EXPERT REVIEWS

The comorbidity of ADHD and autism spectrum disorder

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ADHD and autism spectrum disorder are common psychiatric comorbidities to each another. In addition, there is behavioral, biological and neuropsychological overlap between the two disorders. There are also several important differences between autism spectrum disorder and ADHD. Treatment strategies for the comorbid condition will also be reviewed. Future areas of research and clinical need will be discussed.

KEYWORDS: ADHD • adolescent • ASD • autism spectrum • children • comorbidity • developmental disorder

The comorbidity of ADHD & autism spectrum disorder

ADHD

With a childhood prevalence of between 5 and 8% [1,2], ADHD is characterized by developmentally inappropriate degrees of inattention, impulsiveness and/or hyperactivity that remain relatively persistent over time and result in impairment across multiple domains of daily life activities [1]. ADHD is more commonly diagnosed in males with an average of 3:1 in community samples, which increases to as much as 5:1 to 9:1 in tertiary care or specialty clinics [1]. Approximately two-thirds of children with ADHD grow up to become adults with ADHD [3] and the prevalence rate of ADHD in adults is 4–5% [4].

Much like the DSM-IV-Text Revision [1], the DSM-5 [5] includes nine symptoms of inattention and nine symptoms of hyperactivity/impulsivity. In children and adolescents under age 17, a threshold of six symptoms must occur 'often', be inconsistent with developmental level and negatively impact social and academic activities. Several ADHD symptoms must be present prior to age 12, present in two or more settings and interfere with or reduce the quality of functioning. Finally, the DSM-5 stipulates that the ADHD symptoms cannot be better explained by another disorder [5].

The most common treatment for ADHD is a combination of medication management and a psychosocial intervention, most commonly parent management training aimed at reducing parent–child conflict [6]. Stimulants (methylphenidate, amphetamines), noradrenergic reuptake inhibitors (atomoxetine) and antihypertensive medications (clonidine, guanfacine) are all evidence-based and US FDA-approved medication management strategies for ADHD [7].

Individuals with ADHD often have a co-occurring psychiatric disorder. The most common comorbid condition is oppositional defiant disorder (ODD), with as many as many as 45–65% or more of children with ADHD meeting criteria for ODD [6]. Up to 50% of children with ADHD and ODD progress to conduct disorder (e.g., lying, stealing, fighting and otherwise violating the rights of others) [8]. In addition to externalizing disorders, between 25 and 35% of children with ADHD are also likely to meet criteria for major depression [7,9] or an anxiety disorder [6,10]. With a prevalence rate of nearly four-times what is found in children without ADHD [11], learning disabilities occur in roughly 30% of children with ADHD [12]

Autism spectrum disorder

In DSM-IV-TR, ADHD Criterion E prohibited clinicians from making an ADHD diagnosis in the context of a pervasive developmental disorder (PDD) [1]. (In DSM-IV-TR, PDD refers to a category of conditions including autism, Asperger's disorder and PDD-Not otherwise specified.) In DSM-5, this exclusionary criterion has been removed and clinicians are now able to make an ADHD diagnosis in the context of an autism spectrum disorder. Despite the fact that the DSM-IV-TR prohibited the diagnosis of ADHD in the context of an autism spectrum disorder (ASD), a body of research has emerged examining the comorbidity between the two disorders.

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While a majority of children with ASD (31–95%) have significant symptoms of inattention and/or hyperactivity/impulsivity [13–21], not all children with ASD have these symptoms [21–23]. For example, in a retrospective chart review of 57 children who had been evaluated at a neuropsychological clinic, Goldstein and Schwebach found that just over half (59%) of the children with ASD met diagnostic criteria for ADHD [13]. Of the children with ASD who met criteria for ADHD, 26% met diagnostic criteria for ADHD-Combined type and 33% met diagnostic criteria for ADHD-Inattentive type [13]. Because not all of the children with ASD demonstrated significant evidence of ADHD-like characteristics, the authors concluded that the two disorders are likely independent from each other [13].

Similar to the Goldstein and Schwebach study, Sinzig *et al.* found that the Inattentive subtype of ADHD was the most prevalent ADHD subtype in children with ASD [24]. In the Sinzig study, 46% met criteria for ADHD-Inattentive type, 32% for ADHD-Combined type and 22% for ADHD-Hyperactive/Impulsive type [24]. Others have similarly reported that the Inattentive subtype is the most common in ASD [25]. Similar to the non-ASD population [26,27], ADHD subtype comorbidity in ASD varies with age: the number of children with ASD who meet ADHD symptom criteria for hyperactivity tends to decrease with age, while the number of children with ASD who meet criteria for inattention tends to remain relatively stable [28,29].

Parent and teacher concordance in children with ASD and ADHD symptoms is comparable with that observed in the non-ASD, ADHD population. For example, Pearson *et al.* studied 86 children with ASD (mean age = 9) and assessed parent and teacher concordance on ADHD ratings [30]. Concordance levels were generally in the 0.4–0.6 range for ADHD symptoms and these levels did not vary as a function of child age, gender, medication status, ASD subtype or ASD severity [30]. These concordance rates are comparable with (or somewhat higher than) those in the non-ASD ADHD population [31].

Common features between ASD & ADHD

Biological

Multiple, interacting genetic factors and their interplay with environmental factors constitute the main causative determinants of both ADHD and ASD [32–35]. Although both disorders show substantial heritability and a multifactorial genetic architecture [36,37], identifying causal variants has been challenging. Genetic linkage studies suggested regions of chromosomes 16p13 [38] 2q24, 16p1, 17p11, 5p13 and 15q [39–42] to be involved in both ADHD and ASD. Evidence from family, twin, candidate gene, genome-wide association (GWA) and sequencing studies all suggest that ADHD and ASD originate from partly similar familial/genetic factors [43,44]. A number of known rare mutations that result in syndromes of developmental delay are often associated with symptoms of ASD and ADHD, such as premuations of FMR1 in Fragile X syndrome [45], 22q11 deletion syndrome [46] and microdeletions/duplications at 15q13.2q13.3 spanning gene CHRNA7 [47,48]. An increased burden of rare copy number variants (CNVs) has been implicated in both ASD [49] and ADHD [50]. There is also some evidence for shared common variants in candidate genes such as the dopamine [51,52] and serotonin transporters [53]. When GWA data for five disorders in the Psychiatric Genomics Consortium: ASD, ADHD, bipolar disorder, major depressive disorder and schizophrenia were pooled together, SNPs at four loci reached genome-wide significance ($p < 5 \times 10^{-8}$) including regions on chromosomes 3p21 and 10q24, and SNPs within two L-type voltage-gated calcium channel subunits, CACNA1C and CACNB2 [54].

GWA and sequencing studies have implicated similar neurobiological pathways for ADHD and ASD. For example, both ADHD and ASD involve synaptic mechanisms. Genes in dopaminergic [55], serotoninergic [53], glutamatergic [56,57] and GABAergic [58,59] systems have been implicated in both disorders. Variants in SHANK3-NLGN4-NRXN1 postsynaptic density genes were found in ASD [60]. Genes encoding neuronal cell adhesion molecules (e.g., ASTN2) [61,62], genes involved in synaptic plasticity (e.g., BDNF) were implicated in both ASD and ADHD [63–65]. Indeed, anatomical and functional imaging studies of the human brain have suggested a developmental theory of abnormal connectivity or 'miswiring' for both ADHD and ASD [66–70].

Another example is the mTOR activation pathway. Increased ADHD and ASD symptoms have been found in patients with tuberous sclerosis (TSC) and neurofibromatosis [71–74], two genetic diseases resulted from mutations of mTOR inhibitor genes, TSC1 or TSC2 and NF-1. Other genes in the mTOR pathway that have been implicated in ASD and in developmental abnormalities of the brain include PTEN, EIF4E4 and STRADα [75–77]. Recently, ADHD symptoms were found to be elevated in systemic lupus erythematosus (SLE) patients where the mTOR pathway activation leads to T-cell dysfunction. The ADHD symptoms were relieved by *N*-acetylcysteine (NAC), which acts on the mTOR pathway [78,79]. Interestingly, NAC is an antioxidant, which implicates the redox pathway and oxidative stress has been observed in both ADHD and autism [80,81].

