Attention-Deficit/Hyperactivity Disorder (ADHD) in Preschool-Aged Children:

A Critical Review

Will Anastasiadis

Indiana State University
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Attention-Deficit/Hyperactivity Disorder (ADHD) in Preschool-Aged Children:

A Critical Review

I. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by core symptoms of hyperactivity, impulsivity, and inattention (American Psychiatric Association, 2013). ADHD is a fairly common psychopathology diagnosed in childhood (Kooij et al., 2010; Perou et al., 2013). For instance, a recent study conducted by the Centers for Disease Control and Prevention (CDC) found that approximately 6.1 million (9.4%) U.S. children and adolescents between the ages of 2 and 17 have received an ADHD diagnosis; these prevalence estimates were acquired from a collection of 2016 parent-reported ADHD diagnoses (Danielson et al., 2018). Of those patients diagnosed with ADHD, a weighted estimate of 2.4% (388,000) were between the ages of 2 and 5 (i.e., toddlers and preschool-aged children). Although ADHD was found to be proportionally greater in older school-aged children, there is ongoing controversy surrounding the contemporary diagnosis and treatment of ADHD in preschool-aged children (e.g., Harpin, 2005; Layton, Barnett, Hicks, & Jena, 2018), generating various economic, mental and public health concerns (Zhao et al., 2019).

Misdiagnosis and undertreatment of ADHD are serious burdens for young children at risk, as lack of preventive treatment may ensue long-lasting effects (Harpin, 2005; Upshur, Wenz-Gross, & Reed 2009). Regrettably, prior research also suggests that differentiating ADHD from normative behavior in preschool-aged children is challenging for clinicians (Ford-Jones, 2015). Thus, the purpose of this review is to provide a comprehensive overview of recent research regarding ADHD, with a particular emphasis on the etiology and treatment of preschool-aged
children. In writing this review, the author hopes to provide practitioners and clinical scientists clarity in this fairly contentious area in the ADHD literature.

II. Overview of ADHD

Even though ADHD is categorized as a pervasive neurodevelopmental psychopathology in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5, it is commonly grouped in the literature within a larger subset of externalizing-spectrum disorders with complementary symptom presentations, such as: oppositional defiant disorder (ODD), and conduct disorder (CD; American Psychiatric Association, 2013; Cosgrove et al., 2011; Ralf, Paul, Brian, & Henrik, 2015). ADHD comprises predominant symptoms of hyperactivity, impulsivity, and inattention that impair functioning in two different settings (e.g., academic/work, home), and have a fairly clear symptom onset before age 12 (see Appendix A; American Psychiatric Association, 2013). Our understanding of ADHD nosology shifts with recent hypotheses concerning psychopathological categorization in the DSM-5, resulting in postulated modifications to the traditional categorical approach. For instance, a body of literature utilizing network analyses that measure associations between various disorders has ensued in the recent years, an approach that attempts to represent the relationship between psychopathology via graphical nodes of symptoms (e.g., McElroy, Shevlin, Murphy, & McBride, 2018; Silk et al., 2019).

Because ADHD shares symptoms with other externalizing disorders throughout development (especially ODD; Bendiksen et al., 2017; Kessler et al., 2005; McElroy et al., 2018), there are strong associations between externalizing symptoms (Cosgrove et al., 2011; McElroy et al., 2018), increasing the propensity for lifetime co-occurrence (Ralf et al., 2015). Recent network analyses have also suggested that throughout childhood, ADHD may be slightly associated with the internalizing symptoms related to generalized anxiety disorder; although
strong, internalizing networks are generally less interrelated than the connections found between externalizing symptoms (McElroy et al., 2018). Taken together, data suggests that externalizing symptoms have dynamic interactions amid one another, hypothetically linked by a general deficit in impulse control (i.e., behavioral disinhibition; Cosgrove et al., 2011; Young et al., 2000).

As implied above, the diagnostic criteria of psychiatric disorders in the DSM are regularly revised as new research indicates the need for change. The relatively recent 2013 revision from the DSM-IV to the DSM-5 is no different. ADHD has a long history, shifting from a somewhat enigmatic cluster of disruptive childhood symptoms in the pre- and early-20th century (e.g., Bradley, 1937), to formally acknowledged psychiatric variations, such as: (1) a hyperkinetic reaction of childhood (DSM-II), (2) attention deficit disorder with and without hyperactivity (DSM-III), and finally (3) our contemporary understanding of ADHD (DSM-IV/5) with varying symptom presentations (e.g., predominately inattentive or hyperactive-impulsive, and combined; American Psychiatric Association, 2013; Epstein & Loren, 2013; Lange, Reichl, Lange, Tucha, & Tucha, 2010).

Even though ADHD has had a long history of revisions in prior DSM versions, the most recent shift from the DSM-IV to the DSM-5 was comparatively simple. For example, in the DSM-IV, children, adolescents, and adults all had to meet at least six symptoms for both hyperactive/impulsive and inattentive diagnostic categories (American Psychiatric Association, 2013; Epstein & Loren, 2013). The DSM-5, however, now requires a lower symptom threshold of five in older adolescents (aged 17 and up) and adults (see Appendix A, Criteria A), as research suggests that ADHD symptom presentation may decrease across development (van Lieshout et al., 2016). Additionally, the DSM-5: (1) allows a concurrent diagnosis of Autism Spectrum Disorder, which was exclusionary in the DSM-IV (see Appendix A, Criteria E), (2) increased the
required symptom age of onset to 12, instead of 7, years old (see Appendix A, Criteria B), (3) requires ADHD symptoms to cause functional impairment in more than one setting (see Appendix A, Criteria C), and (4) encourages the use of specifiers and severity modifiers (American Psychiatric Association, 2013; Epstein & Loren, 2013). In the grand scheme of things, the above changes are relatively minute, despite the relative importance and enhanced specificity.

Currently, ADHD is the most prevalent psychiatric disorder diagnosed internationally in childhood (Kooij et al., 2010; Perou et al., 2013), estimated to persist into adulthood in an estimated 50-86.5% of impacted patients (Lara et al., 2009; van Lieshout et al., 2016). Nearly two decades ago, Faraone, Sergeant, Gillberg, and Biederman (2003) conducted an impressive meta-analysis that found a global prevalence of 5% in the pediatric population. Now, recent epidemiological reports show a transnational diagnostic prevalence ratio of roughly 1:10 in childhood (Danielson et al., 2018; Liu, Xu, Yan, Tong, 2018a; Visser et al., 2014), with approximately one-fourth (23%) of diagnosed pediatric patients in the U.S. left untreated in 2016 (Danielson et al., 2018).

Despite this gradual increase in prevalence across time, recent multivariate meta-regression analyses propose that the global diagnosis of ADHD hasn’t necessarily increased; instead, variability may be attributed to methodological and diagnostic heterogeneity in studies assessing disease epidemiology (Liu et al., 2018a; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). In addition, international prevalence rates (with the exception of Africa and the Middle East, due to the lack of current data) suggests that epidemiological trends are relatively stable across geographic location and race, and may fluctuate due to diagnostic variation or perceived psychopathological stigmatization present in other cultures (Faraone et al., 2003; Liu et al., 2018a; Polanczyk et al., 2014). Regardless of this heterogeneity shown in epidemiological
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reports, prevalence data generally indicates that an ADHD diagnosis is less common in girls and women (Owens, Zalecki, Gillette, & Hinshaw, 2017; Quinn & Madhoo, 2014). In fact, studies have found that young males are diagnosed with ADHD two to nine times more often than their female counterparts (Nussbaum, 2012). Overall, epidemiological reports indicate significant heterogeneity between study methodologies. International prevalence data remains fairly stable amid a significant global proclivity towards an ADHD diagnosis in males.

