Examining the Concurrent and Predictive Relations of Working Memory in Childhood Attention-Deficit/Hyperactivity Disorder

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EXAMINING THE CONCURRENT AND PREDICTIVE RELATIONS OF WORKING MEMORY IN CHILDHOOD ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

by

ASHLEY NICOLE SIMONE, M.A.

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements of the degree of

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ABSTRACT

Examining the Concurrent and Predictive Relations of Working Memory in Childhood Attention-Deficit/Hyperactivity Disorder

Advisor: Jeffrey M. Halperin, Ph.D.

Attention-deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity which lead to impairment in multiple settings (American Psychiatric Association, 2013). Childhood ADHD has been concurrently associated with various neurocognitive deficits and one in particular that has been under examination over the past several years is working memory (WM). WM is a temporary storage system that is responsible for maintenance and/or manipulation of information in order to complete complex cognitive and behavioral tasks. Researchers have postulated that WM is one of several potential endophenotypes of ADHD (Castellanos & Tannock, 2002) and/or that WM is a core underlying neurocognitive deficit of the disorder which is responsible for the manifestation of inattentive and/or hyperactive/impulsive behaviors (Rapport et al., 2001). In particular, there has been growing interest in examining WM in this population because several purported interventions for the disorder involve some form of WM training, which are operating under the premise that improved WM will result in a reduction of core ADHD symptomatology. However, the associations between ADHD and WM remain unclear, perhaps in part due to the behavioral and cognitive heterogeneity of this disorder. This dissertation consists of three studies designed to further explore gaps in the literature. The first study examined the specific nature of WM weaknesses in children with ADHD with regard to distinct WM processes (i.e., maintenance and manipulation) and modalities (i.e., auditory-verbal and visuospatial). Analyses revealed significant Group x Condition (p = 0.02) and Group x Modality (p = 0.03) interactions which
indicated differentially poorer performance by those with ADHD on manipulation relative to maintenance and visual-spatial relative to auditory-verbal tasks, respectively, as compared to their typically-developing peers. Study 2 investigated the impact of WM deficits on academic achievement and school functioning in children with ADHD and found a relative double dissociation. Weaknesses in WM, but not ADHD symptom severity, was significantly associated with poorer performance on all measures of academic achievement (all p < 0.01). In contrast, higher levels of inattention and hyperactivity/impulsivity (p < 0.04), but not WM deficits (p > 0.10), were significantly associated with poorer teacher-ratings of behavioral functioning and clinician-ratings of global functioning. The final study examined the longitudinal relations between ADHD and WM by determining whether early preschool WM performance predicted school-aged ADHD symptom severity or whether early ADHD symptoms predicted later WM performance. Analyses revealed that preschool WM did not significantly predict later ADHD symptoms (p > 0.10), but that preschool inattentive symptoms (but not hyperactivity/impulsivity symptoms) significantly predicted school-aged children’s WM ability (p < 0.001). Taken together, findings from these three projects suggest that while on a group-level children with ADHD demonstrate a pattern of WM difficulties, these difficulties may not be evident in all children with the disorder. Also, while WM ability is strongly linked to academic outcomes in children regardless of ADHD status, WM does not appear to be driving the manifestation of behavioral symptoms of the disorder and thus these findings reduce the likelihood that WM represents the core deficit of ADHD.
When I think of who I have become, both personally and professionally, I cannot do so without thinking of my mother. She instilled and fostered my intellectual curiosity and passion for learning. I wholeheartedly dedicate this dissertation to my mother.
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Throughout my graduate education, Dr. Jeffrey Halperin has been an excellent mentor and teacher. Working under his guidance has allowed me to grow and prosper into a more inquisitive, thoughtful, and analytical researcher. I would like to thank him for his continual support over the past seven years, as well as all of the Queens College Preschool Project lab members (co-directors, postdoctoral fellows, graduate and undergraduate research associates) as I have learned so much from all of you and appreciate all of your help with data collection, data input, and conceptualization that has made the following three studies possible. My research career would surely not be where it is today if it were not for all of you. Last, but certainly not least, I would like to thank the countless hours each of the QCPP families spent year after year in this longitudinal study. Following the lives of these parents and children has been undeniably instrumental in shaping my professional and personal life. Recognizing the enduring resilience of these individuals has been undoubtedly inspiring.
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Specific Aims:

Attention-deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity that cause functional impairment in multiple settings. ADHD is highly prevalent, affecting approximately 5-11% of school-aged children, and is more common in boys than girls (American Psychiatric Association, 2013; Walkup et al., 2014; Visser et al., 2014).

A substantial body of research has found that ADHD is associated with various neurocognitive deficits, and one in particular that has received considerable attention is working memory (WM). WM is a temporary storage system that is responsible for maintaining and/or manipulating information in order to complete more complex cognitive and behavioral tasks (Baddeley, 2000). The two WM processes of maintenance versus manipulation of material are closely-linked, yet separable and distinct. Additionally, there are two WM modalities which are also separable, one involved in processing of auditory-verbal information and the other for processing visual-spatial information. Some researchers postulate that WM is an endophenotype of ADHD (Castellanos & Tannock, 2002) or that WM is the core underlying neurocognitive deficit of ADHD (Rapport et al., 2001). In recent years, WM has become an area of particular interest because some emerging interventions for the disorder include WM training, operating under the premise that improved WM will lead to a reduction of ADHD symptomatology. Despite an abundance of research examining WM in childhood ADHD, much is still unknown regarding both the concurrent and predictive relations between ADHD and WM, as well as how WM is affected by the neurocognitive heterogeneity of this disorder.

Two meta-analyses (Martinussen et al., 2005; Kasper et al., 2012) have synthesized previous studies examining the role of WM processes and modalities in childhood ADHD. Overall,
both meta-analyses reported substantial effect sizes for visual-spatial WM, but there were more discrepant findings for auditory-verbal WM (with effect sizes ranging from moderate to large). Additionally, only Martinussen et al. (2005) reported comparisons between children with and without ADHD in regards to WM processes. Specifically, they reported large effect size differences for WM manipulation in the visual-spatial domain (but not for the auditory-verbal domain), with no significant differences reported for WM maintenance. Yet, at this point, it remains unclear whether children with ADHD have specific deficits in the more complex process of manipulation, when maintenance, which is closely linked to attentional control, is held constant. Thus, one need is a comprehensive examination of WM modalities (auditory-verbal vs. visual-spatial) and processes (maintenance vs. manipulation) in a single analytic model using well-matched tasks that allow for the isolation of domain-specific processes to more clearly identify the precise nature of the WM deficits in children with ADHD.

Identifying group-level WM process- and modality-specific differences between children with and without ADHD is important. Yet, it is well-known that the disorder is characterized by neurocognitive heterogeneity, such that not all children with ADHD exhibit significant weaknesses in WM (Nigg & Casey, 2005). WM deficits have also been postulated as underlying learning problems in children with and without ADHD; and interestingly children with ADHD are at much higher risk for experiencing negative academic outcomes than their typically-developing peers (e.g., academic underachievement, school-drop out). Thus, a second critical area of study is to elucidate whether ADHD symptoms and WM are both or independently contributing to various aspects of functioning, such as academic achievement, school behavioral functioning, and global functioning. The demonstration of a link between WM deficits and these functional outcomes could provide considerable support to the further development of interventions targeting WM.
While the examination of concurrent relations between ADHD and WM ability is both relevant and important, research focusing on their longitudinal relations will likely provide greater insights into potential causal pathways. As noted earlier, Rapport et al. (2001) have postulated that WM is a core underlying neurocognitive deficit that is responsible for the manifestation of inattentive and hyperactive/impulsive symptomatology. Consistent with this idea, there are many cognitive training interventions that have been utilized for this population that contain WM paradigms, which operate under the premise that improving WM will lead to a reduction of the core ADHD symptoms (Klingberg et al., 2002). However, development of such interventions may be premature when we do not yet understand the cause-and-effect relations (if one exists) between WM and ADHD symptomatology. To date, very few studies (Brocki et al., 2007; Gau & Chiang, 2013; Schoemaker et al., 2014) have systematically investigated the longitudinal relations between WM and ADHD during early childhood when WM abilities are evolving and ADHD symptoms are first becoming evident. Thus, a third critical area of study is to examine whether early ADHD symptoms from the preschool years predict later WM performance during the school-aged years and/or whether early WM weaknesses predict later ADHD symptom severity.

Based upon these three critical issues and gaps in the field, it is hypothesized that:

1) As compared to their typically-developing peers, children with ADHD will perform a) differentially worse on measures of visual-spatial WM relative to auditory-verbal WM; and b) perform differentially worse on WM manipulation relative to WM maintenance irrespective of modality.

2) WM ability, but not ADHD symptom severity, will be significantly associated with all measures of academic functioning (objective and subjective); whereas, inattentive and hyperactive/impulsive symptom severity, but not WM ability,
would significantly predict teacher ratings of behavioral functioning and clinician ratings of global functioning.

3) Preschool inattentive symptoms will significantly predict later WM performance in school-aged children, above-and-beyond baseline WM functioning in the preschool years, but early WM will not predict later ADHD symptomatology, above-and-beyond baseline inattentive and hyperactive/impulsive symptoms.
Examining the Concurrent and Predictive Relations of Working Memory in Childhood Attention-Deficit/Hyperactivity Disorder

ADHD: General Overview

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity. ADHD is one of the most common psychiatric disorders of childhood, which affects approximately 5-11% of school-aged children (Walkup et al., 2014; Visser et al., 2014; American Psychiatric Association, 2013). The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013) describes three distinct presentations of the disorder, which include the Predominantly Inattentive Presentation, Predominantly Hyperactive/Impulsive Presentation, and the Combined Presentation. The Predominantly Inattentive Presentation describes those individuals who present with six or more inattentive symptoms, such as difficulties sustaining attention, carelessness, forgetfulness, etc., with fewer than six hyperactive/impulsive symptoms. Conversely, individuals diagnosed with the Predominantly Hyperactive/Impulsive Presentation demonstrate significant manifestations of hyperactivity/impulsivity, operationally defined as six or more symptoms, which include restlessness, fidgetiness, intrusiveness, etc., with fewer inattentive symptoms (i.e., < 6). Those individuals diagnosed with the Combined Presentation display significant manifestations of both inattentive and hyperactive/impulsive behaviors, defined as at least six out of the nine symptoms described for each domain. In addition to displaying these symptomatic behaviors, individuals who meet criteria for a diagnosis of ADHD must also demonstrate significant functional impairment in multiple settings, which include home/family life (Kasaei, 2013; Johnston & Mash, 2001), school/work performance (Hinshaw, 1992; Deshazo et al., 2002; Rapport et al., 1999;
LeFever, 2002), and/or peer relationships (Diamantopoulou et al., 2005; Hoza, 2007). Most importantly, longitudinal studies have shown that children with ADHD continue to suffer from lifelong maladjustment/difficulties even as they grow older (Harpin, 2005).