Similar to their shared multifactorial genetic architecture, there are many environmental risk factors implicated in both disorders. Exposure to lead, polychlorinated biphenyls (PCB), mercury, alcohol and cigarette smoke during critical developmental periods, that is, prenatal and early postnatal ages, causes long-term neurodevelopmental consequences and been associated with increased risk for both ADHD and autism [82–86]. Exposure to polybrominated diphenyl ethers (PBDE), used as flame retardants in consumer products in recent years, increases the risk for ADHD symptoms and poor social competence [87,88]. Interestingly, many of these environmental toxins, including PCBs, PBDE, mercury and lead are all well-known anti-thyroid agents with well-characterized teratogenic properties [87,89]. Thyroid hormone is essential for early brain development and affects a wide range of neurodevelopmental processes

such as cell migration, dendrite and axon outgrowth, synapse formation, myelination and gliogenesis [90–92]. It has long been known that maternal hypothyroxinemia can cause profound mental retardation in children and increase the risk of autism [89]. The prevalence of ADHD in children with generalized resistance to thyroid hormone (GRTH) has been reported to be 46%, much higher than the general population (~5%); and the prevalence of thyroid dysfunctions was also found to be increased in children with ADHD (5.4%) compared with the normal population (<1%) [93]. De Cock *et al.* reviewed studies from 21 publications and concluded that exposure to environmental toxins is associated with increased risk for ADHD and ASD, possibly through common mechanisms such as disrupting thyroid hormone function [94].

Other consistent perinatal risk factors shared between the two disorders include low birth weight [95–97] and preterm birth [98–100], both of which increase the incidence of ADHD, ASD and other behavior problems. Maternal obesity and maternal high fat diets also increase the susceptibility of offspring to behavioral disorders including anxiety, depression, ADHD and autism [101]. Maternal stress is also a predictor for autistic- and ADHD-traits in their offspring [102].

Genetic alterations, such as mutations and expression changes of epigenetic genes [103–105] and environmental risk factors including exposure to environmental toxins, maternal behavior, perinatal risk factors, hormonal dysfunction and oxidative stress, all can produce long-lasting trans-generational epigenetic modifications of the genome. Environmental events can lead to DNA methylation and histone acetylation, which can cause abnormal gene expression and cellular dysfunctions, thereby contributing to an array of human diseases including neurodevelopmental and behavioral disorders [106,107]. For example, postnatal stress can alter the DNA methylation of BDNF, a possible risk gene for both ADHD and autism which is involved in neurodevelopment and plasticity [65,108,109]. In fact, epigenetic mechanism may be one of the converging biological pathways underlying the effects and interactions of genome and environment [106,107,110].

Despite these similarities, differences in cortical thickening have been described in ADHD and ASD samples, although no research to our knowledge has considered cortical thickening in the comorbid condition. For example, Shaw *et al.* described a developmental delay in cortical thickening in a large sample of children with ADHD [111]. Conversely, in ASD, others [112,113] have reported on early brain overgrowth followed by greater reductions in gray matter. Unlike other data cited above, these data do not support the argument that ADHD and ASD are related conditions, despite their phenotypic overlap.

In summary, the biological overlap between ADHD and ASD may be substantial. This section provides an overview of some aspects of overlap in genetic, environmental and epigenetic mechanisms from a neurodevelopmental perspective. The research, clinical and social approaches that recognize and address these interactions and overlaps will likely to be more fruitful in the future.

Neuropsychological/cognitive

In addition to biological overlap between the two conditions, there is also neuropsychological/cognitive overlap most of which focuses on attention and executive function vulnerabilities. For example, both ADHD [114,115] and ASD [116–118] are thought to be associated with executive dysfunction.

Several studies have examined executive functioning skills in individuals with ASD compared with those with ADHD. For example, Nyden *et al.* found that both children with ADHD and children with ASD had deficits in inhibition [119]. Geurts *et al.* compared executive functioning abilities in children with ASD and ADHD [120]. Both groups exhibited deficits on multiple aspects of executive functioning and differences between ADHD and ASD groups were most apparent on tasks of planning and cognitive flexibility (ASD < ADHD) and inhibition and verbal fluency (ADHD < ASD). Johnson *et al.*, Ozonoff and Jensen and Happe *et al.* also found both children with ASD and children with ADHD to have executive functioning deficits; however, similar to Geurts *et al.*, children with ASD to have more planning and cognitive flexibility difficulties and children with ADHD to have more inhibition difficulties [117,121,122].

Likewise, Sinzig *et al.* investigated executive functioning in children and adolescents with ADHD (n = 20), ASD with (n = 20) and without (n = 20) comorbid ADHD as well as typically developing controls (n = 20) [123]. Children with ASD performed worse than children with ADHD on tasks of planning and flexibility, whereas children with ADHD performed worse on motor inhibition tasks and spatial working memory tasks [123]. Thus, data suggest that children with ADHD and children with ASD have deficits in executive functioning, although the specific executive deficits may not be identical.

In adult samples, executive dysfunction is common to both conditions. For example, attention-switching problems may be both a symptom overlap as well as a common etiological factor underlying ASD and ADHD [124]. Likewise, other data in adult samples suggest that, while adults with ASD, ADHD and comorbid ASD/ADHD had reduced performance on multiple tests of executive functioning, although no group differences emerged [125].

In addition to executive dysfunction, social cognition (especially theory of mind) has also been empirically explored in both populations. For example, Buitelaar *et al.* examined theory of mind abilities in children with an ASD and ADHD [126]. Both groups had difficulties in theory of mind tasks and were statistically equivalent to each other [126]. Children with ASD [127] and children with ADHD [126,128,129] both have difficulties with theory of mind. Some have proposed that both ADHD and ASD are part of a category of 'empathy disorders' [130]. Other research [131–133], however, suggests that children with ADHD are not as impaired as children with ASD on theory of mind tasks.

Behavioral

ADHD symptoms alone do not differentiate between children with ADHD and those with ASD. For example, approximately 25% of children with ASD meet DSM-IV-TR symptom and

impairment criteria for ADHD-Combined type and approximately 35% meet DSM-IV-TR symptoms and impairment criteria for ADHD-Inattentive type [13,15]. Likewise, children with ASD and ADHD do not differ significantly in the number of ADHD symptoms reported from those with ADHD only [13]. Other data have similarly reported that children with ASD and those with ADHD do not differ significantly in terms of parent report of attention and hyperactivity/impulsivity [134–136].

Children with ADHD have more social problems [137] and ASD behaviors/traits than typically developing children [126,129,135,136,138]. For example, in a large study of clinically referred children with ADHD, between 65 and 85% of the children had clinically significant difficulties in both language and social interaction as assessed with the Autism Criteria Checklist [128]. Likewise, a large population-based twin study demonstrated that children with ADHD have deficits in reciprocal social interactions [139]. Like youth with ASD, children with ADHD also have difficulties with language pragmatics [128,140,141]. Some data suggest that children with ADHD, much like children with ASD, have stereotyped hand and body movements [128] and restricted and repetitive interests [136]. Hyperactive/impulsive symptoms, not inattentive symptoms, may be more closely associated with ASD behaviors [142].

Behaviorally, children with ADHD and ASD appear to be similarly less motivated by social reinforcers. For example in a study comparing the effects of amount and type of reward in children with ADHD and those with ASD, both groups were less strongly motivated by social reinforcers than typically developing control participants yet were equally motivated by monetary reinforcers at levels far above typically developing controls [132].

Despite the similarities, some data suggest that ADHD and ASD are independent from each other. For example, not all children with ADHD have ASD traits; however, in those that do have ASD traits, there is some evidence to suggest that the ASD traits are not better accounted for by ADHD [143]. Likewise, Frazier *et al.* conducted comparative analyses to determine whether inattention and hyperactivity/impulsivity were overrepresented among youth with ASD and whether the inattention and hyperactivity/impulsivity were affected by the children's developmental disorder [22]. Youth with ASD had similar phenotypes regardless of whether they met criteria for ADHD. Similarly, youth who met criteria for ADHD displayed similar characteristics regardless of whether they were diagnosed with an ASD. Furthermore, children with ADHD had a similar age of onset of ADHD symptoms regardless of whether they carried an additional ASD diagnosis. These data suggest that while ASD and ADHD may share behavioral features, the two conditions may be independent from one another.