Aside from prevalence rates, the family burden of pediatric ADHD is noteworthy. A diagnosis of ADHD costs the average U.S. family approximately $15,000 per child across development, an estimate that is roughly five times greater than raising a neurotypical child (Zhao et al., 2019). To put these findings into perspective, data from Zhao and colleagues (2019) further suggests that the cumulative cost of illness equates to an estimated national expenditure of $124.5 billion when factoring in recent U.S. prevalence rates. Clearly, national and global prevalence rates insinuate that ADHD should be considered a societal priority. Course of illness and other prognostic factors directly influence the economic burden from ADHD.

Research suggests that ADHD symptoms typically onset in the prekindergarten years (Polanczyk, 2018; Riddle et al., 2013), and persist into adolescence and adulthood (Lara et al., 2009). Severity of symptoms generally decrease overtime (van Lieshout et al., 2016), hence one might infer that disease prognosis improves as the patient becomes older. However, data further suggests that ADHD symptoms in childhood may result in various long-term outcomes, such as academic failure, psychiatric comorbidity, emotional and executive dysfunction, interpersonal rejection, and other functional impairments (Posner et al., 2005; Uchida, Spencer, Faraone, & Biederman, 2018). This subsequently implies a poor prognosis if the patient goes untreated. As
expected, successful application of evidence-based interventions improves prognosis (e.g., Hart et al., 2016).

The age of onset and developmental course of ADHD are also influenced by a variety of biopsychosocial factors. For example, a recent study conducted by Layton and colleagues (2018) investigated ADHD diagnosis and month of school enrollment in younger children (i.e., between the ages of 4 and 7). In the U.S., several states mandate definitive age-contingent cutoffs for children enrolling in public school, where children must be at least 5 years of age prior to September 1st before beginning kindergarten. Layton and colleagues postulated whether children who were younger in their grade cohort (i.e., students born in August) were diagnosed with ADHD significantly more than their older peers (i.e., students born the prior September). The study utilized past insurance records to obtain medical information (e.g., ADHD diagnosis), and analyzed a total of 407,846 children. Generally, Layton and colleagues confirmed that younger children are diagnosed with ADHD more than their older peers. Thus, implications of this study are slightly provocative, suggesting that younger children are at a higher likelihood of receiving an ADHD diagnosis due to school enrollment; this may be due, in part, to developmentally appropriate behaviors exhibited by younger children that are perceived as aberrant in the classroom. Despite these significant findings, a substantial limitation was the inability to control the process of ADHD assessment. Therefore, definitive conclusions are still ambiguous. Nonetheless, intriguing research considerations from study results are implied, particularly for younger children (e.g., should younger children be held another year from kindergarten to avoid misdiagnosis?). ADHD in prekindergarten children is an exciting area of recent research interest.
III. ADHD in Preschool-Aged Children

The CDC (2019) defines any child between the age of 3 and 5 years as a preschooler. In just a few years, most prekindergarten children experience a copious amount of developmental milestones in various areas of social-emotional, speech-language, cognitive, and physical functioning (Dosman, Andrews, & Goulden, 2012). Hence, The American Academy of Pediatrics (AAP; 2016) highly recommends that clinicians become acutely cognizant of their patient’s developmental trajectory and milestone progress, as deviations from the norm may elicit certain concerns in pediatric patients. In the case of preschool ADHD, developmental surveillance may encompass the identification of deviations in social-emotional capacity (e.g., self-efficacy, impulse-control, compliance, cooperation, communication with others, etc.), physical and cognitive functioning (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2012; Dosman et al., 2012). While moderate levels of hyperactivity, inattention, and impulsivity may be an indicator of typical preschool behavior, pronounced symptoms may warrant a diagnosis of ADHD.

Recent 2016 prevalence data implies that pediatric ADHD is typically diagnosed in older children (e.g., ~2.4% of preschool-aged children vs. ~9.6% school-aged children), with prevalence gradually increasing with age (Danielson et al., 2018), and plateauing in early adulthood. ADHD symptoms identified in preschool typically persist into later childhood and adolescence at a rate of 60-80% (Lahey, Pelham, Loney, Lee, & Willcutt, 2005; Cherkasova et al., 2012). In addition, previous epidemiological trends further suggest that an estimated 70% of preschool children with ADHD have a comorbid psychiatric disorder (Greenhill et al., 2006), with ODD and CD co-occurring in approximately two-fifths of reported cases (Bendiksen et al., 2017). Generally, externalizing symptoms were found to be the most reported concern for preschool children (Egger & Angold, 2006), which somewhat explains the high comorbidity between ADHD and other
externalizing disorders. Consistent with the general population, preschool boys are diagnosed with ADHD more often than their female peers (Lavigne, LeBailly, Hopkins, Gouze, & Binns, 2009). Collectively, global prevalence data remains relatively stable at approximately ~1.9-3.8% across different geographical regions (e.g., Canals, Morales-Hidalgo, Jané, & Domènech, 2016; Gudmundsson et al., 2013; Wichstrøm et al., 2012); although, further research into transnational epidemiological trends is recommended to bolster validity and generalizability. Taken together, even though recent trends suggest that ADHD is diagnosed less in preschool children (despite research suggesting an early symptom onset; Polanczyk, 2018; Riddle et al., 2013), prevalence data collectively imply that symptom presentation in prekindergartners parallels the general population.

Idealistically, ADHD is identified and treated early-on. Unfortunately, this isn’t the case for most young children (Danielson et al., 2018). Differential diagnosis between ADHD and normative behavior can be especially challenging for clinicians, resulting in misdiagnosis (Ford-Jones, 2015). Left untreated, prekindergarten children may be susceptible to a vast amount of functional impairments throughout their disease course, such as peer rejection, poor school readiness, and future psychiatric comorbidity (Graziano, Ros, Hart, & Slavec, 2018; Greenhill et al., 2006; Webster-Stratton, Reid, & Stoolmiller, 2008). Research into the etiological causes of ADHD can help with early identification, and increase the likelihood of treatment.

IV. ADHD Etiology Research

The DSM-5 categorizes ADHD as a neurodevelopmental disorder (American Psychiatric Association, 2013). As such, previous research has insinuated that ADHD possesses a significant neurobiological etiology, influenced by various environmental factors; although, conclusive causal factors are largely unknown. Nevertheless, recent etiological research has focused on gene-
environment interactions (GxE) that may increase the susceptibility in developing ADHD and interrelated symptoms. Findings in behavioral genetics interact with other contemporary etiological hypotheses concerning brain morphology (Dirlikova et al., 2015; Ghassabian et al., 2013), behavioral disinhibition (Barkley, 1997; Young et al., 2009), executive dysfunction (Skogan et al., 2014), parenting (Moghaddam, Assareh, Heidaripoor, Rad, and Pishjoo 2013; Roskam, 2018), and other biopsychosocial factors (Melegari et al., 2015). Hence, ADHD is subsumed to have a multifactorial etiology, with a robust developmental course (American Psychiatric Association, 2013). To help simplify writing, selected acronyms were left undefined, in which the author directs the reader to reference when necessary (see Appendix B).

