADHD patients were identified by means of an ICD-10 GM diagnosis of ADHD. A 1:1 age and gender adjusted reference group without ADHD diagnosis was randomly

selected. Total health claims and health care costs related to ADHD were analysed, in addition to more targeted analyses of the occurrence and costs of pre-defined common comorbidities of, in particular, adult ADHD (SUD, mood and anxiety disorders, obesity). Outcomes were mean costs per patient and occurrence rates of comorbid conditions. Surplus costs of a comorbid condition in persons with ADHD relative to costs of this condition in persons without ADHD were calculated. Subgroup analyses were conducted based on age (0-12 years, 13-17 years, 18-30 years, 30+ years) and gender.

Results: Patients with ADHD were Γé¼1500 more expensive annually than individuals without ADHD ($p < 0.001$). Main cost drivers were inpatient care, psychiatrists and psychotherapists. Mood, anxiety, substance use disorders and obesity were significantly more frequent in ADHD patients and additional costs resulting from the comorbid conditions amounted up to 2800. Costs were slightly higher in women than men and increased with age for both genders. In young adults (18ΓÇô30 years) health care costs dropped notably, especially costs for the medical treatment of ADHD with stimulants and costs for psychiatrists, before rising again in the group of patients over 30 years who had higher comorbidity rates.

Conclusions: Medical costs for ADHD are substantial, in part through frequently occurring comorbid conditions, and particularly in adulthood, and are likely to further accelerate in the coming years. A gap of care was found, starting with the transition age group of patients over 17 years, as indicated by reduced costs per person during young adulthood, as well as an overall strong drop in administrative prevalence. In the future, approaches to improve the situation of care and reduce costs at the same time, i.e. through managed care programmes, should be implemented and benefit from detailed knowledge on age and gender-specific cost-drivers

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Front Biosci (Landmark Ed). 2019 Jan;24:313-33.

ANTIOXIDANT THERAPIES IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Moghadas M, Essa MM, Ba-Omar T, et al.

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder among children and adults. Impulsivity, inattention, and hyperactivity are hallmark of ADHD. While ADHD is not on the autism spectrum, they are related in several ways as they have some overlapping symptoms. The pathogenesis of ADHD has so far remained enigmatic, however, there is some evidence suggesting critical association among ADHD and the level of oxidative stress which trigger cell membrane damage, changes in inner structure and function of proteins, as well as structural damage to DNA which eventually culminate into development of ADHD. Although stimulants as well as some classes of non-stimulants are used to ameliorate symptom of ADHD, various adverse effects have been associated with such compounds. To date, treatment of ADHD is done with a combination of medications, behavior modifications, psycho-education, family therapy and life-style changes. The American Academy of Pediatrics officially promote stimulant medications and/or behavior therapy as 'first line of therapy'. In addition to the presently therapeutic armamentarium, evidences are emerging on relevancy of natural products. There has been an interest on the therapeutic role of antioxidants in the treatment of ADHD. The present review aims to highlight the beneficiary role played by different antioxidants in mitigating the symptoms of ADHD

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Front Human Neurosci. 2019 Feb;13.

DISTINCT METHYLPHENIDATE-EVOKED RESPONSE MEASURED USING FUNCTIONAL NEAR-INFRARED SPECTROSCOPY DURING GO/NO-GO TASK AS A SUPPORTING DIFFERENTIAL DIAGNOSTIC TOOL BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER COMORBID CHILDREN.

Sutoko S, Monden Y, Tokuda T, et al .

Attention deficit/hyperactivity disorder (ADHD) has been frequently reported as co-occurring with autism spectrum disorder (ASD). However, ASD-comorbid ADHD is difficult to diagnose since clinically significant symptoms are similar in both disorders. Therefore, we propose a classification method of differentially recognizing the ASD-comorbid condition in ADHD children. The classification method was investigated based on functional brain imaging measured by near-infrared spectroscopy (NIRS) during a go/no-go task.

Optimization and cross-validation of the classification method was carried out in medicated-naÃ¨ve and methylphenidate (MPH) administered ADHD and ASD-comorbid ADHD children (randomized, double-blind, placebo-controlled, and crossover design) to select robust parameters and cut-off thresholds. The parameters could be defined as either single or averaged multi-channel task-evoked activations under an administration condition (i.e., pre-medication, post-MPH, and post-placebo). The ADHD children were distinguished by significantly high MPH-evoked activation in the right hemisphere near the midline vertex. The ASD-comorbid ADHD children tended to have low activation responses in all regions. High specificity (86 Â± 4.1%; mean Â± SD), sensitivity (93 Â± 7.3%), and accuracy (82 Â± 1.6%) were obtained using the activation of oxygenated-hemoglobin concentration change in right middle frontal, angular, and precentral gyri under MPH medication. Therefore, the significantly differing MPH-evoked responses are potentially effective features and as supporting differential diagnostic tools. (PsycINFO Database Record (c) 2019 APA, all rights reserved)

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Front Human Neurosci. 2019 Feb;13.

A REVIEW OF HETEROGENEITY IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD).

Luo Y, Weibman D, Halperin JM, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects approximately 8% 12% of children worldwide. Throughout an individual s lifetime, ADHD can significantly increase risk for other psychiatric disorders, educational and occupational failure, accidents, criminality, social disability and addictions. No single risk factor is necessary or sufficient to cause ADHD. The multifactorial causation of ADHD is reflected in the heterogeneity of this disorder, as indicated by its diversity of psychiatric comorbidities, varied clinical profiles, patterns of neurocognitive impairment and developmental trajectories, and the wide range of structural and functional brain anomalies. Although evidence-based treatments can reduce ADHD symptoms in a substantial portion of affected individuals, there is yet no curative treatment for ADHD. A number of theoretical models of the emergence and developmental trajectories of ADHD have been proposed, aimed at providing systematic guides for clinical research and practice. We conducted a comprehensive review of the current status of research in understanding the heterogeneity of ADHD in terms of etiology, clinical profiles and trajectories, and neurobiological mechanisms. We suggest that further research focus on investigating the impact of the etiological risk factors and their interactions with developmental neural mechanisms and clinical profiles in ADHD. Such research would have heuristic value for identifying biologically homogeneous subgroups and could facilitate the development of novel and more tailored interventions that target underlying neural anomalies characteristic of more homogeneous subgroups

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Front Integr Neurosci. 2019 Jan;12.

THE EFFECT OF DUAL TASK ON ATTENTIONAL PERFORMANCE IN CHILDREN WITH ADHD.

Caldani S, Razuk M, Septier M, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder without validated objective markers. Oculomotor behavior and executive motor control could potentially be used to investigate attention disorders. The aim of this study was to explore an oculomotor and postural dual task in children with ADHD. Forty-two children were included in the study, gathering children with ADHD (n = 21) (mean 8.15 age Â± years 0.36) and sex-, age-, and IQ-matched typically developing children (TD). Children performed two distinct fixation tasks in three different postural conditions. Eye movements and postural body sway were recorded simultaneously, using an eye tracker and a force platform. Results showed that children with ADHD had poor fixation capability and poor postural stability when compared to TD children. Both groups showed less postural control on the unstable platform and displayed more saccades during the fixation task. Surprisingly, in the dual unstable platform/fixation with distractor task, the instability of children with ADHD was similar to that observed in TD children. 'Top-down' dys-regulation mediated by frontal-striatal dysfunction could be at the origin of both poor inhibitory oculomotor deficits and impaired body stability reported in children with ADHD. Finally, we could assume that the fact both groups of children focused their attention on

a secondary task led to poor postural control. In the future it could be interesting to explore further this issue by developing new dual tasks in a more ecological situation in order to gain more insight on attentional processes in children with ADHD. HIGHLIGHTS Children with ADHD showed poor fixation capability when compared to TD children. 'Top-down' dys-regulation mediated by frontal-striatal dysfunction could be at the origin of both poor inhibitory oculomotor deficits and impaired body stability reported in children with ADHD. Both groups of children focused their attention on the visual fixation task leading to poor postural control. In the future it could be interesting to develop new dual tasks in an ecological situation in order to gain more insight on attentional processes in children with ADHD

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Front Psychol. 2019 Jan;9.

A PILOT STUDY OF BEHAVIORAL, PHYSIOLOGICAL, AND SUBJECTIVE RESPONSES TO VARYING MENTAL EFFORT REQUIREMENTS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Mies GW, Moors P, Sonuga-Barke EJ, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is presumed to involve mental effort application difficulties. To test this assumption, we manipulated task difficulty and measured behavioral, as well as subjective and psychophysiological indices of effort.

Methods: Fifteen adolescent ADHD boys and 16 controls performed two tasks. First, subjective estimates and behavioral and pupillary measures of effort were recorded across five levels of N-back task difficulties. Second, effort discounting was assessed. In the latter, participants made repeated choices between performing a difficult N-back task for a high reward versus an easier N-back task for a smaller reward. Results: Increasing task difficulty led to similar deteriorations in performance for both groups although ADHD participants performed more poorly at all difficulty levels than controls. While ADHD and control participants rated the tasks equally difficult and discounted effort similarly, those with ADHD displayed slightly different pupil dilation patterns with increasing task difficulty. Conclusion: The behavioral results did not provide evidence for mental effort problems in adolescent boys with ADHD. The subtle physiological effects, however, suggest that adolescents with ADHD may allocate effort in a different way than controls

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Gait Posture. 2019 Jan;67:284-89.

POSTURAL INSTABILITY IN ADULT A.

Jansen I, Philipsen A, Dalin D, et al.

BACKGROUND: Apart from inattention, hyperactivity and impulsivity, ADHD in childhood presents with an impairment of motor coordination and balance functions. Until now, literature is scarce about sensorimotor deficits in adult ADHD. This is a pilot study that identifies and quantifies the role of sensory, motor, and central adaptation mechanisms for adult ADHD patients' sensorimotor deficits in a systematic way, using postural control.

METHODS: We analyzed spontaneous and externally perturbed stance in ten adult patients suffering from ADHD. Findings were compared to data from ten matched healthy subjects.

RESULTS: Spontaneous sway amplitudes and velocities were larger in ADHD patients compared to healthy subjects. Furthermore, body excursions as a function of platform tilts were abnormally large in ADHD patients, specifically in the low frequency range. Based on simple feedback model simulations, we found that ADHD patients showed a larger time delay between platform tilts and body response, and a lower value of the integral part of the neural controller, which affects the long-term control of their posture. These postural abnormalities correlated well with the hyperactivity and impulsivity dimensions of the individual ADHD symptoms.

CONCLUSION: We conclude that adult ADHD patients' major postural deficit consists of an impairment of a stable, long-term sensorimotor behavior, which fits very well to the concept of impulsivity and hyperactivity

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Genes. 2019;10.

CLOCK POLYMORPHISMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD): FURTHER EVIDENCE LINKING SLEEP AND CIRCADIAN DISTURBANCES AND ADHD.

Carpena MX, Hutz MH, Salatino-Oliveira A, et al.

Circadian and sleep disorders, short sleep duration, and evening chronotype are often present in attention-deficit/hyperactivity disorder (ADHD). CLOCK, considered the master gene in the circadian rhythm, has been explored by few studies. Understanding the relationship between ADHD and CLOCK may provide additional information to understand the correlation between ADHD and sleep problems. In this study, we aimed to explore the association between ADHD and CLOCK, using several genetic markers to comprehensively cover the gene extension. A total of 259 ADHD children and their parents from a Brazilian clinical sample were genotyped for eight single nucleotide polymorphisms (SNPs) in the CLOCK locus. We tested the individual markers and the haplotype effects using binary logistic regression. Binary logistic and linear regressions considering ADHD symptoms among ADHD cases were conducted as secondary analysis. As main result, the analysis showed a risk effect of the G-A-T-G-G-C-G-A (rs534654, rs1801260, rs6855837, rs34897046, rs11931061, rs3817444, rs4864548, rs726967) haplotype on ADHD. A suggestive association between ADHD and rs534654 was observed. The results suggest that the genetic susceptibility to circadian rhythm attributed to the CLOCK gene may play an important role on ADHD

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Hum Mov Sci. 2019 Feb;63:62-72.

EMPATHY, SOCIAL RELATIONSHIP AND CO-OCCURRENCE IN YOUNG ADULTS WITH DCD.

Tal SM, Kirby A.

Empathy is defined as an emotional or cognitive response to another's emotional state. It is considered essential for navigating meaningful social interactions and is closely linked to prosocial behavior. Developmental coordination disorder (DCD) is characterized by an impairment of motor coordination that has a marked impact on both academic and day-to-day living activities. Children and adolescents with DCD have been shown to have less developed social support and friendships. The research linking empathy and DCD is scarce. The aims of this study are to gain an understanding of the relationship between DCD and empathy in young adults with DCD only, and with DCD coupled with other neurodevelopmental disorders, in comparison with typically developing adults.

METHODS: The study included 212 young adults aged 18-40years. The subjects in this study were from mainstream populations in the UK. The study groups included: (a) "DCD only" with 42 individuals; (b) "DCD+ASD" with 21 individuals; (c) "DCD+ADHD" with 45 individuals; (d) "DCD+ASD+ADHD" with 29 individuals; and (e) the control group of 75 individuals.

RESULTS: ANOVA on the Empathy Questionnaire (EQ) showed a statistically significant difference between groups ($F [4,257]=35.63$; $p<0.001$; $etap(2)=0.409$). No significant differences were found between the DCD-only and the control. MANOVA was performed to assess differences in the Socialising and Friendship Questionnaire (SAF-Q) scores. The results showed a statistically significant difference between groups ($F [8,257]=9.98$; $p<0.001$; $eta=0.162$). Pearson correlation coefficients were performed, revealing significant high correlations between the EQ and the two parts of the SAF-Q ("past" and "currently").

CONCLUSION: The results of this study indicate that social difficulties in the DCD-only group are not due to lack of empathy, but may be driven by an accumulation of external factors. In this study we also concluded that DCD does not appear to be the factor that reduces the ability to empathize, but rather the presence of ADHD and/or ASD

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Hum Mov Sci. 2019.

REDUCED GRAPHOMOTOR PROCEDURAL LEARNING IN CHILDREN AND ADOLESCENTS WITH ADHD.

Duda TA, Casey JE, O'Brien AM, et al.

Purpose: The present study sought to determine if children and adolescents with ADHD demonstrate reduced procedural learning of a graphomotor program.

Method: Thirty-two children and adolescents between age 9 and 15 with (n = 16) and without ADHD (n = 16) participated in the study. Each group of participants practiced a novel grapheme on a digitizing tablet 30 times. Participants with ADHD were off stimulant medication or were medication nave.
Results: Control participants demonstrated significant improvement in graphomotor fluency from the beginning to the end of practice, T = 2, z = 2.534, p =.009, whereas participants with ADHD did not, T = 4, z = 1.810, p =.074.
Conclusions: Consistent with findings in adults with ADHD, results indicate that graphomotor procedural learning in children and adolescents with ADHD is attenuated. Findings have implications for future research that may inform remediation of handwriting difficulties, academic accommodations, and using digitizing technology for neuropsychological assessment

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Indian J Psychiatry. 2019;61:S491-S492.

A STUDY EVALUATING STATUS OF ANXIETY AND DEPRESSION AMONGST PRIMARY CAREGIVERS OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Agrawal A, Koolwal GD, Gehlot S.

Background Attention-deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric condition affecting children across the world. Being a parent to an ADHD child is a challenging and sometimes frustrating task as children impose increased caretaking demands. Parents' mental health can be adversely affected, thus displaying higher levels of depression and anxiety. It is indeed important that we attempt to understand ADHD, interrelationships among causal and controllability attributions and provide balanced and supportive benefits to meet the needs of affected children and their families; hence this study has been planned.
Aim To assess the severity of anxiety and depression among primary caregivers of children with ADHD and its comparison with controls. Methodology This was a cross-sectional study conducted at MDM Hospital, a tertiary care centre associated with Dr. S.N. Medical College, Jodhpur (Rajasthan). Fifty parents of children diagnosed with ADHD, fulfilling the inclusion and exclusion criteria were taken as cases. Fifty suitably matched parents attending the OPD for treatment of their children with minor medical condition comprised the control group. Sociodemographic data of the parents of study group were obtained in a specially designed proforma and Hamilton Rating Scale for Anxiety (HAM-A) and Beck's Depression Inventory (BDI) were used. Obtained data were analysed using appropriate statistics.
Results Results will be discussed at the time of presentation

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Indian J Psychiatry. 2019;61:S527.

IMPACT OF EARLY ADVERSITY ON CORTISOL REACTIVITY AND EXTERNALIZING BEHAVIOR IN CHILDREN OF ALCOHOLICS.

Timothy A, Benegal V, Sharma P.

Background: Children of alcoholics face high early adversity with vulnerability to psychiatric disorders in later life. The pathway to psychiatric disorders may lead through behavioural dyregulation. These children have been shown to have HPA axis impairment. Externalizing behavior and ADHD have also been shown to be independently associated both with hypercortisolism and hypocortisolism. We studied the association of early adversity with cortisol reactivity and externalizing behavior in a sample of COAs and age matched controls.
Methods: We examined children of alcoholics (N=50) and age and ethnicity matched healthy controls (N=50) for exposure to early adversity (both prenatal and postnatal) measured using the WHO Adverse Childhood Experiences Scale and Prenatal Psychosocial profile in a South Indian population. Cortisol reactivitywas tested using Trier Social stress test for children (TSST-C) and measured by ELISA for free salivary cortisol (samples taken at baseline prestressand 6 samples over 1 hr post stress). Externalizing and internalizing behavior were assessed using Strengths and Difficulties Questionnaire with screening for parent reported ADHD Inattentive (ADHD-I) and combined types ADHD-C) with or wthoutODD/CD (on MINI KID plus 6.0).

Results: COA had significantly higher levels of early adversity. Cortisol reactivity was reduced in COA, and negatively correlated with early adversity. Both early adversity and cortisol reactivity correlated with externalizing behavior. Children with ADHD had higher levels of adversityand lower cortisol reactivity compared to those without ADHD. ADHD-I and ADHD-C did not differ in terms of cortisol reactivity. ADHD with or without comorbid ODD/CD did not differ in terms of cortisol reactivity or externalizing behavior.
Conclusion: Our study provides further evidence that early adversity is associated with blunted cortisol reactivity and high externalizing behavior including ADHD. Cortisol reactivity may be the mediating factor between early adversity and behavioural dysregulation and may its effects may stem from genetic or epigenetic changes

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Indian J Psychiatry. 2019;61:S629.

WISC-IV PROFILE OF CHILDREN WITH AND WITHOUT ADHD.

Sharma P, Raman V, Manohari SM.

BACKGROUND AND OBJECTIVES: Studies have shown that children with ADHD have 7-12 IQ (Intelligence Quotient) points lower than their normal controls. The primary aim of the study was to study the association between severity of Attention Deficit Hyperactivity Disorder (ADHD) and IQ scores in children with ADHD. The secondary aim was to study the Wechsler Intelligence Scale for Children-IV (WISC-IV) profile of children with and without ADHD.
METHODOLOGY: The study is a descriptive, cross sectional study. 55 children between 6 and 16 years of age who met criteria for ADHD according to ICD 10 were recruited. 20 children without ADHD of the same age group were recruited as the comparison group. Severity of ADHD was assessed using Conner's Parent rating scale short version. Mini International Neuropsychiatric Interview-KID was used to exclude children with comorbid psychiatric illness. Intelligence was assessed using WISC-IV.
RESULTS: Correlation between severity of ADHD and IQ scores showed that children with more severe ADHD had lower IQ scores ($p<0.001$). There was no significant difference in the mean IQ scores between the two groups ($p = 0.834$). There was no significant difference in the subdomain scores of Verbal Comprehension, Perceptual reasoning, Working memory and Processing speed between the two groups.
CONCLUSIONS: The mean IQ of children with ADHD was in the normal range. However, children with more severe ADHD were found to have lower IQ scores and it was statistically significant. There was no significant difference in the sub-domain scores of WISC-IV between the two groups which is contrary to the available literature. The reasons for these findings will be discussed in the presentation

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Indian J Psychiatry. 2019;61:S609.

TITLE-CLONIDINE IN PRE-SCHOOL ADHD-12 WEEK NATURALISTIC FOLLOW-UP STUDY ON SAFETY AND TOLERABILITY.

Vaidyanathan S, Preeti K, Venkatesh C.

Introduction: Study objective is to report on safety and tolerability of clonidine in pre-school children with ADHD in child guidance clinic in South India.
Methodology: Study was done in child guidance clinic at JIPMER, tertiary teaching hospital. It's a 12 week prospective follow-up study to assess outcomes, safety and tolerability of pharmacotherapy in preschool ADHD children. Children aged 2.5-6 years were screened and after confirmation of diagnosis, ADHD symptom profile assessment was done at baseline and follow-up using Conner's abbreviated rating scale and Clinical global impression-severity scale. Children with autism and social quotient less than 50 were excluded.
Results: Mean age was 4 years. Of 50 children participating in the study, 26% (N=13) were on behavioural intervention and 74% (N=37) were on combination of pharmacotherapy with behavioural interventions. 51% (N=19) of those on medications were on Clonidine, N=7 on risperidone, N=6 were on atomoxetine, N=2 on methylphenidate and N=3 were on combination mediations. The setting being government institution, choice of medication was determined by affordability, availability, growth parameters and comorbidity profile.