Similar to the behavioral presentation of ADHD, the developmental trajectory of the disorder is also quite variable. Typically, the disorder emerges in the preschool years for individuals who exhibit developmentally inappropriate levels of inattentive and hyperactive/impulsive symptomatology (Barkley, Fischer, Edelbrock, & Smallish, 1990; Berwid et al., 2005; Campbell, 1995); at which time, the hyperactive/impulsive symptoms are usually much more salient than the inattentive symptoms. Importantly, during the preschool years some children with the disorder may go undiagnosed, particularly if they present with predominantly inattentive symptoms and few hyperactive/impulsive symptoms. However, as children enter elementary school and the added demands of attention and concentration are imposed in the school setting, some additional children are diagnosed with the disorder. As children progress into adolescence, there is typically a lessening of hyperactive/impulsive symptoms (Hart, Lahey, Loeber, Applegate, & Frick, 1995), and manifestations of inattentive symptoms become more prominent. Moreover, as individuals pass through adolescence and into adulthood, an overall lessening of symptoms and associated impairments is observed for many individuals with the disorder. At this time a substantial portion of cases no longer meet diagnostic criteria for the disorder, while many persist with ADHD (American Psychological Association, 2013; Biederman et al., 1996; Biederman, Petty, Evans, Small, & Faraone, 2010; Faraone, Biederman, & Mick, 2006). Notably, among those no longer meeting full diagnostic criteria for ADHD, many still present with subthreshold levels of symptoms. The vast heterogeneity and variability of the
development of ADHD has made it diagnostically challenging to characterize and also in determining causal factors of the disorder.

**Biological Bases for ADHD**

Studies have shown that youth with ADHD are different from healthy controls in brain structure and functioning, within both subcortical and cortical areas.

Using magnetic resonance imaging (MRI), a recent cross-sectional mega-analysis found that people with ADHD had reduced volume size of the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume as compared to typically-developing individuals (Hoogman et al. 2017). Also, Hoogman and colleagues conducted exploratory lifespan analyses which found much greater effect sizes in youth than adults with ADHD among these subcortical areas, thus suggesting a likely delay in maturation and delay of degeneration in these subcortical areas for those with ADHD. Several other studies have also found reduced volume in components of the basal ganglia, including the globus pallidus, caudate, and putamen, in youth with ADHD (Aylward et al., 1996; Castellanos et al., 1996; Filipek et al., 1997, Semrud-Clikeman et al., 2000; Overmeyer et al., 2001; Castellanos et al., 2002; Semrud-Clikeman et al., 2006; Wellington et al., 2006; Makris et al., 2007; Qui et al., 2009), as well as the cerebellum (Castellanos et al., 2002; Durston et al., 2004), pons (Johnston et al., 2014), and reduced white matter of the brainstem (Johnston et al., 2014). Additionally, one group reported smaller volume of the lateral thalamus was correlated with hyperactivity, whereas larger volume of the medial thalamus was correlated with inattention (Ivanov et al., 2010).

Studies also suggest that youth with ADHD exhibit anatomical differences in the neocortex, such that researchers have reported that children and adolescents with ADHD have reduced volume throughout the cerebral cortex, and specifically in prefrontal areas (Castellanos et
al., 2002; Durston et al., 2004). Additionally, Shaw and colleagues (2007) conducted a longitudinal MRI study which found that peak cortical thickness developed at different time points for children with ADHD versus typically-developing controls. Specifically, they found that peak cortical thickness for nearly half of all cortical points occurred at around 10.5 years of age for children with ADHD, whereas this occurred at around 7.5 years of age for children without ADHD. Further, Shaw and colleagues (2013) suggest that this neurodevelopmental lag of key cortical areas may be specifically related to the behavioral manifestation of ADHD symptoms. For some individuals these cortical areas do begin to “catch-up” in adolescence and/or adulthood; and thus the development of the prefrontal cortex and associated cortical areas may contribute to the diminution of ADHD symptoms that some, but not all, individuals with childhood ADHD experience in adolescence and early adulthood (Halperin & Schulz, 2006; Giedd et al. 2010; Shaw et al., 2013). Consistent with this hypothesis, a recent investigation has shown that ADHD symptom reduction is associated with neuropsychological improvements over time (Rajendran et al., 2013).

Overall, it appears that the development of subcortical and cortical areas is disrupted in youth with ADHD, with recent data pointing to disruptions throughout the catecholamine-rich cortico-striato-thalamo-cortical loop (CSTC; Shaw et al., 2007; Ivanov et al., 2010). Consistent with these MRI data, studies using positron emission tomography (PET) provide compelling evidence for dopaminergic abnormalities in the basal ganglia, and more specifically in the caudate nucleus, in children with ADHD (Mehler-Wex et al., 2006; Volkow et al., 2009; Levy & Dadds, 2014), and animal models and pharmacological data provide compelling support for deficits in noradrenergic functioning (Biederman et al., 1999; Arnsten, 2009; Vanicek et al., 2014).
Treatments for Childhood ADHD

The most commonly utilized and best supported approaches to treating childhood ADHD have been through pharmacological and behavioral interventions. For pharmacologic treatment of ADHD, stimulant medication still remains the most widely used and well-studied approach. Researchers have found that stimulant medications alleviate core symptoms of ADHD and can lead to beneficial outcomes in family life and school productivity (Conners, 2002; Greenhill et al., 1999; Spencer et al., 1996). Despite these efficacious results, there are limitations to using stimulant medications; most notably, there are many parents who refuse to try stimulant medication for their children for a variety of personal reasons (Pisecco et al., 2001; Power et al., 1995). Also, some children experience negative side-effects from stimulants (MTA Cooperative Group, 2004; Swanson et al., 2007; Wigal et al., 2006) which could prevent the continued use of such medications. Additionally, many patients who use stimulant medication discontinue use after a few years or so, despite the fact that the disorder is a chronic, and oftentimes a lifelong condition (Thiruchelvam et al., 2001).

Some families and individuals choose to implement behavioral strategies, while others have utilized both behavior-modification and medication treatment in an effort to improve their child’s ADHD symptoms. The most commonly used and well-studied behavioral interventions for the disorder are parent management training and contingency management in both home and school settings. Studies have shown that these behavioral strategies lead to an improvement in ADHD symptoms, as well as positive functional outcomes (Anastopoulos et al., 1993; Sonuga-Barke et al., 2001; Cunningham et al., 1995). However, despite these beneficial outcomes, behavioral treatments have been shown not to demonstrate as much of a reduction of core ADHD symptoms as compared to stimulant medication use (MTA Cooperative Group, 2004; Sonuga-
Barke et al., 2013). Additionally, the use of behavioral interventions tend to be costly and quite difficult to implement into a family’s day-to-day life.

Moreover, even though both pharmacological and behavioral treatments are effective for alleviating many ADHD symptoms, in general these improvements have only been found to occur during the active treatment phase. That is, studies have failed to show that implementation of these treatments lead to normalization of functioning or significant long-term effects once these interventions have been discontinued. Due to this and other key limitations, it is still necessary to search for and devise better treatment paradigms for childhood ADHD. Hence, research is particularly needed to more precisely delineate the neurological/neuropsychological underpinnings and the cognitive heterogeneity of ADHD, which in turn may help inform the development of more suitable and perhaps personalized treatments for children with the disorder.

**ADHD and Neurocognitive Functioning**

Over the past several decades, a large body of research has found differences in performance between children with and without ADHD on a wide array of neurocognitive measures (Willcutt et al., 2005; Frazier et al., 2004), with clearest evidence for weaknesses in inhibitory control (Barkley, 1997; Oosterlaan et al., 1998), set-shifting (Ware et al., 2012; Sjowall et al., 2013), vigilance (Wilcutt et al., 2005), and working memory (Myatchin et al., 2012; Dovis et al., 2012; Martinussen et al., 2005; Kasper et al., 2012; Bédard et al., 2004). It has further been posited that some of these neurocognitive impairments might represent distinct endophenotypes of ADHD that may help to parse the heterogeneity of the disorder and move the field forward with regard to its genetic underpinnings (Castellanos & Tannock, 2002; Nikolas & Nigg, 2015). An endophenotype is a less complex heritable trait that is thought to underlie a more complex neuropsychiatric disorder that puts an individual at risk or increased vulnerability for developing
the disorder. In order to show that a certain neuropsychological component is an endophenotype of a disorder, biological family members (unaffected by the disorder) and the individuals themselves would all exhibit a deficit in the presumed endophenotype. In relation to ADHD, various executive functions (one in particular being working memory) have been posited as potential endophenotypes of the disorder. Thus, in recent years considerable attention has been devoted to examining working memory (WM) impairments among children and adolescents with ADHD.

**Working Memory**

According to Baddeley and Hitch (1974), WM refers to the ability to maintain and manipulate information in a temporary storage system so that it can be used to guide behavior and complete complex cognitive tasks and guide behavior. Baddeley’s (2000) revised model of WM contains four components: the phonological loop, the visuospatial sketchpad, an episodic buffer, and the central executive. The phonological loop and visuospatial sketchpad comprise two “slave systems” which are short-term storage components responsible for processing and retaining auditory-verbal and visual-spatial information, respectively. The episodic buffer is another slave system which is responsible for integrating information across the phonological loop and visuospatial sketchpad. Lastly, the central executive represents a supervisory component that controls and coordinates information processed by the slave systems.

Another key dissociation related to WM is the distinction between two closely-linked but separable processes: maintenance vs. manipulation. Maintenance involves simple rehearsing of information, while more effortful manipulation requires the rearranging and updating of information. Both of these WM processes occur within each modality-specific slave system of Baddeley and Hitch’s model; however, more complex tasks (i.e., manipulation) require greater
effort to be exerted by the central executive, whereas simpler tasks (i.e., maintenance) require minimal control from this supervisory component. Taken together, this theoretical model posits the existence of two distinct WM modalities/domains (i.e., auditory-verbal and visual-spatial) and two distinct WM processes (WM maintenance and WM manipulation).

**Neural Substrates Implicated in Working Memory**

To date, some research provides support for Baddeley’s model in terms of the neural networks underlying the modalities and processes of WM. Neuroimaging studies have shown particular activation in posterior brain regions, specifically in the parietal lobes, when individuals are storing or maintaining information (Courtney et al., 1996; Crosson et al., 1999; Zurowski et al., 2002). Furthermore, a dorsal-ventral dissociation exists for processing spatial and object information, respectively, in the parietal lobes (Wager & Smith, 2003), which provides support for distinct brain regions being activated for spatial and object information during the maintenance phase (or storage components) of WM. As tasks increase in complexity, greater recruitment of resources from the central executive of WM is required. Additional research has found support for this, such that when individuals complete tasks involving higher executive load, an increase in activation is observed in both the dorsolateral and ventral lateral prefrontal cortices, thus suggesting more frontally-mediated mechanisms underlying manipulation processes (Collette & Van der Linden, 2002). Nevertheless, there are some discrepancies in the literature. Whereas some researchers suggest that activation of the dorsolateral prefrontal cortex is associated with manipulation of visual-spatial information and activation of the ventral lateral prefrontal cortex is associated with manipulation of auditory-verbal information (Goldman-Rakic, 1995; Meyer et al., 2011); others postulate that the two WM modalities may not be distinguishable at the level of neural activation for these more complex manipulation processes (Desposito et al., 1998; Wager
& Smith, 2003). Lastly, a recent review by Baddeley (2012), suggests two key limitations in understanding the neurobiological basis for WM. First, while some researchers have found the above brain regions activated while individuals complete various WM tasks, there has been a lack of consistent replicability of these findings. Second, past research has almost solely focused on localizing the different WM processes and modalities to specific brain areas; this is quite problematic since WM is most likely comprised of a complex network and is probably better understood by examining underlying neural pathways rather than neuroanatomical localization.