Neurogenetics and Neurotransmission

ADHD is fundamentally a heterogeneous neuropsychiatric disorder. Research suggests that ADHD is highly genetic (Demontis et al., 2019; Wallis, Russell, & Muenke, 2008) with an estimated heritability of >75% across development (Rietveld, Hudziak, Bartels, Beijsterveldt, & Boomsma, 2004). In fact, genetic predisposition is currently the strongest contributor to the pathogenesis of ADHD (Nikolas & Burt, 2010). Thus, rapid methodological advances in neurogenetics and developmental neuroscience have greatly enhanced our understanding of the etiological factors involved in ADHD. Candidate genes and significant SNP heritability have been identified in the literature, comprising of various genomic polymorphisms of the following: (1) DAT1 (Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010; Waldman et al., 1998), (2) DRD4 (Martel et al., 2011; Swanson et al., 1998), (3) COMT (Gadow, Roohi, Devincent, Kirsch, & Hatchwell, 2009; Paloyelis et al., 2010), (4) 5-HTTLPR (Baptista et al., 2016; Morgan, Hammen, & Lee, 2016), and (5) SNAP-25 (Brophy, Hawi, Kirley, Fitzgerald, & Gill, 2002; Hawi et al., 2013), to name a few (see Gizer, Ficks, & Waldman, 2009 for a comprehensive meta-analytic...
review). Evidently, previous research indicates that the etiological factors of ADHD symptomology are vastly polygenetic, likely with complex GxE interactions that influence neurotransmission. The well-known neurodevelopmental course of ADHD has catalyzed a demand for neurogenetic etiological research in specific ages, such as preschoolers (Baptista et al., 2016).

Researching the early genetic indicators of ADHD helps improve prognosis for patients. For example, Baptista and colleagues (2016) observed that ADHD symptoms in institutionalized preschoolers are mediated by both 5-HTTLPR polymorphism and environmental stress (i.e., intrusive caregiving). A recent body of literature has indicated that short (s) allele variation of the 5-HTTLPR may serve as an environmentally-contingent risk marker for various psychiatric disorders, including ADHD (Gatt, Burton, Williams, & Schofield, 2015). Generally, results from Baptista and colleagues (2016) suggest more support for the more recent differential-susceptibility hypothesis of psychopathology (i.e., a model that includes the impact of both positive and negative environmental factors on pathogenesis), and less evidence for the more traditional diathesis-stress model (i.e., a framework that exaggerates the influence of negative, and neutralizes positive, environmental factors) in explaining the early etiological factors of ADHD for individuals at a biological risk. In other words, specific protective factors may play a unique resiliency role against the onset of ADHD in preschoolers, despite the significant biological risk factors and relatively early onset. Additionally, despite prior research stating that the etiology of ADHD has little environmental influence (American Psychiatric Association, 2013), data suggest that supportive environmental conditions could be advantageous to young children with a genotypic susceptibility to the disorder (Baptista et al., 2016; Morgan, Hammen, & Lee, 2016); although, the importance of environmental factors generally increases with age (Eilertsen et al., 2018).
Even though Baptista and associates’ (2016) study have interesting implications in enhancing the care for young children diagnosed with ADHD, the findings are fairly limited to the impact of one genetic risk locus. Supplemental research from genome-wide association studies (GWAS; a novel methodological approach that scans the human genome to analyze SNPs potentially involved in the development of pathology) have pioneered recent advances in ADHD neurogenetics (e.g., Demontis et al., 2019; Neale et al., 2008; Shadrin et al., 2018). Analysis across the human genome is invaluable, as it helps to consolidate the vast amount of research on individual risk loci for psychiatric pathogenesis.

A recent GWAS meta-analysis published in Nature Genetics by Demontis and colleagues (2019) sought to pinpoint the first genome-wide ADHD risk loci across the lifespan. The study compared genetic variants across 12 study cohorts, including data from the 23andMe Research Team and the Early Lifecourse and Genetic Epidemiology Consortium. Collectively, the combination of cohorts yielded an impressive 55,374 participants worldwide. Genome-wide results indicated potential risk loci for ADHD symptoms in the FOXP2 and DUSP6 genes. Previous research suggests that the DUSP6 gene helps maintain neurotypical levels of DA in the synaptic cleft (Mortensen, Larsen, Prasad, & Amara, 2008), which is consistent with efficacy research on common ADHD pharmacologic interventions discussed later in this review. Additionally, prior research indicates that mutations of the FOXP2 gene influences the phenotypic development of speech and declarative learning (Schreiweis et al., 2014); this is consistent with problems related to the inattentive symptoms typically seen in children and adolescents with ADHD.

Demontis and colleagues (2019) note important intergenomic variants and genetic overlap of ADHD with other psychiatric problems, such as antisocial behaviors, depressive symptoms,
neuroticism, and schizophrenia. Further research on this genetic overlap, as well as the mechanistic role of \textit{FOXP2} and \textit{DUSP6} in ADHD phenotypic expression, is necessary to substantiate these findings. The genetic architecture of ADHD is indeed complex, but these data serve as a promising foundation for future studies in neuropsychology.

\textbf{Functional Neuroanatomy}

In general, the neuroanatomical organization of the externalizing latent symptoms involved in ADHD is comprised of risk loci in the prefrontal cortex (e.g., Dirlikova et al., 2015), corpus collosum (e.g., Hutchinson, Mathias, & Banich, 2008; Luders et al., 2016), basal ganglia (e.g., Curtin et al., 2018; Teicher et al., 2000), and cerebellum (e.g., Diamond, 2000; Lantieri, Glessner, Hakonarson, Elia, & Devoto, 2010), among others (for a review, see Poissant, Emond, & Joyal, 2009). Thus, research suggests that variation of these brain structures may play a causal role in the manifestation of executive functioning and behavioral deficits frequently found in young children and adolescents with ADHD. Fundamentally, identified risk loci in the genetic code, along with neurotransmitter dysregulation, may give rise to the neuroanatomical correlates of ADHD; similar to any complex psychiatric disorder, exacerbation is then mediated by various environmental factors.

In neurodevelopmental disorders, brain localization of pathology alters throughout time. In the specific case of ADHD, this is combined with a relatively early onset (Halperin & Schulz, 2006; Riddle et al., 2013; Tandon, Si, & Luby, 2011). However, various studies assessing neuroanatomical correlates of ADHD have utilized participants that already have a prior diagnosis of ADHD (i.e., typically older children, largely \textit{a posteriori}). To reprimand this causality dilemma, Ghassabian and colleagues (2013) conducted one of the first \textit{a priori} studies on the neuroanatomical correlates of latent ADHD-like symptoms starting in infancy. Generally, the
research team assessed symptoms that may eventually lead to executive dysfunction or a diagnosis of ADHD. Ghassabian and colleagues analyzed cranial ultrasounds of infant participants (averaging seven weeks postnatal) to assess corpus collosum length, gangliothalamic (i.e., a region incorporating the basal ganglia, caudate nucleus, putamen, globus pallidus, and thalamus) ovoid diameter, and cerebral ventricular volume. The neuroanatomical risk loci measured in this study were chosen based off a broad behavioral neuroanatomy review, seen elsewhere (i.e., Clark, Boutros, & Mendez, 2010). The young participants were later assessed at preschool-age for executive functioning deficits and ADHD-like behavior utilizing the Behavioral Rating Inventory of Executive Functioning – Preschool version (BRIEF-P), and the Child Behavior Checklist for toddlers (CBCL) ADHD problem subscale (Ghassabian et al., 2013).