Other data [144] suggest that children with ASD can be distinguished from those with ADHD based upon symptom profiles. Unusual fascination with repetitive movements, language regression and special abilities may be specific to ASD and overreactivity, meltdowns or aggression appear to be more specific to ADHD [144].

Likewise, ASD and ADHD are both associated with impaired social interaction, yet data suggest that the social interaction impairments are more significant in ASD [135,136]. For example, using a large sample of children with ADHD (n = 821), Mulligan *et al.* documented that children with ADHD are not impaired in the nonverbal communication domain (e.g., eye contact, use of gestures to accompany conversation, and so on) and did not have unusual sensory interests or unusual preoccupations [138]. Others [145] have reported that children with ADHD do not have strong demands for sameness; in fact, a high demand for novelty is thought to be a defining feature of ADHD [1]. The social intent of children with ADHD is less impaired than those with ASD [138], and children with ADHD are more socially motivated than those with ASD [141].

Using latent class analyses, van der Meer *et al.* investigated the behavioral overlap between ADHD and ASD and tested the hypothesis that there may be homogeneous subgroups within the ASD and ADHD population [146]. The authors utilized common ASD and ADHD rating scales for 644 children and adolescents (age 5–17 years) recruited from two sources: 370 children from a random population cohort study and 274 children from a clinical ASD–ADHD genetic study. Five classes emerged: two without behavioral problems, one with only ADHD behavior and two with both clinical symptom levels of ASD and ADHD but with one domain more prominent than the other. The authors concluded that there is support for conceptualizing ADHD and ASD as one overarching disorder (due to ADHD class without ASD symptoms and the absence of an ASD class without ADHD symptoms) albeit with some specificity of cognitive deficits between the five classes.

All of the above suggests that while there are some behavioral similarities between the two disorders, there are also both qualitative and quantitative differences in the behavioral phenotype.

Efficacy of ADHD treatments in ASD

Stimulant medications

In a study examining a nationally representative sample of adolescents [147], the prevalence of psychotropic medication use as a means of treatment was highest (58.2%) among those diagnosed with both ASD and ADHD. The majority of these adolescents were taking multiple medications, and this group had high rates of antipsychotic, antidepressant/anxiolytic and stimulant use in comparison with ASD-only and ADHD-only groups, reflecting a lack of clear treatment guidelines for these individuals [147]. Likewise, despite high rates of ADHD symptoms in individuals with ASD, prescribing physicians often report concerns about prescribing stimulants to individuals with ASD who exhibit ADHD-like symptoms out of concern for inefficacy and/or increased stereotypy [148,149]. Nevertheless, there have been several studies that have assessed the efficacy of stimulant medications in ASD samples.

Using a preschool sample of 14 children aged 3–5 with ASD, Ghuman *et al.* utilized a randomized, double-blind,

placebo-controlled, crossover trial of methyphenidate [150]. The dosing began with a single-blind titration starting at 1.25 mg two-times a day (maximum allowed dose: 10 mg two-times a day) which was followed by a 4-week double-blind crossover phase including 2 weeks of placebo and 2 weeks of methylphenidate. Methylphenidate was superior to the placebo for ADHD symptoms with medium to high effect sizes yet with higher adverse effects than seen in the non-ASD population [150].

Quintana *et al.* conducted a double-blind crossover study to examine the efficacy and side effects of methylphenidate in 10 children (age 7–11) with ASD [151]. Following a 2-week, medication-free baseline period, children were randomly assigned to a methylphenidate (10 mg of methylphenidate each day in the morning and at noon) or placebo. This same procedure continued for the next week, but the methylphenidate dosage was increased to 20 mg. Following that phase of the study, participants then crossed over to the other condition for the next 2 weeks, during which the same procedures were followed. On the final day of each week, participants were observed during a 3 h simulated classroom condition in which demands were matched to participants' mental age. In comparison with placebo condition, methylphenidate decreased children's hyperactivity moderately, but to a statistically significant extent. No statistically significant differences in side effects occurred between methylphenidate condition and placebo and methylphenidate use was not associated with increased stereotypy [151].

In another short-term (21 days) double-blind, placebo-controlled, crossover trial, Handen *et al.* investigated the efficacy of methylphenidate in 13 children (age 5–11) with ASD [152]. Using a 50% reduction in parent-reported ADHD symptoms as evidence of a positive response, 61% of the children were responders. Of the responders, nearly all had a positive response at the lower methylphenidate does (0.3 mg/kg). Methylphenidate response rates did not vary as a function of IQ and there were no significant differences in side effects in the methylphenidate and placebo conditions [152].

The Research Units on Pediatric Psychopharmacology (RUPP) Autism Network conducted a large study of methylphenidate efficacy in ASD [153]. After a 1-week test-dose phase, 66 participants (age 5–13) had a 4-week randomized, double-blind, placebo-controlled, crossover trial using three doses (0.125, 0.250 and 0.500 mg/kg, three times a day). This controlled portion of the study was then followed by an open-label continuation phase for positive responders using the best dose during the randomized phase. All three methylphenidate dosages were statistically superior to placebo with small to medium effect sizes for general behavioral items. Just over half of the participants (57%) were methylphenidate responders at the end of the continuation phase [153].

A larger (n = 174) retrospective study [129] assessed the efficacy of stimulant medications in adolescents with combined ASD and ADHD and those with ADHD alone. After participants in each group received an average of 30 mg of methylphenidate (dose range = 10–50 mg) in three divided doses per day or dextroamphetamine (dose range = 5–30 mg/day) in combination with educational and behavioral interventions as necessary, no statistically significant differences were found to exist in the symptom profile or the side effects between groups. The clinical response to the treatment did not differ between the ASD + ADHD group and the ADHD-only group [129].

In addition to these studies, there are others [154–159] that provide some evidence of the efficacy of stimulant medication use as a means of treating ADHD-like symptoms within individuals with ASD. General conclusions from this volume of literature are:

- IQ and gender are not a determinant of stimulant efficacy
- Effect sizes for the ASD population are somewhat smaller than the non-ASD population
- Fewer individuals in the studies are classified as 'responders' than in the non-ASD population
- Side effects are more common in the ASD population.

Non-stimulant medications

Atomoxetine is a non-stimulant medication that is employed as an ADHD treatment strategy. Relative to the data that have been published on the use of stimulant medications, there are far less data that have been published on atomoxetine. Within the past 3 years, two studies on the efficacy and tolerability of atomoxetine for ASD have been published.

Using an open-label design, Zeiner *et al.* followed 14 males (age 7–17) with ADHD and ASD for 10 weeks [160]. Atomoxetine doses ranged from 0.5 mg/kg/day in week 1 and 1.2–1.4 mg/kg/day over the duration of the remaining 9 weeks. Seven of the 14 males were classified as 'responders' to atomoxetine. Two children ceased atomoxetine treatment due to side effects [160].

In a more carefully controlled study, Harfterkamp *et al.* followed 97 youth aged 6–17 with ADHD and ASD for 8 weeks in a randomly assigned double-blind experiment of 1.2 mg/kg/day atomoxetine or placebo [161]. Results indicated that youth with ADHD and ASD moderately improved their ADHD symptoms and adverse effects were comparable between atomoxetine and placebo conditions.

Another selective norepinephine reuptake inhibitor, reboxetine, has also been tested empirically as a non-stimulant treatment in the ASD population [162]. In a 12-week open-label trial using a sample of 11 adolescents with ASD (mean age = 12) and depressive/ADHD symptoms, reboxetine (maximal dose, 4 mg/day) resulted in statistically significant, albeit modest, decreases in the severity of ADHD symptoms ($p = 0.015$).