**Development of Working Memory**

Neural development begins prenatally and the brain undergoes rapid, non-linear growth, especially throughout the early childhood years (Simmonds et al., 2014). Neuronal growth and migration, as well as the generation of synapses within the cerebral cortex develop at different rates, with development of anterior brain regions (i.e., the prefrontal cortex) occurring later in maturational development. For typically-developing children, research has shown volumetric increases in grey matter of the cerebral cortex, with most growth occurring between birth and 8-years-old; whereas white matter volume of the cerebral cortex has been shown to increase from childhood through adulthood (Belsky & de Haan, 2011). Additionally, imaging studies have demonstrated that peak cortical thickness is achieved at around 7.5 years of age for typically-developing children (Shaw et al., 2007). The developing brain in childhood and adolescence is also marked by the protracted phase of cortical thinning that follows peak cortical thickness (Stiles & Jernigan, 2010). This progressive neuronal growth and myelination of the cerebral cortex which occurs prenatally through early adulthood has been strongly associated to the development of cognitive and behavioral processes (Casey, Giedd, & Thomas, 2000; Nagy, Westerberg, & Klingberg, 2004).
This underlying brain growth appears to correspond with the development of WM. Examination of base rates of simple span tasks reveal that storage capacity of WM maintenance increases rapidly in the early childhood years (e.g., 7-9 years old), and this capacity appears to occur slightly earlier for auditory-verbal information than visual-spatial information (Wechsler, 2003; Kaplan et al., 2004). However, in neither domain does WM storage reach full capacity until later adolescence (Wechsler, 2003; Kaplan et al., 2004). As WM processing grows in complexity (i.e., updating or manipulating information), greater recruitment of frontal brain regions (i.e., dorsal lateral and ventral lateral prefrontal cortices) are required. The capacity of WM manipulation begins developing in childhood but does not incrementally increase until pre-adolescence and does not reach full capacity until early adulthood (Wechsler, 2003; Kaplan et al., 2004). This is consistent with imaging findings that frontal brain regions do not reach full maturity until early adulthood (Fuster, 2002; Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999).

**Working Memory Models in Childhood ADHD**

There are two major models that attempt to explain the role of WM in ADHD. Barkley (1997) suggests that behavioral inhibition is the central deficit in individuals with ADHD and that other executive deficits, including WM deficiencies, occur secondary to or downstream from behavioral disinhibition. According to this model, the core deficit of behavioral disinhibition in children with ADHD compromises working memory (as well as other executive functions) because children cannot delay behavior long enough to deploy these executive processes. In support of this model, several studies have found that children with ADHD perform more poorly on objective tests of behavioral inhibition/response inhibition as compared to their typically-developing peers (Barkley, 1997; Lijffijt et al., 2005; Alderson et al., 2007; Shimoni et al., 2012).
However, the cause-and-effect relation of whether or not behavioral disinhibition leads to poorer recruitment of executive functions, such as working memory, remains unclear.

Conversely, Rapport and colleagues (Rapport, Chung, Shore, & Isaacs, 2001; Alderson, Rapport, Hudec, Sarver, & Kofler, 2010) have hypothesized that impaired WM is the core underlying neurocognitive deficit that leads to the dysregulated behavior typical of children with ADHD (i.e., deficits in attention and behavioral inhibition). In support of this hypothesis, these investigators have conducted several novel experiments which suggest that WM performance in children with ADHD mediates the relations between ADHD and response inhibition (Alderson et al., 2010; Raiker et al., 2012), as well as between ADHD and activity level (Rapport et al., 2009). However, even with this evidence it remains unclear whether WM is responsible for the manifestation of inattentive and/or hyperactive/impulsive behaviors, or if WM is downstream from or secondary to ADHD symptomatology. Furthermore, if WM does underlie the core ADHD symptoms, it still remains to be investigated which WM components are responsible for this. Thus, the predictive nature between WM and ADHD has yet to be clarified and systematically studied.

**Previous Research Investigating WM Deficiencies in Childhood ADHD**

Considerable research has attempted to clarify the concurrent relations between childhood ADHD and WM. Two recent meta-analyses (Martinussen et al., 2005; Kasper et al., 2012) have nicely synthesized research pertaining to WM modalities (i.e., auditory-verbal and visual-spatial) and to some extent WM processes (i.e., maintenance and manipulation) in children with ADHD. Together these meta-analyses included 66 different studies that have examined WM in children with ADHD. Both meta-analyses indicated that children with ADHD have substantially poorer visual-spatial WM compared to their typically-developing peers, with large effect sizes ranging from 0.74 to 1.06. However, conclusions regarding the auditory-verbal domain were less
consistent. Martinussen et al. (2005) found more limited group differences in auditory-verbal WM (mean effect size = 0.43), whereas Kasper et al. (2012) reported substantial auditory-verbal WM deficits (effect size = 0.69). Furthermore, only the meta-analysis from Martinussen et al. (2005) reported effect sizes for WM processes and found that overall there was a large effect size (d = 1.06) for WM manipulation in the visual-spatial domain, but not in the auditory-verbal domain, and more modest effect sizes for WM maintenance (d = 0.43). Taken together, despite extensive research in this area (Bédard et al., 2004; Kerns et al., 2001; de Jong et al., 2009; Gau et al., 2009; Healy et al., 2006; Manassis et al., 2007; McInnes et al., 2003; Nyman et al., 2010; Gau & Chiang, 2013; Sjowall et al., 2013; Udal, Oygarden, Egeland, Malt, Lovdahl, Pripp, & Groholt, 2012a; Karalunas et al., 2013; Nikolas et al., 2013; Udal, Oygarden, Egeland, Malt, & Groholt, 2012b; Dovis et al., 2012; Dovis et al., 2013; Takács et al., 2014; Tseng et al., 2013; Vance et al., 2013; Rhodes et al., 2012; Fried et al., 2012; Myatchin et al., 2012; Strand et al., 2012), there are discrepancies in the literature and it remains unclear, as a group, where the particular WM impairments lie for children with ADHD. More precisely, it remains unclear whether children with ADHD have specific deficits in the more complex process of manipulation, when maintenance, which is closely linked to attentional control, is held constant; or if children with ADHD are deficient in both WM processes (maintenance and manipulation).

To date, there have been two research groups to concurrently examine both WM processes and both WM modalities in a single study. McInnes et al. (2003) administered tasks to assess WM maintenance and manipulation in both domains (auditory-verbal and visual-spatial). This could have allowed them to parse the differences in WM processes and modalities within one unified model. However, they analyzed each WM process within each domain separately, precluding the parsing of specific WM weaknesses while controlling for other related processes. They reported
that children with ADHD performed significantly worse than controls on tasks assessing visual-spatial maintenance and manipulation and auditory-verbal manipulation; however, no significant differences were found between the groups on WM maintenance of auditory-verbal information. In a similarly designed study, Fair et al. (2012) administered both the forward (maintenance) and backward (manipulation) conditions of the digit span task and a computerized version of the spatial span task, which would have also allowed them to parse the differences in these WM processes. However, even though they separately analyzed the two forms of WM processes, which they defined as encoding/span [maintenance] and WM [manipulation], they collapsed their findings across both modalities (i.e., auditory-verbal and visual-spatial). To date, there have yet to be any studies to systematically examine both WM processes and modalities in a single analytic model which would allow for one to see specific or global deficits of WM processes. Thus, it is unclear what larger effect sizes in WM manipulation means (as reported in many studies and the meta-analysis from Martinussen et al., 2005); it may represent a specific deficit in WM manipulation or it may merely be due to the fact that manipulation tasks require both maintenance and manipulation. Similarly, it remains to be investigated, whether both WM modalities are impaired in children with ADHD, or if one is differentially worse than the other in this population.

Furthermore, most research investigating WM in youth with ADHD has been concurrent in nature. That is, there have only been a small number of studies to systematically examine the longitudinal/predictive relations between ADHD and WM. While Gau and Chiang (2013) found that early inattentive symptoms were significantly related to WM in early adolescence, their study was conducted by obtaining reports of childhood ADHD symptoms retrospectively from parents, and as we know, retrospective reports have been shown to be particularly suspect (Miller, Newcorn, & Halperin, 2010). Longitudinal studies utilizing prospective data of preschoolers
(Brocki et al., 2007; Schoemaker et al., 2014) have found somewhat divergent results. Schoemaker and colleagues (2014) found evidence for WM deficits in ADHD over time (including during the preschool years), whereas Brocki and colleagues (2007) found no longitudinal relations between ADHD and WM; and importantly, they did not find any relation between early WM scores and ADHD symptom severity in early childhood either. This could be due to the lack of sensitivity in their measures. To date, no study has longitudinally examined the extent to which early WM predicts change in ADHD severity over time and vice versa, the extent to which early ADHD predicts change in WM ability. Due to such limited research examining these predictive relations, and because there are discrepancies of findings across studies, future research is needed to clarify WM’s role in the development of ADHD symptomatology. Without conducting additional longitudinal studies in this area, it becomes difficult to determine if a causal relation exists between WM and ADHD.

A significant limitation in much of the previous research examining WM in children with ADHD is the age-range of the samples studied. The majority of studies (Ferrin et al., 2012; Gau et al., 2013; Myatchin et al., 2012; Rhodes et al., 2012; Vance et al., 2013) have utilized age ranges spanning as much as a nine years within a given cohort. As WM, like other executive functions, undergoes rapid non-linear growth throughout childhood and early adolescence (Simmonds et al., 2014), collapsing data across these wide age ranges complicates efforts to determine the specific chronological age(s) at which WM differences occur. Moreover, combining ages into a single cohort may decrease the likelihood of detecting subtle specific differences in WM processes and modalities between children with and without ADHD over early development.
Working Memory Treatments for ADHD

Understanding the nature of WM deficits in children with ADHD has important clinical implications because recent interventions for the disorder specifically focus on WM training with the assumption that improved WM will result in a reduction of core ADHD symptoms (Klingberg et al., 2002; Beck et al., 2010). Perhaps the most widely publicized and empirically investigated of these is Cogmed Working Memory Training (CWMT; Klingberg et al., 2005; Klingberg, 2010). However, recent data (Chacko et al., 2014; van-Dongen-Boomsma et al., 2014), reviews (Rapport et al., 2013), and meta-analyses (Cortese et al., 2015) have suggested that CWMT may not yield real-world improvements of ADHD behavior, but instead primarily improve proficiency on proximal cognitive (i.e., working memory) tests with limited generalization. More importantly, it may be somewhat premature to utilize such interventions before we fully understand the degree to which WM deficits play a causal role in ADHD.