Results indicated a significant correlation between corpus collosum length measured in infancy, and specific BRIEF-P executive functioning subscales (i.e., inhibition and emotional control) measured years later in the same participants. Furthermore, Ghassabian and colleagues (2013) found no significant correlations between CBCL ADHD ratings, which is contradictory to prior studies evidencing this connection (Hutchinson et al., 2008). Although the neuroanatomical correlations are exclusive to deficits in executive functioning, and not in predicting ADHD onset, the study’s methodology in assessing cognitive and behavioral impairments may be of concern (Ghassabian et al., 2013; Mahone et al., 2002). The BRIEF-P assesses behavioral, emotional, and cognitive functioning through parent and teacher (or, day care provider) self-report (Gioia, Espy, & Isquith, 2003). Even though the BRIEF-P is widely used in many ADHD assessment batteries (Sherman & Brooks, 2010), solely utilizing a self-report measure to assess executive functioning is generally not recommended; other more objective measures (e.g., the Conners Continuous Performance Test II) may supplement the assessment of executive functioning deficits (Huang-
Pollock, Karalunas, Tam, & Moore, 2012). Additionally, Ghassabian and colleagues (2013) neglected to assess symptomology in more than one setting (i.e., outside of sheer parent report), despite the current diagnostic necessity for ADHD symptoms to be present in two or more settings in the DSM-5 (American Psychiatric Association, 2013). Notwithstanding these limitations, the perusal of early brain structure correlates highlights the need for translational research in clinical neuroscience. Future studies replicating these results with slight methodological modifications would help shed clarity in this area of ADHD literature.

While Ghassabian and colleagues (2013) focused in brain regions of the limbic and related systems, other studies have explored ADHD correlates in the frontal lobe. Intriguingly, data from a research team at Johns Hopkins University suggests that sex differences in frontal lobe brain morphology may play a role in the differential prevalence rates and symptom presentation found between gender in ADHD (Dirlikova et al., 2015). To examine potential sex differences, Dirlikova and colleagues utilized MRI brain scans to compare cortical thickness and surface area in subdivisions of the frontal lobe between school-aged neurotypical participants and patients diagnosed with ADHD. Results indicated that on average, boys with ADHD (when compared to their neurotypical male peers) showed surface area reductions in the posterior frontal lobe regions (e.g., the premotor cortex). Conversely, brain scans signified that girls with ADHD had surface area reductions in the anterior frontal lobe (e.g., the prefrontal cortex). These data are in line with common trends in ADHD symptom expression between gender; prior epidemiological research suggests that females are diagnosed more with ADHD-PI vs. males with ADHD-C (Hinshaw et al., 2006; Arnett, MacDonald, & Pennington 2013). Bearing in mind the insufficient recognition of gender-specific presentations in the assessment of ADHD (Owens et al., 2017; Quinn & Madhoo, 2014), these results further clarify the causal factors underpinning gender stratification.
in ADHD diagnosis (Dirlikova et al., 2015). Nonetheless, future research in clinical science is necessary to connect these findings to the aberrant behaviors typically expressed in ADHD. Clinical application of this research may help decrease the potential for underdiagnosis of ADHD in female patients.

Aside from sex differences, neuroimaging studies for ADHD are frequently conducted in participants aged six and above (e.g., Dirlikova et al., 2015). Considering the early pathogenesis of ADHD (Halperin & Schulz, 2006; Riddle et al., 2013), the same John Hopkins research group mentioned above sought to investigate potential age- and sex-dependent brain morphologies found in younger children (4 – 5 years old) in a later study (Rosch et al., 2018). Instead of primarily focusing on frontal lobe regions, Rosch and colleagues (2018) investigated neuroanatomical correlates of ADHD in other specific subcortical areas (e.g., thalamus, basal ganglia), due to the dearth of recent research on this brain region in school-aged participants with ADHD (e.g., Seymour et al., 2017; Qiu et al., 2009).

Data suggest that sexually dimorphic brain morphologies exist between neurotypical participants and preschoolers diagnosed with ADHD (Rosch et al., 2018). Specifically, significant subcortical reductions were seen in young females with ADHD when compared to their neurotypical peers; this finding was absent between male groups. These data are somewhat provocative, as the results generally contradict prior findings (i.e., Seymour et al., 2017) that school-aged boys exhibit greater subcortical reductions than their female counterparts. Perhaps, the gender-specific neurodevelopmental trajectory influences symptom presentation of ADHD, as previous data from the neuroscience literature suggests that females and males differ throughout the course of typical neurodevelopment (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997). In spite of the contradictory findings and unbalanced participant sample size between sexes,
replication of this study may indicate convincing sex differences in the early onset of ADHD. In sum, although many brain regions have been identified to influence the development of ADHD, the above data suggests that some brain loci may play a larger role in the pathogenesis than others.

**Behavioral Inhibition and Executive Functioning**

Over two decades ago, Barkley (1997) proposed a hybrid neuropsychological model for ADHD that hypothetically unified deficits in four intermediate executive functions (i.e., working memory, self-regulation of affect-motivation-arousal, internalization of speech, and reconstitution) with poor *behavioral inhibition* (i.e., inhibition of impulses). Barkley postulated that poor behavioral inhibition was the core dysfunction (the primary causal factor) in patients with ADHD, setting the foundation for potential deficits in the four intermediate executive functions. Under Barkley’s original model, both executive dysfunction and disrupted behavioral inhibition directly influence goal-directed motor responses; the onset of which starts at a fairly young age (i.e., preschool years).

Since the model’s 1997 debut, Barkley’s theory has received substantial research attention; his article earned approximately ~8,000 citations at the time of this review. Contemporary studies related to Barkley’s model of ADHD have involved further investigation of behavioral disinhibition (e.g., Young et al., 2009), emotional dysregulation (e.g., Musser & Nigg, 2019; Shaw, Stringaris, Nigg, & Leibenluft, 2014), response to reinforcement (e.g., Bubnik, Hawk, Pelham, Waxmonsky, Rosch, 2014; Luman et al., 2010), and executive dysfunction (e.g., Skogan et al., 2014; Marotta et al., 2017) as potential causal factors. Complementing previous research in behavioral neuroscience, Barkley’s (1997) intent was to relate his unifying model back to neuropsychological factors, a phenomenon that largely occurs in today’s behavioral and cognitive literature on ADHD etiology.
Expanding on Barkley’s (1997) model, Young and colleagues (2009) conducted a longitudinal twin study investigating the impact of behavioral disinhibition and executive dysfunction in the manifestation of externalizing disorders and other latent symptoms. As mentioned earlier in this review, ODD and ADHD are frequently comorbid (Kessler, 2005; McElroy et al., 2018). The culmination of specific externalizing symptoms (e.g., novelty seeking) subsequently establishes the nosology of common externalizing spectrum disorders found in the DSM-5, such as ODD and ADHD (American Psychiatric Association, 2013; Young et al., 2009). Young and colleagues (2009) tested the developmental patterns and genetic correlates of behavioral disinhibition, and its relationship to a similar (and more recent) executive function: *response inhibition* (i.e., a higher order cognitive ability associated with both impulse inhibition and executive control). Generally, the researchers desired to measure the developmental pattern across externalizing disorders through the measurement of latent risk factors.

In regards to the etiological factors of ADHD and its relationship with other externalizing disorders, Young and colleagues concluded that ADHD is rather stable concerning behavioral disinhibition, particularly in early to late adolescence. In other words, what can be implied from these findings are that the latent symptoms of ADHD: (1) have an early onset, (2) are stable across time, (3) are highly genetic, and (4) are influenced by executive dysfunction. This seemed to differ from other externalizing disorders, as data from Young and colleagues suggest that symptom presentation for conduct and related disorders fluctuated throughout development. Despite the potential implications, this research is not without its limitations. While Young and colleagues found differences between symptom onset and presentation, this isn’t necessarily “cutting-edge,” as other previous data already implied that externalizing spectrum disorders have many shared characteristics due to high comorbidity (e.g., Kessler, 2005). Additionally, Young and colleagues
neglected to longitudinally assess all measured facets of executive functioning. However, like ADHD symptoms, prior studies have implied that executive functioning has a relatively early and stable onset (e.g., Friedman et al., 2008), which may serve as an explanation for this limitation. Perhaps, supplementary investigation of executive dysfunction among relatively young children (preschoolers) can help clarify this gap in the data.