The alpha-2 adrenergic agonists guanfacine and clonidine are US FDA approved for ADHD but have not been widely studied for ADHD in the context of ASD. Handen *et al.* reported a 6-week double-blind placebo-controlled crossover trial of 11 children treated with guanfacine and placebo [163]. Guanfacine led to significant decreases in hyperactivity and better Global Improvement Ratings. Five of 11 patients were

classified as responders based on a 50% decrease in hyperactivity scores. Several side effects were reported, including drowsiness and irritability. Similarly, an open-label trial of clonidine in children with ASD reported modest improvements in ADHD symptoms and largely tolerable side effects [164].

While not FDA-approved for the treatment of ADHD, atypical antipsychotic medications such as risperidone and aripiprazole are FDA-approved for the treatment of disruptive behavior disorders including aggression and severe behavioral problems in ASD [165,166]. While ADHD is frequently categorized as a disruptive behavior disorder, the severity of the disruptive behaviors for which the atypical antipsychotic medications are FDA-approved far exceeds the typical level of disruption observed in ADHD. There are, however, data suggesting that children with ADHD (and no other psychiatric comorbidity) account for one in seven prescriptions of atypical antipsychotic medications [167]. Nevertheless, these medications should be used cautiously among youth with ADHD.

Behavioral treatments

Compared with the data that have been published on pharmacological interventions, far less data have been published on the efficacy of behavioral interventions for the comorbid ADHD/ASD population. Presently, to our knowledge, no studies have directly compared the effects of psychosocial treatments in children with ASD only, ADHD only and comorbid ASD and ADHD. Antshel *et al.* have come the closest to testing this research question. In their sample of 83 children (74 males, 9 females) with an ASD (mean age = 9.5 years; SD = 1.2) and common comorbid psychiatric disorders, children with ASD + ADHD benefitted much less from a 10-week social skills training program than children with ASD only and ASD + anxiety disorder [168]. These data suggest that an ASD intervention may not be as effective in the presence of comorbid ADHD.

Expert commentary

Twenty years ago when the DSM-IV was published, ADHD and ASD were thought to share behavioral symptoms so much that the zeitgeist of the time was to disallow an ADHD diagnosis in the context of ASD. Since that time, much data have been published suggesting that while many (even most) individuals with ASD may have ADHD symptoms, not all individuals with ASD have impairing inattentive and/or hyperactive symptoms. Thus, within the past 20 years, there seems to have been an increasing recognition that the two disorders are related with one another yet not completely overlapping. Today, the DSM-5 recognize that when ADHD can be diagnosed in the presence of ASD, the ADHD diagnosis carries important implications for treatment response such that medications used to treat ADHD are also effective for treating ADHD in the presence of ASD.

What is also clear from the research reviewed above is the heterogeneity of findings. This may be a function of several variables including the ASD samples (e.g., clinical characteristics, comorbid neurological conditions, severity of ASD, IQ, age, and so on), the manner in which ADHD was assessed (e.g., diagnosis, symptoms), and the manner in which treatment efficacy was assessed (e.g., how being a treatment 'responder' was operationalized).

In addition to the heterogeneity of the findings, there are also gaps in the literature base. For example, ADHD and ASD are both disorders that typically begin to impair functioning in childhood. Not surprisingly, it is clear from the data that have been reviewed above that the majority of empirical studies have focused on the middle childhood (age 6–11 years) population. Thus, we know far more about ADHD and ASD in this developmental period. Adopting a lifespan developmental approach to the study of the comorbid condition is needed.

Further, while clear treatment parameters guide the management of symptoms among those with ADHD, evidence suggests that individuals with comorbid ASD may be receiving variable treatment due to the murkier recommendations set forth by less convincing research [169]. Thus, it is particularly crucial to further research and understand efficacious pharmacological treatments for individuals with coexisting ADHD and ASD. There is, however, a sufficient evidence base to recommend treating ADHD in the context of ASD with either stimulant medication or atomoxetine. More work is needed to better understand the effects of guanfacine and clonidine.

Likewise, the empirical literature that has assessed the efficacy of psychosocial/behavioral interventions in the comorbid ADHD and ASD population is strikingly scant. While it is tempting to assume that the comorbid state would benefit from the same behavioral interventions that are effective in the ADHD or ASD population, this has not been assessed. In fact, there is evidence to suggest that social skills training, an effective intervention for ASD, is negatively mediated by the presence of ADHD.

With the publication of the DSM-5 and the removal of the ASD exclusionary criteria for the diagnosis of ADHD, there may be an increase in the research base on the comorbid state. With the exclusionary criteria removal, clinicians may be less likely to engage in diagnostic overshadowing or the attribution of certain behaviors to one condition without considering the other [170].

Five-year view

There are many research opportunities and unanswered questions that remain about ADHD in the context of ASD and could be considered in the next 5 years. Most fundamentally, future research should continue to focus on this comorbidity. Using the framework adopted by Biederman *et al.*, future research should consider these competing hypotheses for explaining the comorbidity between ADHD and ASD the comorbid disorders are the expression of phenotypic variability of the same DSM-5 disorder, each disorder is a separate DSM-5 disorder, ADHD and ASD possess common vulnerabilities, the comorbid ADHD and ASD state represents a homogeneous subgroup with the ADHD (or ASD) population, one condition is a developmental precursor to the other

condition, and one disorder increases the risk for the second disorder [171]. Evidence to distinguish one condition from another, and evidence for distinct comorbid subtypes can be organized into the framework originally developed by Robins and Guze, which assesses evidence in multiple domains clinical description, laboratory studies, delimitation from other disorders, follow-up studies and family studies [172].

In addition to further examining the explanations for the comorbidity between ADHD and ASD, future research in the next 5 years should examine clinically relevant topics. For example, to date treatment studies have overwhelmingly focused on methylphenidate. Mixed amphetamine preparations have received very little, if any, research focus and more studies of non-stimulants are needed. Likewise, no existing ASD and ADHD treatment studies have combined behavioral and medication management, the primary treatment strategy employed for managing ADHD. Furthermore, rather than employing ADHD symptoms as outcome measures, the use of quality of life scale, ecologically valid indices of functioning (e.g., grades, sociometric ratings, etc.) may also advance our knowledge. Improvements in core ADHD symptoms in children with ASD may not necessarily be the most sensitive outcome measure. Finally, all of the existing ADHD and ASD treatment studies have focused on child variables with very little focus on family level variables (e.g., parenting efficacy, parenting stress, parent mental health, etc.) as either independent or dependent variables.

In addition to treatment research goals, assessment strategies also need to be further refined. Assessment instruments are not validated generally, but rather, are validated for use within a specific population. A fruitful future research avenue in this population is to study the diagnostic efficiency of ADHD diagnostic criteria in ASD. Knowing the base rates of ADHD symptoms in the ASD population appears a critical first step toward further validating the negative predictive power and positive predictive power of various assessment instruments. This will permit us to then glean which ADHD symptoms have clear advantages as an inclusion criterion and exclusion criterion and may enhance the predictive and discriminant validity of our ADHD diagnostic instruments. Given diagnostic overshadowing, it is also conceivable that false-negative ADHD diagnoses are common in children with ASD. Future research should consider which diagnostic algorithm may best avoid type I and II errors in the diagnosis of ADHD in individuals with ASD.

Finally, we can expect that the next 5 years will teach us much about the etiologic overlap between ASD and ADHD. Ongoing genetic studies of these disorders should clarify the degree to which they share both common and rare variants. This work will, hopefully, uncover new biological pathways underlying these disorders, which could lead to new and more effective treatments.

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Key issues

- In the DSM-IV-TR, ADHD Criterion E prohibits clinicians from making an ADHD diagnosis in the context of autism spectrum disorder (ASD). In the DSM-5, this exclusionary criterion has been removed and clinicians are now able to make an ADHD diagnosis in the context of ASD.
- A majority of children with ASD (31–95%) have significant symptoms of inattention and/or hyperactivity/impulsivity, not all children with ASD have these symptoms.
- ADHD-Inattentive type is somewhat more common in ASD than ADHD-Combined type.
- ASD and ADHD are both associated with impaired social interaction, yet data suggest that the social interaction impairments are more significant in ASD.
- Genetic linkage studies suggested regions of chromosomes 16p13, 2q24, 16p1, 17p11, 5p13 and 15q to be involved in both ADHD and ASD.
- Genes in dopaminergic, serotoninergic, glutamatergic and and GABAergic systems have been implicated in both disorders.
- ADHD and ASD are thought to be associated with (or defined by) executive dysfunction although the specific executive domains that are negatively impacted may differ. Children with ASD have more planning and cognitive flexibility difficulties and children with ADHD have more inhibition difficulties.
- Atomoxetine and methylphenidate both show evidence for treating ADHD symptoms within individuals with ASD. However, effect sizes from the ASD population are somewhat smaller than the non-ASD population and side effects are more common in the ASD population.