Cardiac clearance was obtained when child's age was less than 4 years. At end of 3 months, 1 child on clonidine had excess sedation for which clonidine was changed to atomoxetine. No other side-effects were noted. Mean dose of clonidine was 50 microgram. Pre-schoolers with ADHD on clonidine for 12 weeks showed improvement in attention deficits and aggressiveness.
Conclusions: The study adds to limited literature and improves our understanding of safety of clonidine in pre-schoolers with ADHD. Given the lack of anti-ADHD medication in current NMH program, including clonidine can address over-prescription of antipsychotics in children. Further study with larger sample is indicated

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Indian J Psychiatry. 2019;61:S368-S369.
EEG FINDING AND IMPLICATION OF CLINICAL SEIZURE'S ABSENCE OR PRESENCE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.
Baruah J, Phookun HR.
BACKGROUND : Epilepsy and attention deficit hyperactivity disorder (ADHD) are often seen to be comorbid conditions and have significant effects on the social and behavioural development of children . Many of the ADHD children have abnormal electroencephalograph (EEG) results, compared to that of healthy children AIMS . To correlate the EEG findings in established cases of ADHD. and to find the association of clinically absent seizure and abnormal EEG finding.
MATERIALS AND METHODS: Patients(50 sample) already diagnosed as ADHD attending a tertiary care hospital, age 5 to 18 were enrolled for the study. Detailed history from parents taken. Epilepsy already diagnosed by neurologists. IQ test done on all the patients. EEG was advised to all the patients. Data analysis was done using SPSS 21.0 Software version.
RESULTS AND DISCUSSION: In our study 11 patients i.e. (22%) had epilepsy , similarly another study has mentioned a bidirectional relationship of ADHD and epilepsy in two cohort studies. Also a study done in 2018 have mentioned has mentioned that individuals with epilepsy had a statistically significant increased risk of ADHD. Out of the 50 patients ,11 of them had clinical seizure.(22%). 52% of the patients of ADHD had abnormal EEG irrespective of clinical presence of seizures. Similarly in a study done in 2014 has revealed that about half (48.3%) of the children with ADHD had abnormal EEG findings It was seen that out of the 50 patients ,39(78%) patients had no clinical seizure but 16(41%) patients out of them had an abnormal EEG ($p<.003$). Similar to our study a study done in north east India in 2016 out of 113 patients having various psychiatric diagnosis in children(including ADHD) 26.54% had abnormal EEG and had significant correlation.
CONCLUSION: From the present study it is reflected that ADHD is not a disease of single entity, multiple comorbid conditions including epilepsy and abnormal EEG finding

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Indian J Psychiatry. 2019;61:S360.
A STUDY ON EFFECT OF SLEEP TRAINING PROGRAM IN CHILDREN WITH ADHD: A COMPARATIVE PROSPECTIVE STUDY.
Dani AP, Shah HR, Kamath R.
Background: ADHD is one of the most common neuropsychiatric disorder affecting children. Sleep problems are common in them and lead to impairment of behavior, quality of life and functioning.
Aims: To study complementary effect of sleep training program in ADHD children receiving tablet Methylphenidate in following aspects: sleep; quality of life (QOL); social, behavioral, emotional and executive functioning of children; and their parent's mental state.
Settings and Design: A comparative and prospective study, conducted in child mental health services of a tertiary care municipal hospital.
Methods and materials: The children were diagnosed as ADHD using DSM 5 criteria. 100 participants (parent-child dyad) were selected and randomly equally divided into 2 groups- A and B. Semi-structured proforma was filled and scales applied to children- Children's sleep habit questionnaire, Strengths and Difficulties Questionnaire, Pediatric QOL Inventory, Stroop test and Verbal fluency test and to

parentDepression Anxiety Stress Scale-21. Then, participants in group A received sleep intervention in the form of a validated module. Scales were reapplied after 12 weeks.
Statistical Analysis: Chi-square test, Paired-t test, Unpaired-t test, Wilcoxon signed rank test, Mann Whitney U test, Spearman's correlation test and Logistic regression analysis were used for data analysis. 'p'value<0.05- significant. SPSS version 20 software was used for data analysis.
Results and Conclusion: We found significant post intervention improvement in sleep, QOL, social, behavioral and executive functioning in child and emotional factors in parents. Thus combination of sleep intervention and Methylphenidate was more effective in improving all these factors than Methylphenidate alone

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Indian J Psychiatry. 2019;61:S474.
CORRELATION OF SOCIAL COGNITION AND AGGRESSION IN CHILDREN AND ADOLESCENTS WITH ADHD.
Dutta BK.
Background:- Adequate social functioning and healthy peer relationships are considered primary conditions for children's primal development, and having healthy satisfying relationships in future. There is ample evidence that in children and adolescents with ADHD, symptoms interfere and reduce the quality of social, academic and occupational functioning. The term social functioning encompasses social skills and interactions, social cognition and behaviours displayed by the individual, which can affect adaptation in school, home and community environments. The present study attempted to find correlation of ADHD with social cognition deficits and its role in aggression and other areas of dys-functioning.
Material and Methods: the main objectives of this study was to study the various presentations of ADHD, and its correlation with social cognition especially 'theory of mind' construct, and to understand the impact of aggression, if present on social functioning in children with ADHD. About 20 subjects between the ages of 8 and 16 years of age were administered ADHD Rating Scale 5 (Home Version), Children's Aggression Scale, Strength and Difficulties Questionnaire (SDQ), Children Global Assessment Scale (CGAS) and SOCRATIS Theory of Mind (TOM) tasks.
Results: It has been observed that in first and second order theory of mind tasks, scores progressively declined as the ratings on ADHD increased (p=0.01, 95% CI 0.81-0.151), especially hyperactivity symptoms (ADHD HI scores, p=0.004, 95% CI 0.83-0.235), also as externalising symptoms rise as per SDQ ratings (p=0.16, 95% CI 0.69-0.141). However, TOM tasks showed gradual improvements with corresponding age of the participants.
Conclusions: Poor social cognition in children and adolescents with ADHD leads to impaired social and adaptive functioning. Social cognitive remediation programs including learning strategies and positive appraisals may help to benefit these patient

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Indian J Psychiatry. 2019;61:S445.
ADHD PARENT TRAINING WORKSHOP.
Srivastava C, Agrawal V.
Outline: ADHD is a chronic and pervasive developmental disorder that has maladaptively high levels of impulsivity, hyperactivity and inattention. It is pervasive across different settings. ADHD in young children, especially if left untreated, marks a significant risk for later development of oppositional defiant disorder (ODD), conduct disorder (CD), and more serious antisocial behavior in adolescence. It is therefore important to recognize and treat these children early. Early interventions focus more on parent training and behaviour management and less on medications. Parent training helps both in core ADHD symptoms and the ODD symptoms, therefore being of potential benefit in reducing the more serious conduct problems as the child grows up. This workshop aims to provide a practical overview on parent training for children with ADHD.

The principles of parent training that will be discussed in the workshop will be helpful both in routine clinical settings of a busy psychiatrist and in focused parent training programs

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Indian Journal of Public Health Research and Development. 2019;10:1048-52.

ASSESSMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDERS AMONG PRIMARY SCHOOL CHILDREN IN AL-NAJAF CITY.

Al-Fatlawi DAH, Al-Dujaili AH.

(ADHD) or Attention-deficit hyperactivity is a disorder characterized by persistent and developmentally inappropriate pattern of hyperactivity, inattention, and impulsivity which result in functional or developmental impairment. The worldwide prevalence of ADHD is about 2.5% for adults and 5% for children, affect about 3ΓÇô5 % of school age children. The prevalence rate in Arab world was between 2.7 and 20.5% for school aged students. The ratio of male to female 4:1 in childhood and in adulthood. A descriptive cross sectional study was carried out in order to assess (ADHD) among primary school children through ConnerΓÇÖs classroom rating scale, and to find the relationship between ADHD and socio-demographical data. The study has begun from November 1, 2017 through September 18, 2018. A Probability (simple random Sample) of (500) primary school child are included in the study. The data are collected through the utilization of the developed questionnaire by using an self-report technique. The validity of the questionnaire is determined through (Face Validity), and the reliability was achieved through the application of Alpha CronbachΓÇÖs technique. The findings of the present study indicate that the overall assessment of attention deficient hyperactivity disorder in primary school children is about 25%

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Indian Journal of Public Health Research and Development. 2019;10:417-21.

RISK FACTORS AFFECTING ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG EARLY CHILDHOOD IN THE AGRICULTURAL AREA IN INDONESIA.

Istiklaili F, Suwandono A, Suhartono S, et al.

Background: ADHD (Attention Deficit Hyperactivity Disorder) is a behavioral disorder the most common among children. This disorder is often found in early childhood and school age. The purpose of this study was to determine the incidence and risk factors for ADHD in early childhood in agricultural areas.

Method: This study used a cross-sectional design. The subjects of this study were 1,113, kindergarten students aged 5-7 years in the agricultural area of Brebes Regency, Central Java, Indonesia. The independent variables in this study were age, sex, history of preterm birth, education level and parental work, and the dependent variable is the incidence of ADHD. The multivariate logistic regression test is used to determine variables which are risk factors.

Results: The study showed that from 1.113 total subjects. there were 480 (43.1%) subjects in ADHD diagnosis. History of preterm birth (OR = 1.577; 95% CI = 1.128-2.205), low fatherΓÇÖs education level (OR = 1.422; 95% CI = 1.106-1.827), low motherΓÇÖs education level (OR = 1.312; 95% CI = 1.008-1.708), parental involvement in agriculture (OR = 1.580; 95% CI = 1.231-2.028) and gender (OR = 3.126; 95% CI = 2.442-4.001) proved to be an independent risk factor for ADHD.

Conclusion: The incidence of ADHD in early childhood in agricultural areas reached 43.1%. History of preterm birth, the low father education level, the parental involvement in agriculture and the male gender are independent risk factors for early childhood ADHD incidence in agricultural areas

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Int J Pediatr Otorhinolaryngol. 2019 Mar;118:165-69.

AURAL AND NASAL FOREIGN BODIES IN CHILDREN - EPIDEMIOLOGY AND CORRELATION WITH HYPERKINETIC DISORDERS, DEVELOPMENTAL DISORDERS AND CONGENITAL MALFORMATIONS.

Schuldt T, Grossmann W, Weiss NM, et al.

OBJECTIVES: Foreign body incorporation in children is often a serious situation. Attention deficit hyperactivity disorder (ADHD) could be a risk factor for self-insertion of foreign bodies. Large cohort analyses are missing.

METHODS: This was a retrospective analysis of patients' records from a health insurance company representing 2.19% of the German population and 1.75% of German children and adolescents. According to the International Classification of Diseases, children in the age range between 1 and 18 years have been screened for foreign bodies in ear, nasal sinus and nostrils as well as for hyperkinetic disorders (F90), disorders of psychological development (F80-F89), and congenital malformations, deformations and chromosomal abnormalities (Q00-Q99).

RESULTS: In total, 12887 children (6609 male; 6278 female) have been treated in 16929 cases. The majority (n=10041 (77.9%)) presented with foreign body incorporation on a single occasion. On average, 1.31 cases of foreign body treatment were recorded per child; 14.1% of children with foreign body treatment (FBT) also had a record of hyperkinetic disorder, 52.7% had a disorder of psychological development, and 50.8% a congenital malformation. Mean occurrence of FBT was 174.8 days before the diagnosis of a hyperkinetic disorder but 517.2 days after the diagnosis of a psychological development disorder and 683.1 days after the diagnosis of a congenital malformation, deformation or chromosomal abnormality.

CONCLUSION: Patients with disorders of psychological development as well as children with congenital malformations are high-risk patients for nasal and aural foreign bodies. The prevalence of a hyperkinetic disorder in patients with FBT is much higher than in the normal population. ADHD is a risk factor for foreign bodies

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Int J Epidemiol. 2017;46:1633-40.

MATERNAL ALCOHOL USE DURING PREGNANCY AND OFFSPRING ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD): A PROSPECTIVE SIBLING CONTROL STUDY.

Eilertsen EM, Gjerde LC, Reichborn-Kjennerud T, et al.

Background: Maternal alcohol use during pregnancy has repeatedly been associated with development of attention-deficit hyperactivity disorder (ADHD) in the offspring. It is, however not known whether this reflects a direct casual intra-uterine effect or a non-causal relationship due to confounding. We used three different approaches to control for measured and unmeasured confounding: statistical adjustment for covariates, negative control comparison against maternal pre-pregnancy alcohol use, and comparison among differentially exposed siblings.

Methods: The sample comprised 114 247 children (34 283 siblings) from 94 907 mothers, recruited to the Norwegian Mother and Child Birth Cohort Study between 1999 and 2008. Self-reported measurements of alcohol use were obtained in week 30 during the pregnancy. Mothers rated offspring ADHD symptoms at 5 years on two measures. Clinical ADHD diagnoses were obtained from the Norwegian Patient Registry.

Results: We found an overall positive association between maternal alcohol use during pregnancy and offspring ADHD symptoms, which was only marginally attenuated after inclusion of measured covariates. Both the negative control and the sibling comparison analysis further attenuated the estimated association, but it remained greater than zero [b -+ 0.017, 95% confidence interval (CI) -+ 0.005-0.030). No association was found between maternal alcohol use during pregnancy and offspring ADHD diagnosis.

Conclusions: For offspring ADHD symptoms we found a weak, but possibly causal association with maternal alcohol use during pregnancy, but no such effect was observed for clinical ADHD diagnosis

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Int J Psychiatry Med. 2019.

EFFECT OF ADENOTONSILLECTOMY ON SLEEP PROBLEMS, ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS, AND QUALITY OF LIFE OF CHILDREN WITH ADENOTONSILLAR HYPERTROPHY AND SLEEP-DISORDERED BREATHING.

Türkoğlu S, Tahsin SB, Sapmaz E, et al.

Objective: Chronic adenotonsillar hypertrophy is the most common etiologic reason for upper airway obstruction in childhood and has been found to be associated with a variety of psychiatric disorders and poor quality of life. In the present study, we investigated the impact of adenotonsillectomy on attention deficit hyperactivity disorder symptoms, sleep problems, and quality of life in children with chronic adenotonsillar hypertrophy.

Methods: The parents of children with chronic adenotonsillar hypertrophy filled out the ConnersΓÇÖs Parent Rating Scale-Revised Short form (CPRS-RS), Children's Sleep Habits Questionnaire (CSHQ), and Pediatric Quality of Life Inventory, Parent version (PedsQL-P) before and six months after adenotonsillectomy.

Results: A total of 64 children were included in the study (mean age = 6.8 -¦ 2.4 years; boy:girl ratio= 1). The mean attention deficit hyperactivity disorder index and oppositionality subdomain scores of the CPRS-RS and all of the CSHQ subdomain scores (bedtime resistance, sleep-onset delay, sleep anxiety, night waking, parasomnias, sleep-disordered breathing, and daytime sleepiness) except for sleep duration significantly decreased after adenotonsillectomy ($p < 0.05$). The PedsQL-P total score and both PedsQL-P physical health and psychosocial health subdomain scores were significantly higher at six months after adenotonsillectomy ($p < 0.001$).

Conclusions: Child and adolescent psychiatrists should check the symptoms of chronic adenotonsillar hypertrophy to identify children with chronic adenotonsillar hypertrophy who suffer from sleep disturbance, attention deficit hyperactivity disorder symptoms, and oppositionality. Adenotonsillectomy seems to be beneficial for coexisting attention deficit hyperactivity disorder and sleep disorder symptoms and quality of life in these children

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J Affect Disord. 2019 Mar;246:633-39.

GENETIC RISK FOR BIPOLAR DISORDER AND PSYCHOPATHOLOGY FROM CHILDHOOD TO EARLY ADULTHOOD.

Mistry S, Escott-Price V, Florio AD, et al.

BACKGROUND: Studying the phenotypic manifestations of increased genetic liability for Bipolar Disorder (BD) can increase understanding of this disorder. AIMS: We assessed whether genetic risk for BD was associated with childhood psychopathology and features of hypomania in young adulthood within a large population-based birth cohort.

METHODS: We used data from the second Psychiatric Genetics Consortium Genome Wide Association Study (GWAS) for Bipolar Disorder to construct a polygenic risk score (PRS) for each individual in the Avon Longitudinal Study of Parents and Children (ALSPAC). Linear and logistic regression models were used to assess associations between the BD-PRS and emotional/behavioural difficulties, attention deficit hyperactivity disorder (ADHD) and borderline personality disorder (BPD) traits in childhood, as well as hypomania in early adulthood (sample sizes from 2654 to 6111).

RESULTS: The BD-PRS was not associated with total hypomania score, but was weakly associated with a binary measure of hypomania (OR=1.13, 95%CI 0.98,1.32; p=0.097), and particularly at higher hypomania symptom thresholds (strongest evidence OR=1.33, 95%CI 1.07, 1.65; p=0.01). The BD-PRS was also associated with ADHD (OR=1.31, 95%CI 1.10, 1.57; p=0.018), but not with other childhood psychopathology.

LIMITATIONS: The PRS only captures common genetic variation and currently explains a relatively small proportion of the variance for BD.

CONCLUSIONS: The BD-PRS was associated with ADHD in childhood, and weakly with adult hypomania, but not with other psychopathology examined. Our findings suggest that genetic risk for BD does not appear to manifest in childhood to the same extent as schizophrenia genetic risk has been reported to do

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J Affect Disord. 2019 Feb;244:33-41.

IMPULSIVITY AND ITS ASSOCIATION WITH CHILDHOOD TRAUMA EXPERIENCES ACROSS BIPOLAR DISORDER, ATTENTION DEFICIT HYPERACTIVITY DISORDER AND BORDERLINE PERSONALITY DISORDER.

Richard-Lepouriel H, Kung AL, Hasler R, et al.

BACKGROUND: Impulsivity is a core feature of the attention-deficit/hyperactivity disorder (ADHD) and is one of the DSM-V diagnostic criteria for borderline personality disorder (BPD). Impulsivity is also present in bipolar disorder (BD). Impulsivity has been linked to adverse behavior (suicidality,...) and to traumatic childhood experiences. Our study explored impulsivity in BPD, BD, ADHD and healthy controls (CTRL) and investigated the impact of early trauma on impulsivity.

METHODS: 744 patients with BD (n=276), BPD (n=168), ADHD (n=173) or a combination (BPD_BD, n=29; BPD_ADHD, n=94, BD_BPD_ADHD n=13) and 47 controls were included. All subjects were completed the Baratt Impulsivity Scale (BIS-10) and the Childhood Trauma Questionnaire (CTQ).

RESULTS: BD reported the same levels of impulsiveness as CTRL. When BPD and BD are co-morbid, impulsivity increased to reach the level of BPD. Impulsiveness was significantly associated to traumatic childhood event for BD and CTRL, not for BPD and AHDH.

LIMITATIONS: Impulsivity was assessed on the basis of a self-report questionnaire and not by the mean of an objective measure such as a neuropsychological test. Moreover, we don't know what treatment our pathological subjects were receiving. But, ADHD and BPD, despite the probable treatment, were more impulsive than healthy CTRLs who did not take medications.

CONCLUSIONS: Impulsivity is probably not a feature of BD but is associated with the presence of traumatic childhood experiences, especially for euthymic patients, unlike BPD and ADHD. So, it seems essential to assess the presence of early trauma to reduce the impulsivity and improve the evolution of BD

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J Affect Disord. 2019 Feb;244:107-12.

ADULT OUTCOMES OF CHILDHOOD DISRUPTIVE DISORDERS IN OFFSPRING OF DEPRESSED AND HEALTHY PARENTS.

Diaz AP, Svob C, Zhao R, et al.

BACKGROUND: Longitudinal studies of children with disruptive disorders (DDs) have shown high rates of antisocial personality disorder (ASPD) and substance use in adulthood, but few have examined the contribution of parental disorders. We examine child-/adulthood outcomes of DDs in offspring, whose biological parents did not have a history of ASPD, bipolar disorder, or substance use disorders.

METHOD: Offspring (N=267) of parents with or without major depression (MDD), but no ASPD or bipolar disorders were followed longitudinally over 33 years, and associations between DDs and psychiatric and functional outcomes were tested.

RESULTS: Eighty-nine (33%) offspring had a DD. Those with, compared to without DDs, had higher rates of MDD (adjusted odds ratio, AOR=3.42, p<0.0001), bipolar disorder (AOR=3.10, p=0.03), and substance use disorders (AOR=5.69, p<0.0001) by age 18, as well as poorer school performance and global functioning. DDs continued to predict MDD and substance use outcomes in adulthood, even after accounting for presence of the corresponding disorder in childhood (MDD: hazards ratio, HR=3.25, p<0.0001; SUD, HR=2.52, p<0.0001). Associations were similar among the offspring of parents with and without major depression. DDs did not predict adulthood ASPD in either group. LIMITATIONS: Associations are largely accounted for by conduct disorder (CD), as there were few offspring with ADHD, and oppositional defiant disorder (ODD) was not diagnosed at the time this study began.

CONCLUSION: If there is no familial risk for ASPD, bipolar disorder or substance use, childhood DDs do not lead to ASPD in adulthood; however, the children still have poorer prognosis into midlife. Early treatment of children with DD, particularly CD, while carefully considering familial risk for these disorders, may help mitigate later adversity

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J Autism Dev Disord. 2019 Jan;49:227-35.

PREVALENCE OF PSYCHOTROPIC MEDICINE USE IN AUSTRALIAN CHILDREN WITH AUTISM SPECTRUM DISORDER: A DRUG UTILIZATION STUDY BASED ON CHILDREN ENROLLED IN THE LONGITUDINAL STUDY OF AUSTRALIAN CHILDREN.