A later study conducted by Skogan and colleagues (2014) investigated executive dysfunction as a causal factor in nonclinical preschool children with and without elevated externalizing symptomology (specific to ADHD and ODD). Relaying back to Barkley’s (1997) seminal model and previous research on etiological relationships between latent externalizing symptomology (e.g., Young et al., 2009), Skogan and colleagues (2014) sought to explore the developmental trajectory of behavioral dimensions and cognitive mechanisms found in common externalizing psychopathologies; particularly, the development of working memory and response inhibition. The concurrent early onset of executive functions and aberrant ADHD-like behavior makes the investigation in preschoolers meaningful for etiology research. Generally, data suggests that higher ADHD-like symptoms were associated with decreased working memory and response inhibition (Skogan et al., 2014). Conversely, as compared to ADHD symptomology, ODD-like symptoms were less related with prodromal executive dysfunction. Nonetheless, these results should be interpreted with slight caution; the interpretation of cognitive ability in preschool-aged children, such as the Stanford-Binet subscales used in Skogan and colleagues (2014) study, may have construct instability in younger children (Lichtenberger, 2005).

Results from Skogan and colleagues (2014) are largely consistent with, and further supplement, Young and colleagues (2009) findings on the developmental trajectories of executive dysfunction in ADHD. Taken together, despite the high comorbidity between externalizing
spectrum disorders, the etiology of ADHD is consistently associated with high executive dysfunction with low behavioral inhibition across time (Barkley, 1997; Skogan et al., 2014; Young et al., 2009). Subsequently, this postulation supplements psychiatry research on temperament and etiology found elsewhere (e.g., Melegari et al., 2015). ADHD etiological research in cognitive and behavioral science are far from complete, as many recent studies recommend the further integration of a neurobiological framework (e.g., Marotta et al., 2017; Shaw et al., 2014). Notwithstanding the etiological implications, other recent research suggests that behavioral inhibition had less of an effect on the developmental trajectory of common externalizing disorders than ineffective parenting (Roskam, 2018); this seems to slightly contradict the significant neurobehavioral and cognitive etiological data mentioned above.

**Parenting**

ADHD unequivocally has a robust biological etiology (Demontis et al., 2019; Gizer, et al., 2009). Nonetheless, due to the early onset of ADHD, many researchers have also investigated the potential role of parenting behavior in the pathogenesis of ADHD (Modesto-Lowe, Danforth, & Brooks, 2008). Largely, research on parenting has involved investigating the influence of parental attribution (Park, Johnston, Colalillo, & Williamson, 2018; Wong et al., 2018), traditionally negative parenting styles (i.e., authoritarian, permissive, uninvolved; Hutchison, Feder, Abar, & Winsler, 2016; Moghaddam et al., 2013; Roskam, 2018), and other ineffective parenting techniques (Mokrova, O’Brien, Calkins, & Keane, 2010). Of all mentioned etiological factors in this review, the implications of parental behavior may vary considerably due to other environmental factors, such as culture (e.g., Rodríguez, Donovich, & Crowley, 2009). Therefore, a slight word of caution is advised in the generalization and application of theories on parenting and the pathogenesis of ADHD; the author encourages a holistic and thorough approach to ADHD
research and diagnosis. Nonetheless, the role of parenting may play a unique part in the development of ADHD in younger populations, as there is relatively strong evidence to support that dysfunctional patterns of externalizing behavior may manifest from various parental-based factors that reinforce the child’s negative behavior (Mokrova et al., 2010; Roskam, 2018), and thus predict future ADHD-like symptomology.

Clearly, examining early indicators of externalizing behavior is beneficial in assessing the etiology and prognosis of ADHD. Despite the practical advantages, prior studies have largely neglected to exclusively measure the continuity and change of externalizing symptoms throughout time between different theoretical models (Roskam, 2018). Hence, Roskam (2018) sought to investigate the developmental trajectory (i.e., from 3 to 14 years of age) of aberrant levels of externalizing behavior, with hopes in identifying early indicators, and establishing predictive trends, across common theories of etiology. This study complements data from other studies on parenting (e.g., Park et al., 2018; Mokrova et al., 2010), as Roskam (2018) stressed the potential influence of parenting on psychiatric pathogenesis at a relatively young age.

In regards to early indicators of externalizing disorders, coercive parenting (i.e., a cycle of harsh discipline, rejection, neglect, etc.) was found to strongly impact the onset and developmental trajectory (Roskam, 2018). In fact, of all the common etiological theories measured by Roskam (i.e., executive functioning, attachment, and other cognitive abilities) early maternal coercive parenting had the most predictive risk for ineffective externalizing behavior. In other words, data suggests that early exposure to traditionally negative parenting styles, such as authoritarian parenting in mothers, may significantly impact the onset and trajectory of ADHD (particularly hyperactive/impulsive symptoms).
Despite the intriguing findings, and as stated before in this review, etiological data resulting from parenting is uniquely sensitive to cross-cultural variability (e.g., Rodríguez et al., 2009). Roskam (2018) collected data in a predominately French-speaking area of Belgium. Thus, considering the individualistic nature of the Belgian culture (Green, Deschamps, & Páez, 2005), future studies should analyze the developmental trajectory of externalizing behavior in collectivistic nations where the impact of parenting style may produce differential behavioral outcomes (Rudy & Grusec, 2006). Indeed, Roskam’s (2018) findings may be of importance in individualistic cultures, but lack global generalizability.

Notwithstanding the potential influence of parenting style on ADHD, a causality dilemma emerges from much of the parenting literature. Data supports that a child’s negative behavior may influence their parent’s stress and style of parenting (Gordon & Hinshaw, 2017; Muñoz-Silva, Lago-Urbano, Sanchez-Garcia, & Carmona-Márquez, 2017). These findings imply that the etiology of ineffective parenting practices may be influenced by typical ADHD symptoms, such as hyperactivity and impulsivity. Consequently, this might further exacerbate the child’s symptoms, promoting a vicious cycle of family disarray (Mokrova et al., 2010). This may explain, in part, the strong empirical support for family-based interventions for ADHD in younger children, such as behavioral parent training (Mulqueen, Barley, & Blotch, 2015; Modesto-Lowe et al., 2008). Hence, treatment may help alleviate this cyclical maladaptive pattern, regardless of this causality dilemma found in the parenting etiology literature.

**Final Remarks on Etiology**

The etiology of ADHD, as with other complex psychiatric disorders, is fairly complex. As detailed above, ADHD may be impacted by a host of biopsychosocial factors, of which either exacerbate the symptomology or protect against the pathogenesis. Aside from all the theories and
paradigms, most studies have generally adopted a neurodevelopmental perspective to the psychopathology. Thus, continuous research into the etiology of ADHD in preschool-aged children is a rich area of investigation, as future studies may considerably enhance our understanding of neurodevelopment and ADHD. Alas, deriving a definitive “formula” for the pathogenesis of ADHD is inconclusive at the moment; certainly, the derivation of which would pioneer promising directions for future treatment and preventive care.

V. Evidence-Based Interventions for ADHD

Two decades ago, the Multimodal Treatment of ADHD (MTA) Cooperative Group (1999) published the largest National Institutes of Mental Health (NIMH)-funded control treatment study to date for pediatric ADHD, measuring the comparative efficacy of (1) medication management, (2) behavioral intervention (e.g., modification), and (3) multimodal (combined) treatment. Generally, the research team found that all intervention groups yielded significant reductions in ADHD symptom presentation throughout time; although, medication management and combined treatment were found to be the most efficacious in treating symptoms. Presently, evidence-based treatment for children and adolescents diagnosed with ADHD encompass an individualized combination of psychosocial intervention and adjunct stimulant or non-stimulant pharmacotherapy (Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). The MTA Cooperative Group (1999) has laid the foundation for recent clinical trials that test treatment efficacy for pediatric ADHD.