References

1 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR(4th Edition)*. American Psychiatric Association, Washington, DC (2000).

2 Barbaresi WJ, Katusic SK, Colligan RC *et al*. How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. *Arch. Pediatr. Adolesc. Med*. 156(3), 217–224 (2002).

3 Antshel KM, Barkley R. Developmental and behavioral disorders grown up: attention deficit hyperactivity disorder. *J. Dev. Behav. Pediatr*. 30(1), 81–90 (2009).

4 Kessler RC, Adler L, Barkley R *et al*. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am. J. Psychiatry* 163(4), 716–723 (2006).

5 American Psychiatric Association. In: *Diagnostic and Statistical Manual of Mental Disorders (5th Edition)*. American Psychiatric Publishing, Washington, DC (2013).

6 Mta Collaborative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Arch. Gen. Psychiatry* 56(12), 1073–1086 (1999).

7 Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 46(7), 894–921 (2007).

8 Van Lier PA, Van Der Ende J, Koot HM, Verhulst FC. Which better predicts conduct problems? The relationship of trajectories of conduct problems with ODD and ADHD symptoms from childhood into adolescence. *J. Child Psychol. Psychiatry, and allied disciplines* 48(6), 601–608 (2007).

9 Biederman J, Ball SW, Monuteaux MC *et al*. New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *J. Am. Acad. Child Adolesc. Psychiatry* 47(4), 426–434 (2008).

10 Carlson CL, Tamm L, Gaub M. Gender differences in children with ADHD, ODD, and co-occurring ADHD/ODD identified in a school population. *J. Am. Acad. Child Adolesc. Psychiatry* 36(12), 1706–1714 (1997).

11 Blanchard LT, Gurka MJ, Blackman JA. Emotional, developmental, and behavioral health of American children and their families: a report from the 2003 National Survey of Children's Health. *Pediatrics* 117(6), e1202–e1212 (2006).

12 Dupaul G, Stoner G. *ADHD In The Schools: Assessment And Intervention Strategies*. Guilford Press, NY, USA (2003).

13 Goldstein S, Schwebach AJ. The comorbidity of pervasive developmental disorder and attention deficit hyperactivity disorder: results of a retrospective chart review. *J. Autism Dev. Disord*. 34(3), 329–339 (2004).

14 Sturm H, Fernell E, Gillberg C. Autism spectrum disorders in children with normal intellectual levels: associated impairments and subgroups. *Dev Med. Child Neurol.* 46(7), 444–447 (2004).

15 Yoshida Y, Uchiyama T. The clinical necessity for assessing Attention Deficit/Hyperactivity Disorder (AD/HD) symptoms in children with high-functioning Pervasive Developmental Disorder (PDD). *Eur Child Adolesc. Psychiatry* 13(5), 307–314 (2004).

16 Ehlers S, Gillberg C. The epidemiology of Asperger syndrome. A total population study. *J. Child Psychol. Psychiatry* 34(8), 1327–1350 (1993).

17 Yoshida Y, Uchiyama T. The clinical necessity for assessing attention deficit/hyperactivity disorder (AD/HD) symptoms in children with high-functioning pervasive developmental disorder (PDD). *Eur Child Adolesc. Psychiatry* 13(5), 307–314 (2004).

18 Leyfer OT, Folstein SE, Bacalman S *et al*. Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. *J. Autism Dev. Disord*. 36(7), 849–861 (2006).

19 Keen D, Ward S. Autistic spectrum disorder. *Autism* 8(1), 39–48 (2004).

20 Sturm H, Fernell E, Gillberg C. Autism spectrum disorders in children with normal intellectual levels: Associated impairments and subgroups. *Dev. Med.Child Neurol*. 46(7), 444–447 (2004).

21 Goldstein S, Schwebach AJ. The comorbidity of pervasive developmental disorder and attention deficit hyperactivity disorder: Results of a retrospective chart review. *J. Autism Dev. Disord*. 34(3), 329–339 (2004).

22 Frazier JA, Biederman J, Bellordre CA *et al*. Should the diagnosis of attention-deficit/hyperactivity disorder be considered in children with pervasive developmental disorder? *J. Attention Disord*. 4(4), 203–211 (2001).

23 Ghaziuddin M, Tsai LY, Alessi N. ADHD and PDD. *J. Am. Acad. Child Adolesc. Psychiatry* 31(3) 567 (1992).

24 Sinzig J, Walter D, Doepfner M. Attention deficit/hyperactivity disorder in children and adolescents with autism spectrum disorder: symptom or syndrome? *J. Atten. Disord*. 13(2), 117–126 (2009).

25 Gjevik E, Eldevik S, Fjaeran-Granum T, Sponheim E. Kiddie-SADS reveals high rates of DSM-IV disorders in children and adolescents with autism spectrum disorders. *J. Autism Dev. Disord*. 41(6), 761–769 (2011).

26 Dupaul GJ, Ervin RA, Hook CL, Mcgoey KE. Peer tutoring for children with attention deficit hyperactivity disorder: Effects on classroom behavior and academic performance. *J. Appl. Behav. Anal*. 31(4), 579–592 (1998).

27 Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: Impact of remission definition and symptom type. *Am. J. Psychiatry* 157(5), 816–818 (2000).

28 Sinzig J, Walter D, Doepfner M. Attention deficit/hyperactivity disorder in children and adolescents with autism spectrum disorder: Symptom or syndrome? *J. Atten. Disord*. 13(2), 117–126 (2009).

29 Lee DO, Ousley OY. Attention-deficit hyperactivity disorder symptoms in a clinic sample of children and adolescents with pervasive developmental disorders. *J. Child Adolesc. Psychopharmacol*. 16(6), 737–746 (2006).

30 Pearson DA, Aman MG, Arnold LE *et al*. High concordance of parent and teacher attention-deficit/hyperactivity disorder ratings in medicated and unmedicated children with autism spectrum disorders. *J. Child Adolesc. Psychopharmacol*. 22(4), 284–291 (2012).

31 Dupaul G, Power T, Anastopoulos A. *Adhd Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. Guilford Press, New York (1998).

32 Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics* 113(5), e472–e486 (2004).

33 Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. *Biol. Psychiatry* 44(10), 951–958 (1998).

34 Faraone SV, Mick E. Molecular genetics of attention deficit hyperactivity disorder. *Psychiatric Clin. North Am*. 33(1), 159–180 (2010).

35 Mick E, Faraone SV. Genetics of attention deficit hyperactivity disorder. *Child Adolesc.*

Psychiatr. Clin. North Am. 17(2), 261–284, vii–viii (2008).

36 Faraone SV, Perlis RH, Doyle AE *et al.* Molecular genetics of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 57(11), 1313–1323 (2005).

37 Bailey A, Le Couteur A, Gottesman I *et al.* Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol. Med.* 25(1), 63–77. (1995).

38 Smalley SL, Kustanovich V, Minassian SL *et al.* Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *Am. J. Hum. Gene.* 71(4), 959–963 (2002).

39 Bakker SC, Van Der Meulen EM, Buitelaar JK *et al.* A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *Am. J. Hum. Genet.* 72(5), 1251–1260 (2003).

40 Fisher SE, Francks C, Mccracken JT *et al.* A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *Am. J. Hum. Gene.* 70(5), 1183–1196 (2002).

41 Ogdie MN, Macphie IL, Minassian SL *et al.* A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: suggestive linkage on 17p11. *Am. J. Hum. Genet.* 72(5), 1268–1279 (2003).