Rasmussen L, Pratt N, Roughead E, et al.

Based on data from the Longitudinal Study of Australian Children linked with pharmacy dispensing data from the Australian Government's Pharmaceutical Benefits Scheme, we calculated the 1-year prevalence of psychotropic medicine supply in children and adolescents with Autism Spectrum Disorder (ASD) as reported by parents in 2014. The majority of children and adolescents with ASD in Australia were not treated with psychotropic medicine. One-third had claims for at least one psychotropic medication, most commonly medications for attention-deficit/hyperactivity disorder (ADHD), and antidepressants. Antipsychotics were supplied to less than one in twenty children and approximately one in ten adolescents. In line with findings from North America, psychotropic medicine was more often supplied to children and adolescents with ASD and comorbid ADHD

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J Abnorm Child Psychol. 2019 Mar;47:421-32.

STRESSFUL LIFE EVENTS, ADHD SYMPTOMS, AND BRAIN STRUCTURE IN EARLY ADOLESCENCE.

Humphreys KL, Watts EL, Dennis EL, et al.

Despite a growing understanding that early adversity in childhood broadly affects risk for psychopathology, the contribution of stressful life events to the development of symptoms of attention-deficit/hyperactivity disorder (ADHD) is not clear. In the present study, we examined the association between number of stressful life events experienced and ADHD symptoms, assessed using the Attention Problems subscale of the Child Behavior Checklist, in a sample of 214 children (43% male) ages 9.11-13.98 years (M = 11.38, SD = 1.05). In addition, we examined whether the timing of the events (i.e., onset through age 5 years or after age 6 years) was associated with ADHD symptoms. Finally, we examined variation in brain structure to determine whether stressful life events were associated with volume in brain regions that were found to vary as a function of symptoms of ADHD. We found a small to moderate association between number of stressful life events and ADHD symptoms. Although the strength of the associations between number of events and ADHD symptoms did not differ as a function of the age of occurrence of stressful experiences, different brain regions were implicated in the association between stressors and ADHD symptoms in the two age periods during which stressful life events occurred. These findings support the hypothesis that early adversity is associated with ADHD symptoms, and provide insight into possible brain-based mediators of this association

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J Abnorm Child Psychol. 2019 Mar;47:557-67.

EX-GAUSSIAN, FREQUENCY AND REWARD ANALYSES REVEAL SPECIFICITY OF REACTION TIME FLUCTUATIONS TO ADHD AND NOT AUTISM TRAITS.

Adamo N, Hodsoll J, Asherson P, et al.

Both attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have been linked to increased reaction time variability (RTV), a marker of attentional fluctuation. Here we test whether specificity to either trait emerges when we examine (1) detailed ex-Gaussian and frequency RTV subcomponents, (2) effects while controlling for the other trait and (3) improvement in the RTV measures following rewards or a faster event rate. 1110 children aged 7-10 years from a population-based sample completed a Go/No-Go task under three conditions (slow, fast and incentives). We measured RTV with standard deviation of RT (SDRT), ex-Gaussian distribution measures (Sigma and Tau), RT fluctuations in cycles of ~14-90 s in all conditions (Slow-4 and Slow-5), and RT fluctuations in cycles of 2-14 s in the fast condition (Slow-2 and Slow-3). Parent-rated ADHD and ASD traits were obtained. All refined RTV components were linked to ADHD traits only and not to ASD traits, while Sigma did not relate to either trait. Although both ADHD and ASD social-communication traits were associated with SDRT, the association with social-communication impairments disappeared when controlling for ADHD traits. A reward-induced

improvement in RTV measures, indicating malleability, emerged in relation to ADHD traits but not ASD traits. Under closer inspection, specificity emerges of high RTV to ADHD traits. For the clinician, our findings indicate that attentional fluctuation in children with high ASD traits may be due to co-occurring ADHD traits and emphasise how the effectiveness of rewards does not generalise from ADHD to ASD traits

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J Abnorm Child Psychol. 2019 Mar;47:381-92.

BIDIRECTIONAL ASSOCIATIONS BETWEEN PEER RELATIONS AND ATTENTION PROBLEMS FROM 9 TO 16 YEARS.

Ji L, Pan B, Zhang W, et al.

We examined the bidirectional relations between peer relations and attention problems from middle childhood through adolescence. Using data from the Longitudinal Study of Chinese Children and Adolescents (LSCCA, N = 2157, 51.9% male), three key aspects of peer relations (acceptance, rejection, and victimization) were assessed annually from 9 to 16 years of age. Attention problems were assessed at 9 and 15 years. Latent growth modeling indicated that greater attention problems at age 9 were linked with a lower intercept for peer acceptance, and higher intercepts for rejection and victimization. Also, prior lower acceptance and greater rejection and victimization, along with a higher increase over time in rejection and lower decrease over time in victimization, predicted attention problems at age 15. Cross-lagged analysis showed that attention problems were associated with less subsequent peer acceptance and greater subsequent rejection and victimization. Only peer rejection (but neither victimization nor acceptance) predicted more subsequent attention problems. Findings point to bidirectional associations between attention problems and peer relations in the developmental transition across adolescence. Evidence for differential bidirectionality of attention problems with the multiple peer experience (group versus dyadic; good versus bad) emerged, and future replications are needed

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J Abnorm Child Psychol. 2019 Mar;47:433-46.

DO WORKING MEMORY DEFICITS UNDERLIE READING PROBLEMS IN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)?

Kofler MJ, Spiegel JA, Soto EF, et al.

Reading problems are common in children with ADHD and show strong covariation with these childrenâ€™s underdeveloped working memory abilities. In contrast, working memory training does not appear to improve reading performance for children with ADHD or neurotypical children. The current study bridges the gap between these conflicting findings, and combines dual-task methodology with Bayesian modeling to examine the role of working memory for explaining ADHD-related reading problems. Children ages 8â€“13 (M = 10.50, SD = 1.59) with and without ADHD (N = 78; 29 girls; 63% Caucasian/Non-Hispanic) completed a counterbalanced series of reading tasks that systematically manipulated concurrent working memory demands. Adding working memory demands produced disproportionate decrements in reading comprehension for children with ADHD (d = â^'0.67) relative to Non-ADHD children (d = â^'0.18); comprehension was significantly reduced in both groups when working memory demands were increased. These effects were robust to controls for foundational reading skills (decoding, sight word vocabulary) and comorbid reading disability. Concurrent working memory demands did not slow reading speed for either group. The ADHD group showed lower comprehension (d = 1.02) and speed (d = 0.69) even before adding working memory demands beyond those inherently required for reading. Exploratory conditional effects analyses indicated that underdeveloped working memory overlapped with 41% (comprehension) and 85% (speed) of these between-group differences. Reading problems in ADHD appear attributable, at least in part, to their underdeveloped working memory abilities. Combined with prior cross-sectional and longitudinal findings, the current experimental evidence positions working memory as a potential causal mechanism that is necessary but not sufficient for effectively understanding written language

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J Affective Disord. 2019;250:397-403.

CHARACTERIZATION OF CORTICAL AND SUBCORTICAL ABNORMALITIES IN DRUG-NAIVE BOYS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Lu L, Zhang L, Tang S, et al.

Background: The current study was designed to investigate the anatomical differences in cortical and subcortical morphometry between drug-naive boys with attention-deficit/hyperactivity disorder (ADHD) and healthy controls (HCs) using three-dimensional T1-weighted imaging and to explore the effects of age on morphometric abnormalities.

Methods: Fifty-three drug-naive boys with ADHD and 53 HCs underwent high-resolution anatomical magnetic resonance (MR) imaging using a 3-T MR scanner. The FreeSurfer image analysis suite was used to obtain measures of cortical volume, thickness, and surface area, as well as the volumes of 14 subcortical structures. Statistically significant differences in measures between children with ADHD and HCs were evaluated using a least general linear model, with the intracranial volume and age as covariates.

Results: Compared to HCs, boys with ADHD exhibited an increased cortical volume in the left frontal eye field (FEF), a decreased surface area in the left ventral frontal cortex (VFC), and a decreased volume in the right putamen (cluster-wise $p < 0.05$; Monte Carlo-corrected). Moreover, we also observed age-related differences in FEF and VFC between groups.

Limitations: The cross-sectional study design limited inferences about the effects of age on regions displaying morphometric differences.

Conclusions: To our knowledge, this study is the first to characterize the cortical morphometry, including volume, thickness and surface area, of drug-naive boys with ADHD at the whole brain level; which provided detailed information about neuroanatomical alterations in attention systems beyond effects reported in previous studies at the lobe and sub-lobe levels. Based on our results, boys with ADHD presented significant alterations in cortical and subcortical morphology in several important nodes of the attention network

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J Child Adolesc Psychopharmacol. 2019;29:90-99.

ATTENDANCE AND ENGAGEMENT IN PARENT TRAINING PREDICT CHILD BEHAVIORAL OUTCOMES IN CHILDREN PHARMACOLOGICALLY TREATED FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND SEVERE AGGRESSION.

Joseph HM, Farmer C, Kipp H, et al.

Objectives: We examined the association of parent training (PT)-related factors with therapeutic success in the Treatment of Severe Childhood Aggression (TOSCA) study. Our aims were (1) to evaluate demographic and clinical characteristics as predictors of parent attendance and engagement in PT and (2) to examine the associations of parent attendance and engagement in PT with study-targeted child behavior outcomes (i.e., attention-deficit/hyperactivity disorder [ADHD] and disruptive behavior symptoms). TOSCA was a randomized clinical trial evaluating the effect of placebo versus risperidone when added to PT and psychostimulant for childhood ADHD with severe aggression.

Methods: Data for 167 parents and children 6-12 years old with ADHD, oppositional defiant disorder (ODD) or conduct disorder, and severe physical aggression were examined. Analyses used generalized linear models.

Results: Most parents (72%) attended seven or more of nine sessions. The average parental engagement, that is, the percentage of PT elements fully achieved across participants and sessions, was 85%. The average therapist rating of goal completion was 92%. Parents of non-white and/or Hispanic children ($p = 0.01$) and children with lower intelligence quotient ($p = 0.02$) had lower PT attendance; parents with lower family incomes ($p = 0.01$) were less engaged. Attendance and engagement predicted better scores on the primary child behavior outcomes of disruptive behavior (Nisonger Child Behavior Rating Form Disruptive Behavior Total) and ADHD and ODD symptoms, adjusting for baseline severity.

Conclusions: When the clinical picture is sufficiently severe to warrant prescribing an atypical antipsychotic, PT is feasible for families of children with ADHD and co-occurring severe aggression. The promotion of attendance and engagement in PT is important to enhance clinical outcomes among this challenging population. Methods for overcoming barriers to participation in PT deserve vigorous investigation, particularly for those with low family income, non-white race, Hispanic ethnicity, or when children have lower cognitive level

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J Child Adolesc Psychopharmacol. 2019;29:80-89.

DASOTRALINE IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: A SIX-WEEK, PLACEBO-CONTROLLED, FIXED-DOSE TRIAL.

Findling RL, Adler LA, Spencer TJ, et al.

Objective: Dasotraline is a potent inhibitor of presynaptic dopamine and norepinephrine reuptake with a pharmacokinetic profile characterized by slow absorption and a long elimination half-life. The aim of this study was to evaluate the efficacy and safety of dasotraline in children with attention-deficit/hyperactivity disorder (ADHD).

Methods: Children aged 6-12 years with a Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of ADHD were randomized to 6 weeks of double-blind once-daily treatment with dasotraline (2 or 4 mg) or placebo. The primary efficacy endpoint was change from baseline in the ADHD Rating Scale Version IV-Home Version (ADHD RS-IV HV) total score at week 6.

Results: A total of 342 patients were randomized to dasotraline or placebo (mean age 9.1 years, 66.7% male). Treatment with dasotraline was associated with significant improvement at study endpoint in the ADHD RS-IV HV total score for the 4 mg/day dose versus placebo (-17.5 vs. -11.4; $p < 0.001$; effect size [ES], 0.48), but not for the 2 mg/day dose (-11.8 vs. -11.4; ns; ES, 0.03). A regression analysis confirmed a significant linear dose-response relationship for dasotraline. Significant improvement for dasotraline 4 mg/day dose versus placebo was also observed across the majority of secondary efficacy endpoints, including the Clinical Global Impression (CGI)-Severity score, the Conners Parent Rating Scale-Revised scale (CPRS-R) ADHD index score, and subscale measures of hyperactivity and inattentiveness. Discontinuation rates due to adverse events (AEs) were higher in the dasotraline 4 mg/day group (12.2%) compared with the 2 mg/day group (6.3%) and placebo (1.7%). The most frequent AEs associated with dasotraline were insomnia, decreased appetite, decreased weight, and irritability. Psychosis-related symptoms were reported as AEs by 7/219 patients treated with dasotraline in this study. There were no serious AEs or clinically meaningful changes in blood pressure or heart rate on dasotraline.

Conclusion: In this placebo-controlled study, treatment with dasotraline 4 mg/day significantly improved ADHD symptoms and behaviors, including attention and hyperactivity, in children aged 6-12 years. The most frequently reported AEs observed on dasotraline included insomnia, decreased appetite, decreased weight, and irritability

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J Child Psychol Psychiatry. 2019 Mar;60:259-66.

INVESTIGATING THE CHILDHOOD SYMPTOM PROFILE OF COMMUNITYÂ€• BASED INDIVIDUALS DIAGNOSED WITH ATTENTIONÂ€• DEFICIT/HYPERACTIVITY DISORDER AS ADULTS.

Taylor MJ, Larsson H, Gillberg C, et al.

Background: Attention-deficit/hyperactivity disorder (ADHD) is currently defined as a disorder with onset during childhood. Although ADHD occurs in adults as well as children, recent debate has focused on whether adult ADHD represents a continuation of a child-onset disorder or if ADHD may, in at least some cases, have an adult onset. We therefore aimed to test the hypothesis of adult-onset ADHD using a sample born relatively recently (1992-1999) in order to minimize confounding by secular changes in diagnostic practices.

Methods: We identified 74 individuals with a community diagnosis of ADHD first assigned during adulthood. We also identified individuals with childhood (N = 194) and adolescent (N = 394) community diagnoses of

ADHD. These groups were compared with a comparison group (N = 14,474) on their childhood ADHD and neuropsychiatric symptoms, and rate of other psychiatric diagnoses during childhood.
Results: Having an adulthood community diagnosis of ADHD was associated with a mean increase in childhood ADHD symptoms of approximately three times that of the comparison group. Individuals with an adult community diagnosis of ADHD also displayed more autistic traits, motor problems, learning difficulties, tics, and oppositional behavior. Forty two percent of these individuals, compared with 1% of comparison cases, had a psychiatric diagnosis other than ADHD as children. In post-hoc analyses of 21 ADHD cases showing few or no ADHD symptoms in childhood, we were unable to detect any other childhood symptomatology in only nine cases, of whom six were female.
Conclusions: Our results indicate that alternative explanations for data that appear to show adult onset ADHD, such as sex biases in diagnostic practices, need rigorous testing before adult onset ADHD can be accepted as a valid clinical construct

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J Child Psychol Psychiatry. 2019 Jan;60:43-53.
INFANT TEMPERAMENT REACTIVITY AND EARLY MATERNAL CAREGIVING: INDEPENDENT AND INTERACTIVE LINKS TO LATER CHILDHOOD ATTENTIONâ€• DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS.
Miller NV, Degnan KA, Hane AA, et al.
Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with origins early in life. There is growing evidence that individual differences in temperament reactivity are predictive of ADHD symptoms, yet little is known about the relations between temperament reactivity in early infancy and later ADHD symptoms or the combined effect of reactivity with early environmental factors on ADHD symptom development. Using a 9-year prospective longitudinal design, this study tested the independent and interactive contributions of infant reactivity and maternal caregiving behaviors (MCB) on parent- and teacher-reported childhood ADHD symptoms.
Methods: Participants included 291 children (135 male; 156 female) who participated in a larger study of temperament and social emotional development. Reactivity was assessed by behavioral observation of negative affect, positive affect, and motor activity during novel stimuli presentations at 4 months of age. MCB were observed during a series of semistructured mother infant tasks at 9 months of age. Finally, ADHD symptoms were assessed by parent- and teacher-report questionnaires at 7 and 9 years, respectively.
Results: Reactivity was predictive of ADHD symptoms, but results were sex specific. For boys, infant motor activity was positively predictive of later ADHD symptoms, but only at lower quality MCB. For girls, infant positive affect was positively predictive of later ADHD symptoms at lower quality MCB, and unexpectedly infant positive affect and motor activity were negatively predictive of later ADHD symptoms at higher quality MCB.
Conclusions: These results point to early parenting as a moderating factor to mitigate temperament-related risk for later ADHD, suggesting this as a potential intervention target to mitigate risk for ADHD among reactive infants

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J Clin Child Adolesc Psychol. 2019 Jan;48:153-65.
EMOTION DYSREGULATION ACROSS EMOTION SYSTEMS IN ATTENTION DEFICIT/HYPERACTIVITY DISORDER.
Musser ED, Nigg JT.
Children with attention deficit/hyperactivity disorder (ADHD) display alterations in both emotion reactivity and regulation. One mechanism underlying such alternations may be reduced coherence among emotion systems (i.e., autonomic, facial affect). The present study sought to examine this. One hundred children (50 with ADHD combined presentation), 7-11 years of age (62% male, 78% White), completed an emotion induction and suppression task. This task was coded for facial affect behavior across both negative and positive emotion eliciting task conditions. Electrocardiogram and impedance cardiography data were acquired throughout the task. Time-linked coherence of facial affect behavior and autonomic reactivity and regulation were examined during the induction conditions using hierarchical linear modeling. Although ADHD

and typically developing children did not differ with respect to rates of facial affect behavior displayed (all Fs < 2.09, ps > .29), the ADHD group exhibited reduced coherence between facial affect behavior and an index of parasympathetic functioning (i.e., respiratory sinus arrhythmia), γ_{10} = -0.03, SE = 0.02, t(138) = -1.96, p = .05. In contrast, children in the control group displayed a significant, positive, γ_{10} = 0.06, SE = 0.01, t(138) = 4.07, p < .001, association between facial affect behavior and respiratory sinus arrhythmia. Children with ADHD may receive conflicting emotional signals at the levels of facial affective behavior and parasympathetic functioning when compared to typically developing youth. Weakened coherence among these emotion systems may be an underlying mechanism of emotion dysregulation in ADHD. Implications for etiology and treatment are discussed

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J Clin Child Adolesc Psychol. 2019 Jan;48:80-92.

NEUROPSYCHOLOGICAL PREDICTORS OF ODD SYMPTOM DIMENSIONS IN YOUNG CHILDREN.

Griffith SF, Arnold DH, Rolon-Arroyo B, et al.

Oppositional defiant disorder (ODD) is a commonly diagnosed childhood behavior disorder, yet knowledge of relations between ODD and early neuropsychological functions, particularly independent of attention deficit/hyperactivity disorder (ADHD), is still limited. In addition, studies have not examined neuropsy chological functioning as it relates to the different ODD symptom dimensions. Structural equation modeling was used to investigate how preschool neuropsychological functioning predicted negative affect, oppositional behavior, and antagonistic behavior symptom dimensions of ODD in 224 six-year-old children, oversampled for early behavior problems. Working memory, inhibition, and sustained attention predicted negative affect symptoms of ODD, controlling for ADHD, whereas delay aversion uniquely predicted oppositional behavior, controlling for ADHD. Delay aversion also marginally predicted antagonistic behavior, controlling for ADHD. Results demonstrate that different ODD symptom dimensions may be differentially predicted by different neuropsychological functions. The findings further underscore the importance of future research on ODD to take into account the possible heterogeneity of both symptoms and underlying neuropsychological functioning

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Journal of Clinical Medicine. 2019;8.

DIFFERENTIAL EFFICACY OF NEUROFEEDBACK IN CHILDREN WITH ADHD PRESENTATIONS.

Cueli M, Rodrìguez C, Cabaleiro P, et al.

Training in neurofeedback (NF) reduces the symptomatology associated with attention deficit with hyperactivity disorder (ADHD). However, ADHD differs in terms of the type of presentation, i.e., inattentive (ADHD-I), impulsive/hyperactive (ADHD-HI), or combined (ADHD-C). This study examines the efficacy of NF in ADHD presentations. Participants were 64 students (8ΓÇô12 years old). Cortical activation, executive control, and observed symptomatology by parents were assessed. Results indicated that ADHD-C and ADHD-HI demonstrated greater improvements than ADHD-I. It was concluded that this kind of training produces an improvement and that it is necessary to explore it further in terms of the protocol used

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J Indian Assoc Child Adolesc Ment Health. 2019;15:39-48.

PSYCHIATRIC CO-MORBIDITIES IN ATTENTION DEFICIT HYPERACTIVE DISORDER (ADHD): A RETROSPECTIVE CLINICAL CHART REVIEW FROM A TERTIARY HOSPITAL IN NORTH INDIA.

Arya S, Jangid P, Verma P, et al.

Background: ADHD is one of the most common disorders seen in children and the presenting complaint of the parents is not able to manage the child. ADHD is highly co-morbid with various psychiatric illnesses which further add to diagnostic and management difficulties.