Although the efficacy of psychostimulant medication is extremely well supported in the ADHD treatment literature for most ages (Faraone & Buitelaar, 2010), long-term effects generally remain unknown (Hinshaw & Arnold, 2015; Schweren et al., 2018). It is recommended that ADHD intervention starts at a relatively young age, considering the early onset and
neurodevelopmental course (American Psychiatric Association, 2013; Halperin & Schulz, 2006; Riddle et al., 2013), to help mitigate future symptoms (Childress & Stark, 2018). However, data further suggests that stimulant medication presents an increased risk for unwanted side effects (Greenhill et al., 2006; Hinshaw & Arnold, 2015); thus, psychosocial therapies are deemed the first-line of treatment for preschool-aged children diagnosed with ADHD (Childress & Stark, 2018). Regardless of the long-term effects, the pharmacological treatment of ADHD has elicited public controversy and misconception, partly due to medication abuse (King et al., 2018; Sepúlveda et al., 2011) and public debate about if ADHD is a “real” psychiatric disorder (McLeod, Fettes, Jensen, Pescosolido, & Martin, 2007). Because of this increased publicity, the multimodal treatment of ADHD will continue to be a research priority in the clinical science field.

Psychosocial Treatment

Traditionally, evidence-based interventions for children and adolescents with ADHD have encompassed a combination of pharmacotherapy and psychosocial treatment (MTA Cooperative Group, 1999); although, other studies have found conflicting results (e.g., Pelham et al., 2000). Specific to psychosocial treatment, the AAP (2011) clinical practice guidelines for ADHD strongly recommends behavior therapy, as it is one of the only evidence-based non-pharmacological interventions for pediatric ADHD across development. For most pediatric patients, symptom relief is enhanced by adjunct pharmacologic interventions; however, this isn’t necessarily the case for preschool-aged children. Behavior therapy is considered the first line of treatment for prekindergarten patients with ADHD (AAP, 2011; Childress & Stark, 2018; Mulqueen et al., 2015).

Generally, behavior therapy for externalizing behavior includes three main components: (1) child intervention (e.g., intensive behavior modification), (2) parental/caregiver intervention
(e.g., behavioral parent training), and (3) school/academic intervention (e.g., daily report cards [DRCs]; Hinshaw & Arnold, 2015). The combination of the above three components is necessary for longer-term efficacy of in-session behavior therapy. Concurrent parent and teacher psychoeducation occurs throughout the child’s therapeutic process, and is critical for subsequent generalizability of applied behavioral techniques. Based upon Skinnerian (operant) conditioning and social learning theory, behavior therapy for the treatment of ADHD is centered upon the ABC (Antecedent, Behavior, Consequence) model of behavior (O’Leary, & O’Leary, 1972). An assessment of the child’s antecedents and consequences in their environment helps identify dysfunctional target behaviors for treatment; typically, in behavior therapy, modification of behavior occurs through a token economy system.

As mentioned earlier in this review, the MTA Cooperative Group (1999) compared the efficacy of behavior therapy with pharmacologic treatment. Specifically, an intensive children’s summer treatment program (STP) served as the study’s behavior therapy of choice. The STP was created by William Pelham in the early 1980’s (Fabiano, Schatz & Pelham, 2014), and has received extensive support ever since the initial creation (e.g., Pelham et al., 2000; Verret, Guay, Berthiaume, Gardiner, & Béliveau, 2012; Yamashita et al., 2010). Presently, the STP is practiced internationally in various settings (e.g., academic institutions, children’s hospitals, etc.), and is well-recognized with a strong evidence base (Fabiano et al., 2014; Hinshaw & Arnold, 2015).

The STP is a manualized six to nine week research-based program that combines behavioral parent training, contingency management, and generalization (Fabiano et al., 2014; Pelham, Greiner, & Gnagy, 1997). Throughout the day, pediatric patients (aged 5-12, depending on the setting) are exposed to a variety of structured recreational and academic-like activities; this includes a rigorously enforced reward and response cost point system, where patients can earn and
lose points for effective and ineffective behaviors. The behaviors are operationally defined and monitored by paraprofessional staff and doctoral-level supervisors throughout most daily activities. Implemented point system behaviors are categorized (e.g., interval, frequency, positive, negative) and include (but are not limited to), the following: (1) good sportsmanship (positive, interval), (2) standardized attention (positive, frequency), (3) intentional aggression (negative, frequency), (4) cursing/swearing (negative, frequency), among many others. The point system is the primary technique employed in the STP, in which pediatric patients can earn points for functional reinforcers at home (e.g., by utilizing a DRC), and program-wide field trips at the end of each week; functional reinforcers are tailored to each child’s performance through the constant tracking of point system behaviors. Since patients with ADHD typically suffer from overwhelming symptoms of inattention and disorganization, the STP’s intensive structure significantly helps with subsequent symptom relief by providing consistent structure (Fabiano et al., 2014; Pelhem et al., 1997). Additionally, in line with Skinnerian conditioning, the labeled behavior is postulated to generate learning and generalization. Evidently, the above program requires extensive training and resources, of which may be an issue for some settings (e.g., rural areas with less available assets).

Although the STP is ideal for school-aged children, behavioral treatments for ADHD and related disorders should feasibly start at a young age in order to improve prognosis (Polanczyk, 2018; Webster-Stratton et al., 2008). Of recently, the STP has expanded to prekindergartners (i.e., the summer treatment program for prekindergartners; STP-PreK), and has since received ample empirical support for treating externalizing behavioral problems (e.g., Graziano et al., 2018; Graziano, Slavec, Hart, Garcia, & Pelhem, 2014; Hart et al., 2016; Hart, Maharaj, & Graziano, 2019). The creation of the STP-PreK was multifaceted, adopting various empirically-supported techniques utilized in the children’s STP, and incorporating a particular focus on bolstering both
executive functioning (EF) and emotional regulation (ER) in preschool patients (Graziano et al., 2014). Prior studies have indicated that increased self-regulation (i.e., combined EF and ER) predicts academic success (Ursache, Blair, & Raver, 2012). Generally, the program was implemented to decrease the risk for externalizing behavior disorders (e.g., ADHD, ODD, etc.), improve school readiness for preschoolers, and further generalize the STP intervention into academic settings by intervening the transitional summer before kindergarten. Graziano and colleagues (2014) conducted the first pilot study introducing the structure, pertinence, and efficacy of the newly modified STP.

Similar to the original STP, the STP-PreK is a manualized behavioral treatment program that runs approximately 8-weeks throughout the summer months (Graziano et al., 2014), with more emphasis on the academic learning center and less on periods of structured recreational activity. The STP-PreK was meant to combat early symptoms of clinically elevated externalizing behavior problems. As such, children were exposed to a behavioral modification program throughout the day; the primary goal being to increase prosocial, and shape ineffective, classroom behavior. Instead of utilizing only points for contingency management (which may be developmentally abstract for the younger kids), an additional visual response cost system utilizing tangible chips was employed in the classroom. Ineffective behavior (e.g., violation of posted activity rules) resulted in public labeling of behavior and/or time outs. A child’s effective behavior (e.g., contributing, helping a peer, etc.) could result in exchanging their points/chips for functional reinforcers, social reinforcement (e.g., public validation/praise), behavior-contingent home rewards, and (if the group generally displayed a high frequency of effective behavior) attainment of reinforcing group contingencies.
Aside from behavior modification, and similar to the children’s STP, concurrent behavioral parent training is a crucial feature of the STP-PreK; although, the curriculum offered in the STP-PreK parent training is slightly different than what is offered in the original STP. The STP-PreK uses the School Readiness Parenting Program (SRPP), a curriculum adapted to pre-kindergarten students partially based on parent-child interaction therapy (PCIT), as their behavioral parent training of choice (Graziano et al., 2014). Similar to the children’s STP, the first half of the SRPP teaches parents how to implement behavioral strategies at home, focused on effective parenting (e.g., labeled praise, appropriate time outs, etc.). The second half of the STP-PreK SRPP diverges from the original STP, focusing on the process of achieving early educational milestones through school-readiness group discussions. Taken together, the STP-PreK has generated promising data demonstrating effectiveness in increasing self-regulation and school readiness with children at risk for externalizing behavior disorders (e.g., Hart et al., 2019).