Concluding Summary

Taken together, children with ADHD have been shown to exhibit weaknesses in WM as compared to their typically-developing peers, but several critical issues and gaps remain in the literature. First, it is unclear whether children with ADHD are globally or specifically impaired in the various WM processes and modalities. Second, as many youth with ADHD also present with academic difficulties, it is worthwhile to examine whether academic performance and school behavioral functioning are related to WM deficiencies or ADHD symptomatology, or both. Finally, while some researchers have postulated that WM weaknesses are responsible for the behavioral manifestation of ADHD symptoms, it remains to be investigated whether a true longitudinal association exists between these variables.
Based upon the need to investigate these areas, the following three studies were conducted to examine these concurrent and predictive relations between WM and ADHD. It was hypothesized that:

1) As compared to their typically-developing peers, children with ADHD will perform a) differentially worse on measures of visual-spatial WM relative to auditory-verbal WM; and b) perform differentially worse on WM manipulation relative to WM maintenance irrespective of modality.

2) WM ability, but not ADHD symptom severity, will be significantly associated with all measures of academic functioning (objective and subjective); whereas, inattentive and hyperactive/impulsive symptom severity, but not WM ability, would significantly predict teacher ratings of behavioral functioning and clinician ratings of global functioning.

3) Preschool inattentive symptoms will significantly predict later WM performance in school-aged children, above-and-beyond baseline WM functioning in the preschool years, but early WM will not predict later ADHD symptomatology, above-and-beyond baseline inattentive and hyperactive/impulsive symptoms.

GENERAL METHODS

The sections below outline the general methodology which was used for the following three studies of this dissertation. For all three studies, the child participants were recruited in the same way, and ADHD diagnoses for the child participants were also obtained similarly for each of the following three studies.

Participants
All participants were initially recruited in their preschool years (3-4 years-old, N=216) as part of a larger longitudinal investigation examining early development of children with and without ADHD. Children were recruited via school screenings and direct referrals into the study by preschools, as well as pediatric and mental health outpatient clinics in the New York Metropolitan area. To be included in the initial study, preschool children had to be English-speaking and attending school and/or daycare. Exclusionary criteria at the time of initial recruitment were: FSIQ < 80 as assessed by the Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III; Wechsler, 2006), systemic medication use (including treatment for ADHD), and presence of a neurological disorder, post-traumatic stress disorder, and/or pervasive developmental disorder. At their initial evaluation (ages 3-4 years), parents/caregivers and teachers rated all children using the ADHD-Rating Scale-IV (ADHD-RS-IV; DuPaul, Power, Anastopoulus, & Reid, 1998), which consists of the 18 ADHD symptom criteria listed in the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition Text Revision (DSM–IV–TR; American Psychiatric Association, 2000). Children rated as having six or more different symptoms, as defined by a rating of pretty much or very much, in either the inattentive or hyperactive/impulsive domain, as endorsed by a combination of parent/caregiver and/or teacher reports, were deemed to be “at-risk” for developing ADHD. Therefore, these children did not necessarily meet full diagnostic criteria for ADHD (as presented in DSM-IV or DSM-5) at initial recruitment. However, they did show elevated levels of ADHD symptoms and were symptomatic in at least one setting. Children who were rated as having fewer than three symptoms in both symptom domains as endorsed by both parent/caregiver and teacher ratings were classified as “typically-developing.”
As part of their 8-year-old evaluation, children received a comprehensive psychiatric evaluation which consisted of a semi-structured interview with the parent/caregiver, along with several parent and teacher rating scales. Children were determined to have an ADHD diagnosis if they met full DSM-5 diagnostic criteria for one of the three major ADHD presentations at the 8-year-old evaluation.

Materials

*Diagnostic Measures*

**ADHD-RS-IV.** Parents and teachers completed the ADHD Rating Scale-IV (DuPaul, Power, Anastopoulos, & Reid, 1998) at both the baseline and 8-year-old follow-up evaluation. This scale includes that 18 symptoms for ADHD listed in the DSM. Parents and teachers indicated the extent to which participants exhibited each of these behaviors on a 4-point Likert scale (0 = *not at all*, 1 = *somewhat*, 2 = *pretty much*, and 3 = *very much*). Coefficient alpha for the parent scales at baseline and 8-year-old evaluations were .95 and .97, respectively; analogous values for teacher ratings were .97 and .96, respectively.

**Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (KSADS-PL).** At the 8-year-old follow-up parents and/or caregivers were administered the KSADS-PL, a semi-structured clinical interview (Kaufman, Birmaher, Brent, Rao, & Ryan, 1996) designed to assess the presence of childhood psychiatric disorders. The interviewers were well-trained psychology graduate students or post-doctoral fellows, blind to the children’s baseline status, and were supervised by doctoral-level licensed psychologists to arrive at diagnoses for the child participants.

*Intelligence Measures*
Wechsler Preschool and Primary Scale of Intelligence – Second Edition (WPPSI-III). Preschool children were administered all of the primary subtests from the WPPSI-III in order to determine their general intellectual ability at the initial evaluation. Preschoolers with a total full scale IQ of less than 80 were excluded from the longitudinal study.

Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV). At the 6-year-old follow-up, children were administered all of the primary subtests from the WISC-IV in order to re-evaluate their general intellectual ability. For all of the following studies, the General Ability Index (GAI) was calculated which is based on the sum of scaled scores from the Verbal Comprehension and Perceptual Reasoning subtests. The GAI was used in some of the analyses for the following studies instead of the WISC-IV Full Scale IQ in order to reduce overlap with measures of WM.

Procedure

At the initial preschool evaluation, parents and teachers completed the ADHD-RS to assess children’s ADHD symptom severity, along with several other scales assessing a broader array of psychopathological conditions, impairment, and temperament, which are not part of the present dissertation research.

Following their initial evaluation, the children and their families received annual follow-up evaluations in which the children completed a variety of neuropsychological and academic tests, while their parents/caregivers have completed various rating scales and a semi-structured clinical interview. Additionally, the children’s teachers also completed a set of rating scales during each follow-up period which were incorporated into determining diagnoses for the children via the semi-structured clinical interview.
All of the following studies were approved by the institutional review board (IRB) of the City University of New York. Following a full description of the study and their rights as participants, parents/caregivers signed IRB-approved informed consent forms and children provided verbal assent at the 8-year-old evaluation.
STUDY 1

Good Holders, Bad Shufflers:

An Examination of Working Memory Processes and Modalities in Children with ADHD

(Simone, Bédard, Marks, & Halperin, 2016)

To parse the specific WM deficiencies in children with ADHD, this study examined two distinct WM modalities (auditory-verbal vs. visual-spatial) and both WM processes (maintenance vs. manipulation) in a single analytic model using well-matched tasks. By conducting a design such as this, the aim was to isolate deficits in domain-specific processes in order to more clearly identify the precise nature of WM deficits exhibited by children with ADHD. Specifically, we investigated whether children with ADHD are deficient in the simpler process of WM maintenance, or if they are selectively deficient in the more complex process of WM manipulation above-and-beyond their WM maintenance ability. While previous studies have utilized tasks to examine the various WM components (McInnes et al., 2003; Fair et al., 2012), to the best of our knowledge, there are no studies which have investigated all of these WM components in a single analytic model that allows for the parsing of distinct processes. Thus, the following were hypothesized:

a. As compared to their typically-developing peers (non-ADHD comparison children), children with ADHD will perform differentially worse on measures of visual-spatial WM relative to auditory-verbal WM

b. As compared to their typically-developing peers (non-ADHD comparison children), children with ADHD will perform differentially
worse on WM manipulation relative to WM maintenance irrespective of modality.

Method

Participants

Children were classified as ADHD if they were deemed “at-risk” during the baseline evaluation (thus had clear evidence of early onset of symptoms) and met full DSM-5 diagnostic criteria for one of the three major ADHD presentations at the 8-year-old evaluation. The non-ADHD comparison group consisted of children who were deemed “typically developing” at the baseline evaluation and did not have an ADHD diagnosis at the 8-year-old evaluation. The final sample consisted of 63 children with ADHD (M = 8.58 years; SD = 0.31; 75% male) and 51 non-ADHD comparison children (M = 8.52 years; SD = 0.30; 63% male). Among those with ADHD, 18 (28.57%), 7 (11.11%), and 38 (60.32%) met criteria for the Predominantly Inattentive, Predominantly Hyperactive-Impulsive, and Combined presentations, respectively. As shown in Table 1, the ADHD and non-ADHD groups differed significantly in parent and teacher ratings of ADHD symptoms at the time of their baseline and 8-year-old evaluations. Further, the ADHD group had a significantly lower WISC-IV General Ability Index (GAI) as measured at age 6, as well as lower socioeconomic status (SES). The groups did not differ significantly in age, gender distribution, or race/ethnicity.
Table 1: Descriptive characteristics of the sample

<table>
<thead>
<tr>
<th></th>
<th>Non-ADHD (N = 51)</th>
<th>ADHD (N = 63)</th>
<th>t / χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, Mean (SD)</td>
<td>8.52 (0.30)</td>
<td>8.58 (0.30)</td>
<td>1.04</td>
<td>0.30</td>
</tr>
<tr>
<td>Sex: % males</td>
<td>62.75</td>
<td>74.60</td>
<td>0.42</td>
<td>0.30</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td>1.76</td>
<td>0.25</td>
</tr>
<tr>
<td>Non-Hispanic, White</td>
<td>35.29</td>
<td>47.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>64.71</td>
<td>52.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WISC-IV GAI Composite Score at 6-years-old, Mean (SD)</td>
<td>110.43 (13.05)</td>
<td>103.57 (14.71)</td>
<td>2.60</td>
<td>0.01</td>
</tr>
<tr>
<td>SES at Baseline, Mean (SD)</td>
<td>70.08 (16.35)</td>
<td>59.29 (2.47)</td>
<td>3.21</td>
<td>0.002</td>
</tr>
<tr>
<td>ADHD-RS Parent Report at Baseline, Mean (SD)</td>
<td>8.33 (4.63)</td>
<td>29.38 (9.78)</td>
<td>14.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADHD-RS Teacher Report at Baseline, Mean (SD)</td>
<td>4.10 (4.46)</td>
<td>29.29 (14.02)</td>
<td>12.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADHD-RS Parent Report at 8-years-old, Mean (SD)</td>
<td>5.43 (4.99)</td>
<td>26.68 (11.81)</td>
<td>11.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADHD-RS Teacher Report at 8-years-old, Mean (SD)</td>
<td>5.36 (7.05)</td>
<td>25.22 (13.76)</td>
<td>12.32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Materials

Diagnostic Measures

ADHD-RS-IV. See above.