Method: The case records of Child Guidance Clinic (CGC) (2012-2017) of Postgraduate Institute of Medical Sciences (PGIMS) Rohtak, Haryana were manually screened to collect information about children with a diagnosis of ADHD. Relevant details were noted and data were analyzed.
Results: 436 children were diagnosed with ADHD. Most common age of presentation was 8 years (n=68), with majority of children being males (80%) presenting between 5-7 years of age (44.5%) and belonging to urban background (n=253, 57.76%). The overall prevalence of psychiatric co-morbidities was 35%, with mental retardation being the most common (38.16%) followed by oppositional defiant disorder (27.63%), conduct disorder (16.45%) and seizure disorder (11.84%).
Conclusion: Seeing the high co-morbidity, it becomes important to screen all the patients diagnosed with ADHD for psychiatric co-morbidities

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J Pers Soc Psychol. 2019 Mar.

THE ROLE OF EFFORTFUL CONTROL IN THE DEVELOPMENT OF ADHD, ODD, AND CD SYMPTOMS.

Atherton OE, Lawson KM, Ferrer E, et al.

Many adolescents have difficulty regulating their impulses and become prone to externalizing problems (e.g., attention-deficit/hyperactivity disorder [ADHD], oppositional defiant disorder [ODD], and conduct disorder [CD]) and other adverse consequences. Using multimethod data from a longitudinal study of Mexican-origin youth (N = 674), assessed annually from age 10 to 16, we examined the relations between effortful control and ADHD, ODD, and CD symptoms over time. Bivariate latent growth curve models showed negative correlations between the trajectories of effortful control and ADHD, ODD, and CD, indicating that steeper decreases in effortful control were related to steeper increases in ADHD, ODD, and CD symptoms. Using a novel statistical technique, the factor of curves model (FOCUS), we found that ADHD, ODD, and CD share a common 'externalizing' trajectory during adolescence. Although effortful control was strongly associated with this common trajectory, it had few unique associations with the individual disorder trajectories, above and beyond their shared trajectory. When we extended the FOCUS model to include the effortful control trajectory as an indicator, we found that ADHD and ODD had strong loadings, whereas effortful control and CD had comparatively weak loadings on the shared developmental trajectory. Follow-up analyses showed that a two-factor solution, with externalizing symptom trajectories on one factor and the effortful control facet trajectories on a separate factor, was a better fit to the data than a one-factor solution. Finally, parent ASPD symptoms were related to increases in CD, but had no significant influence on effortful control, ADHD, or ODD. We discuss the implications for personality and externalizing problem development

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J Psychopathol Behav Assess. 2019.

IQ AND ACADEMIC ACHIEVEMENT IN CHILDREN WITH ADHD: THE DIFFERENTIAL EFFECTS OF SPECIFIC COGNITIVE FUNCTIONS.

Calub CA, Rapport MD, Friedman LM, et al.

The co-occurrence of lower full-scale intellectual abilities (FSIQ) and academic achievement deficits in children with ADHD is well established; however, the extent to which the relation reflects the influence of a general factor (g) deficiency or deficiencies in one or more specific intellectual abilities remains speculative and was the focus of the current investigation. Twenty-eight boys with ADHD-combined presentation and 26 neurotypical (NT) boys between 8 and 12-áyears of age were administered the WISC-IV and standardized measures of reading and math. FSIQ and achievement scores in both reading and math were significantly lower for the ADHD relative to the NT group; however, examination of WISC-IV index scores revealed that group level differences in FSIQ resulted from lower scores on two of the four specific intellectual ability indicesΓÇöWorking Memory (WMI) and Verbal Comprehension (VCI). Bias-corrected bootstrapped mediation analyses revealed that both WMI and VCI contributed uniquely to the ADHD-Academic Achievement relation. The contribution of WMI to ADHD-related academic underachievement reflected lower scores on the Letter-Number Sequencing (LNS) but not the Digit Span (DS) subtest. Both LNS and VCI explained ADHD-related differences in reading, whereas LNS alone explained ADHD-related differences in

math. Collectively these findings suggest that strengthening deficient higher-level WM abilities, in conjunction with empirically based academic instruction, is needed to improve learning outcomes in children with ADHD

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J Am Acad Child Adolesc Psychiatry. 2019;58:392-94.

EDITORIAL: TRANSCUTANEOUS TRIGEMINAL NERVE STIMULATION FOR CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.

Grigolon RB, Blumberger DM, Daskalakis ZJ, et al.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of 9.5% of school-aged children and 4.4% of adults in the United States. ADHD is defined by clinically significant and developmentally inappropriate levels of inattention and hyperactivity/impulsivity. Executive functioning and control and attention regulation are the neuropsychological deficits commonly associated with ADHD.1

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J Am Acad Child Adolesc Psychiatry. 2019;58:401-02.

EDITORIAL: DOES A DIAGNOSIS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD DETERMINE AN INCREASED RISK FOR FUTURE CRIMINALITY?

Greenhill LL.

Problems with occupational performance, emotional adjustment, legal involvement, and educational attainment are common in adults who had been diagnosed during childhood with attention-deficit/hyperactivity disorder.1 The National Institute of Health (NIMH) Multimodal Treatment Study of Attention-Deficit/Hyperactivity Disorder (ADHD) (MTA study) reported that of their cohort of 579 youth diagnosed with ADHD, combined type, age 7 to 9 years, half endorsed 4 persistent symptoms of ADHD when evaluated 16 years later at a mean age of 24.7 years.2 In fact, 41% persisted in meeting full ADHD symptomatic and impairment criteria as adults. This subgroup continued to experience problems with incomplete postsecondary education, job instability, lower current income, receipt of public assistance, and risky sexual behavior.3 Although the persistence of ADHD symptoms in the MTA study follow-up study was not associated with increased jail time, other studies concluded that a childhood diagnosis of ADHD was associated with a two- to threefold increased risk of later arrests, convictions, and incarcerations.4 Furthermore, although ADHD medications were not associated with better outcomes after 16 years of follow-up of the MTA cohort,5 Lichtenstein et al.6 reported that ADHD medication exerted a possible protective effect against incarceration

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J Am Acad Child Adolesc Psychiatry. 2019.

COMMON POLYGENIC VARIATIONS FOR PSYCHIATRIC DISORDERS AND COGNITION IN RELATION TO BRAIN MORPHOLOGY IN THE GENERAL PEDIATRIC POPULATION.

Alemany S, Jansen PR, Muetzel RL, et al.

Objective: This study examined the relation between polygenic scores (PGSs) for 5 major psychiatric disorders and 2 cognitive traits with brain magnetic resonance imaging morphologic measurements in a large population-based sample of children. In addition, this study tested for differences in brain morphology-mediated associations between PGSs for psychiatric disorders and PGSs for related behavioral phenotypes.
Method: Participants included 1,139 children from the Generation R Study assessed at 10 years of age with genotype and neuroimaging data available. PGSs were calculated for schizophrenia, bipolar disorder, major depression disorder, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, intelligence, and educational attainment using results from the most recent genome-wide association studies. Image processing was performed using FreeSurfer to extract cortical and subcortical brain volumes.
Results: Greater genetic susceptibility for ADHD was associated with smaller caudate volume (strongest prior = 0.01: +¦ = 0.07, p =.006). In boys, mediation analysis estimates showed that 11% of the association between the PGS for ADHD and the PGS attention problems was mediated by differences in caudate volume

(n = 535), whereas mediation was not significant in girls or the entire sample. PGSs for educational attainment and intelligence showed positive associations with total brain volume (strongest prior = 0.5: +¦ = 0.14, p = 7.12 +ù 10-8; and +¦ = 0.12, p = 6.87 +ù 10ΓêÆ7, respectively).
Conclusion: The present findings indicate that the neurobiological manifestation of polygenic susceptibility for ADHD, educational attainment, and intelligence involve early morphologic differences in caudate and total brain volumes in childhood. Furthermore, the genetic risk for ADHD might influence attention problems through the caudate nucleus in boys

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J Am Acad Child Adolesc Psychiatry. 2019;58:443-52.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDHOOD AND ADOLESCENCE AND THE RISK OF CRIME IN YOUNG ADULTHOOD IN A DANISH NATIONWIDE STUDY.
Mohr-Jensen C, M++ller BC, Boldsen SK, et al.
Objective: To determine the risk of long-term conviction and incarceration associated with childhood attention-deficit/hyperactivity disorder (ADHD), and to identify risk and protective factors including associations with active treatment with ADHD medication.
Method: All participants with ADHD who were 4 to 15 years of age during 1995 to 2005 were matched by year of birth and sex to a random sample of participants without ADHD from the Danish population using nationwide registers. Using Cox proportional hazard models, we estimated the risk of conviction and incarceration associated with ADHD in childhood and estimated associations with active treatment and outcome.
Results: The ADHD cohort were followed up at a mean of 22.0 (SD = 5.8) years. Of 4,231 individuals with ADHD, 1,355 (32.0%) had received at least one conviction, compared to 3,059 (15.6%) of the 19,595 participants without ADHD (p < 0.001). ADHD was significantly associated with conviction (hazard ratio [HR] = 2.4, 95% CI = 2.3-2.6) and incarceration (HR = 3.0, 95% CI = 2.8-3.3). Subsequent to adjustment for various risk factors, ADHD exposure was still significantly related to conviction (HR = 1.6, 95% CI = 1.5-1.8) and incarceration (HR = 1.7, 95% CI = 1.5-1.9). Comorbidity with substance use disorder, oppositional-defiant disorder/conduct disorder, low family socioeconomic status, parental incarceration, and parental relationship status all significantly increased the risk of conviction and incarceration. Crime rates increased with the number of associated risks but were reduced during periods of taking ADHD medication.
Conclusion: In addition to ADHD, a broad range of individual, familial, and social factors increase the risk of antisocial development. The findings imply that ADHD medication may contribute to crime prevention

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J Am Acad Child Adolesc Psychiatry. 2019;58:403-11.
DOUBLE-BLIND, SHAM-CONTROLLED, PILOT STUDY OF TRIGEMINAL NERVE STIMULATION FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
McGough JJ, Sturm A, Cowen J, et al.
Objective: Trigeminal nerve stimulation (TNS), a minimal-risk noninvasive neuromodulation method, showed potential benefits for attention-deficit/hyperactivity disorder (ADHD) in an unblinded open study. The present blinded sham-controlled trial was conducted to assess the efficacy and safety of TNS for ADHD and potential changes in brain spectral power using resting-state quantitative electroencephalography.
Method: Sixty-two children 8 to 12 years old, with full-scale IQ of at least 85 and Schedule for Affective Disorders and SchizophreniaΓÇôdiagnosed ADHD, were randomized to 4 weeks of nightly treatment with active or sham TNS, followed by 1 week without intervention. Assessments included weekly clinician-administered ADHD Rating Scales (ADHD-RS) and Clinical Global Impression (CGI) scales and quantitative electroencephalography at baseline and week 4.
Results: ADHD-RS total scores showed significant group-by-time interactions (F1,228 = 8.12, p =.005; week 4 Cohen d = 0.5). CGI-Improvement scores also favored active treatment (¤ç21,168 = 8.75, p =.003; number needed to treat = 3). Resting-state quantitative electroencephalography showed increased spectral power in

the right frontal and frontal midline frequency bands with active TNS. Neither group had clinically meaningful adverse events.
Conclusion: This study demonstrates TNS efficacy for ADHD in a blinded sham-controlled trial, with estimated treatment effect size similar to non-stimulants. TNS is well tolerated and has minimal risk. Additional research should examine treatment response durability and potential impact on brain development with sustained use.
Clinical trial registration information: Trigeminal Nerve Stimulation for ADHD; http://clinicaltrials.gov/; NCT02155608

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J Am Acad Child Adolesc Psychiatry. 2019;58:412-22.
SEX DIFFERENCES IN COMORBIDITY PATTERNS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER.
Ottosen C, Larsen JT, Faraone SV, et al.
Objective: To investigate sex differences in associations between attention-deficit/hyperactivity disorder (ADHD) and a spectrum of comorbid disorders.
Method: The study population included all children born in Denmark from 1981 through 2013 (N = 1,665,729). Data were merged from Danish registers and information was obtained on birth characteristics, socioeconomic status, familial psychiatric history, and diagnoses of ADHD (n = 32,308) and comorbid disorders. To estimate absolute and relative risks of comorbid disorders, incidence rates and adjusted hazard ratios (HRs) with 95% CIs were calculated for female and male individuals. In addition, interactions between ADHD and sex in association with comorbid disorders were estimated as HR ratios (HRRs) in female and male individuals (95% CIs).
Results: Individuals diagnosed with ADHD had significantly increased absolute and relative risks of all 12 comorbid psychiatric disorders investigated. ADHD-sex interactions were found for some comorbid disorders. Compared with male individuals, ADHD in female individuals showed a stronger association with autism spectrum disorder (HRR 1.86, 95% CI 1.62ΓÇô2.14), oppositional defiant/conduct disorder (HRR 1.97, 95% CI 1.68ΓÇô2.30), intellectual disability (HRR 1.79, 95% CI 1.54ΓÇô2.09), personality disorders (HRR 1.23, 95% CI 1.06ΓÇô1.43), schizophrenia (HRR 1.21, 95% CI 1.02ΓÇô1.43), substance use disorders (HRR 1.21, 95% CI 1.07ΓÇô1.38), and suicidal behavior (1.28, 95% CI 1.12ΓÇô1.47). The remaining disorders showed no significant sex differences in association with ADHD.
Conclusion: This study indicates that the association between ADHD and several comorbid disorders is stronger in female than in male individuals. These important findings add to the literature on sex differences in ADHD and suggest that female individuals diagnosed with ADHD are a more vulnerable group of patients

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J Am Acad Child Adolesc Psychiatry. 2019;58:433-42.
SHORTENED SLEEP DURATION CAUSES SLEEPINESS, INATTENTION, AND OPPOSITIONALITY IN ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: FINDINGS FROM A CROSSOVER SLEEP RESTRICTION/EXTENSION STUDY.
Becker SP, Epstein JN, Tamm L, et al.
Objective: Although poor sleep is often reported in adolescents with attention-deficit/hyperactivity disorder (ADHD), prior studies have been correlational. This study investigated whether sleep duration is causally linked to sleepiness, inattention, and behavioral functioning in adolescents with ADHD.
Method: A total of 72 adolescents (aged 14ΓêÆ17 years) entered a 3-week sleep protocol using an experimental crossover design. The protocol included a phase stabilization week, followed in randomized counterbalanced order by 1 week of sleep restriction (6.5 hours) and 1 week of sleep extension (9.5 hours). Sleep was monitored with actigraphy and daily sleep diaries, with laboratory visits at the end of each week. Analyses included 48 adolescents who had complete actigraphy data and successfully completed the sleep protocol (defined a priori as obtaining 1 hour actigraphy-measured sleep duration during extension compared to restriction). Parent and adolescent ratings of daytime sleepiness, ADHD symptoms, sluggish cognitive

tempo (SCT), and oppositional behaviors were the primary measures. The A-X Continuous Performance Test (CPT) was a secondary measure.
Results: Compared to the extended sleep week, parents reported more inattentive and oppositional symptoms during the restricted sleep week. Both parents and adolescents reported more SCT symptoms and greater daytime sleepiness during restriction compared to extension. Adolescents reported less hyperactivity-impulsivity during sleep restriction than extension. No effects were found for parent-reported hyperactivity-impulsivity, adolescent-reported ADHD inattention, or CPT performance.
Conclusion: This study provides the first evidence that sleep duration is a causal contributor to daytime behaviors in adolescents with ADHD. Sleep may be an important target for intervention in adolescents with ADHD. Clinical trial registration information: Cognitive and Behavioral Effects of Sleep Restriction in Adolescents With ADHD; https://clinicaltrials.gov/; NCT02732756

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Minerva Pediatr. 2019;71:135-38.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND ENURESIS: A STUDY ABOUT EFFECTIVENESS OF TREATMENT WITH METHYLPHENIDATE OR DESMOPRESSIN IN A PEDIATRIC POPULATION.
Ferrara P, Sannicandro V, Ianniello F, et al.
BACKGROUND: The aim of this study was to evaluate the effectiveness of treatment with methylphenidate or desmopressin (dDAVP) in patients with comorbid attention-deficit/hyperactivity disorder (ADHD) and enuresis.
METHODS: We enrolled 103 patients affected by ADHD and 125 patients with monosymptomatic nocturnal enuresis (NE). Data were collected between January 2014 and December 2015. The study was carried out in compliance with the Helsinki Declaration.
RESULTS: About children with ADHD, 9/103 (8.7%) were also suffering from NE; of those 8/9 followed treatment with methylphenidate and cognitive behavioral therapy. After 3 months 2/8 (25%, CI 95%: 8-65%) showed improvements, remaining 75% has been increased dosage of methylphenidate. After 6 months a response was achieved in 6/8 (75%, CI 95%: 35-96%) children and 1/8 was lost to follow-up. Furthermore the drug withdrawal showed a recurrence of symptoms both ADHD and NE in 1/7 (14.3%, CI 95%: 0.3-57%) vs. 6/7 (85.7%, CI 95%: 42-99%) that not presented recurrences. About children with NE enrolled at Campus Bio-Medico University it was found that 4/125 (3.8%) children were also suffering from ADHD; 3/4 (75%) treated with dDAVP and motivational therapy, of those 2/3 (66.7%, CI 95%: 9-99%) showed no improvements of symptoms vs. 1/3 (33.3%, CI 95%: 0.8-90%) that showed partial response with a reduction of wet-nights.
CONCLUSIONS: It is important the service of recruitment of patients with NE. In fact considering NE in a Child Neuropsychiatry Service where patients belong to a diagnosis of ADHD and NE is an incidental finding, this one is not considered as the addressee of treatment, but the therapy is directed to the neuro-behavioral problem using specific drugs and therapies, which are resolutive in the enuretic disorder

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N Engl J Med. 2019 Mar;380:1128-38.
PSYCHOSIS WITH METHYLPHENIDATE OR AMPHETAMINE IN PATIENTS WITH ADHD.
Moran LV, Ongur D, Hsu J, et al.
BACKGROUND: The prescription use of the stimulants methylphenidate and amphetamine for the treatment of attention deficit-hyperactivity disorder (ADHD) has been increasing. In 2007, the Food and Drug Administration mandated changes to drug labels for stimulants on the basis of findings of new-onset psychosis. Whether the risk of psychosis in adolescents and young adults with ADHD differs among various stimulants has not been extensively studied.
METHODS: We used data from two commercial insurance claims databases to assess patients 13 to 25 years of age who had received a diagnosis of ADHD and who started taking methylphenidate or amphetamine between January 1, 2004, and September 30, 2015. The outcome was a new diagnosis of psychosis for which an antipsychotic medication was prescribed during the first 60 days after the date of the onset of psychosis. To estimate hazard ratios for psychosis, we used propensity scores to match patients

who received methylphenidate with patients who received amphetamine in each database, compared the incidence of psychosis between the two stimulant groups, and then pooled the results across the two databases.
RESULTS: We assessed 337,919 adolescents and young adults who received a prescription for a stimulant for ADHD. The study population consisted of 221,846 patients with 143,286 person-years of follow up; 110,923 patients taking methylphenidate were matched with 110,923 patients taking amphetamines. There were 343 episodes of psychosis (with an episode defined as a new diagnosis code for psychosis and a prescription for an antipsychotic medication) in the matched populations (2.4 per 1000 person-years): 106 episodes (0.10%) in the methylphenidate group and 237 episodes (0.21%) in the amphetamine group (hazard ratio with amphetamine use, 1.65; 95% confidence interval, 1.31 to 2.09).
CONCLUSIONS: Among adolescents and young adults with ADHD who were receiving prescription stimulants, new-onset psychosis occurred in approximately 1 in 660 patients. Amphetamine use was associated with a greater risk of psychosis than methylphenidate

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Neuropsychopharmacology. 2019 Jan;44:226-27.
THE VENTROMEDIAL PREFRONTAL CORTEX: A PUTATIVE LOCUS FOR TRAIT INATTENTION.
Albaugh MD, Potter AS.

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NeuroRegulation. 2017;4:153.
THE EFFECTS OF MISDIAGNOSED ATTENTION-DEFICIT/HYPERACTIVITY (ADHD) MAY DECREASE CHILDREN'S IQ, AND THE EFFICACY OF QEEG AND NEURO FEEDBACK IN THE ASSESSMENT AND TREATMENT OF MISDIAGNOSED ADHD CHILDREN: A CLINICAL CASE SERIES.
Surmeli T.
Background. In children with ADHD, some studies support the effect of stimulant medication on academic achievement and some do not. One problem may be the incorrect diagnosis of ADHD using subjective measures and another may be the inefficacy of treatment. If the problem is not addressed properly it may cause a decline in IQ scores as seen in our population. Neuro feedback was chosen as a treatment since there is evidence that neuro feedback in ADHD and LD has shown to be effective in this population and has also shown to be effective in improving IQ scores.
Methods. In this clinical case series, we analyzed the results of 21 medicated ADHD-diagnosed children and adolescents who did not show any substantial improvement and who had WISC-R results at least six months prior to coming to us. All the subjects were withdrawn from medication and tests were performed to determine the diagnosis and establish a baseline (qEEG Neurometric Analysis, WISC-R, TOVA, and subjective questionnaires). These children were administered a qEEG-guided Neuro feedback protocol. The rationale being that NF would be effective in this population and another consideration was the parents' wishes of having a non medication alternative.
Results. At the end of the treatment all the tests were readministered and compared against baseline values. The results showed an increase in IQ scores with improvement in the all tests administered.
Conclusions. In this group, incorrect diagnoses, ineffective treatment, and the side effects of medication may cause a decline in the intellectual development of the children as observed by a decline in IQ scores. This decline was reversed with Neuro feedback treatment which not only showed improvement in objective measures (IQ scores) but on subjective measures also (rating scales). The implication for a clinical practice is that the overreliance on subjective measures may lead to an incorrect diagnosis and an ineffective treatment, having untoward effects on the child's intellectual development. Another finding of this study is that Neuro feedback treatment may be an effective treatment in this group of children

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NeuroRegulation. 2017;4:140.