Studies on the STP-PreK are ongoing, and the author of this review predicts that research will proceed in the upcoming years. The most recent randomized control study for the STP-PreK was conducted by Hart and colleagues (2019) who measured the comparative efficacy between 4-week and 8-week doses of the STP-PreK, and traditional school-based interventions (e.g., behavioral consultation; BC) in preschoolers at risk for developing externalizing behavior problems. School readiness and kindergarten success were measured by level of functioning (e.g., adaptive, academic, behavioral), social-emotional skills, and self-regulation (EF and ER) between all intervention groups. Results indicated that even though all three interventions were found to have relatively long-term effects on school readiness and kindergarten success, both the 4-week and 8-week STP-PreK groups exhibited higher immediate results in level of functioning, emotional skills, and self-regulation (Hart et al., 2019). This suggests that both intensive behavioral-based
summer immersion, and generalized behavioral programs in the school setting, are effective in improving prognosis for preschoolers with externalizing behavioral problems. Future dismantling studies assessing individual components of the STP-PreK is necessary to bolster clinical utility, further clarifying the above results and uniform efficacy between shorter and longer treatment.

Prior research suggests that the psychosocial treatment of ADHD for young children largely revolves around the implementation of behavior therapy (AAP, 2011; Fabiano et al., 2009; Pelham, Wheeler, & Chronis, 1998). There are several other forms of empirically-supported and behaviorally-based interventions for use with preschool-aged children not detailed in this review (e.g., The Incredible Years; Webster-Stratton et al., 2008); thus, the reader is directed to Young and Amarasinghe (2010) for a succinct review of other non-pharmacological treatments for ADHD. To sum, outcome data suggests that the STP-PreK and related evidence-based behavioral interventions are effective, providing hope for the thousands of children in need of symptom relief.

**Pharmacotherapy**

Pharmacotherapy for the treatment of ADHD has shown to be quite effective in acutely alleviating externalizing symptoms in pediatric patients (MTA Cooperative Group, 1999; Van der Oord et al., 2008). Prior research suggests that neurotransmitter dysfunction from genetic variation may give rise to the symptoms seen in children with ADHD (e.g., Demontis et al., 2019; Gizer et al., 2009). Consequently, research suggests that ADHD symptoms can be effectively treated by both stimulant (e.g., AMPH, MPH) and non-stimulant (e.g., ATX) medication regimes in most age groups (e.g., Childress et al., 2015; Dougherty et al., 2016; Liu et al., 2018b; Nakanishi et al., 2017).

Despite the potential efficacy of psychostimulant medication, long-term effects are largely contested in the current literature. For instance, Schweren and colleagues (2018) found that
frequently-used stimulant medication had neither beneficial nor detrimental longitudinal effects on ADHD symptoms, social-emotional functioning, and cognition (e.g., working memory). Study results, however, may be attributed to a potential decrease in ADHD symptom severity shown throughout the course of normative development from childhood into young adulthood (van Lieshout et al., 2016). Nonetheless, data implies that physicians should carefully consider the advantages and disadvantages of ADHD prescription medication across all ages, since the long-term effects of medication on ADHD symptom presentation and the brain are currently undetermined (Schweren et al., 2018; Vitiello et al., 2015). Additionally, the addictive properties of ADHD medications is a growing public health concern. Recent studies have found that children and adolescents may partake in prescription misuse and abuse (King et al., 2018; Lakhan & Kirchgessner, 2012; Wilens et al., 2007). Perhaps, this is due to intriguing data suggesting a link between neural reward processing and prescription psychostimulants (Schweren et al., 2017). In preschool-aged children, there is even more mixed evidence and hesitations on the long-term efficacy and safety of prescription medications for ADHD.

Currently, data supports the treatment efficacy of a MPH (stimulant), or a ATX (non-stimulant), derivative for preschoolers with ADHD (Childress & Stark, 2018; Liu et al., 2018b; Ghuman et al., 2009ab; Greenhill et al., 2006; Wigal et al., 2007); although, MPH and ATX are not approved for preschool use by the Food and Drug Administration (FDA; Childress & Stark, 2018). While studies have indicated that AMPH (e.g., Adderall) is fairly efficacious in school-aged children (Childress et al., 2015; Faraone & Buitelaar, 2010), and despite approval for preschool use by the FDA (Childress & Stark, 2018), a prescription of a AMPH derivative (e.g., Adderall) currently lacks empirical support, eliciting various safety and related concerns (AAP, 2011; Bourgeois, Kim, & Mand, 2014; Childress & Stark, 2018). ATX and MPH are both widely
used across the lifespan, with research suggesting a differential neural locus of effect (Nakanishi et al., 2017). MPH, commonly prescribed as Ritalin or Concerta, is made of two enantiomers (i.e., dextorotary \([d\text{-}\text{threo-MPH}]\) and levorotary \([l\text{-}\text{threo-MPH}]\), with \(d\text{-}\text{threo-MPH}\) holding increased receptor affinity and potency) that jointly act as an indirect DA agonist and NE transporter inhibitor (Heal & Pierce, 2006; Nakanishi et al., 2017). Whereas ATX, commonly prescribed as Strattera, acts as a potent selective NE reuptake inhibitor, with concurrent (but slight) modulation of DA neurotransmission in the prefrontal cortex and other brain regions (Nakaishi et al., 2017). Both drug derivatives exogenously modulate the amount of extracellular DA and NE. Yet, the AAP (2011) recommends the use of MPH as a second-line treatment for prekindergarten children with ADHD, following an unsuccessful trial of behavioral therapy.

About a decade ago, Greenhill and colleagues (2006) conducted the largest MPH (specifically, immediate-release; MPH-IR) intervention study to date for preschoolers with ADHD, called the \textit{Preschoolers with ADHD Treatment Study} (PATS), to build upon prior studies assessing MPH in younger children (e.g., Handen, Feldman, Lurier, & Murray, 1999). Similar to the previously mentioned MTA (1999) study, PATS was funded by the NIMH with an impressive study cohort of preschool children (aged 3 to 5.5 years). To assess efficacy and safety of prescription MPH-IR in preschoolers, PATS incorporated a six-center, randomized, controlled research design following children across 70-weeks. Results indicated that if a treatment regime calls for a prescription of MPH, dosage should start low and gradually increase to an optimal amount (approximately \(14.2 \pm 8.1\) mg/day) to maximize therapeutic effects and subsequent symptom relief.