42 Nijmeijer JS, Arias-Vasquez A, Rommelse NN *et al.* Identifying loci for the overlap between attention-deficit/hyperactivity disorder and autism spectrum disorder using a genome-wide QTL linkage approach. *J. Am. Acad. Child Adolesc. Psychiatry* 49(7), 675–685 (2010).

43 Rommelse NN, Franke B, Geurts HM, Hartman CA, Buitelaar JK. Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Eur. Child Adolesc. Psychiatry* 19(3), 281–295 (2010).

44 Vorstman JA, Ophoff RA. Genetic causes of developmental disorders. *Curr. Opin. Neurol.* 26(2), 128–136 (2013).

45 Farzin F, Perry H, Hessl D *et al.* Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *J. Dev. Behav. Pediatr.* 27(2 Suppl. 2), S137–S144 (2006).

46 Niklasson L, Rasmussen P, Oskarsdottir S, Gillberg C. Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. *Res. dev. Disabil.* 30(4), 763–773 (2009).

47 Miller DT, Shen Y, Weiss LA *et al.* Microdeletion/duplication at 15q13.2q13.3 among individuals with features of autism and other neuropsychiatric disorders. *J. Med. Genet.* 46(4), 242–248 (2009).

48 Williams NM, Franke B, Mick E *et al.* Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3. *Am. J. Psychiatry* 169(2), 195–204 (2012).

49 Sebat J, Lakshmi B, Malhotra D *et al.* Strong association of de novo copy number mutations with autism. *Science* 316(5823), 445–449 (2007).

50 Williams NM, Zaharieva I, Martin A *et al.* Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *Lancet* 376(9750), 1401–1408 (2010).

51 Gadow KD, Nolan EE, Sverd J, Sprafkin J, Schneider J. Methylphenidate in children with oppositional defiant disorder and both comorbid chronic multiple tic disorder and ADHD. *J. Child Neurol.* 23(9), 981–990 (2008).

52 Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. *Hum. Genet.* 126(1), 51–90 (2009).

53 Sinzig J, Lehmkuhl G. What do we know about the serotonergic genetic heterogeneity in attention-deficit/hyperactivity and autistic disorders? *Psychopathology* 40(5), 329–337 (2007).

54 Smoller JW, Craddock N, Kendler K *et al.* Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* 381(9875), 1371–1379 (2013).

55 Nieoullon A. Dopamine and the regulation of cognition and attention. *Prog. Neurobiol.* 67(1), 53–83 (2002).

56 Yang Y, Pan C. Role of metabotropic glutamate receptor 7 in autism spectrum disorders: a pilot study. *Life Sci.* 92(2), 149–153 (2013).

57 Elia J, Glessner JT, Wang K *et al.* Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. *Nat. Genet.* 44(1), 78–84 (2011).

58 Wang GX, Ma YH, Wang SF, Ren GF, Guo H. Association of dopaminergic/GABAergic genes with attention deficit hyperactivity disorder in children. *Mol. Med. Rep.* 6(5), 1093–1098 (2012).

59 Piton A, Jouan L, Rochefort D *et al.* Analysis of the effects of rare variants on splicing identifies alterations in GABA(A) receptor genes in autism spectrum disorder individuals. *Eur. J. Hum. genet.* (2012).

60 Marshall CR, Noor A, Vincent JB *et al.* Structural variation of chromosomes in autism spectrum disorder. *Am. J. Hum. Genet.* 82(2), 477–488 (2008).

61 Glessner JT, Wang K, Cai G *et al.* Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature* 459(7246), 569–573 (2009).

62 Lesch KP, Timmesfeld N, Renner TJ *et al.* Molecular genetics of adult ADHD: converging evidence from genome-wide association and extended pedigree linkage studies. *J. Neural Trans.* 115, 1573–1585 (2008).

63 Banaschewski T, Becker K, Scherag S, Franke B, Coghill D. Molecular genetics of attention-deficit/hyperactivity disorder: an overview. *Eur. Child Adolesc. Psychiatry* 19(3), 237–257 (2010).

64 Conner AC, Kissling C, Hodges E *et al.* Neurotrophic factor-related gene polymorphisms and adult attention deficit hyperactivity disorder (ADHD) score in a high-risk male population. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 147B(8), 1476–1480 (2008).

65 Shinawi M, Sahoo T, Maranda B *et al.* 11p14.1 microdeletions associated with ADHD, autism, developmental delay, and obesity. *Am. J. Med. Genet. A.* 155A(6), 1272–1280 (2011).

66 Konrad K, Eickhoff SB. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Hum. Brain Mapp.* 31(6), 904–916 (2010).

67 Plessen KJ, Bansal R, Zhu H *et al.* Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry* 63(7), 795–807 (2006).

68 Ecker C, Suckling J, Deoni SC *et al.* Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. *Arch. Gen. Psychiatry* 69(2), 195–209 (2012).

69 Jou RJ, Jackowski AP, Papademetris X, Rajeevan N, Staib LH, Volkmar FR. Diffusion tensor imaging in autism spectrum disorders: preliminary evidence of abnormal neural connectivity. *Aust. NZ J. Psychiatry* 45(2), 153–162 (2011).

70 Clegg J, Gillott A, Jones J. Conceptual issues in neurodevelopmental disorders: lives out of synch. *Curr. opin. Psychiatry* 26(3), 289–294 (2013).

71 Garg S, Lehtonen A, Huson SM *et al.* Autism and other psychiatric comorbidity in neurofibromatosis type 1: evidence from a population-based study. *Dev. Med. Child Neurol.* 55(2), 139–145 (2013).

72 Lo-Castro A, D'agati E, Curatolo P. ADHD and genetic syndromes. *Brain Dev.* 33(6), 456–461 (2010).

73 Gutierrez GC, Smalley SL, Tanguay PE. Autism in tuberous sclerosis complex. *J. Autism. Dev. Disord.* 28(2), 97–103 (1998).

74 Kehrer-Sawatzki H, Vogt J, Mussotter T, Kluwe L, Cooper DN, Mautner VF. Dissecting the clinical phenotype associated with mosaic type-2 NF1 microdeletions. *Neurogenetics* 13(3), 229–236 (2012).

75 Buxbaum JD, Cai G, Chaste P *et al.* Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 144B(4), 484–491 (2007).

76 Mcbride KL, Varga EA, Pastore MT *et al.* Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. *Autism Res.* 3(3), 137–141 (2010).

77 Neves-Pereira M, Muller B, Massie D *et al.* Deregulation of EIF4E: a novel mechanism for autism. *J. Med. Genet.* 46(11), 759–765 (2009).

78 Lai ZW, Hanczko R, Bonilla E *et al. N*-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 64(9), 2937–2946 (2012).

79 Garcia RJ, Francis L, Dawood M, Lai ZW, Faraone SV, Perl A. Brief report: attention deficit and hyperactivity disorder scores are elevated and respond to *N*-acetylcysteine treatment in patients with systemic lupus erythematosus. *Arthritis Rheum.* 65(5), 1313–1318 (2013).

80 Bradstreet JJ, Smith S, Baral M, Rossignol DA. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. *Altern. Med. Rev.* 15(1), 15–32 (2010).

81 Marazziti D, Baroni S, Picchetti M *et al.* Psychiatric disorders and mitochondrial dysfunctions. *Eur. Rev. Med. Pharmacol. Sci.* 16(2), 270–275 (2012).

82 Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology* 13(4), 417–423 (2002).

83 Langley K, Rice F, Van Den Bree MB, Thapar A. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. *Minerva. Pediatr.* 57(6), 359–371 (2005).

84 Winneke G. Developmental aspects of environmental neurotoxicology: lessons from lead and polychlorinated biphenyls. *J. Neurol. Sci.* 308(1–2), 9–15 (2011).

85 Williams JH, Ross L. Consequences of prenatal toxin exposure for mental health in children and adolescents: a systematic review. *Eur. Child Adolesc. Psychiatry* 16(4), 243–253 (2007).

86 Zhang X, Lv CC, Tian J *et al.* Prenatal and perinatal risk factors for autism in China. *J. Autism Dev. Disord.* 40(11), 1311–1321 (2010).

87 Messer A. Mini-review: polybrominated diphenyl ether (PBDE) flame retardants as potential autism risk factors. *Physiol. Behav.* 100(3), 245–249 (2010).