EARLY DETECTION AND TREATMENT OF ATTENTION DEFICITS IN PRETERM INFANTS.

Harmony T.

This study described the application of a scale for evaluation and treatment of early attention deficits in infants, the 'Infant Scale of Selective Attention' (EEAS). It is well known that attention deficit begins in infancy and adversely affects individuals throughout life; thus, the challenge is to find ways to diagnose and treat it early in life, during infancy, to try to prevent children from developing attentiondeficit/ hyperactivity disorder. EEAS measures the infant's overall ability to detect, locate, track, and respond selectively to visual and auditory stimuli. Also, an intervention program was designed to stimulate attention in infants with delayed attention. This program was applied daily, from 3 to 8 months corrected age. Monthly behavioral measures from 3 to 8 months and event-related potentials (ERP) recordings for a two-tone oddball paradigm were collected in 10 full-term and 21 preterm infants with white matter injury and attention deficits. Eleven preterm infants participated in the attention stimulation program (experimental group) and 10 did not (control group). The behavioral study showed that the experimental group had a faster rate of improvement in attention than the control group. ERPs showed that deviant stimuli were automatically detected and could involuntarily capture attention but only in the healthy and treated groups

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Neurosci Biobehav Rev. 2019 Jan;96:93-115.

OVERLAPS AND DISTINCTIONS BETWEEN ATTENTION DEFICIT/HYPERACTIVITY DISORDER AND AUTISM SPECTRUM DISORDER IN YOUNG ADULTHOOD: SYSTEMATIC REVIEW AND GUIDING FRAMEWORK FOR EEG-IMAGING RESEARCH.

Lau-Zhu A, Fritz A, McLoughlin G.

Attention deficit/hyperactivity disorders (ADHD) and autism spectrum disorders (ASD) frequently co-occur. However, we know little about the neural basis of the overlaps and distinctions between these disorders, particularly in young adulthood - a critical time window for brain plasticity across executive and socioemotional domains. Here, we systematically review 75 articles investigating ADHD and ASD in young adult samples (mean ages 16-26) using cognitive tasks, with neural activity concurrently measured via electroencephalography (EEG) - the most accessible neuroimaging technology. The majority of studies focused on event-related potentials (ERPs), with some beginning to capitalise on oscillatory approaches. Overlapping and specific profiles for ASD and ADHD were found mainly for four neurocognitive domains: attention processing, performance monitoring, face processing and sensory processing. No studies in this age group directly compared both disorders or considered dual diagnosis with both disorders. Moving forward, understanding of ADHD, ASD and their overlap in young adulthood would benefit from an increased focus on cross-disorder comparisons, using similar paradigms and in well-powered samples and longitudinal cohorts

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Neurosci Biobehav Rev. 2019;100:1-8.

BRAIN ALTERATIONS IN CHILDREN/ADOLESCENTS WITH ADHD REVISITED: A NEUROIMAGING META-ANALYSIS OF 96 STRUCTURAL AND FUNCTIONAL STUDIES.

Samea F, Soluki S, Nejati V, et al.

The findings of neuroimaging studies in children/adolescents with ADHD, and even those of previous meta-analyses, are divergent. Here, Activation Likelihood Estimation meta-analysis, following the current best-practice guidelines, was conducted. We searched multiple databases and traced the references up to June 2018. Then, we extracted the reported coordinates reflecting group comparison between ADHD and healthy subjects from 96 eligible studies, containing 1914 unique participants. The analysis of pooled structural and functional, sub-analyses restricted to modality, and in-/decreased contrast did not yield any significant findings. However, further sub-analyses in the task-fMRI experiments (neutral stimuli only) led to aberrant activity in the left pallidum/putamen and decreased activity (male subjects only) in the left inferior frontal gyrus. The overall findings indicate a lack of regional convergence in children/adolescents with ADHD, which might be due to heterogeneous clinical populations, various experimental design, preprocessing, statistical

procedures in individual publications. Our results highlight the need for further high-powered investigations, but may also indicate ADHD pathophysiology might rest in network interactions rather than just regional abnormality

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Nutritional Neuroscience. 2019.

RESTING-STATE NETWORKS AND NEUROMETABOLITES IN CHILDREN WITH ADHD AFTER 10 WEEKS OF TREATMENT WITH MICRONUTRIENTS: RESULTS OF A RANDOMISED PLACEBO-CONTROLLED TRIAL.

Borlase N, Melzer TR, Eggleston MJF, et al.

Children with attention-deficit/hyperactivity disorder (ADHD) show significant abnormalities on MR imaging in network communication and connectivity. The prefrontal-striatal-cerebella circuitry, involved in attention is particularly disrupted. Neurometabolites, the biochemical structures that support neurological structural integrity, particularly in the prefrontal cortex and striatum are associated with symptoms. This study aimed to explore changes in neurometabolite levels through treatment with vitamins and minerals (micronutrients), hypothesising that treatment would impact neural circuitry and correspond to a reduction in symptoms. Twenty-seven non-medicated children (M = 10.75 years) with DSM5 diagnosed ADHD were randomised to receive daily micronutrients or placebo for 10 weeks. Main outcome measures included the Clinical Global Impression-Improvement Scale and ADHD-RS-IV Clinician Ratings of ADHD symptoms. Magnetic resonance spectroscopy of the bilateral pre-frontal cortex and bilateral striatum, resting state fMRI and structural images were acquired 1 week pre-treatment, and in the last week of intervention. Results did not show any significant differences in the measured brain metrics and the levels of neurometabolites between treatment and placebo groups after ten weeks of treatment with micronutrients. In the treatment group there was a trend for: decreased choline in the striatum; decreased glutamate in the prefrontal cortex; increased grey matter in the anterior thalamus; increased white matter in the fornix and improved network integrity of the default mode network, dorsal attention network and frontal executive network. The small sample size of the current study limits results, future studies with higher power are warranted to explore any association between micronutrient treatment and neurological changes

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Pediatr Surg Int. 2019 Feb;35:215-20.

ACQUIRED ISOLATED HYPOGANGLIONOSIS AS A DISTINCT ENTITY: RESULTS FROM A NATIONWIDE SURVEY.

Obata S, Yoshimaru K, Kirino K, et al.

PURPOSE: Acquired isolated hypoganglionosis (A-IH) is a late-onset intestinal pseudo-obstruction disorder and shows different pathophysiological findings from congenital isolated hypoganglionosis (C-IH). In this study, we retrospectively examined five cases of A-IH and investigated the features of A-IH.

METHODS: Five cases of A-IH were extracted from a nationwide retrospective cohort study in 10 years, from which totally 355 cases of Allied Disorders of Hirschsprung's Disease (ADHD) were collected.

RESULTS: Ages of onset were between 13 and 17 years in three cases, and 4 years and 4 months in ones. Initial symptoms were abdominal distension and/or chronic constipation in 4 cases, whereas one exhibited intestinal perforation. Affected lesions varied from case to case, extending various length of intestinal tracts. All cases underwent multiple operations (average: 4.6 times), such as enterostomy, resection of dilated intestines, and/or pull-through. Pathological findings showed the decreased numbers of ganglion cells and degeneration of ganglion cells, whereas the size of the plexus was normal. Currently, all cases were alive and almost all eat regular food without requiring parenteral feeding.

CONCLUSION: A-IH is rare, but distinct entity characterized by different clinical courses and pathological findings from those of C-IH. The outcome is considered to be favorable after a resection of affected intestine

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Pediatrics. 2019;143.

PRENATAL COTININE LEVELS AND ADHD AMONG OFFSPRING.

Sourander A, Sucksdorff M, Chudal R, et al.

OBJECTIVES: An association between maternal smoking during pregnancy and offspring attention-deficit/hyperactivity disorder (ADHD) has been shown across several studies based on self-reports. No previous studies have investigated the association of nicotine exposure measured by cotinine levels during pregnancy and offspring ADHD.

METHODS: In this population-based study, 1079 patients born between 1998 and 1999 and diagnosed with ADHD according to the International Classification of Diseases and 1079 matched controls were identified from Finnish nationwide registers. Maternal cotinine levels were measured by using quantitative immunoassays from maternal serum specimens collected during the first and second trimesters of pregnancy and archived in the national biobank.

RESULTS: There was a significant association between increasing log-transformed maternal cotinine levels and offspring ADHD. The odds ratio was 1.09 (95% confidence interval [CI] 1.06-1.12) when adjusting for maternal socioeconomic status, maternal age, maternal psychopathology, paternal age, paternal psychopathology, and child's birth weight for gestational age. In the categorical analyses with cotinine levels in 3 groups, heavy nicotine exposure (cotinine level .50 ng/mL) was associated with offspring ADHD, with an odds ratio of 2.21 (95% CI 1.63-2.99) in the adjusted analyses. Analyses by deciles of cotinine levels revealed that the adjusted odds for offspring ADHD in the highest decile was 3.34 (95% CI 2.02-5.52).

CONCLUSIONS: The study reveals an association with and a dose-response relationship between nicotine exposure during pregnancy and offspring ADHD. Future studies incorporating maternal smoking and environmental, genetic, and epigenetic factors are warranted

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PLoS ONE. 2019;14.

DISRUPTED REINFORCEMENT LEARNING DURING POST-ERROR SLOWING IN ADHD.

Chevrier A, Bhaijiwala M, Lipszyc J, et al.

ADHD is associated with altered dopamine regulated reinforcement learning on prediction errors. Despite evidence of categorically altered error processing in ADHD, neuroimaging advances have largely investigated models of normal reinforcement learning in greater detail. Further, although reinforcement leaning critically relies on ventral striatum exerting error magnitude related thresholding influences on substantia nigra (SN) and dorsal striatum, these thresholding influences have never been identified with neuroimaging. To identify such thresholding influences, we propose that error magnitude related activities must first be separated from opposite activities in overlapping neural regions during error detection. Here we separate error detection from magnitude related adjustment (post-error slowing) during inhibition errors in the stop signal task in typically developing (TD) and ADHD adolescents using fMRI. In TD, we predicted that: 1) deactivation of dorsal striatum on error detection interrupts ongoing processing, and should be proportional to right frontoparietal response phase activity that has been observed in the SST; 2) deactivation of ventral striatum on post-error slowing exerts thresholding influences on, and should be proportional to activity in dorsal striatum. In ADHD, we predicted that ventral striatum would instead correlate with heightened amygdala responses to errors. We found deactivation of dorsal striatum on error detection correlated with response-phase activity in both groups. In TD, post-error slowing deactivation of ventral striatum correlated with activation of dorsal striatum. In ADHD, ventral striatum correlated with heightened amygdala activity. Further, heightened activities in locus coeruleus (norepinephrine), raphe nucleus (serotonin) and medial septal nuclei (acetylcholine), which all compete for control of DA, and are altered in ADHD, exhibited altered correlations with SN. All correlations in TD were replicated in healthy adults. Results in TD are consistent with dopamine regulated reinforcement learning on post-error slowing. In ADHD, results are consistent with heightened activities in the amygdala and non-dopaminergic neurotransmitter nuclei preventing reinforcement learning

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Postgrad Med. 2019.

A RANDOMIZED, DOUBLE-BLIND, 3-WAY CROSSOVER, ANALOG CLASSROOM STUDY OF SHP465 MIXED AMPHETAMINE SALTS EXTENDED-RELEASE IN ADOLESCENTS WITH ADHD.

Wigal S, Lopez F, Frick G, et al.

Objectives: To evaluate the duration of efficacy, safety, and tolerability of SHP465 mixed amphetamine salts (MAS) extended-release versus placebo and immediate-release MAS (MAS IR) in adolescents with attention-deficit/hyperactivity disorder (ADHD).

Methods: This phase 2, randomized, 3-period, 3-treatment crossover study compared SHP465 MAS (25/50 mg) with placebo and MAS IR (12.5 mg) in 13ΓÇô17-year-old adolescents with ADHD having ADHD Rating Scale, Version IV (ADHD-RS-IV) total scores ΓëÑ24. A laboratory classroom served as a controlled environment during 16-hour observations, with efficacy assessed on the last day of each 7-day treatment period. The primary efficacy analysis compared SHP465 MAS with placebo on Permanent Product Measure of Performance (PERMP) total score averaged over the 16-hour postdose period using a mixed linear model. Comparisons were also conducted between MAS IR and placebo (for assay sensitivity) and between SHP465 MAS and MAS IR. PERMP problems attempted and answered correctly and ADHD symptoms based on ADHD-RS-IV; participant self-report; Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale; and Revised ConnerΓÇÖs Parent Rating Scale scores were also evaluated. Safety and tolerability assessments included treatment-emergent adverse events and vital signs.

Results: The intent-to-treat population included 84 participants. Least squares mean (95% CI) PERMP total score treatment differences significantly favored SHP465 MAS (combined 25/50 mg) over placebo for the average of all postdose assessment time points (41.26 [32.24, 50.29]; P <-á0.0001) and each postdose assessment time point (all P <-0.0001). Similar results were observed for MAS IR versus placebo (all postdose assessment time points averaged: nominal P <-0.0001; each postdose assessment time point: all nominal P <-0.004). The safety and tolerability of SHP465 MAS were consistent with previous reports.

Conclusions: SHP465 MAS significantly improved PERMP total scores versus placebo from 2 to 16-áhours postdose in adolescents with ADHD. The safety and tolerability profile of SHP465 MAS was consistent with previous reports of SHP465 MAS in individuals with ADHD

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Prenatal Diagnosis. 2018;38:5-6.

THE COMBINATIVE EFFECT OF TESTOSTERONE TREATMENT AND THE TIMING OF DIAGNOSIS ON NEUROCOGNITIVE ABILITIES AND ADHD IN 47, XXY (KLINEFELTER SYNDROME).

Samango-Sprouse C, Lasutschinkow P, Chea S, et al.

Objectives: 47, XXY (KS) is the most frequently occurring X and Y chromosomal disorder (1:660). These boys may exhibit motor planning deficits and delays, language-based learning disabilities (LLD), ADHD, and executive dysfunction. Testosterone replacement has been shown to mitigate some neurodevelopmental differences. Few studies have documented the possible beneficial combinative effect of prenatal diagnosis and testosterone treatment on intellectual capabilities and behavior.

Methods: 288 males with 47, XXY were evaluated using the Child Behavior Checklist (CBCL), Weschler Intelligence Scale for Children (WISC), and the Leiter International Performance Scale (LIPS). 78.5% were prenatally diagnosed with the remainder diagnosed postnatally. 71.5% received some type of testosterone treatment, and 28.5% received none. Treatment included early hormonal treatment (E) before 5 years, hormonal booster treatment (B) between 5 and 10 years, testosterone treatment after 10 years (T), and combinations of the three. Treatment was based on the patient's pediatric endocrinologist's assessment of the size of phallus in comparison to neurotypical boys of the same age.

Results: Boys who received both E + B had significantly reduced ADHD symptoms on the CBCL in comparison to boys with B (P = 0.007). Treated, prenatally diagnosed boys performed better than treated postnatally diagnosed in PIQ (P = 0.038) and PSI (P = 0.002). Boys with prenatal diagnosis and treated with any testosterone performed significantly better in VIQ (P = 0.005), PRI (P = 0.003), PSI (P = 0.023), and WMI (P = 0.001) than untreated boys. Prenatal boys who received E + B + T did significantly better than untreated boys with prenatal diagnosis (P = 0.012) on VIQ and PRI on the WISC. On the LIPS, boys who received E + B + T performed significantly better when compared to untreated boys (P = 0.020) and boys with some but not all testosterone treatment (P = 0.019).

Conclusions: This study has further expanded our knowledge of the positive impact of testosterone treatment on the neurodevelopmental outcome of boys with 47, XXY and suggests that receiving multiple testosterone treatments (E + B + T) results in the most positive outcome. For the first time, a combinative effect of hormonal treatment and diagnosis suggests that boys with 47, XXY may need treatment at several life stages to optimize neurodevelopmental outcome. Further exploration of the most advantageous timing and dosage for boys with 47, XXY is warranted. Additional study is required to investigate the relationship between repeated treatments of testosterone during childhood and maximum neurodevelopmental outcome

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Prog Neuropsychopharmacol Biol Psychiatry. 2019 Mar;90:134-41.

SIGNIFICANTLY LOWER SERUM AND HAIR MAGNESIUM LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER THAN CONTROLS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Huang YH, Zeng BY, Li DJ, et al.

The pathophysiology of attention deficient hyperactivity disorder (ADHD) is still obscure. Some studies have discussed that magnesium levels are lower in the serum and erythrocytes of children with ADHD. However, these findings are controversial. The aim of our study is to identify whether magnesium levels are in fact lower in children with ADHD. We conducted a thorough search of the literature and examined the connection between magnesium insufficiency and ADHD. A total of twelve studies were included into the current meta-analysis. The results of our meta-analysis found that peripheral blood magnesium levels, either in plasma, serum, or whole blood, of children diagnosed with ADHD were significantly lower than those in controls (k = 8, Hedges' g = âˆ’0.547, 95% CI = âˆ’0.818 to âˆ’0.276, p < .001). The subgroup meta-analysis with serum sample sources also suggested that peripheral serum magnesium levels of children diagnosed with ADHD were significantly lower than those in controls (k = 6, Hedges' g = âˆ’0.733, 95% CI = âˆ’0.911 to âˆ’0.555, p < .001). The subgroup meta-analysis focusing on subjects with ADHD diagnosed by definite diagnostic criteria also suggested significantly lower peripheral serum magnesium levels in ADHD children than those in controls (k = 4, Hedges' g = âˆ’0.780, 95% CI = âˆ’0.985 to âˆ’0.574, p < .001). We also noted that magnesium levels in the hair of children diagnosed with ADHD were significantly lower than those in controls (k = 4, Hedges' g = âˆ’0.713, 95% CI = âˆ’1.359 to âˆ’0.067, p = .031). In this meta-analysis, we found that children diagnosed with ADHD have lower serum and hair magnesium levels than children without ADHD. Further study may be needed to investigate the behavioral influence on ADHD due to lower magnesium levels, the association between brain and serum magnesium levels, and the effects brought about by larger longitudinal cohort studies

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Psychiatr Genet. 2019 Apr;29:37-43.

FAMILIAL ASSOCIATION OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER WITH AUTOIMMUNE DISEASES IN THE POPULATION OF SWEDEN.

Li X, Sjostedt C, Sundquist J, et al.

AIMS: In the era of genome-wide association studies, familial risks are used to estimate disease heritability and success in gene identification. We wanted to estimate associations of 42 autoimmune diseases with attention-deficit hyperactivity disorder (ADHD) between individuals and family members.

PARTICIPANTS AND METHODS: The availability of a Multigeneration Register in Sweden provides reliable access to family data that covers the last century. An open cohort design of the diseases in individual and family members was obtained through linkage to the Hospital Discharge Register. Standardized incidence ratios were calculated as relative risks for ADHD in family members of affected patients compared with those without affected family members.