Noting the results from PATS, Ghuman and colleagues (2009b) later published a randomized, placebo-controlled, crossover study on the short-term efficacy and safety of MPH for
preschoolers diagnosed with concurrent ADHD and developmental disabilities (DD; i.e., intellectual disability and pervasive developmental disorder). Young children with DD typically have co-occurring outcomes akin to ADHD, and thus are treated with an ADHD treatment regime, despite the lack of empirical backing in co-occurring prognostic outcome (Aman et al., 2014; Lecavalier, 2006; Ghuman et al., 2009b). Compared to placebo and baseline, MPH significantly improved parental report of ADHD and related symptoms overtime. Even though prescription MPH is empirically supported to suppress some symptoms of ADHD and related disorders, a slew of adverse side effects have developed in a significant amount of preschool-aged children prescribed MPH (e.g., PATS found up to 30% of children experienced aversive side effects), which included emotional outbursts, social withdrawal and lethargy, digestive problems, insomnia, hypophagia, and other pharmacokinetic-induced effects (Greenhill et al., 2006; Wigal et al., 2007). This may, in part, explain the FDA’s hesitation in approving MPH for common use in prekindergarten children (Childress & Stark, 2018).

Other avenues towards safely medicating young children with impairing externalizing symptoms have recently become a research priority. For instance, the utilization of ATX has received empirical support in the current preschool ADHD treatment literature (Liu et al., 2018b; Ghuman et al., 2009ab). Although not overtly recommended by the AAP (2011) or FDA (Childress & Stark, 2018), ATX is categorized by the Drug Enforcement Administration (DEA) as a non-controlled substance (i.e., low addictive potential), with promising therapeutic effects for the treatment of externalizing symptoms; conversely, stimulant medications are classified as controlled-substances by the DEA due to an increased risk for dependency.

Ghuman and associates (2009a) conducted a recent pilot study of open-label ATX, testing the efficacy and safety of ATX for preschoolers. Accordingly, findings indicated that prescription
ATX significantly decreased parent ratings of ADHD symptoms when compared to baseline, with some adverse side effects. Approximately two-thirds (66.7%) of preschool participants in the study experienced side effects, with most side effects reported in the study related to elevated conduct problems, and less concerning physiological dysfunction. Considering Ghuman and associates (2009a) conducted one of the first studies on ATX in prekindergarten participants, future randomized, double-blind clinical trials are necessary to bolster ATX prescriptive recommendation for preschool-aged children and earn subsequent approval for use by the FDA.

Controversy surrounding the prescription of various ADHD medications in preschool children is justifiable. Despite the potential efficacy in reducing ADHD symptoms, there are various potential side effects, and very little research on the long-term effects and efficacy of psychostimulants and non-stimulants (Ghuman & Ghuman, 2013; Schweren et al., 2018). Future randomized controlled trials on preschool children should continue to assess all aspects of effects (e.g., side effects, optimal and non-optimal dosage, pharmacodynamics and pharmacokinetics, the long-term impact on drug efficacy, etc.) generated from prescription ADHD medications. For now, physicians and prescribing psychologists entertain a tough role in deciding whether or not to medicate a preschool child with impairing externalizing symptoms.

VI. Clinical Implications and Future Directions

As illustrated by this review, ADHD is a fairly prevalent neuropsychiatric disorder with a host of potential causal factors and proposed interventions. Early studies (pre-21st century) have largely focused on the impact of ADHD in school-aged children. Therefore, ADHD in prekindergartners is a relatively novel area of interest. Considering the recency of research in ADHD among preschoolers, the identification and treatment is relatively more ambiguous in younger children for clinicians, increasing the proclivity for misdiagnosis and undertreatment for
children at risk. Hence, the author recommends future research and clinical focus in three broad areas: (1) sex differences; translating current and future research into practice by increasing gender-dependent assessment and treatment, (2) pharmacogenetics; modifying the safety and efficacy of prescription medication through the integration of research on genomic pathogenesis, and (3) accessibility of treatment; proactively pursuing research into cost-effective behavioral programs to combat socioeconomic barriers. A brief rationale for each recommendation is detailed below.

**Sex Differences**

Prevalence data repeatedly indicates that, across the lifespan, ADHD is diagnosed significantly more in males. However, biopsychosocial research further suggests that ADHD symptoms present differently in female patients, with inattention being the predominant symptom presentation throughout development (Dirlikova et al., 2015; Hinshaw et al., 2006; Owens et al., 2017; Quinn & Madhoo, 2014). Collectively, this implies that an increased international awareness of sex-differences present in ADHD is necessitated for preventative care.

**Pharmacogenetics**

Considering the strong neurobiological etiology of ADHD, medication management could significantly improve prognosis for young children. Although ATX and MPH have shown to be efficacious, these prescriptions have yet to meet FDA approval guidelines for use in preschool-aged children (Childress & Stark, 2018; Greenhill et al., 2006). Perhaps, the recent focus on GWAS in the psychiatric literature can help to pioneer advances in pharmacogenetics, drug development, and long-term effects. Nonetheless, future randomized, double-blind, placebo-controlled trials in all ADHD medication derivatives (AMPH, MPH, ATX, etc.) will help to resolve this discrepancy.
Accessibility of Treatment

Behavioral therapy is currently the first line treatment for preschool-aged patients with ADHD (AAP, 2011). Despite the strong evidence base, most programs are resource and labor intensive, serving as an unfortunate socioeconomic barrier for several families and communities in need of empirically-supported interventions. In order to make these treatment programs more accessible, future research is recommended to test the effectiveness of modified (less labor-intensive) programs.

Evidently, there is a comparative lack of ADHD literature on preschool-aged children when compared to their school-aged and adolescent counterparts. However, research interest in this population is rapidly emerging. The continual pursuit for future studies on ADHD in preschoolers will provide clinicians with the necessary evidence-based techniques to effectively support their pediatric patients.
References


ADHD IN PRESCHOOL CHILDREN

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ADHD IN PRESCHOOL CHILDREN


Appendix A

DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder (F90.X)

Note. Criteria from the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
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A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   
   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
   
   b. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
   
   c. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
   
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
   
   e. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
   
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
   
   g. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
   
   h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
   
   i. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).

2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
   
   Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
   
   a. Often fidgets with or taps hands or feet or squirms in seat.
   
   b. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
d. Often unable to play or engage in leisure activities quietly.
e. Is often “on the go,” acting as if “driven by a motor” (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
f. Often talks excessively.
g. Often blurts out an answer before a question has been completed (e.g., completes people’s sentences; cannot wait for turn in conversation).
h. Often has difficulty waiting his or her turn (e.g., while waiting in line).
i. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people’s things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).

B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

- **314.01 (F90.2) Combined presentation**: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- **314.00 (F90.0) Predominantly inattentive presentation**: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- **314.01 (F90.1) Predominantly hyperactive/impulsive presentation**: If Criterion A2 (hyperactivity/impulsivity) is met but Criterion A1 (inattention) is not met over the past 6 months.

Specify if:

- In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

- **Mild**: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in only minor functional impairments.
- **Moderate**: Symptoms or functional impairment between “mild” and “severe” are present.
- **Severe**: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.
Appendix B

Selected Neuroscience Acronyms

5-HT = 5-hydroxytryptamine [serotonin]
5-HT2A = serotonin 2A receptor; chromosome 13
5-HTR2A = serotonin 2A receptor gene; chromosome 13
5-HTTLRP = serotonin-transporter-linked polymorphic region in SLC6A4; chromosome 17
AMPH = amphetamine or dextroamphetamine
ATX = atomoxetine
COMT = catechol-O-methyltransferase transporter; chromosome 22
DA = dopamine
DAT1 = dopamine transporter; chromosome 5
DUSP6 = dual specificity phosphate 6; chromosome 12
FOXP2 = forkhead box protein P2; chromosome 7
MPH = methylphenidate
MRI = magnetic resonance imaging
NE = norepinephrine
SLC6A4 = solute carrier family 6 member 4; chromosome 17
SNAP25 = synaptosomal nerve-associated protein 25 gene; chromosome 20
SNPs = single nucleotide polymorphisms