88 Gascon M, Vrijheid M, Martinez D *et al.* Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. *Environ. Int.* 37(3), 605–611 (2011).

89 Roman GC. Autism: transient in utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *J. Neurol. Sci.* 262(1–2), 15–26 (2007).

90 Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. *J. Neuroendocrinol.* 20(6), 784–794 (2008).

91 Lima FR, Trentin AG, Rosenthal D, Chagas C, Moura Neto V. Thyroid hormone induces protein secretion and morphological changes in astroglial cells with an increase in expression of glial fibrillary acidic protein. *J. Endocrinol.* 154(1), 167–175 (1997).

92 Oppenheimer JH, Schwartz HL. Molecular basis of thyroid hormone-dependent brain development. *Endocr. Rev.* 18(4), 462–475 (1997).

93 Weiss RE, Stein MA, Trommer B, Refetoff S. Attention-deficit hyperactivity disorder and thyroid function. *J. Pediatr.* 123(4), 539–545 (1993).

94 De Cock M, Maas YG, Van De Bor M. Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. *Acta Paediatr.* 101(8), 811–818 (2012).

95 Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. *Pediatrics* 121(6), 1155–1164 (2008).

96 Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV. Impact of low birth weight on attention-deficit hyperactivity disorder. *J. Dev. Behav. Pediatr.* 23(1), 16–22 (2002).

97 Botting N, Powls A, Cooke RW, Marlow N. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *J. Child Psychol. Psychiatry* 38(8), 931–941 (1997).

98 Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. *J. Pediatr.* 156(4), 525–531 e522 (2010).

99 Indredavik MS. Extremely preterm children at increased risk of autism spectrum disorders. *Evid. Based Ment. Health* 13, 92 (2010).

100 Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 288(6), 728–737 (2002).

101 Sullivan EL, Nousen L, Chamlou K. Maternal high fat diet consumption during the perinatal period programs offspring behavior. *Physiol. Behav.* doi:10.1016/j.physbeh.2012.07.014 (2012) (Epub ahead of print).

102 Ronald A, Pennell CE, Whitehouse AJ. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. *Front. Psychol.* 1, 223 (2010).

103 Dasbanerjee T, Middleton FA, Berger DF, Lombardo JP, Sagvolden T, Faraone SV. A comparison of molecular alterations in environmental and genetic rat models of ADHD: A pilot study. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 147B(8), 1554–1563 (2008).

104 Carney RM, Wolpert CM, Ravan SA *et al.* Identification of MeCP2 mutations in a series of females with autistic disorder. *Pediatr. Neurol.* 28(3), 205–211 (2003).

105 Amir RE, Van Den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat. Genet.* 23(2), 185–188 (1999).

106 Latham KE, Sapienza C, Engel N. The epigenetic lorax: gene-environment interactions in human health. *Epigenomics* 4(4), 383–402 (2012).

107 Keverne EB. Significance of epigenetics for understanding brain development, brain evolution and behaviour. *Neuroscience* doi:10.1016/j.neuroscience.2012.11.030 (2012) (Epub ahead of print).

108 Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol. Psychiatry* 65(9), 760–769 (2009).

109 Gadow KD, Roohi J, Devincent CJ, Kirsch S, Hatchwell E. Association of COMT (Val158Met) and BDNF (Val66Met) gene polymorphisms with anxiety, ADHD and tics in children with autism spectrum disorder. *J. Autism Dev. Disord*. 39(11), 1542–1551 (2009).

110 Nigg JT. Future Directions in ADHD Etiology Research. *J. Clin. Child Adolesc*. 41(2), 524–533 (2012).

111 Shaw P, Eckstrand K, Sharp W *et al*. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc. Natl Acad. Sci.USA* 104(49), 19649–19654 (2007).

112 Hazlett HC, Poe MD, Gerig G *et al*. Early brain overgrowth in autism associated with an increase in cortical surface area before age 2 years. *Arch. Gen. Psychiatry* 68(5), 467–476 (2011).

113 Hardan AY, Libove RA, Keshavan MS, Melhem NM, Minshew NJ. A preliminary longitudinal magnetic resonance imaging study of brain volume and cortical thickness in autism. *Biol. Psychiatry* 66(4), 320–326 (2009).

114 Nigg JT, Blaskey LG, Huang-Pollock CL, Rappley MD. Neuropsychological executive functions and DSM-IV ADHD subtypes. *J. Am. Acad. Child Adolesc. Psychiatry* 41(1), 59–66 (2002).

115 Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol. Bull* 121(1), 65–94 (1997).

116 Russell J. *Autism as an executive disorder*. Oxford University Press, New York (1997).

117 Ozonoff S, Jensen J. Brief report: specific executive function profiles in three neurodevelopmental disorders. *J. Autism Dev. Disord*. 29(2), 171–177 (1999).

118 Hill EL. Executive dysfunction in autism. *Trends Cogn. Sci*. 8(1), 26–32 (2004).

119 Nyden A, Gillberg C, Hjelmquist E, Heimann M. Executive function/attention deficits in boys with Asperger syndrome, attention disorder and reading/writing disorder. *Autism* 3, 213–228 (1999).

120 Geurts HM, Verte S, Oosterlaan J, Roeyers H, Sergeant JA. How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *J. Child Psychol. Psychiatry* 45(4), 836–854 (2004).

121 Johnson KA, Robertson IH, Kelly SP *et al*. Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. *Neuropsychologia* 45(10), 2234–2245 (2007).

122 Happe F, Booth R, Charlton R, Hughes C. Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. *Brain Cogn*. 61(1), 25–39 (2006).

123 Sinzig J, Morsch D, Bruning N, Schmidt MH, Lehmkuhl G. Inhibition, flexibility, working memory and planning in autism spectrum disorders with and without comorbid ADHD-symptoms. *Child Adolesc. Psychiatry Ment. Health* 2(1), 4 (2008).

124 Anholt GE, Cath DC, Van Oppen P *et al*. Autism and ADHD symptoms in patients with OCD: are they associated with specific OC symptom dimensions or OC symptom severity? *J. Autism Dev. Disord*. 40(5), 580–589 (2010).

125 Nyden A, Niklasson L, Stahlberg O *et al*. Adults with autism spectrum disorders and ADHD neuropsychological aspects. *Res. Dev. Disabilities* 31(6), 1659–1668 (2010).

126 Buitelaar JK, Van Der Wees M, Swaab-Barneveld H, Van Der Gaag RJ. Theory of mind and emotion-recognition functioning in autistic spectrum disorders and in psychiatric control and normal children. *Dev. Psychopathol*. 11(1), 39–58 (1999).

127 Brune M, Brune-Cohrs U. Theory of mind–evolution, ontogeny, brain mechanisms and psychopathology. *Neurosci. Biobehav. Rev*. 30(4), 437–455 (2006).

128 Clark T, Feehan C, Tinline C, Vostanis P. Autistic symptoms in children with attention deficit-hyperactivity disorder. *Eur Child Adolesc. Psychiatry* 8(1), 50–55 (1999).

129 Santosh PJ, Baird G, Pityaratstian N, Tavare E, Gringras P. Impact of comorbid autism spectrum disorders on stimulant response in children with attention deficit hyperactivity disorder: a retrospective and prospective effectiveness study. *Child Care Health Dev*. 32(5), 575–583 (2006).

130 Gillberg CL. The Emanuel Miller Memorial Lecture 1991. Autism and autistic-like conditions: subclasses among disorders of empathy. *J. Child Psychol. Psychiatry* 33(5), 813–842 (1992).

131 Dyck MJ, Ferguson K, Shochet IM. Do autism spectrum disorders differ from each other and from non-spectrum disorders on emotion recognition tests? *Eur Child Adolesc. Psychiatry* 10(2), 105–116 (2001).

132 Demurie E, Roeyers H, Baeyens D, Sonuga-Barke E. Common alterations in sensitivity to type but not amount of reward in ADHD and autism spectrum disorders. *J. Child Psychol. Psychiatry* 52(11), 1164–1173 (2011).