RESULTS: Among a total of 86 493 patients, 18 153 had a family history of autoimmune diseases. ADHD was associated with 14 autoimmune diseases in the first-degree relatives, including ankylosing spondylitis (standardized incidence ratio:1.13), celiac disease (1.16), Crohn's disease (1.07), diabetes mellitus type 1 (1.19), discoid lupus erythematosus (1.26), glomerular nephritis chronic (1.13), Hashimoto/hypothyroidism

(1.11), lupoid hepatitis (1.44), multiple sclerosis (1.11), psoriasis (1.18), Reiter's disease (1.38), rheumatoid arthritis (1.07), Sjogren's syndrome (1.21), and ulcerative colitis (1.05).
CONCLUSION: Familial associations with several autoimmune diseases suggest genetic sharing and challenge to gene identification

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Psychiatry and Clinical Psychopharmacology. 2019.
NEUROLOGICAL DEFICITS AND COMORBIDITY IN CHILDREN WITH READING DISORDER.
Naz S, Najam N.
OBJECTIVES: Neuropsychological deficits were compared between three groups, i.e. RD (n = 12), RD (ADHD) (n = 12), and control group (n = 24) on neuropsychological tasks assessing Visuoconstructional ability, Postural Stability, and Language Laterality.
METHODS: Forty-eight children (age M = 12.5 years; 29 females, 19 males) were selected through purposive sampling procedure, from local primary schools. The participants were initially selected on the basis of Teachers Evaluation Checklist and then screened for RD and ADHD (combined type) using the Bangor Dyslexia Test and ADHD Clinical Parent Form, respectively. The groups were matched on nonverbal IQ (not less than on RSPM), Reading achievement estimate (Γëñ90 on WRAT-3), age (11.5ΓÇô15.3 years), and income. Visuoconstructional ability was assessed by scores on Rey Osterrieth Complex Figure Task (RCFT), while Postural Stability was measured by scores on Postural Stability subtest of Dyslexia Screening Instrument. Language Laterality was analysed through Dichotic Listening Words Test (DLWT).
RESULTS AND CONCLUSIONS: Results indicated that the group with RD (ADHD) performed significantly poor on all these tasks as compared to NC and RD (pure) group. Although the results are restricted to limited sample size, findings of the study may help in isolating the specific neuropsychological deficits related to reading disability and comorbidity which can provide important clinical information regarding etiology of the RD-ADHD connection and future treatment

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Psychiatry Res. 2019;274:189-94.
CHANGES IN SERUM MIRNA-LET-7 LEVEL IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER TREATED BY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OR ATOMOXETINE: AN EXPLORATORY TRIAL.
Cao P, Wang L, Cheng Q, et al.
We aimed to investigate whether microRNA-let-7d (miRNA-let-7d) and miRNA-107 may serve as diagnostic and therapeutic biomarkers of attention deficit hyperactivity disorder (ADHD). The relative expression level of miRNA-let-7d and miRNA-107 in patients with ADHD and in a healthy control group was detected by real-time polymerase chain reaction. The blood samples were collected at 6 weeks after repetitive transcranial magnetic stimulation (rTMS) or atomoxetine (ATX) in ADHD patients, and the relative expression levels of the two miRNAs before and after treatments were compared. There were significant differences in the expression level of miRNA-let-7d between ADHD patients and healthy children, as well as before and after rTMS or ATX treatment in ADHD patients. However, the expression of miRNA-107 showed no significant difference between ADHD patients and healthy children or before and after rTMS (or ATX treatment). These results suggest that serum miRNA-let-7d may serve as a potential diagnostic and therapeutic biomarker for children with ADHD

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Psychiatry Res. 2019;275:39-45.
SLEEP ALTERATIONS IN PEDIATRIC BIPOLAR DISORDER VERSUS ATTENTION DEFICIT DISORDER.
Estrada-Prat X, +ülvarez-Guerrico I, Batlle-Vila S, et al.
Bipolar disorder (BD) and attention deficit/hyperactivity disorder (ADHD) share numerous clinical features, which can make the differential diagnosis challenging. Studies conducted in adults suggest that patients with BD and ADHD have different sleep patterns. However, in pediatric populations, data on these potential

differences are scant. The present preliminary study was conducted to identify potential differences in sleep alterations among youths diagnosed with BD or ADHD compared to healthy controls (HC). A total of 26 patients diagnosed with BD (n = 13) or ADHD (n = 13) were compared to 26 sex- and age-matched HC ([HCBD], n = 13, and [HCADHD], n = 13). All participants underwent polysomnography. The mean duration of stage N2 sleep was shorter in the BD group than in controls (HCBD). The BD group also had higher (non-significant) REM density (REMd) scores than controls while mean REMd scores were lower in the ADHD group versus controls. Compared to the ADHD group, the BD group presented a shorter N2 stage, a longer first REM sleep duration (R1), and greater REMd. According to our findings, these three variablesΓÇöN2 stage, REMd, and R1ΓÇöappear to differentiate patients with BD from those with ADHD and from HC

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Psychol Rep. 2019 Feb;122:61-78.

ROLE OF FAULT ATTRIBUTIONS AND OTHER FACTORS IN ADULTS' ATTITUDES TOWARD HYPOTHETICAL CHILDREN WITH AN UNDESIRABLE CHARACTERISTIC.

Wadian TW, Sonnentag TL, Jones TL, et al.

A total of 184 adults read descriptions of six hypothetical children with various undesirable characteristics (i.e., being extremely overweight, extremely aggressive, extremely shy, a poor student, a poor athlete, displaying symptoms of attention deficit hyperactivity disorder). Following each description, the participants were asked to rate how much they disagree or agree that the child, the child's parents, and the child's biological condition (i.e., "something wrong inside the child's body or brain") are at fault for the onset and the perpetuation of the undesirable characteristic. In addition, the participants were asked to rate their attitude toward each child using a 100-point "feeling thermometer." Analyses of the participants' various fault attribution ratings revealed that they tended to agree more strongly that a child's parents and his/her biological condition are at fault for the onset and the perpetuation of the child's undesirable characteristic than is the child him/herself. Despite the participants' reluctance to blame a hypothetical child for his/her undesirable characteristic, regression analyses revealed that, in general, the more they blamed the child for the onset of his/her undesirable characteristic, the more negative their attitude was toward the child. However, the participants' ratings of the extent to which the child's parents or biological condition are at fault for the onset and the perpetuation of the child's undesirable characteristic were not found to be associated with their attitude toward any of the children. Similarities and differences between the present findings and those reported in prior studies involving younger individuals are addressed

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Psychol Rep. 2019 Feb;122:23-35.

EXPLORING THE EFFECTS OF WORKING MEMORY ON TIME PERCEPTION IN ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Lee HY, Yang EL.

Children with attention deficit hyperactivity disorder (ADHD) are often reported to have deficits of time perception. However, there is a strong relation between performance on tasks of working memory and time perception. Thus, it is possible that the poor performance of children with ADHD on time perception results from their deficit of working memory. In this study, the working memory of participants was separately assessed; therefore, we could explore the relationship between working memory and time perception of children with ADHD. Fifty-six children with ADHD and those of healthy controls completed tasks measuring working memory and time perception. The results showed that the time discrimination ability of children with ADHD was poorer than that of controls. However, there was a strong association between time perception and working memory. After controlling working memory and intelligence, the time discrimination ability of children with ADHD was not significantly poorer than that of controls. We suggest that there is an interdependent relationship between time perception and working memory for children with ADHD

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Psychol Addict Behav. 2019 Mar.

CIGARETTE AND E-CIGARETTE USE AND SOCIAL PERCEPTIONS OVER THE TRANSITION TO COLLEGE: THE ROLE OF ADHD SYMPTOMS.

Dvorsky MR, Langberg JM .

Cigarette and electronic cigarette (e-cigarette) use prevalence increases during adolescence and peaks in young adulthood, with substantial increases during the transition from high school to college especially more recently for e-cigarette use. It is important to identify the underlying factors that serve as risk factors for tobacco use and social perceptions about cigarette and e-cigarette use. It is unknown whether attention-deficit/hyperactivity disorder (ADHD) symptoms are associated with social perceptions about tobacco or increased tobacco use during the high school to college transition. This three timepoint prospective longitudinal study evaluates the reciprocal relationship between ADHD symptoms and social perceptions about tobacco as well as the frequency of cigarette and e-cigarette use in a sample of 150 high school seniors (Mage = 18.25, 66.0% female, 65.3% White) across the transition to college. ADHD symptoms in high school predicted increases in e-cigarette use during the first semester of college, and this association maintained through the end of the first year. ADHD symptoms predicted changes in social perceptions about cigarette and e-cigarette use after the transition to college. ADHD symptoms were predicted by social perceptions about e-cigarettes at the beginning of college. Understanding the psychosocial mechanisms underlying the pathways from ADHD symptoms to e-cigarette use may advance tobacco use etiology and prevention efforts, which is important considering the rapid growth in e-cigarette use among emerging adults

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Psychoneuroendocrinology. 2019;104:49-54.

PRENATAL TESTOSTERONE EXPOSURE IS ASSOCIATED WITH DELAY OF GRATIFICATION AND ATTENTION PROBLEMS/OVERACTIVE BEHAVIOR IN 3-YEAR-OLD BOYS.

Körner LM, Pause BM, Meinlschmidt G, et al.

Sex differences in self-control become apparent during preschool years. Girls are better able to delay their gratification and show less attention problems and overactive behavior than boys. In this context, organizational effects of gonadal steroids affecting the neural circuitry underlying self-control could be responsible for these early sex differences. In the present study testosterone levels measured in amniotic fluid (via ultra performance liquid chromatography and tandem mass spectrometry) were used to examine the role of organizational sex hormones on self-control. One hundred and twenty-two 40-month-old children participated in a delay of gratification task (DoG task) and their parents reported on their attention problems and overactive behavior. Girls waited significantly longer for their preferred reward than boys, and significantly more girls than boys waited the maximum period of time, providing evidence for sex differences in delay of gratification. Boys that were rated as suffering from more attention problems and overactive behavior waited significantly shorter in the DoG task. Amniotic testosterone measures were reliable in boys only. Most importantly, boys who waited shorter in the DoG task and boys who were reported to suffer from more attention problems and overactive behavior had higher prenatal testosterone levels. These findings extend our knowledge concerning organizational effects of testosterone on the brain circuitry underlying self-control in boys, and are of relevance for understanding how sex differences in behavioral disorders are connected with a lack of self-control

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Qual Life Res. 2019 Jan;28:241-51.

PSYCHOMETRIC PROPERTIES OF A MODIFIED VERSION OF THE WEISS FUNCTIONAL IMPAIRMENT RATING SCALE-PARENT REPORT (WFIRS-P) IN A CLINICAL SAMPLE OF CHILDREN WITH AGGRESSIVE BEHAVIOR.

Kernder T, Doepfner M, Dose C, et al.

PURPOSE: To evaluate the psychometric properties of a German modification of the Weiss Functional Impairment Rating Scale-Parent Report for children with aggressive and oppositional behavior problems (WFIRS-P for ODD/CD).

METHODS: Data were collected from a clinical sample of children (6-12 years; 96% boys) with oppositional defiant disorder (ODD) and conduct disorder (CD) (N = 219). The WFIRS-P conceptual framework was evaluated using confirmatory factor analyses (CFA). Reliability was estimated using internal consistency (Cronbach's alpha) and omega statistics. Validity was assessed through correlations between WFIRS-P for ODD/CD domain scores and parent-rated scales on symptoms of ODD, CD, attention-deficit/hyperactivity disorder (ADHD), a broad range of other behavioral and emotional problems, and scales on health-related quality of life and family burden.
RESULTS: CFA of the WFIRS-P for ODD/CD revealed that a bifactor model, with a general factor accounting for common variance (omegaH = 0.23-0.48) and independent specific group factors accounting for additional variance in item scores (omegaS = 0.37-0.60), best fits the data. Thus, CFA confirmed the theoretical assumption of a general construct of impairment (total scale) and additional specific impairments (subscales, e.g., family, social activities). Cronbach's alpha coefficient exceeded 0.70 for all subscales. Omega statistics showed that both the general construct and specific factors accounted for item variance. As expected, correlations with symptoms scales for ODD/CD and ADHD were low to moderate.
CONCLUSIONS: The use of the parent-rated WFIRS for ODD/CD in identifying ODD- and CD-related impairment in children is psychometrically supported. The scale can be employed to assess functional impairment in children with aggressive behavior problems

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Res Dev Disabil. 2019;89:22-28.

INTERNET ADDICTION AND ATTENTION-DEFICIT / HYPERACTIVITY DISORDER SYMPTOMS IN ADOLESCENTS WITH AUTISM SPECTRUM DISORDER.

Kawabe K, Horiuchi F, Miyama T, et al.

Aim: Several studies have reported that internet addiction (IA) is more prevalent in adolescents with autism spectrum disorder (ASD). However, the characteristics of ASD adolescents with IA are unclear. The objective of this study was to investigate the prevalence of IA in ASD adolescents, and compare the characteristics between the IA and the non-IA groups in adolescents with ASD.
Methods: The study included 55 participants who were outpatients at Ehime University Hospital and Ehime Rehabilitation Center for Children in Japan, aged 10ΓÇô19 years, diagnosed with ASD. Patients and their parents answered several questionnaires including the Young's Internet Addiction Test (IAT), Strengths and Difficulties Questionnaire (SDQ), Autism Spectrum Quotient (AQ), and Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHD-RS).
Results: Based on the total IAT score, 25 out of 55 participants were classified as having IA. Although there were no significant differences in AQ and Intelligence Quotient, the higher scores of ADHD symptoms in SDQ and ADHD-RS were observed in the IA group than the non-IA group. The IA group used portable games more often than the non-IA group.
Conclusion: The ADHD symptoms were strongly associated with IA in ASD adolescents. More intensive prevention and intervention for IA are needed especially for the ASD adolescents with ADHD symptoms

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Soc Sci Med. 2019.

ASSOCIATIONS BETWEEN NEIGHBORHOOD, FAMILY FACTORS AND SYMPTOM CHANGE IN CHILDHOOD ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Sharp W, Mangalmurti A, Hall C, et al.

Transactional theories view development as partly shaped by processes proximal to a child, which in turn interact with more distal neighborhood and societal contexts. Here we apply this theory to parse the interplay between neighborhood and familial factors on age-related change in symptoms of inattention and hyperactivity-impulsivity (ADHD). A cohort of 190 children (96 with ADHD) had a range of neighborhood and familial factors ascertained and had repeated clinical assessments over an average of 2.5 years at a U.S. research center. Using mixed model regression, we found an association between neighborhood wealth, but not the built environment, and the annual rate of change of inattentive but not hyperactive-impulsive

symptoms. Following the transactional model, we asked if familial processes explain (mediate), modify (moderate), or act alongside this effect of neighborhood wealth on the change in a child's symptoms of inattention with age. We found evidence for moderation. Specifically, several family level variables ΓÇô parental economic/education status and degree of family conflict and order moderated the effects of neighborhood wealth on the change in a child's inattentive symptoms. Children living in relatively affluent neighborhoods showed improvement with age in inattention, largely independent of variation in a wide range of familial factors. By contrast, children living in less affluent neighborhoods showed clinical deterioration only if the family had high levels of conflict or if the parents were of lower economic/educational status. Such work might help identify children whose familial and neighborhood contexts place them at risk of having ADHD symptoms persist or increase with age

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The American Journal of Psychiatry. 2019 Jan;176:67-76.

BRAIN MECHANISMS OF ATTENTION ORIENTING FOLLOWING FRUSTRATION: ASSOCIATIONS WITH IRRITABILITY AND AGE IN YOUTHS.

Tseng WL, Deveney CM, Stoddard J, et al.

Objective: Childhood irritability is a common, impairing problem with changing age-related manifestations that predict long-term adverse outcomes. However, more investigation of overall and age-specific neural correlates is needed. Because youths with irritability exhibit exaggerated responses to frustrating stimuli, the authors used a frustration functional MRI (fMRI) paradigm to examine associations between irritability and neural activation and tested the moderating effect of age.

Method: The authors studied a transdiagnostic sample of 195 youths with varying levels of irritability (disruptive mood dysregulation disorder, N = 52; anxiety disorder, N = 42; attention deficit hyperactivity disorder, N = 40; and healthy volunteers, N = 61). Irritability was measured by parent and child reports on the Affective Reactivity Index. The fMRI paradigm was a cued-attention task differentiating neural activity in response to frustration (rigged feedback) from activity during attention orienting in the trial following frustration.

Results: Whole-brain activation analyses revealed associations with irritability during attention orienting following frustration. Irritability was positively associated with frontal-striatal activation, specifically in the dorsolateral prefrontal cortex, inferior frontal gyrus, and caudate. Age moderated the association between irritability and activation in some frontal and posterior regions (the anterior cingulate cortex, medial frontal gyrus, cuneus, precuneus, and superior parietal lobule [F = 19.04-28.51, df = 1, 189, partial eta squared = 0.09-0.13]). Specifically, higher irritability was more strongly related to increased activation in younger youths compared with older youths.

Conclusions: Following frustration, levels of irritability correlated with activity in neural systems mediating attention orienting, top-down regulation of emotions, and motor execution. Although most associations were independent of age, dysfunction in the anterior cingulate cortex and posterior regions was more pronounced in young children with irritability

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Transl Psychiatry. 2019;9.

DISENTANGLING POLYGENIC ASSOCIATIONS BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, EDUCATIONAL ATTAINMENT, LITERACY AND LANGUAGE.

Verhoef E, Demontis D, Burgess S, et al.

Interpreting polygenic overlap between ADHD and both literacy-related and language-related impairments is challenging as genetic associations might be influenced by indirectly shared genetic factors. Here, we investigate genetic overlap between polygenic ADHD risk and multiple literacy-related and/or language-related abilities (LRAs), as assessed in UK children (N 5919), accounting for genetically predictable educational attainment (EA). Genome-wide summary statistics on clinical ADHD and years of schooling were obtained from large consortia (N 326,041). Our findings show that ADHD-polygenic scores (ADHD-PGS) were inversely associated with LRAs in ALSPAC, most consistently with reading-related abilities, and

explained 1.6% phenotypic variation. These polygenic links were then dissected into both ADHD effects shared with and independent of EA, using multivariable regressions (MVR). Conditional on EA, polygenic ADHD risk remained associated with multiple reading and/or spelling abilities, phonemic awareness and verbal intelligence, but not listening comprehension and non-word repetition. Using conservative ADHD-instruments (P-threshold < 5 10-8), this corresponded, for example, to a 0.35 SD decrease in pooled reading performance per log-odds in ADHD-liability (P = 9.2 10-5). Using subthreshold ADHD-instruments (P-threshold < 0.0015), these effects became smaller, with a 0.03 SD decrease per log-odds in ADHD risk (P = 1.4 10-6), although the predictive accuracy increased. However, polygenic ADHD-effects shared with EA were of equal strength and at least equal magnitude compared to those independent of EA, for all LRAs studied, and detectable using subthreshold instruments. Thus, ADHD-related polygenic links with LRAs are to a large extent due to shared genetic effects with EA, although there is evidence for an ADHD-specific association profile, independent of EA, that primarily involves literacy-related impairments

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HOW ONLINE ADHD-RELATED INFORMATION AFFECTS CHINESE PARENTS□ÇÖ DECISIONS?

Yu X-H, Zhong L, Huang J.

Background: Attention deficit hyperactivity disorder (ADHD) is a major public health problem in China. Parents of children with confirmed, or suspected ADHD often face a difficult process in making decisions concerning diagnosis and treatment. The internet is a major source of information for parents. The purpose of this study is to survey Chinese parental motivation and experience in using the internet to retrieve ADHD-related information, and how well online information is associated with making decisions.

Methods: Parents were recruited to fill out an online questionnaire in the health portal. A total of 404 valid questionnaires were collected.

Results: A total of 47.8% of parents agree that the internet helps them to understand the potential treatment options, but 77.7% of all parents still have conflict during decision-making.

Conclusions: Parents search for ADHD-related information online, but their acquisition skills need to be improved. Internet information affects their health decisions. Parents still have highly conflicting decision-making. Improving the ability of parents to obtain information on the Internet may reduce the conflict in decision-making

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REVIEW

Early motor signs of attention-deficit hyperactivity disorder: a systematic review

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Abstract
ADHD is a common neurodevelopmental disorder with onset of symptoms typically in early childhood. First signs of the disorder, including language delay, motor delay and temperament characteristics, may be evident as early as infancy. The present review describes published evidence about early motor signs of either children with later symptoms of ADHD or a later diagnosis of the disorder. Nine published cohort studies were included after a systematic search of related terms in PubMed and PsycInfo databases. Study eligibility criteria included: (1) report on early motor function or any motor-related signs; (2) the presence of a participants' assessment by/at 12 months of age; (3) report of a later presence of ADHD symptoms. The limited number of reports included suggests an association between mild early neurological markers and later developmental coordination disorder and motor overflow movements. Unfortunately, due to their small sample sizes and focus on group reports rather than individuals, they have limited power to find strong associations. Early motor indicators of ADHD, if present, appear to be non-specific, and therefore not yet useful in clinical screening. Spontaneous motility seems to be a promising measure for early ADHD detection, although further studies with large cohorts are recommended to determine its clinical role in children at risk for ADHD.

Keywords Attention-deficit hyperactivity disorder (ADHD) · Early motor signs · Infancy · General movements (GMs)

Introduction

ADHD is a common neurodevelopmental disorder with symptoms typically emerging during early school years and a worldwide prevalence estimated between 5 and 7% [1, 2].

ADHD is characterized by a persistent pattern of inattention and/or hyperactivity–impulsivity which hinders adaptive functioning or compromises development [3]. To be diagnosed with ADHD, symptoms of the disorder must be observed in two or more settings and have negative effects on fundamental aspects of the child's daily activities. Co-occurring psychiatric conditions are frequently observed, including oppositional defiant disorder (ODD), conduct disorder, anxiety disorders, depression, autism spectrum disorder (ASD) and learning disabilities [4–9]. Children with ADHD also often face difficulties in everyday life, including in their social relationships, academic performance and achievements, and low self-esteem [10]. In addition, they may experience deficits in visuospatial and verbal working memory, vigilance, inhibitory control and planning, problems with coordination of gross and fine motor functions, sequencing of movements [11], difficulties with working memory and self-regulation of emotions, language and speech deficits, arousal and activation and temporal information processing and timing [11–17].

Investigating early motor signs during the first year of life could be of high importance for the study of early

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biomarkers of common neurodevelopmental disorders, such as ADHD and ASD, which may share neurobiological underpinnings [18–21]. There is evidence that children with ADHD have worse gross motor and fine motor skills than their typically developing peers [22]. Two hypotheses on the source of the motor disadvantages in individuals with ADHD have been put forward. The first hypothesis attributes these motor abnormalities to the core triad of ADHD symptoms: hyperactivity, impulsivity and inattention. According to this theory, inattention [22] and vigilance problems [23] affect motor skill development. The second hypothesis attributes the motor delays to a likely presence of a comorbid disorder such as developmental coordination disorder (DCD) or ASD [23, 24]. Overall, research indicates that attention and impulse control are strongly predictive of gross and fine motor skill development in children with ADHD [24].

The neurobiological basis for the primary theory is that delays in brain maturation are associated with delays in motor development and specific motor skills [25] in the ADHD population. More specifically, motor control and executive function rely on the integrity of the thalamus, known to be affected in individuals with ADHD [26]. In addition, cortical thickness structure abnormalities and hypoactivation in the right globus pallidus, the right frontal cerebellum and frontal region, reported to be present in ADHD, are responsible, among other functions, for precise motor control.