Working Memory Measures

Auditory-Verbal WM. Auditory-verbal WM was assessed using the Digit Span subtest from the Wechsler Intelligence Scale for Children - Fourth Edition Integrated (WISC-IV Integrated; Kaplan et al., 2004). The Digit Span subtest contains two conditions, Digit Span Forward and Digit Span Backward. Digit Span Forward requires participants to listen to a series
of number sequences and recite back each sequence in the same order. Digit Span Backward requires individuals to recite back each number sequence in the reverse order.

**Visual-spatial WM.** Visual-spatial WM was assessed using the Spatial Span subtest from the WISC-IV Integrated (Kaplan et al., 2004). Similar to Digit Span, the Spatial Span subtest has two conditions, Spatial Span Forward and Spatial Span Backward. In Spatial Span Forward, participants watch the examiner point-out a series of block sequences; examinees must touch the blocks in the same order. For Spatial Span Backward, participants are required to touch the blocks in the reverse order.

Both of these tasks (Digit Span and Spatial Span) begin with a two-span sequence and the sequence length progresses by one until the final nine-span sequence is reached for the forward conditions and eight-span sequence for the backward conditions. There are two trials for each span. The tasks are discontinued when the participant fails both trials of the same span length or completes the final sequence.

For both WM modalities, within each of these subtests the forward condition served as a measure of WM maintenance and the backward condition served as a measure of WM manipulation. For all WM measures, raw scores rather than scaled scores served as the primary dependent measures because of the greater sensitivity and variability that they provide, as well as their ability to allow for direct comparisons across the forward and backward conditions. The narrow age-range of the sample (i.e., all 8-year-olds) as well as the close correspondence in age across groups (i.e., <1 month difference) makes the use of raw scores particularly appropriate for the present study.

**Procedure**
Children were tested individually at age 8 years by a member of the research team while a different evaluator interviewed the child’s parent/caregiver using the K-SADS-PL. Both examiners were blind to the child’s prior diagnostic status. The full evaluation lasted approximately 2-3 hours, during which children completed the WM tasks as well as other neuropsychological and academic measures. All children completed the Spatial Span task first and then the Digit Span task. Children were given a small prize at the end of the session for participating in the study. Parents received compensation for their time and expenses associated with study participation.

Statistical Analysis

A 3-way Group x Modality x Condition (2 x 2 x 2) analysis of variance (ANOVA) was conducted to determine main and interaction effects related to WM modalities (visual-spatial and auditory-verbal) and WM processes (maintenance and manipulation of information). Group (ADHD vs. non-ADHD) served as the between group variable, and Modality (Auditory-Verbal vs. Visual-Spatial) and Condition (Forward vs. Backward) served as within group variables. A significant main effect of Group would suggest that overall the groups performed significantly different on the WM measures. A main effect of Modality would indicate significant differences in performance across auditory-verbal WM and visual-spatial WM. A main effect of Condition would point to a significant difference in performance across maintenance and manipulation processes. While these main effects are noteworthy (and expected), specific interaction effects are of primary interest. A Group x Modality interaction would indicate that one group performed differentially worse across one of the WM modalities (i.e., auditory-verbal or visual-spatial). A Group x Condition interaction would indicate that one group performed differentially worse in one of the WM processes (i.e., maintenance or manipulation). Further, a 3-way Group x Modality x
Condition interaction would suggest that one group performed differentially worse on a specific WM process in one of the WM domains. Where significant interactions emerged, post-hoc tests comparing the two groups on key data points were conducted to elucidate the nature of specific interactions. Bonferroni’s correction was employed to control for multiple contrasts. As four post-hoc tests were conducted, an alpha of .0125 (.05/4) was required in these individual contrasts for statistical significance. Effect sizes are reported as partial eta squared ($\eta^2_p$), with .02, .13 and .26 reflecting small, medium, and large effect sizes, respectively (Miles & Shevlin, 2001).

It is through our unique statistical analysis (2 x 2 x 2 ANOVA) that we will be able to make direct comparisons among WM processes and modalities within this population. While some may suggest to utilize analysis of covariance to control for pre-existing group differences in one variable (e.g., WM maintenance) when determining group differences on a different variable (e.g., WM manipulation), compelling statistical (Miller & Chapman, 2001) and conceptual (Dennis et al. 2009) arguments have been made as to why such an approach (i.e., analysis of covariance) should not be employed and would likely misrepresent the true findings. Additionally, researchers also use ANCOVA to control for variables on which clinical groups differ (such as IQ) and the use of such covariates are also likely to misrepresent the true findings. As such, ANCOVA was not utilized in the present study to assess for differences between WM maintenance and manipulation, as well as visual-spatial and auditory-verbal WM, and no covariates were incorporated into our primary analyses (such as GAI).

Using the same analytic approach, secondary analyses were conducted to examine ADHD presentation differences in WM. As there were only 7 children with ADHD, Predominantly Hyperactive/Impulsive presentation, these analyses were restricted to those with ADHD,
Predominantly Inattentive presentation (ADHD-I) and ADHD, Combined Presentation (ADHD-C).

Results

Descriptive statistics for the different WM measures as a function of group are displayed in Table 2.

Table 2: Group scores on each working memory task

<table>
<thead>
<tr>
<th>Working Memory Measures</th>
<th>Non-ADHD (N = 51)</th>
<th>ADHD (N = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span Forward Raw Score, Mean (SD)</td>
<td>7.90 (1.85)</td>
<td>7.56 (1.41)</td>
</tr>
<tr>
<td>Digit Span Backward Raw Score, Mean (SD)</td>
<td>6.63 (1.51)</td>
<td>5.73 (1.50)</td>
</tr>
<tr>
<td>Spatial Span Forward Raw Score, Mean (SD)</td>
<td>6.80 (1.69)</td>
<td>5.92 (2.13)</td>
</tr>
<tr>
<td>Spatial Span Backward Raw Score, Mean (SD)</td>
<td>6.12 (1.83)</td>
<td>4.43 (2.10)</td>
</tr>
<tr>
<td>Digit Span Forward Scaled Score, Mean (SD)</td>
<td>10.31 (2.76)</td>
<td>9.86 (2.35)</td>
</tr>
<tr>
<td>Digit Span Backward Scaled Score, Mean (SD)</td>
<td>11.12 (2.89)</td>
<td>9.44 (2.93)</td>
</tr>
<tr>
<td>Spatial Span Forward Scaled Score, Mean (SD)</td>
<td>11.31 (2.87)</td>
<td>9.95 (3.46)</td>
</tr>
<tr>
<td>Spatial Span Backward Scaled Score, Mean (SD)</td>
<td>12.16 (2.85)</td>
<td>9.51 (3.33)</td>
</tr>
</tbody>
</table>

ADHD vs. Non-ADHD children

There was a significant main effect of Group (F(1,112)=17.31, p<0.001, $\eta^2_p=0.13$), indicating that 8-year-old children with ADHD performed worse across all WM tasks compared to their non-ADHD peers. Also observed was a main effect of Modality (F(1,112)=56.01, p<0.001, $\eta^2_p=0.33$), such that participants performed worse on the visual-spatial compared to the auditory-verbal tasks. Lastly, a main effect of Condition (F(1,112)=82.53, p<0.001, $\eta^2_p=0.42$), indicated poorer performance on the backward relative to forward conditions.

As depicted in Figure 1, there was a significant Group x Condition interaction (F(1,112)=5.45, p=0.02, $\eta^2_p=0.05$). Post hoc analyses revealed that the groups differed significantly on backward (F(1,112)=21.81, p<0.001, $\eta^2_p=0.163$), but only marginally on forward tasks (F(1,112)=5.349, p=0.02, $\eta^2_p=0.046$) after Bonferroni correction.
Additionally, there was a significant interaction of Group x Modality (F(1,112)=4.79, p=0.03, $\eta^2_p=0.04$). Post hoc analyses revealed that the groups significantly differed on auditory-verbal (F(1,112)=7.682, p=0.007, $\eta^2_p=0.064$), as well as visual-spatial WM tasks (F(1,112)=16.395, p<0.001, $\eta^2_p=0.128$; see Figure 2). However, those with ADHD performed differentially worse on visual-spatial relative to auditory-verbal WM tasks.
Figure 2. Performance of children with ADHD and their non-ADHD peers on auditory-verbal and visual-spatial tasks collapsed across condition. Bars indicate standard error (SE).

Group x Modality Interaction: $F(1,112) = 4.79$, $p = 0.03$, $\eta^2_p = 0.04$
Auditory-verbal WM: $F(1,112) = 7.682$, $p = 0.007$, $\eta^2_p = 0.064$
Visual-spatial WM: $F(1,112) = 16.395$, $p < 0.001$, $\eta^2_p = 0.128$

Finally, neither the Condition x Modality interaction ($F(1,112)=3.59$, $p>0.05$, $\eta^2_p=0.03$) nor the three-way interaction ($F(1,112)=0.28$, $p>0.05$, $\eta^2_p=0.002$) were significant.

**ADHD-I vs. ADHD-C**

Secondary analyses examining differences between children with ADHD-I and ADHD-C yielded a significant main effect of Modality ($F(1, 54)=38.12$, $p<0.001$, $\eta^2_p=0.41$), indicating that children performed worse on the visual-spatial compared to the auditory-verbal tasks. Also, a main effect of Condition ($F(1, 54)=76.10$, $p<0.001$, $\eta^2_p=0.59$) indicated lower scores on the backward relative to the forward conditions. The main effect of Group was not significant ($p=0.767$), indicating that overall performance across presentations did not differ.
Nevertheless, a significant Group x Condition interaction emerged \((F(1,54)=7.31, p=0.009, \eta^2_p=0.12)\), such that children with ADHD-I, compared to those with ADHD-C, performed differentially worse on backward versus forward tasks (see Figure 3). Post hoc tests did not reveal significant group differences on forward or backward tasks (both \(p>.10\)). However, children with ADHD-I had a significantly greater difference between forward and backward scores as compared to the ADHD-C group \((t=2.70, p=.009)\). The Group x Modality \((F(1,54)=2.54, p=0.12, \eta^2_p=0.04)\) and 3-way \((F(1,54)=2.41, p=0.13, \eta^2_p=0.04)\) interactions were not significant.

Discussion

Study 1 was designed to systematically examine components of WM (i.e., auditory-verbal maintenance, auditory-verbal manipulation, visual-spatial maintenance, and visual-spatial
manipulation) in children with ADHD within a single analytic model, and represents the first of its kind to parse distinct memory processes while accounting for global attentional and mnemonic abilities. Overall, the data indicated that, as compared to their non-ADHD peers, children with ADHD exhibited incrementally greater deficits in visual-spatial versus auditory-verbal WM; however, for children with ADHD, impairments were evident in both domains. In addition, those with ADHD demonstrated significantly greater deficits in WM manipulation relative to WM maintenance as compared with their non-ADHD peers. Taken together the findings suggest that children with ADHD are not globally impaired across WM processes, but rather have a pattern of relative strengths and weaknesses.