133 Buhler E, Bachmann C, Goyert H, Heinzel-Gutenbrunner M, Kamp-Becker I. Differential diagnosis of autism spectrum disorder and attention deficit hyperactivity disorder by means of inhibitory control and 'theory of mind'. *J. Autism Dev. Disord*. 41(12), 1718–1726 (2011).

134 Jensen VK, Larrieu JA, Mack KK. Differential diagnosis between attention-deficit/hyperactivity disorder and pervasive developmental disorder–not otherwise specified. *Clinical pediatrics* 36(10), 555–561 (1997).

135 Luteijn EF, Serra M, Jackson S *et al*. How unspecified are disorders of children with a pervasive developmental disorder not otherwise specified? A study of social problems in children with PDD-NOS and ADHD. *Eur Child Adolesc. Psychiatry* 9(3), 168–179 (2000).

136 Hattori J, Ogino T, Abiru K, Nakano K, Oka M, Ohtsuka Y. Are pervasive developmental disorders and attention-deficit/hyperactivity disorder distinct disorders? *Brain Dev*. 28(6), 371–374 (2006).

137 Antshel KM, Remer R. Social skills training in children with attention deficit hyperactivity disorder: a randomized-controlled clinical trial. *J. Clin. Child Adolesc. Psychol. 53* 32(1), 152–165 (2003).

138 Mulligan A, Anney RJ, O'regan M *et al*. Autism symptoms in attention-deficit/hyperactivity disorder: a familial trait which correlates with conduct, oppositional defiant, language and motor disorders. *J. Autism Dev. Disord*. 39(2), 197–209 (2009).

139 Reiersen AM, Constantino JN, Volk HE, Todd RD. Autistic traits in a population-based ADHD twin sample. *J. Child Psychol. Psychiatry* 48(5), 464–472 (2007).

140 Bishop DV, Baird G. Parent and teacher report of pragmatic aspects of communication: use of the children's communication checklist in a clinical setting. *Dev. Med. Child Neurol*. 43(12), 809–818 (2001).

141 Geurts HM, Luman M, Van Meel CS. What's in a game: the effect of social

motivation on interference control in boys with ADHD and autism spectrum disorders. *J. Child Psychol. Psychiatry* 49(8), 848–857 (2008).

142 Ames CS, White SJ. Are ADHD traits dissociable from the autistic profile? Links between cognition and behaviour. *J. Autism Dev. Disord.* 41(3), 357–363 (2011).

143 Grzadzinski R, Di Martino A, Brady E *et al.* Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? *J. Autism Dev. Disord.* 41(9), 1178–1191 (2011).

144 Mayes SD, Calhoun SL, Mayes RD, Molitoris S. Autism and ADHD: overlapping and discriminating symptoms. *Res. Autism Spectrum Disord.* 6(1), 277–285 (2012).

145 Anckarsater H, Stahlberg O, Larson T *et al.* The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *Am. J. Psychiatry* 163(7), 1239–1244 (2006).

146 van der Meer JM, Oerlemans AM, Van Steijn DJ *et al.* Are autism spectrum disorder and attention-deficit/hyperactivity disorder different manifestations of one overarching disorder? Cognitive and symptom evidence from a clinical and population-based sample. *J. Am. Acad. Child Adolesc. Psychiatry* 51(11), 1160–1172 e1163 (2012).

147 Frazier TW, Shattuck PT, Narendorf SC, Cooper BP, Wagner M, Spitznagel EL. Prevalence and correlates of psychotropic medication use in adolescents with an autism spectrum disorder with and without caregiver-reported attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 21(6), 571–579 (2011).

148 Handen BL, Taylor J, Tumuluru R. Psychopharmacological treatment of ADHD symptoms in children with autism spectrum disorder. *Int. J. Adolesc. Med. Health* 23(3), 167–173 (2011).

149 Mcpheeters ML, Warren Z, Sathe N *et al.* A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics* 127(5), e1312–e1321 (2011).

150 Ghuman JK, Aman MG, Lecavalier L *et al.* Randomized, placebo-controlled, crossover study of methylphenidate for attention-deficit/hyperactivity disorder symptoms in preschoolers with developmental disorders. *J. Child Adolesc. Psychopharmacol.* 19(4), 329–339 (2009).

151 Quintana H, Birmaher B, Stedge D *et al.* Use of methylphenidate in the treatment of children with autistic disorder. *J. Autism Dev. Disord.* 25(3), 283–294 (1995).

152 Handen BL, Johnson CR, Lubetsky M. Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J. Autism Dev. Disord.* 30(3), 245–255 (2000).

153 Network RUOPPA. Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch. Gen. Psychiatry* 62(11), 1266–1274 (2005).

154 Birmaher B, Quintana H, Greenhill LL. Methylphenidate treatment of hyperactive autistic children. *J. Am. Acad. Child Adolesc. Psychiatry* 27(2), 248–251 (1988).

155 Strayhorn JM Jr., Rapp N, Donina W, Strain PS. Randomized trial of methylphenidate for an autistic child. *J. Am. Acad. Child Adolesc. Psychiatry* 27(2), 244–247 (1988).

156 Aman MG, Langworthy KS. Pharmacotherapy for hyperactivity in children with autism and other pervasive developmental disorders. *J. Autism Dev. Disord.* 30(5), 451–459 (2000).

157 Di Martino A, Melis G, Cianchetti C, Zuddas A. Methylphenidate for pervasive developmental disorders: safety and efficacy of acute single dose test and ongoing therapy: an open-pilot study. *J. Child Adolesc. Psychopharmacol.* 14(2), 207–218 (2004).

158 Stigler KA, Desmond LA, Posey DJ, Wiegand RE, Mcdougle CJ. A naturalistic retrospective analysis of psychostimulants in pervasive developmental disorders. *J. Child Adolesc. Psychopharmacol.* 14(1), 49–56 (2004).

159 Nickels K, Katusic SK, Colligan RC, Weaver AL, Voigt RG, Barbaresi WJ. Stimulant medication treatment of target behaviors in children with autism: a population-based study. *J. Dev. Behav. Pediatr.* 29(2), 75–81 (2008).

160 Zeiner P, Gjevik E, Weidle B. Response to atomoxetine in boys with high-functioning autism spectrum disorders and attention deficit/hyperactivity disorder. *Acta Paediatr.* 100(9), 1258–1261 (2011).

161 Harfterkamp M, Van De Loo-Neus G, Minderaa RB *et al.* A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 51(7), 733–741 (2012).

162 Golubchik P, Sever J, Weizman A. Reboxetine treatment for autistic spectrum disorder of pediatric patients with depressive and inattentive/hyperactive symptoms: an open-label trial. *Clin. Neuropharmacol.* 36(2), 37–41 (2013).

163 Handen BL, Sahl R, Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. *J. Dev. Behav. Pediatr.* 29(4), 303–308 (2008).

164 Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. *Brain Dev.* 30(7), 454–460 (2008).

165 Maher AR, Theodore G. Summary of the comparative effectiveness review on off-label use of atypical antipsychotics. *J. Manag. Care Pharm.* 18(5 Suppl. B), S1–S20 (2012).

166 Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst. Rev.* 9, CD008559 (2012).

167 Matone M, Localio R, Huang YS, Dosreis S, Feudtner C, Rubin D. The relationship between mental health diagnosis and treatment with second-generation antipsychotics over time: a national study of U.S. Medicaid-enrolled children. *Health Services Res.* 47(5), 1836–1860 (2012).

168 Antshel KM, Polacek C, Mcmahon M *et al.* Comorbid ADHD and anxiety affect social skills group intervention treatment efficacy in children with autism spectrum disorders. *J. Dev. Behav. Pediatr.* 32(6), 439–446 (2011).

169 Frazier TW, Shattuck PT, Narendorf SC, Cooper BP, Wagner M, Spitznagel EL. Prevalence and correlates of psychotropic medication use in adolescents with an autism spectrum disorder with and without caregiver-reported attention-deficit/hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* 21(6), 571–579

170 Jopp DA, Keys CB. Diagnostic overshadowing reviewed and reconsidered. *Am. J. Ment. Retard.* 106(5), 416–433 (2001).

171 Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am. J. Psychiatry* 148(5), 564–577 (1991).

172 Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am. J. Psychiatry* 126(7), 983–987 (1970).