The second theory—of the comorbidity between ADHD and DCD as the potential cause of motor delays—is also supported by neurological findings. Although the comorbidity of ADHD and DCD is not often taken into account, a high percentage of children with ADHD (30–50%) experiences co-occurring DCD with a familial correlation of 0.38 [27–31]. Almost half of individuals with ADHD (34% out of 63%) have been reported to show motor difficulties within the DCD range, particularly in manual dexterity. These difficulties result in low self-esteem and reduced popularity in children [29, 30]. At present, there is evidence that a dopamine-induced imbalance of basal ganglia neuro circuits could also be involved in the underlying neurobiological mechanisms [32, 33]. Thus, health care professionals should be aware of the high prevalence of this co-occurring motor condition.

Cerebellar abnormalities in children with DCD could also explain postural control and balance problems. Children with ADHD without co-occurring DCD have shown fine motor fluency and flexibility, but when a co-occurring DCD condition is present, fine motor difficulties are observed [34]. However, few studies have focused on brain region atypicalities in ADHD children with co-occurring DCD. McLeod et al [35]. found that these children have increased functional connectivity between the primary motor cortex and brain regions involved in motor control, and claimed this is fundamental for their ability to organize and successfully execute movement [36]. However, motor abnormalities in ADHD cannot be attributed only to the co-occurence with DCD, since children with ADHD without DCD do also have motor difficulties, although these are less prominent [37].

Since ADHD symptoms usually emerge during the early school years, both clinical and neurobiological research have focused on school-aged children, adolescents and adults. Interest in early signs of ADHD is, however, rapidly growing. Recent studies report initial evidence of some indicators appearing prior to school-age, including difficult temperament, and language and motor delay [38, 39]. Still, a little is known about whether early signs of ADHD can be reliably observed during the first year of life. This may be partly due to the relative immaturity of cognitive functions related to sustained attention and focused activity during the first months of life, and to the consequent difficulty in reliably assessing them. Increasing evidence suggests that specific motor behaviors observed during the first months of life may be a marker of neurodevelopmental disorders, which show clinical and genetic overlap with ADHD [40]. Some authors suggest that increased activity in infancy could be considered an early sign of ADHD [38, 41–45]. However, other researchers argue that the quality of movements in infancy per se does not predict the disorder [46–48].

To shed light on early motor signs in ADHD and their emergence, we systematically reviewed the publications investigating motor behavior during the first year of life in infants who later develop subclinical ADHD symptoms or are diagnosed with the disorder.

Methods

A systematic literature search was performed in PubMed and PsycInfo databases including the following keywords: (1) "ADHD" OR "Attention deficit hyperactivity disorder" OR "Attention deficit-hyperactivity disorder"; (2) AND "infant*" OR "infancy" OR "neonatal" OR "newborn" OR "baby"; AND "movement*" OR "motor" OR "sensory-motor" OR "sensori-motor" OR "motion". A systematic review of the references of the included papers was also performed to ensure a thorough search. The first search was performed in July 2016, and once more in January 2017, which yielded one additional relevant article.

Study eligibility criteria included: (1) report on early motor function or any motor-related signs; (2) the presence of a participants' assessment by/at 12 months of age; (3) report of a later presence of ADHD symptoms. The first selection was based on the study titles, as identified by one of the authors (AA). Second, abstracts were independently screened for eligibility by two authors (AA and OC). Two authors (AA and OC) independently performed the data

extraction and discussed their findings to reach a consensus. Full texts of potentially relevant papers were read to ascertain whether the study met all selection criteria.

The following data were extracted from the included articles: type of study (e.g., longitudinal, cross-sectional, or case control, both retrospective and prospective), source population (e.g., population-based or hospital referrals), participants' age range, type and timing of early motor signs, type and timing of ADHD diagnosis (based on the DSM-5) [3], or ADHD-specific symptoms (based on interviews/questionnaires), and the study outcome assessment.

Quality ratings were conducted using a modified Methodological Quality Checklist [49] developed for assessing the methodological quality of both randomized and non-randomized studies. Two of the authors (AA and OC) performed the quality ratings independently, and when necessary, reached a decision by consensus. Thirteen out of the 27 items of the scale were used in the present study, after removing those that applied only to randomized trials and intervention studies. This modified scale yielded a final rating from 0 to 14 points (see Table 1). The same approach was previously used in a systematic review on ADHD [50].

Results

In total, 417 articles were identified via the database search on both PubMed and PsycInfo; 30 studies were selected for review. Nine articles were included after completing the selection process (see flow diagram in Fig. 1). All included publications were cohort studies. The findings of all reviewed articles are reported in Table 2. Design and outcome measures differed substantially among the studies, which made a formal meta-analysis not feasible. The quality ratings of the included studies ranged between 11 and 14 out of 14 (see Table 1). Overall, the reports were of good quality.

Spontaneous movements during the first 3 months of age

Three prospective studies [42–44] explored very early motor signs of ADHD. They focused on the quality of spontaneous motility, as assessed by the General Movements (GMs) approach with infants at risk for neurodevelopmental delays. General movements are distinct spontaneous movement patterns that infants exhibit without external stimulation [53]. Investigations of early motor indicators of ADHD through the evaluation of GMs have included both healthy infants and those with increased risk for neurodevelopmental delays. Consistent with the GM method, the investigators evaluated infants several times in the first months of life and then followed up with standardized behavioral assessments at school-age. One study [42] reported that infants with definitely abnormal GMs including extremely reduced complexity, variability and fluency were at significantly increased risk to develop cerebral palsy. Furthermore, a significant association was found between milder GM abnormalities and attention problems at 4–9-year follow-up (odds ratio 6.88, 95% CI 1.39–33.97) assessed by the DSM-IV ADHD questionnaire. In particular, unlike infants with normal fidgety movements at 3–4 months, children with mildly abnormal GMs were significantly more distractible, inattentive and hyperactive as assessed by the Groningen Perinatal Project Questionnaire (GPPQ) and the DSM-IV ADHD Questionnaire for Attention-Deficit/Hyperactivity Disorder. Another study [40] indicated that abnormal GMs at both writhing and fidgety age were significantly associated with the presence of ADHD only when it was co-occurrent with another psychiatric diagnosis, but not when it was present in isolation. Furthermore, abnormal GMs at fidgety age were related to a higher total score on the DSM-IV ADHD questionnaire, and in particular, to higher subscores for hyperactivity and impulsivity, and lower subscores for inattention. Another report of GMs with preterm born infants, however, showed no significant association between GMs and attention problems at 7–11 years, as assessed by a separate subscale of the Child Behavior Checklist (CBCL) [55]. This dissociation was even stronger when children with cerebral palsy were excluded from the analysis [44].

Motor signs during the first year

Of the included reports, four were large longitudinal cohort studies exploring early neurodevelopment in the general population [38, 46, 48] or in families with lower socioeconomic status [45]. Neurodevelopmental characteristics of children with ADHD symptoms or an ADHD diagnosis were compared to the same characteristics of control children.

A retrospective chart review study of 58 children diagnosed with ADHD at school-age and 58 controls that participated in a population-based developmental program at a 'Well-Baby' clinic evaluated longitudinal data from birth, 1-, 3-, 9- and 18-month visits [38]. Higher incidence of emergency caesarian sections, smaller head circumference at 3 months and feeding or sleeping difficulties before 6 months were all identified as early signs significantly correlated with ADHD. However, the only motor-related early sign identified was a delay in gross motor development, as assessed by the Denver Developmental Screening Test (DDST) [54]. A delay in gross motor movements was identified at 9 months of age in 34.5% of the ADHD group compared to 13.8% of the controls. The most reported deviation from typical gross motor development was the refusal to maintain supine position, which led to difficulties in head control, and thus, to general motor development difficulties. The delay was reported to be relatively mild, and attributed

Table 1 Quality ratings of studies

	References								
	Johnson et al. [47]	Jaspers et al. [46]	Jeyaseelan et al. [41]	Hadders-Algra and Groothuis [42]	Hadders-Algra et al. [43]	Butcher et al. [44]	Lemcke et al. [48]	Gurevitz et al. [38]	Jacobvitz and Sroufe [45]
Reporting									
1. Is the hypothesis/aim/objective of the study clearly described?	I	I	I	I	I	I	I	I?	I
2. Are the main outcomes to be measured clearly described in the "Introduction" or "Method" section?	I	I	I	I	I	I	0?	I	I
3. Are the characteristics of the patients included in the study clearly described?	I	I	I	I	I	I	I	I	I
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	2	2	2	2	0?	1?	1	1	2
6. Are the main findings of the study clearly described?	I	I	I	I	I	I	I	I	I

Table 1 (continued)

	References								
	Johnson et al. [47]	Jaspers et al. [46]	Jeyaseelan et al. [41]	Hadders-Algra and Groothuis [42]	Hadders-Algra et al. [43]	Butcher et al. [44]	Lemcke et al. [48]	Gurevitz et al. [38]	Jacobvitz and Sroufe [45]
7. Does the study provide estimates of the random variability in the data for the main outcomes?	I	I	I	I		0 I	I (CI)	I	I
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	I	I	I	I	I	I	I (≤ 0.01)	I	I ($p<0.09$)
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	I	I	I	I	I	I	I	0 Unable to determine	I

Table 1 (continued)

	References								
	Johnson et al. [47]	Jaspers et al. [46]	Jeyaseelan et al. [41]	Hadders-Algra and Groothuis [42]	Hadders-Algra et al. [43]	Butcher et al. [44]	Lemcke et al. [48]	Gurevitz et al. [38]	Jacobvitz and Sroufe [45]
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	I	I	I	I	I	I	I	0 Unable to determine	I
13. If any of the results of the study were based on "Data dredging", was this made clear?	I	I	I	I	I	I	I	I	I
14. Were the statistical tests used to assess the main outcomes appropriate?	I	I	I	I	I	I	I	I	I
15. Were the main outcome measures used accurate (valid and reliable)?	I	0 ADHD outcome was based only on the DSM-IV scale (7 items)	0 Possible follow-up bias	I	I	I	I	I	I
16. Did the study have sufficient power to detect a clinically important effect?	I (80%)	0 No calculation of the sample size	0 Small sample size	0 No calculation of the sample size	0 Small sample size	0 Small sample size	I?	I	0 Small sample size. Not calculated
Quality rating score									

Yes = I, No = 0, Unable to determine = 0

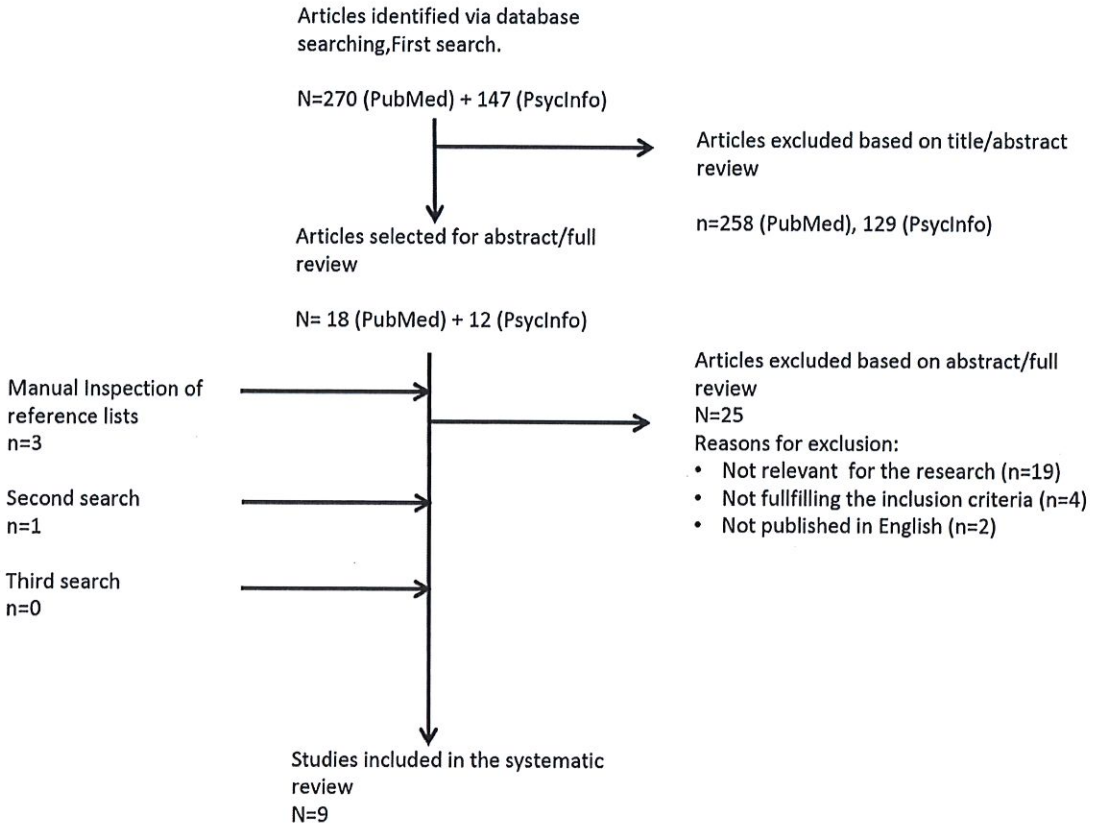

Fig. 1 Selection process

to physical characteristics including lax ligaments and hypotonia. Importantly, some children in the ADHD group were early achievers and some were late achievers, with both subgroups reported by the authors as showing "extreme" motor behavior.

A prospective study exploring early development in 267 infants from families with lower socioeconomic status [45] also included a smaller retrospective evaluation of 34 hyperactive children and 34 age-matched controls. The presence of hyperactivity was determined at around 6 years of age from subscores of the teacher-administered CBCL [55]. Thirty-eight child behavior variables were obtained during the first 2.5 years of life including neonatal behavioral assessments, mother-administered Carey questionnaire evaluating temperament, activity and attention, and other ratings of activity at 3 and 6 months of age [56]. Children who were hyperactive in kindergarten had been motorically less mature at 7 days old as assessed by the motor maturity Brazelton factor [57]. However, this was the only variable, out of the 38, which differentiated hyperactive children from typical children.

Another large study by Lemcke et al. [48] included 2034 children with a diagnosis of ADHD, who came from a large population-based cohort from the Danish National Birth Cohort (DNBC). As part of the DNBC, 76,286 mothers were interviewed about their child's development at 6 and 18 months. Children were followed up between 8 and 14 years of age, when they were assessed for the presence of ADHD based on International Classification of Diseases, 10th Revision (ICD-10) criteria. The interview at 6 months of age explored specific aspects of motor development, such as the infant holding their head straight while being picked up, sitting up while on an adult's lap, rolling over from back to stomach, crawling on the stomach. When comparing the ADHD group with the total study cohort, the only significant finding in the ADHD group was a higher number of infants who could not sit up straight when put on lap at 6 months ($p \leq 0.001$).

Similarly, Jaspers et al. [46] studied early indicators of ADHD (and ASD) in a population of 1816 subjects who took part in a prospective cohort study among (pre-)adolescents in the general population. Early indicators were obtained by identifying correlations between routine data from the community pediatric services during the first year of life and ADHD-risk as measured by parent-administered CBCL between 11 and 17 years old. Early motor indicators

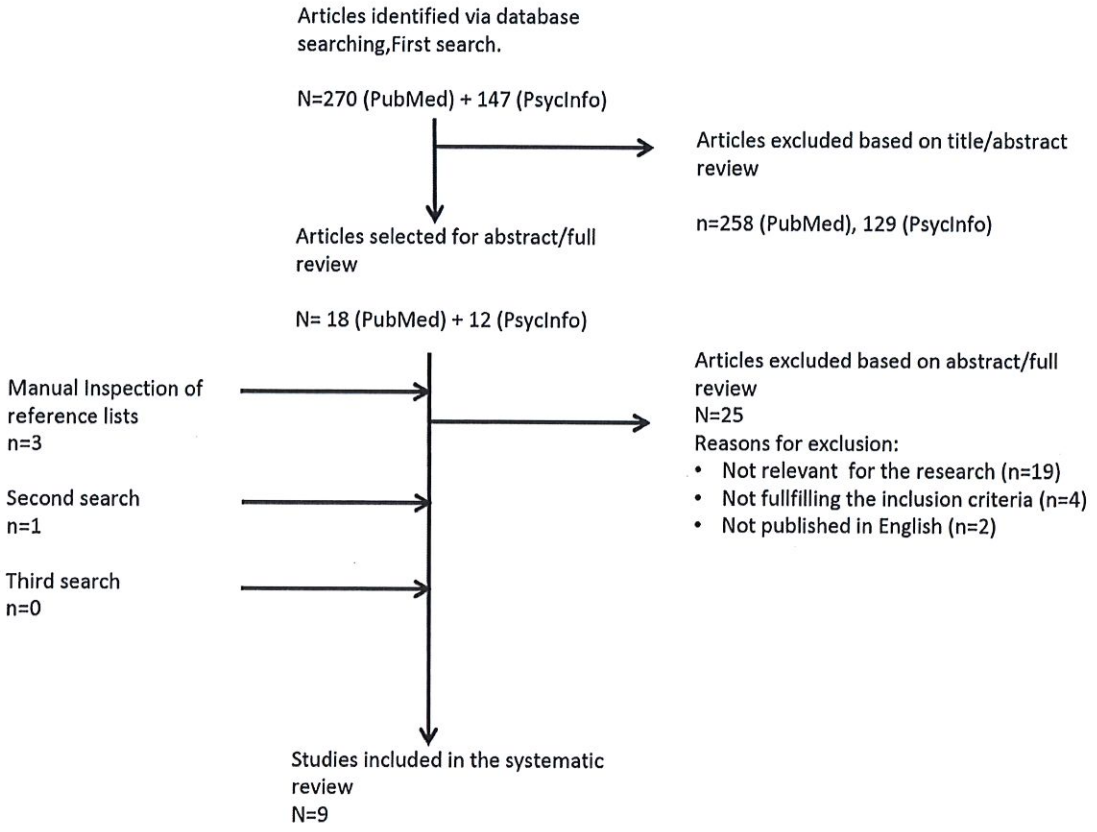

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Table 2 Studies included in the current systematic review

Study	Population	Participants	Study design	Early marker (EM) (*n* variables)	Age at EM	Outcome measures (OM)	Age at OM	Summary of results
Johnson et al. [47]	Community-based, within ALSPAC	16 ADHD, 120 controls	Retrospective longitudinal	Body movements (14)	12 months	ADHD diagnosis based on DSM-IV	7 years	No correlation between motion variables at 12 months and ADHD diagnosis at 7 years
Jaspers et al. [46]	Dutch pre-adolescents	348 adolescents with ASD, 419 adolescents with ADHD	Prospective cohort (TRAILS) based on PCH setting	Gross motor skills (16), fine motor skills and adaptation (11), communication and social behavior (10)	Birth, 18 months	CSBQ, CBCL, DSM-IV, oriented attention-hyperactivity problem scale, PCH	10–12 years	Good gross motor skills within the first year significantly correlated with development of ADHD
Jeyaseelan et al. [41]	Neonatal patients	45 extremely low birth weight (< 1000 g) and/or very preterm (< 27 weeks GA) infants	Retrospective longitudinal	NSMDA, neurological status, infant movement patterns, postural development and motor responses to sensory input	12, 24 months	CRSR, ADHD-RS	7–9 years	Motor development of ELBW 24 month infants correlated with specific clinical measures of attention at school-age, independent of biological and social factors
Hadders-Algra and Groothuis [42]	Children from the study of Hadders-Algra et al. [51, 52] (cohort of a larger study)	52 children: 28 healthy term infants, 24 at high-risk for neurodevelopmental disorders	Longitudinal	GM complexity, GM variation, GM fluency	2–4 weeks (low-risk group), 1–6 weeks (high-risk group)	Neurological examination and evaluation of behavior by parental questionnaires GPPQ, DSM-IV based questionnaire adapted for ADHD	4–9 years	Mildly abnormal GMs were associated with the development of MND, ADHD and aggression
Hadders-Algra et al. [43]	Neonatal patients, cohort from a larger study (1988–1993)	41 infants:25 low-risk full-term infants, 16 infants at high-risk for neurodevelopmental disorder	Follow-up prospective	Two forms of normal GMs (normal–optimal, normal–suboptimal) and two forms of abnormal (mildly and definitely abnormal)	Multiple ages during the first postnatal months	ADHD diagnosis, TRF questionnaire based on DSM-IV, CBCL	4–9 years, 9–12 parents completed CBCL and DSMq	Abnormal GMs at 'writhing' and 'fidgety' age are linked to ADHD along with a psychiatric comorbidity, but no isolated ADHD

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Table 2 (continued)

Study	Population	Participants	Study design	Early marker (EM) (*n* variables)	Age at EM	Outcome measures (OM)	Age at OM	Summary of results
Butcher et al. [44]	Neonatal intensive care unit patients (1993–1998)	65 infants born at ≤33 gestational weeks	Follow-up	Spontaneous movement (GMs) quality as an indicator of intelligence and behavior at school-age	4–6 week intervals between birth, and at 6 months post-term	Neurological status assessed with Touwen's test, CBCL with a separate subscale for attention problems	7–11 years (intelligence and behavior)	Spontaneous movements at 11–16 weeks seem to predict both motor development and intelligence. FM quality is strongly associated with later neurological dysfunction. No significant correlation with attention problems
Lemcke et al. [48]	Large population-based birth cohort from a network database	2034 singletons from Danish health registers with a clinical diagnosis of ADHD	Retrospective	Activity and motor development, mothers interviewed about child's development and temperament	Birth, at 6 and 18 months	ADHD diagnosis based on DSM-IV	8–14 years old	Mothers of children later diagnosed with ADHD reported more or less activity along with a limited cautiousness and a delay in language development. Majority of the children did not show deviations in motor development. There were early and late achievers of independent walking

Table 2 (continued)

Study	Population	Participants	Study design	Early marker (EM) (*n* variables)	Age at EM	Outcome measures (OM)	Age at OM	Summary of results
Gurevitz et al. [38]	Children followed up in well-baby-care clinics	58 children diagnosed with ADHD, 58 typical children	Retrospective	Gross and fine motor (general tone, head and neck control, hyperlaxity of ligaments, physical/neurological abnormalities), language and speech, and cognition and communication	0–1, 3, 9 and 18 months	ADHD diagnosis, family, perinatal and postnatal history, biometric parameters of the infant/toddler, DDST, common difficulties during the first 3 months, sleep and feeding problems, child temperament description by parents and pediatricians, behavior characteristics, abnormal findings on physical examination	Early childhood	Motor (hypotonia and lax ligaments) and language development delay, along with difficult temperament
Jacobvitz and Sroufe [45]	cohort from a larger study of 267 families	34 hyperactive (24 males, 10 females), 34 control children (24 males, 10 females)	Longitudinal	Neonatal status (orientation, arousal, motor maturity, physical ability/body tonus and quieting/consolability), newborn ratings, Carey Infant Temperament Questionnaire, EASI Temperament Survey, home and laboratory observations	Day 7, day 10, 6 months	Teachers completed the Achenbach "Child Behavior Checklst" at the end of kindergarten	5 or 6 years	Hyperactive kindergarteners were less motorically mature on the 7/10 day (isolated finding). Only one out of 38 variables differentiated hyperactive children from controls

ADHD attention-deficit hyperactivity disorder, *ASD* autism spectrum disorder, *TRAILS* tracking adolescents' individual lives survey, *PCH* preventive child healthcare, *CSBQ* children's social behavior questionnaire, *CBCL* child behavior checklist, *ESSENCE* syndromes eliciting neurodevelopmental clinical examinations, *IDD* intellectual developmental disorder, *DCD* developmental coordination disorder, *NTR* Netherlands twin register, *SES*: socioeconomical status, *ELBW* extremely low birthweight, *NSMDA* neurosensory motor developmental assessment, *GMs* general movements, *MND* minor neurological dysfunction, *DBNC* Danish national birth cohort

as assessed by the Van Wiechen scheme [58] explored the scores of gross and fine motor skills and social behavior. This study reports that good gross motor skills within the first year were significantly correlated with the development of ADHD problems.