Our findings are largely consistent with and expand upon previously published literature as described in two meta-analyses that have systematically examined research on WM deficits in children with ADHD (Martinussen et al. 2005; Kasper et al. 2012). Martinussen et al. (2005) reported statistically large differences between children with and without ADHD in visual-spatial WM, but only a moderate effect size for differences in auditory-verbal WM. Consistent with our results, these findings suggest that children with ADHD perform significantly worse on visual-spatial WM tasks relative to auditory-verbal WM tasks. However, while this meta-analysis did differentiate between the WM processes of maintenance vs. manipulation of information, they did not examine manipulation after controlling for the processes associated with maintenance such as attention and rehearsal. Thus, our finding of a selective deficit in WM manipulation, after accounting for these other factors, expands upon previous findings.

Nevertheless, the findings of the current study, as well as those of Martinussen et al. (2005), were somewhat discrepant from the more recent meta-analytic review by Kasper and colleagues (2012), which found relatively large effect sizes differentiating children with ADHD from controls.
for both visual-spatial and auditory-verbal WM. Processing demands associated with maintenance and manipulation were not differentiated in this meta-analysis, and thus our findings expand upon previous research.

The distinction between maintenance and manipulation processes is critical to understanding the nature of the WM deficit among children with ADHD. Several studies have independently examined performance on forward and backward tasks in children with and without ADHD, with some examining differences on both measures (Udal et al., 2012a) and others examining differences only on backward tasks (Gau et al., 2013; Sjowall et al., 2012; Udal et al., 2012b; Karalunas et al., 2013; Nikolas et al., 2013). However, findings on backward tasks are difficult to interpret when performance on more rudimentary (forward) tasks requiring attention and sequencing are not accounted for within the model. Our data demonstrate that youth in the present sample are deficient in WM manipulation independent of or above and beyond other potentially more global impairments.

Rapport et al. (2001) have hypothesized that WM is the core deficit that underlies the dysregulated behavior typically observed in children with ADHD. In support of this hypothesis, these investigators have conducted several novel experiments which suggest that WM performance in children with ADHD mediates the relations between ADHD and response inhibition (Alderson et al., 2010), as well as between ADHD and activity level (Rapport et al., 2009). However, these studies do not clarify which WM processes in particular, underlie the core ADHD symptoms. While our data cannot directly address the extent to which WM deficiencies are a core deficit in ADHD or an epiphenomenon of other deficits (Barkley, 1997), the results of this study clearly indicate the presence of visual-spatial WM and WM manipulation deficits which are not accounted
for by attentional lapses. Nevertheless, given the heterogeneity of ADHD and our effect sizes, it is unlikely that WM deficits underlie the difficulties for all children with ADHD.

Our secondary analyses examining the different ADHD Presentations also provided interesting and unique findings. Several investigators (Yang et al., 2013; Skogli et al., 2013; Solanto et al. 2007) have examined differences between Predominantly Inattentive and Combined Presentations of ADHD on a range of executive function measures finding relatively few differences. Similar to others, our analyses did not yield main effects of Group, which could superficially lead to the conclusion that children with ADHD, Predominantly Inattentive and Combined Presentations do not differ in WM. However, the results from our data analytic approach indicated that children with ADHD-I have differentially greater impairments in WM manipulation relative to maintenance, as compared to youth with ADHD-C. Importantly, although of interest, these findings from secondary analyses will require replication.

Study 1 has important clinical implications as recent efforts have centered on the use of WM training as a therapeutic intervention for youth with ADHD. Perhaps the most widely publicized and empirically investigated of these is Cogmed Working Memory Training (CWMT; Klingberg et al., 2005; Klingberg, 2010), a computerized training program in which individuals learn and perform various WM tasks in an effort to improve their WM capacity. However, recent data (Chacko et al., 2014; van-Dongen-Boomsma et al., 2014) and reviews (Rapport et al., 2013) have suggested that CWMT may not yield real-world improvements of ADHD behavior, but instead primarily improve proficiency on proximal cognitive (i.e., working memory) tests. Overall, our findings suggest that children with ADHD are impaired on WM manipulation (with maintenance relatively intact) and have more severe deficits in the visual-spatial domain relative to the auditory-verbal domain. These findings could potentially help inform WM treatment
paradigms, in order to tailor them in such a way that incorporates the specific WM deficiencies we observed in our results. However, even with efforts to refine working memory training programs, it may actually be more important to emphasize that ADHD is a heterogeneous disorder, with some youth presenting with unambiguous working memory deficiencies and others exhibiting a markedly different, possibly more intact neurocognitive profile. Thus, since ADHD encompasses such heterogeneity, those children who present with WM deficits may be the ones who are better suited to benefit from WM treatments, while others with ADHD who exhibit intact WM might be less likely to experience profitable outcomes from these interventions. Overall, interventions for ADHD may need to be tailored in such a way that incorporates the array of weaknesses which children with this disorder exhibit.

The current study had a number of notable strengths. First, we utilized a well-studied sample that has been routinely followed-up as a part of a larger longitudinal research project. Thus, the sample is well-characterized for both the presence and absence of ADHD (at both baseline and 8-year-old follow-up). Second, this study is unique with regard to the narrow age-range of the participants (i.e., restriction to 8-year-old youth at the time of the WM assessment). Chronological age is of particular importance because the neurocognitive processes under examination progressively develop as children age, and tremendous brain growth occurs in late childhood and adolescence (Shaw et al., 2007). This narrow age range also facilitated the use of raw scores rather than scaled scores, with the former being more sensitive to individual differences. Perhaps most importantly, this was the first study to our knowledge to examine the various WM components in a single model using well-matched tests, which facilitated comparisons of distinct WM processes (i.e., maintenance vs. manipulation) and modalities (i.e., visual-spatial vs. auditory-verbal WM) while accounting for possible weaknesses in other processes and modalities.
Nevertheless, this study also had some limitations. While the narrow age-range is largely viewed as a strength, caution must be used when generalizing the results to other ages. Further, the current study only examined the participants at one point in time. It would be beneficial to examine the same children over various time points to identify developmental trajectories of these WM components and their potential correspondence to symptom expression. Therefore, future research should employ longitudinal designs when examining the various components of WM in children with ADHD. Additionally, the tasks used to assess WM manipulation were restricted to memory span tasks. Some researchers (Rapport et al., 2008; Engle et al., 1999) have argued that simple span tasks are not taxing enough to assess central executive control of WM. While this may be true in some samples, we do not believe this to be the case in this study as none of the tasks employed were hampered by ceiling effects, and the backward span tasks in both domains were sensitive enough to reveal group differences. Furthermore, the study included only a single measure to assess each WM process within each modality (i.e., auditory-verbal maintenance, visual-spatial maintenance, auditory-verbal manipulation, and visual-spatial manipulation). While the use of a single task might increase measurement error, these well-matched tasks allowed us to make direct comparisons of performance between the WM processes and modalities, and enabled us to parse the specific nature of WM impairments in this sample. Nevertheless, future research is needed to replicate these findings using additional WM tasks to form aggregated and/or latent constructs of WM.

Overall, this study found that children with ADHD exhibited specific deficits in WM manipulation, while WM maintenance was relatively intact. Additionally, we found that children with ADHD exhibited deficits across both WM modalities, with greater group differences in the visual-spatial relative to the auditory-verbal domain. To the best of our knowledge, this was the
first study to systematically examine both WM processes along with modalities, in an effort to examine specific versus global impairments of WM in children with ADHD.
STUDY 2

Low Working Memory Rather than ADHD Symptoms

Predicts Poor Academic Achievement in School-Aged Children

(Simone, Marks, Bédard, & Halperin, in press)

While examining group-level WM differences between children with and without ADHD is of great importance, it is also important to acknowledge and study the neurocognitive heterogeneity of the disorder. Particularly, not all children with ADHD exhibit weaknesses in WM (Nigg & Casey, 2005). In addition to poor WM, relative to their typically-developing peers, children and adolescents with ADHD present with significantly higher rates of academic underachievement (DeShazo, Lyman, & Grofer, 2002; Hinshaw, 1992), as well as school drop-out (Loe & Feldman, 2007; Trampush, Miller, Newcorn, & Halperin, 2009). It has been estimated that 20 – 50% of children with ADHD meet criteria for a learning disability (LD; Pastor & Reuben, 2008; Pliszka, 2000). Yet, many children with ADHD have been shown to have poor academic functioning, even in the absence of a frank LD. As WM has also been linked to poor academic achievement in children (regardless of ADHD diagnosis; Alloway & Alloway, 2010), some investigators (Rogers, Hwang, Toplak, Weiss, & Tannock, 2011; Sjowall & Thorell, 2014) have begun to examine whether WM ability mediates the relation between ADHD symptoms and academic outcomes in school-aged children. Specifically, Rogers and colleagues (2011) found that in adolescents with ADHD, auditory-verbal and visual-spatial WM partially mediated the relation between inattentive symptoms and performance on tests of reading, but not mathematics, achievement. Similarly, Sjowall and Thorell (2014) found that WM (collapsed across auditory-verbal and visual-spatial tasks) partially mediated the relation between ADHD symptoms and teacher ratings of children’s math and language skills. Given the heterogeneity of WM impairment
in samples of children with ADHD, it is still unclear whether ADHD and WM ability uniquely contribute to poor academic outcomes. Further, there have been inconsistent findings regarding the relations between ADHD, WM, and mathematics outcomes, which could be due to the different academic outcome assessments used (i.e., tests versus teacher ratings). Thus, it is important to examine within a single sample of children whether ADHD symptoms and WM ability both, or differentially, contribute to objective tests and subjective ratings of academic achievement.

To date, two studies (Alloway, Gathercole, & Elliott, 2010; Holmes et al., 2014) have compared children with ADHD to non-ADHD children with low WM and found that the groups did not appear to differ on tests of academic achievement. Alloway and colleagues (2010) divided their sample based on teacher ratings of WM (irrespective of ADHD diagnosis) and found that the low WM group performed substantially poorer on all academic achievement measures relative to those with average WM, but that the groups did not differ on teacher ratings of classroom functioning. In contrast, Holmes and colleagues (2014) found that teachers rated children with ADHD as having significantly more hyperactivity and impulsivity than their non-ADHD low WM peers. Based on these findings, it would appear that WM is contributing to poorer academic achievement in children (regardless of ADHD status), and the contribution of WM to behavioral dysfunction in children with or without ADHD is unclear. Further, it remains uncertain whether both ADHD symptom domains (inattentive and hyperactive/impulsive), as well as WM ability significantly contribute to poorer academic and behavioral functioning in school-aged children.

Study 2 examined the extent to which WM ability (auditory-verbal and visual-spatial), inattentive symptoms, and/or hyperactive/impulsive symptoms significantly contribute to academic, behavioral, and global functioning among 8-year-old children. Children completed tests of academic achievement; teachers rated the children on academic and behavioral functioning in
the classroom; and clinicians judged overall global functioning. As findings regarding distinct associations of modality-specific WM processes and academic abilities are mixed (Brady, 1991; Jorm, 1983; McLean & Hitch, 1999; Schuchardt, Maehler, & Hasselhorn, 2008; Swanson & Sachse-Lee, 2001), we made no specific hypotheses regarding differential relations between WM modalities and academic achievement. Therefore, irrespective of modality, we hypothesized that:

1) WM ability, but not ADHD symptom severity, would be significantly associated with all measures of academic functioning (objective tests and subjective ratings).

2) Inattentive and hyperactive/impulsive symptom severity, but not WM ability, would significantly predict teacher ratings of behavioral functioning and clinician ratings of global functioning.

If these hypotheses are supported, it would suggest a double dissociation whereby WM ability would be linked to learning and academic problems rather than behavioral functioning in school-aged children; and inattentive and hyperactive/impulsive symptoms, but not WM ability, would be more closely associated with poorer behavioral functioning.

Method

Participants

For Study 2, children were re-evaluated at eight years of age in which approximately 160 had complete data (with the exception of teacher ratings of school behavioral functioning). Fifty-three were typically-developing at preschool and did not have ADHD at 8-years-old; 11 were typically-developing at preschool and did have ADHD at 8-years-old; 21 were at-risk for ADHD at preschool and did not have ADHD at 8-years-old; 75 were at-risk for ADHD at preschool and did have ADHD at 8-years-old. The children who returned for this follow-up evaluation did not differ from those lost to follow-up on any key demographic variables assessed at the initial
evaluation, which included age, socioeconomic status (SES), WPPSI-III IQ scores, or parent- and teacher-ratings of ADHD.

At 8-years-old the sample was predominantly male (75.6%) and largely middle class, but included youth from a range of socioeconomic backgrounds (see Table 3). The children were of varied racial and ethnic backgrounds: White/Caucasian (58.8%), Other/Mixed Race (18.1%), Asian/Pacific Islander (12.5%), and Black/African-American (10.6%); 70.0% were non-Hispanic (70.0%). ADHD symptom severity and diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (K-SADS-PL; Kaufman, Birmaher, Brent, Rao, & Ryan, 1996), which was administered to a parent or caregiver. Of the children assessed at 8-years-old, 53.8% met criteria for a DSM-5 (American Psychiatric Association, 2013) ADHD diagnosis (Inattentive Presentation = 15.6%, Hyperactive/Impulsive Presentation = 5.0%, Combined Presentation = 29.4%, Not Otherwise Specified = 3.8%). Several children in the sample met criteria for internalizing (20.6%) and externalizing disorders (8.8%). In accordance with DSM-5 (American Psychiatric Association, 2013), 4.4% (n = 7) of our sample met diagnostic criteria for a specific learning disorder (LD; i.e., having a score falling 1.5 standard deviations or lower than the population mean on any of the academic achievement measures). Of these children, all but one was deemed at-risk for developing ADHD at the baseline evaluation and met diagnostic criteria for ADHD at the 8-year-old evaluation.

Materials

Diagnostic Measures


Working Memory Measures
Auditory-Verbal Working Memory was assessed using the WMI of the WISC-IV Integrated (Kaplan et al., 2004). This index is comprised of the Digit Span and Letter-Number Sequencing subtests.

Visual-Spatial Working Memory was assessed using the Spatial Span subtest from the WISC-IV Integrated which contains two conditions, Spatial Span Forward and Spatial Span Backward. As the Spatial Span subtest does not calculate a standardized score for the total performance on both the forward and backward conditions, we averaged the scaled scores for these two conditions to arrive at a combined scaled score of visual-spatial WM.

Within our sample, the WMI and averaged Spatial Span scaled scores demonstrated a moderate, positive correlation ($r = 0.576$, $p < .001$), suggesting some overlap between these measures, but that they are relatively distinct from each other. Among those who did and did not meet criteria for ADHD, 34.5% and 13.7% fell below the 25%ile on the WMI ($X^2 = 9.07, p = .003$) and 24.4% and 5.5% fell below the 25%ile on the Spatial Span tests ($X^2 = 10.91, p = .001$), respectively. Thus, more children with ADHD had WM difficulties relative to controls, but even with this liberal cut score, the majority of children with ADHD had normatively intact WM ability.
Table 3: Descriptive characteristics of the sample of children at 8-years-old

<table>
<thead>
<tr>
<th></th>
<th>Full Sample</th>
<th>Non-ADHD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>Age in years</td>
<td>160</td>
<td>8.56 (0.31)</td>
<td>7.91 – 9.33</td>
</tr>
<tr>
<td>Socioeconomic Status (SES)</td>
<td>160</td>
<td>63.91 (17.94)</td>
<td>20 – 97</td>
</tr>
<tr>
<td>WPPSI-III Full Scale IQ at 3-4 years old</td>
<td>160</td>
<td>107.35 (13.41)</td>
<td>80 – 144</td>
</tr>
<tr>
<td>Working Memory Index (WMI)</td>
<td>157</td>
<td>99.68 (13.99)</td>
<td>65 – 135</td>
</tr>
<tr>
<td>Spatial Span Averaged Scaled Score</td>
<td>160</td>
<td>110.57 (12.67)</td>
<td>75 – 130</td>
</tr>
<tr>
<td>KSADS Inattentive Severity Score</td>
<td>160</td>
<td>115.51 (10.80)</td>
<td>65 – 131</td>
</tr>
<tr>
<td>KSADS Hyperactive/Impulsive Severity Score</td>
<td>160</td>
<td>112.68 (11.90)</td>
<td>65 – 131</td>
</tr>
<tr>
<td>Gender (%) males</td>
<td>75.6</td>
<td>70.3</td>
<td>80.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian (%)</td>
<td>58.8</td>
<td>52.7</td>
<td>64.0</td>
</tr>
<tr>
<td>Black/African-American (%)</td>
<td>10.6</td>
<td>5.4</td>
<td>15.1</td>
</tr>
<tr>
<td>Asian/Pacific Islander (%)</td>
<td>12.5</td>
<td>20.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Other/Mixed Race (%)</td>
<td>18.1</td>
<td>21.6</td>
<td>15.1</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic (%)</td>
<td>70</td>
<td>74.3</td>
<td>66.3</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>30</td>
<td>25.7</td>
<td>33.7</td>
</tr>
</tbody>
</table>

*SD = Standard Deviation; KSADS = Kiddie-Schedule of Affective Disorders and Schizophrenia; WIAT-II = Wechsler Individual Achievement Test, Second Edition; NICHQ = National Institute of Children’s Healthcare Quality Vanderbilt Assessment Scale, Teacher Version
†p < 0.01
‡p<0.001

**Academic Achievement Measures**


Children were administered several subtests from the WIAT-II which is a comprehensive battery assessing various aspects of academic achievement in children. Each subtest is administered separately with its own instructions, which include reversal and discontinue rules. For each subtest, raw scores are calculated and then transformed into individual standard scores (M = 100, SD = 15).
**Word Reading.** The Word Reading subtest requires individuals to read a series of American English words. The task begins with simpler words and progresses in word complexity and is discontinued when the participant is unable to accurately read six consecutive words or the final word of the test is read.

**Pseudoword Decoding.** This subtest requires individuals to read a series of nonsense words phonetically. The task begins with simpler nonsense words and progresses in complexity. The task is discontinued when the participant is unable to accurately read six consecutive nonsense words or the final nonsense word of the test is read.

**Spelling.** The Spelling subtest requires individuals to listen to sentences read aloud by an examiner and then write a specific word from that sentence. The task begins with simpler words and progresses in word complexity. The task is discontinued when the participant is unable to accurately spell six consecutive words or the final word of the test is administered.

**Reading Comprehension.** This subtest requires individuals to read a series of short sentences and passages and then answer questions about what they previously read. Participants begin the task based on their current grade level (or most recent grade level completed) and the task is discontinued when the participant reaches the final sentence or passage within their grade section.

**Numerical Operations.** The Numerical Operations subtest requires individuals to complete various mathematical problems (e.g., addition, subtraction, percentages, fractions, etc.) which increase in complexity as the task progresses. The task is discontinued when the participant completes six problems incorrectly or when the final problem is reached.

Table 4 shows correlations among the WM, academic achievement, and ADHD symptom severity scores. As shown in Table 4, all of the WM, academic achievement measures, preschool
IQ, and ADHD symptom domains are moderately correlated; thus suggesting that while there is some overlap between these variables, they are all relatively distinct from each other.

Table 4: Pearson Bivariate Correlations for WM, preschool IQ, academic achievement measures, and symptom severity scores

<table>
<thead>
<tr>
<th></th>
<th>Spatial Span Averaged Scale Score</th>
<th>WPPSI FSIQ</th>
<th>Word Reading</th>
<th>Reading Comprehension</th>
<th>Pseudoword Decoding</th>
<th>Numerical Operations</th>
<th>Spelling</th>
<th>Inattentive Severity Score</th>
<th>Hyperactive/Impulsive Severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMI</td>
<td>.576**</td>
<td>.533**</td>
<td>.563**</td>
<td>.500**</td>
<td>.533**</td>
<td>.591**</td>
<td>.555**</td>
<td>-.375**</td>
<td>-.241**</td>
</tr>
<tr>
<td>Spatial Span Averaged Scaled Score</td>
<td>1</td>
<td>.414**</td>
<td>.367**</td>
<td>.346**</td>
<td>.309**</td>
<td>.459**</td>
<td>.360**</td>
<td>-.388**</td>
<td>-.304**</td>
</tr>
<tr>
<td>WPPSI-III FSIQ</td>
<td></td>
<td>1</td>
<td>.378**</td>
<td>.538**</td>
<td>.319**</td>
<td>.459**</td>
<td>.284**</td>
<td>-.309**</td>
<td>-.205*</td>
</tr>
<tr>
<td>Word Reading</td>
<td></td>
<td></td>
<td>1</td>
<td>.583**</td>
<td>.860**</td>
<td>.576**</td>
<td>.803**</td>
<td>-.213**</td>
<td>-.195*</td>
</tr>
<tr>
<td>Reading Comprehension</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>.507**</td>
<td>.550**</td>
<td>.503**</td>
<td>-.247**</td>
<td>-.204*</td>
</tr>
<tr>
<td>Pseudoword Decoding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>.552**</td>
<td>.753**</td>
<td>-.226**</td>
<td>-.191*</td>
</tr>
<tr>
<td>Numerical Operations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>.617**</td>
<td>-.238**</td>
<td>-.158*</td>
</tr>
<tr>
<td>Spelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>-.256**</td>
<td>-.161*</td>
</tr>
<tr>
<td>Inattentive Severity Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>.759**</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

School Functioning Measure

National Institute for Children’s Health Quality (NICHQ) Vanderbilt Assessment Scale – Teacher Version (Wolraich et al., 2003). The NICHQ was used to assess children’s overall school/classroom functioning. Teachers completed these rating scales, which probed for the student’s performance in mathematics, reading, and written expression. Teachers also rated the students on their behavioral functioning in the classroom: 1) relationship with peers, 2) following directions, 3) disrupting the classroom, 4) assignment completion, and 5) organizational skills. For
each of the above academic and behavioral dimensions, teachers rated students on a 5-point Likert scale (1 = excellent, 2 = above average, 3 = average, 4 = somewhat of a problem, and 5 = problematic). For our analyses, we used the sum of each of these scales (i.e., three items of academic functioning and five items of behavioral functioning) as our outcome measure. For our sample, coefficient alphas for the teacher-reported academic functioning and behavioral functioning scales were 0.81 and 0.88, respectively.