Motor signs at 1 year

Two studies explored motor signs at 12 months of age. Johnson et al. [46] studied 16 children with ADHD (based on DSM-IV criteria), and 120 control children. Both groups were extracted from a focus study group within a larger community-based cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). As part of the ALSPAC focus study group, 1240 infants at 1 year took part in a video-recorded parent–infant interaction in a naturalistic environment [59]. Software was used to track 8 body markers [(nose (N), right (RH) and left hand (LH), right (RE) and left elbow (LE), right (RS) and left shoulder (LS) and pelvis (P)]. Thirteen motion summaries were used to determine robust indexes of motor activity including speed, acceleration along with their variability, acceleration, periodicity and agitation. Finally, 14 out of 104 variables were chosen for further investigation, including the speed and variability of 5 markers (N, RH, LH, LE, LS), the agitation of 3 (N, LH, LE) and rhythmic movement of one marker (RH). No significant association was found between the motion variables examined and the diagnosis of ADHD at 7 years. A correlation between motor activity and scores on the inattentiveness subscale of the ADHD diagnostic interview was found in male participants, but considered questionable by the authors due to the small size of the subsample ($n = 14$).

Lastly, motor signs of extremely low birth weight and very preterm infants were evaluated at 12 months with the Neurosensory Motor Developmental Assessment (NSMDA) and these scores were examined together with clinical and psychometric measures of attention at 7–9 years of age [41]. At 12 months, NSMDA evaluated gross and fine motor function, motor patterns, neurological status, postural development, and the reaction to sensory input. Measures of attention in childhood included the Conner's Rating Scale Revised-Long Form (CRSR) and Du Paul ADHD Rating Scale IV (ADHD-RS).

Discussion

ADHD is a neurodevelopmental disorder characterized by a pattern of inattention and/or impulsivity and hyperactivity across different contexts. Since early identification of ADHD is essential to optimize the quality of life, there is growing research interest in the investigation of early clinical and behavioral features of children later diagnosed with ADHD. To further investigate this topic, we reviewed the literature summarizing the full spectrum of motor impairments which might be potential early indicators of ADHD. In particular, we included studies which report motor skills of infants during the first year of life who subsequently (1) received a formal psychiatric diagnosis of ADHD based on DSM-IV or the ICD-10, or (2) whose behaviors were related to high levels of ADHD symptoms, as identified by questionnaires.

Diagnosis of ADHD and early motor signs

Four of nine studies presented included a formal diagnosis of ADHD through a psychiatric assessment [36, 42, 47, 48]. The clinical diagnosis of ADHD was either based on the criteria of the DSM-IV or the ICD-10. In these studies, children with ADHD showed atypical motor development detectable in the first 9 months [47], but not as late as 12 months, when compared to typically developing infants.

The first detectable abnormalities of motor development, GMs, in children later diagnosed with ADHD seem to be associated more strongly with ADHD when it is co-occurring with other psychiatric disorders than with ADHD alone. This is consistent with previous reports suggesting that ADHD with a co-occurring disorder is a probably more severe form of ADHD [60, 61]. Indeed, although children diagnosed with cerebral palsy were excluded from Hadders-Algra's [42] study, to avoid bias related to the known association between cerebral palsy and behavioral problems, their study population was at high risk for neurodevelopmental problems [43]. Therefore, the relationship found in this study between abnormal GMs and ADHD still suggests that the vulnerability of periventricular white matter, typical of preterm subjects and associated to abnormal GMs, may contribute to the development of ADHD with co-occurring conditions [62, 63]. In any case, the results of Hadders-Algra [42] should be considered as preliminary, since its sample size was insufficient to reach definite conclusions [43].

During the time of spontaneous motility (0–5 months) and beyond, at least up to 9 months, a delay in gross motor function was significantly more common in infants who later developed ADHD. At 3 and 9 months, Gurevitz et al. [38] reported a delay in gross motor development as assessed by the Denver Developmental Screening Test, while at 6 months Lemcke et al. [48] found a significantly higher number of infants who could not sit up straight when put on lap in the ADHD group. Motor delay seems to be no longer present at 12 months, according to the findings by Johnson et al. [46], who found no significant association between a series of motor variables at 12 months with the clinical diagnosis of ADHD at 7 years of age. As the authors hypothesized, their inconclusive outcome could be due to the small sample size of the study.

Auerbach et al. [64], examining 7-month-old infants at risk of ADHD based on mother reports and observational measures, found that children with later ADHD were significantly different from the control group in respect of behavioral states, interest and activity level.

Overall, these results support the hypothesis of a link between mild neurological markers and developmental coordination disorder, and motor overflow movements, all of which are more common in children with ADHD [64]. Nevertheless, non-specific factors related to physical characteristics, such as lax ligaments and hypotonia, are also likely to have contributed to the described gross motor delay.

Symptoms of ADHD and early motor signs

Results are more inconsistent when it comes to the relationship between early motor signs and later subclinical ADHD symptoms. Some reports state that early spontaneous motility is correlated with attention problems, including less motoric maturity at 7 days of life in children who are later hyperactive in kindergarten. Similarly, Jeyaseelan et al. [41] found a correlation between decreased motor and sensory assessment scale scores (NSMDA) and psychometric measures of verbal attention span at 12 months. However, Jaspers et al. [46] found that ADHD problems were significantly correlated with good gross motor skills, as defined by the authors, within the first year of life.

There are multiple possible reasons for these inconsistent findings. The populations that were studied are extremely heterogeneous and have different degrees of risk for ADHD, from infants with clinical signs of early hyperactivity to those who are born preterm or were small for gestational age. The assessments used to test the presence and characteristics of early motor signs were also heterogeneous, including parental questionnaires, qualitative and quantitative assessments of motor behavior, and early attentional measures. Finally, the diagnostic instruments that were used to evaluate later presence of ADHD symptoms differed among studies, making comparisons very challenging.

The limitation of our review is that the studies which are included have small sample sizes and focus on group reports rather than individuals, so they have limited power to find strong associations. Although the studies are of high quality according to the rating scheme, the outcome measures have questionable accuracy (see Table 1).

Concluding remarks

In summary, there are a limited number of reports investigating gross motor function in the first year of life in children who later have ADHD symptoms or are diagnosed with ADHD. Early detection of ADHD-related motor abnormalities would be important to provide a timely diagnosis, and most importantly, early intervention, especially in case of a very strong association between ADHD and early motor signs. This would assist clinicians in the continuous development and implementation of interventions at a very critical period of child development, when the brain is rapidly developing and neuroplasticity is highest. Unfortunately, data emerging from this review show that early motor signs, if present, seem to be non-specific, and therefore not yet worth implementing in clinical screening protocols. Some qualities of spontaneous motility seem promising as an early detection tool for risk of ADHD, although further studies based on the individual, with larger cohorts and more specific and semi-quantitative scoring systems, are necessary to determine their clinical role in populations at risk for ADHD.

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Conflict of interest None.

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ORIGINAL ARTICLE

Attention-deficit/hyperactivity disorder and enuresis: a study about effectiveness of treatment with methylphenidate or desmopressin in a pediatric population

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ABSTRACT

BACKGROUND: The aim of this study was to evaluate the effectiveness of treatment with methylphenidate or desmopressin (dDAVP) in patients with comorbid attention-deficit/hyperactivity disorder (ADHD) and enuresis.

METHODS: We enrolled 103 patients affected by ADHD and 125 patients with monosymptomatic nocturnal enuresis (NE). Data were collected between January 2014 and December 2015. The study was carried out in compliance with the Helsinki Declaration.

RESULTS: About children with ADHD, 9/103 (8.7%) were also suffering from NE; of those 8/9 followed treatment with methylphenidate and cognitive behavioral therapy. After 3 months 2/8 (25%, CI 95%: 8-65%) showed improvements, remaining 75% has been increased dosage of methylphenidate. After 6 months a response was achieved in 6/8 (75%, CI 95%: 35-96%) children and 1/8 was lost to follow-up. Furthermore the drug withdrawal showed a recurrence of symptoms both ADHD and NE in 1/7 (14.3%, CI 95%: 0.3-57%) *vs.* 6/7 (85.7%, CI 95%: 42-99%) that not presented recurrences. About children with NE enrolled at Campus Bio-Medico University it was found that 4/125 (3.8%) children were also suffering from ADHD; 3/4 (75%) treated with dDAVP and motivational therapy, of those 2/3 (66.7%, CI 95%: 9-99%) showed no improvements of symptoms *vs.* 1/3 (33.3%, CI 95%: 0.8-90%) that showed partial response with a reduction of wet-nights.

CONCLUSIONS: It is important the service of recruitment of patients with NE. In fact considering NE in a Child Neuropsychiatry Service where patients belong to a diagnosis of ADHD and NE is an incidental finding, this one is not considered as the addressee of treatment, but the therapy is directed to the neuro-behavioral problem using specific drugs and therapies, which are resolutive in the enuretic disorder.

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KEY WORDS: Attention deficit disorder with hyperactivity - Enuresis - Methylphenidate - Deamino arginine vasopressin.

Nocturnal enuresis (NE) is a common pediatric disorder, it can be defined as intermittent incontinence occurring exclusively during sleep periods.[1] NE should not be used to refer to daytime incontinence. The achievement of sphincter control is related to the maturation of a variety of functions relating to both the psychomotor development and the interaction with the social

context in which the child grows. The main aim of treatment is the resolution of the disorder from a physical point of view, but the psychological aspects should not be underestimated. The pathogenetic mechanisms of NE have to be clarified completely, probably its etiology is multifactorial.[2] The factors involved in NE are: genetic predisposition, sleep disorders, hyperactivity of detrusor muscle and nocturnal polyuria.

Disorder attention deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, characterized by inattention, hyperactivity, impulsivity. The etiology of this disorder is multifactorial, contribute both biological factors and socio-environmental factors.[3]

Epidemiological studies show that ADHD is present in about 5-10% of the population under the age of 18 years, with variations between one country and another. The prevalence of ADHD in the Italian pediatric population aged 6 to 18 years, however, is highly variable, because studies conducted in the past have used different diagnostic procedures.[4]

Recently it has been studied correlation between NE and ADHD.[5-7] Studies have shown a high incidence of psychiatric symptoms in children with sphincter incontinence: 20-30% of children with NE, 20-40% of children with daytime incontinence and 30-50% of children with fecal incontinence. The 16.8% of preschool children with any sphincter disorder presents symptoms consistent with ADHD.[8]

The hypothesis is that the ADHD drug treatment can also solve the micturition disorder. The aim of this study is to evaluate response to therapy in patients with ADHD and EN.

Materials and methods

We enrolled at Child Neuropsychiatry Service, "A. Gemelli" Hospital, Rome, 103 patients affected by ADHD (G1), ranging in age from 5 to 15 years, who met 6 or more criteria about Inattention and Hyperactivity/Impulsivity of the DSM-IV-R, moreover, we selected at Service of Pediatrics, Campus Bio-Medico University, Rome, 125 patients with monosymptomatic NE (G2), ranging in age from 5 to 15 year (Table I). The criteria of the DSM-IV-R for NE are repeated voiding of urine into bed or clothes with a frequency of twice a week for at least three consecutive months, chronological age is at least 5 years of age, these symptoms must not be due to a general medical condition.

Data were collected between January 2014 and December 2015. The retrospective-prospective study was carried out in compliance with the Helsinki Declaration and any informed consent from human subjects was obtained as required.

In G1, 9 of them were also affected by EN. In this group methylphenidate is the drug therapy prescribed by a 10-40 mg/day dose, while the recommended behavioral therapy is Cognitive-Behavioral Therapy. In G2, 4 of them were also affected by ADHD. They followed drug therapy with dDAVP 120 µg/day and cognitive-behavioral therapy. In both groups therapy was taken for 12 months.

In the first phase was studied correlation between voiding disorders and ADHD, and the hypothesis that drug treatment with methylphenidate may also resolve voiding disorder. In the second phase, patients were selected and was administered drug therapy and behavioral therapy. In the last phase, patients were called back to

TABLE I.—*Summary of 9 patients affected by NE in G1.*

Patient	Age (years)	Gender	Other comorbidities	Criteria ADHD DSM-IV-R
1	6	M	ODD	7/9 (A1) 9/9 (A2)
2	7	F	Epilepsy	7/9 (A1) 6/9 (A2)
3	13	M	LD	9/9 (A1) 9/9 (A2)
4	5	M	ODD, epilepsy	6/9 (A1) 7/9 (A2)
5	8	M	None	6/9 (A1) 9/9 (A2)
6	9	M	OCD	6/9 (A1) 8/9 (A2)
7	6	M	None	7/9 (A1) 7/9 (A2)
8	8	M	Epilepsy	8/9 (A1) 9/9 (A2)
9	6	F	ODD	8/9 (A1) 8/9 (A2)

ODD: oppositional defiant disorder; LD: learning disorder; OCD: obsessive-compulsive disorder. A1: diagnostic criteria for inattention; A2: diagnostic criteria for hyperactivity-impulsivity.

verify changes in symptomatology and if they still met diagnostic criteria of DSM-IV-R. During therapy, pharmacological and behavioral, patients were followed at 3, 6 and 12 months.

Results

Of the 103 patients with ADHD in G1 and treated with methylphenidate and behavioral therapy, 9 (8.7%) suffered also from NE. 8/9 followed the treatment *vs.* 1/9 lost to follow-up.

After 3 months 2/8 (25%, CI 95%: 8-65%) showed improvements, remaining 75% has been increased dosage of methylphenidate. After 6 months a response was achieved in 6/8 (75%, CI 95%: 35-96%) children and 1/8 was lost to follow-up. Furthermore the drug withdrawal showed a recurrence of symptoms both ADHD and NE in 1/7 (14.3%, CI 95%: 0.3-57%) *vs.* 6/7 (85.7%, CI 95%: 42-99%) that not presented recurrences.

About the 125 children in G2 it was found that 4/125 (3.8%) children were also suffering from ADHD; of those 3/4 (75%) were treated with dDAVP and motivational therapy. 2/3 (66.7%, CI 95%: 9-99%) showed no improvements of symptoms *vs.* 1/3 (33.3%, CI 95%: 0.8-90%) that showed partial response with a reduction of wet-nights. Odd ratio for treatment with methylphenidate and cognitive behavioral therapy in respect to treatment with dDAVP and motivational therapy was 0.08 (CI 95%: 0.001-4.04) with no statistical significance.

Discussion

ADHD and NE are common disorders in childhood and may be present in comorbidity. It has been suggested a common etiology and this is confirmed in recent studies.[9-13]

In G1, therapy (methylphenidate and cognitive behavioral therapy) showed a significant effect also in resolution of NE: 25% after 3 months and 75% after 6 months had a complete resolution of symptoms. Moreover after suspension of therapy there were not relapses.

In G2, therapy (dDAVP and cognitive behavioral therapy) showed a partial response of NE in only 1 (33.3%) patient. This not reflected international literature because the response to dDAVP and behavioral therapy of NE is clearly higher than 50%.[14-17]

These results demonstrate how place of recruitment of patients with NE is important. In fact, considering NE in a Child Neuropsychiatry Service where patients coming for a diagnosis of ADHD and NE is an incidental finding, this is not regarded as addressee of treatment, which is directed to the neuro-behavioral problems, *i.e.* ADHD, using specific drugs and therapies, which in 66.6% of cases are effective even in resolution of NE.

However, considering ADHD in a pediatric clinic where patients coming for a diagnosis of NE and ADHD is an incidental finding, this is not considered as first addressee of treatment, which is directed to micturition disease, using drugs and specific therapies, which are not effective in resolution of ADHD.

Limitations of the study

Results obtained demonstrate that the response to dDAVP and behavioral therapy is not comparable to that obtained with same therapy in patients affected by NE but not by ADHD.

However, due to our low number of patients, there is a need to conduct larger studies on this topic to provide important information about correlation between ADHD and NE, and consequently to suggest a new potential approach in treating ADHD and NE.

Conclusions

We want to give more resonance to a new hypothetical kind of aid to treat these two conditions: associate methylphenidate with dDAVP and motivational and behavioral therapy, to obtain improvement in symptoms and more radical resolution of these two conditions that could be invalidating in childhood.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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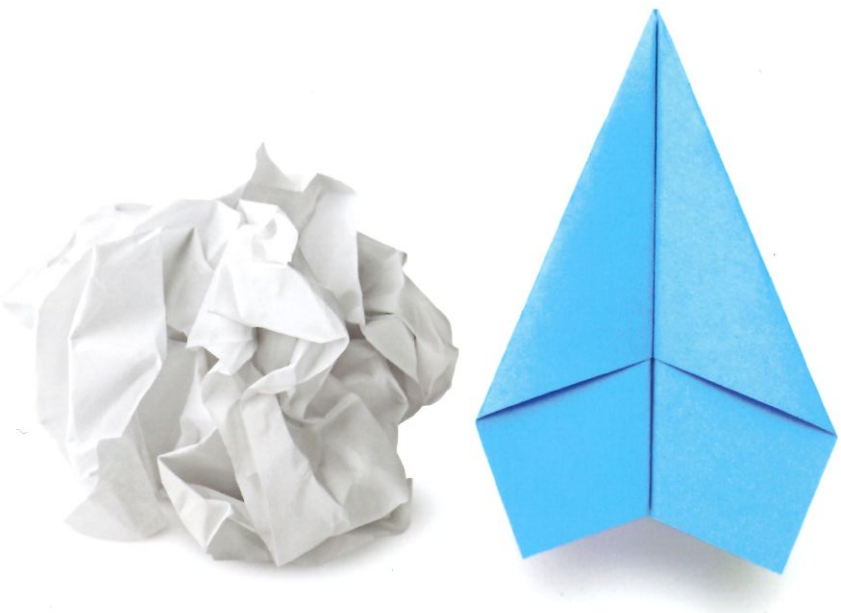
Gian Marco Marzocchi
Elena Bongarzone

Disattenti e iperattivi

Cosa possono fare genitori e insegnanti



Disattenti e iperattivi

Faticano a mantenere l'attenzione, non riescono a controllare l'impulsività né a rispettare le regole a scuola, nei giochi e nelle attività di gruppo. La causa non è un'educazione inadeguata o un eccesso di vivacità, e la soluzione non passa per rimproveri e punizioni. Sono bambini con deficit d'attenzione e iperattività (Adhd). Che cosa sappiamo di questo disturbo? Quali sono i trattamenti, quale può essere il ruolo delle famiglie e della scuola nel ridurre gli aspetti più negativi e condurre il bambino verso un'esistenza più serena?

Gian Marco Marzocchi

Insegna Psicologia della disabilità e dell'integrazione scolastica e Applied cognitive development nell'Università di Milano - Bicocca. Tra i suoi libri «Le funzioni esecutive in età evolutiva» (con S. Valagussa, Franco Angeli, 2011).

Elena Bongarzone

Psicologa clinica, lavora con ragazzi con disturbi dell'apprendimento e disturbi dell'attenzione/iperattività.

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