Global Functioning Measure

Following a comprehensive evaluation, which included the K-SADS-PL interview with parents and rating scale data from parents and teachers, each child’s case was presented to a group of clinicians who independently rated the child on the Children’s Global Assessment Scale (CGAS; Schaffer et al., 1983) based on the child’s lowest level of functioning over the previous evaluation year. Scores on this scale range from 1 to 100, with scores below 60 typically representing impaired functioning (Shaffer et al., 1983). Median scores across clinicians were calculated for each child, and this score was used in the final analyses. Across the 160 participants assessed at age 8, the number of clinician-raters varied from 4 through 13. Reliability among raters was calculated separately for each number of raters (except 4 and 13 where there was only one case each) using intra-class correlations (ICC). Reliability was excellent with ICC values ranging from 0.938 – 0.976.

Procedure

Children were tested individually by a member of the research team while a different evaluator interviewed the child’s parent/caregiver using the K-SADS-PL. Both examiners were blind to the child’s prior diagnostic status. The full evaluation lasted approximately 2-3 hours, during which children completed the academic tests, WM tasks, as well as other
neuropsychological measures. Children were given a small prize at the end of the session for participating in the study. Parents received compensation for their time and expenses associated with study participation.

Statistical Analyses

Multiple linear regressions were conducted to assess whether WM ability and ADHD symptom severity (inattentive and hyperactive/impulsive symptoms) significantly contributed to each outcome variable (i.e., academic achievement tests, teacher-rated academic functioning, teacher-rated behavioral functioning, and clinician-rated global functioning). As SES has been shown to be a strong predictor of academic outcomes (Sirin, 2005), as well as health and social-emotional functioning in children (Bradley & Corwyn, 2002), it was entered into the first step of each model to control for its effects on the dependent variables.

For the second step, WM ability (either auditory-verbal or visual-spatial), and K-SADS inattentive and hyperactive/impulsive symptom severity were added into the model to determine their individual associations with the outcome variables. For the final step, interaction variables between centered WM x inattentive symptoms and centered WM x hyperactive/impulsive symptoms were added into the model.

The first set of regression analyses was conducted with auditory-verbal WM (AVWM) ability, and then a second set of analyses using the same statistical procedures was conducted with visual-spatial WM.

Results

Auditory-Verbal WM (see Table 5)

Academic Achievement Tests
Word Reading: SES and AVWM significantly contributed to Word Reading, accounting for 12.5% and 23.9% of the variance, respectively. Inattentive and hyperactive/impulsive symptom severity, as well as the two interaction terms, was not significantly related to Word Reading scores.

Reading Comprehension: SES and AVWM were significantly associated with Reading Comprehension and accounted for 17.5% and 16.3% of the variance, respectively. Neither ADHD symptom domain nor their interactions with AVWM significantly predicted Reading Comprehension scores.

Pseudoword Decoding: Again, SES and AVWM significantly contributed to Pseudoword Decoding accounting for 9.8% and 22.3% of the variance, respectively. None of the other predictor variables were significantly related to Pseudoword Decoding scores.

Numerical Operations: SES and AVWM were significantly related to Numerical Operations scores and accounted for 11.7% and 26.9% of the variance, respectively. Inattentive and hyperactive/impulsive symptom severity, as well as their interactions with AVWM, were not significantly related to Numerical Operations.

Spelling: Similar to the other WIAT-II subtests, SES and AVWM significantly contributed to Spelling scores accounting for 8.8% and 24.4% of the variance, respectively. Neither of the ADHD symptom domain nor their interactions with significantly predicted Spelling scores.

School Functioning as Rated by Teachers

As shown in Table 5, after accounting for SES, AVWM and inattentive symptom severity significantly contributed to classroom academic functioning accounting for 20.4% and 6.1% of the variance, respectively. None of the other predictor variables were significantly associated with teacher ratings of academic functioning. In contrast, after accounting for SES, inattentive symptom severity and hyperactive/impulsive symptom severity were significantly associated with
classroom behavioral functioning, in which inattentive symptom severity accounted for 28.5% of the variance and hyperactive/impulsive symptom severity accounted for an additional 2.9% of the variance. Neither AVWM nor any of the other predictor variables were associated with teacher ratings of behavioral functioning.

Global Functioning as Rated by Clinicians

Similar to teacher ratings of behavioral functioning, both inattentive and hyperactive/impulsive symptom severity significantly contributed to clinician ratings of children’s overall global functioning, in which inattentive symptom severity contributed 64.4% of the variance and hyperactive/impulsive symptom severity contributed an additional 2.6% of the variance.
Table 5: Multiple Linear Regressions with Auditory-Verbal WM – Final Model

<table>
<thead>
<tr>
<th>Academic Achievement Tests</th>
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</tr>
<tr>
<td>WMI</td>
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<td>7.124</td>
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<td>K-SADS Hyperactive/Impulsive Symptom Severity</td>
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<tr>
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<td><strong>Clinician Rated Children's Global Assessment Scale</strong></td>
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<td>-0.090</td>
<td>0.928</td>
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</table>

Bold denotes significant predictor variables
Visual-Spatial WM (see Table 6)

Academic Achievement Tests

Word Reading: SES and VSWM significantly contributed to Word Reading, accounting for 12.3% and 10.0% of the variance, respectively. Inattentive and hyperactive/impulsive symptom severity, as well as the two interaction terms were not significantly related to Word Reading scores.

Reading Comprehension: SES and VSWM significantly contributed to Reading Comprehension, accounting for 17.3% and 8.0% of the variance, respectively. In addition, the interaction between VSWM x hyperactive/impulsive symptom severity was significantly associated with Reading Comprehension and accounted for an additional 3.7% of the variance. The nature of this interaction was such that children with higher hyperactive/impulsive symptom severity and lower VSWM had differentially poorer reading comprehension scores when compared to children with low levels of hyperactive/impulsive symptoms irrespective of VSWM and those with high levels of symptoms but stronger VSWM (see Figure 4). None of the other predictor variables were significantly related to Reading Comprehension scores.

![Figure 4. Interaction of hyperactivity/impulsivity symptom severity and visual-spatial working memory on reading comprehension scores. Error bars represent standard deviation (SD).](image-url)

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Pseudoword Decoding: SES and VSWM significantly contributed to Pseudoword Decoding, accounting for 9.8% and 7.0% of the variance, respectively. Inattentive and hyperactive/impulsive symptom severity and the two interaction terms were not significantly related to Pseudoword Decoding scores.

Numerical Operations: SES and VSWM significantly contributed to Numerical Operations, accounting for 12.6% and 19.4% of the variance, respectively. Inattentive and hyperactive/impulsive symptom severity, as well as the two interaction terms were not significantly related to Numerical Operations.

Spelling: SES and VSWM significantly contributed to Spelling, accounting for 8.6% and 11.5% of the variance, respectively. Inattentive and hyperactive/impulsive symptom severity, as well as the two interaction terms were not significantly related to Spelling.

School Functioning as Rated by Teachers

As displayed in Table 6, SES, VSWM, and inattentive symptom severity significantly contributed to classroom academic functioning. After accounting for SES, VSWM and inattentive symptom severity contributed 6.5% and 15.2% of the variance, respectively. Hyperactive/impulsive symptom severity and the two interaction terms were not significantly associated with teacher ratings of academic functioning.

Both inattentive and hyperactive/impulsive symptom severity significantly contributed to classroom behavioral functioning, in which inattentive symptom severity accounted for 29.1% of the variance and hyperactive/impulsive symptom severity accounted for an additional 2.9% of the variance. SES, VSWM, and the two interaction terms were not significantly associated with teacher ratings of behavioral functioning.

Global Functioning as Rated by Clinicians
Both inattentive and hyperactive/impulsive symptom severity significantly contributed to clinician ratings of children’s overall global functioning, in which inattentive symptom severity accounted for 64.6% of the variance and hyperactive/impulsive symptom severity accounted for an additional 2.5% of the variance. SES, VSWM, and the two interaction terms were not significantly related to clinician ratings of children’s global functioning.
Table 6: Multiple Linear Regressions with Visual-Spatial WM – Final Model

<table>
<thead>
<tr>
<th>Academic Achievement Tests</th>
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<th>p value</th>
</tr>
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<tr>
<td><strong>Word Reading</strong></td>
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**Bold** denotes significant predictor variables.
Discussion

To the best of our knowledge this was the first systematic examination of differential relations of both WM modalities, as well as inattentive and hyperactive/impulsive symptom severity with academic, behavioral, and global functioning in children. As hypothesized, our data indicated that, regardless of which WM modality was assessed (auditory-verbal or visual-spatial), WM ability was significantly associated with all tests of academic achievement, but not with measures of behavior problems or overall global impairment. In contrast, inattentive and hyperactive/impulsive symptoms were associated with measures of behavior problems and global functioning, but not with academic achievement. These findings indicate that compromised WM ability is specifically related to poor academic achievement in children and that the presence of inattentive and hyperactive/impulsive symptoms per se have little to no relation to academic skills. Moreover, while SES was also shown to significantly predict academic achievement, the amount of additional variance accounted for by WM ability across many tests of academic achievement was nearly double what SES accounted for alone.

Interestingly, teacher-ratings of school-based academic performance yielded a somewhat different pattern of predictors. Across both modalities, WM and inattentive symptoms (but not hyperactive/impulsive symptoms) significantly contributed to teachers’ ratings of academic functioning (math, reading, and written expression). This discrepancy between objective test measures and teacher ratings of academic performance may be accounted for by either a difference between skills and performance in children with ADHD, or by negative biases affecting teacher ratings. For the first scenario, several studies (Barkley & Fischer, 2011; Barkley & Murphy, 2010) have shown that children’s performance on tests in an individual setting is often not strongly predictive to real-world environments (e.g., in school) and thus their behavioral dysregulation.
prevents them from communicating such knowledge in the classroom. Not surprisingly, inattentive symptom severity is more closely linked to classroom performance than hyperactivity/impulsivity, and more closely associated with classroom performance than test performance. Alternatively, teacher-ratings might be affected by halo effects (Abikoff, Courtney, Pelham Jr., & Koplewicz, 1993). Specifically, behavior management issues may elicit a negative bias from classroom instructors, which in turn, influences their ratings of students’ academic functioning. Nevertheless, for the latter to be the case, one could reasonably assume that both hyperactivity/impulsivity and inattention in the classroom would elicit a negative response bias from teachers, yet we only found evidence for inattention symptoms to significantly contribute to teacher-ratings of school functioning.

As hypothesized, we also found that both inattentive and hyperactive/impulsive symptoms, but not WM ability, significantly predicted both teachers’ and clinicians’ ratings of impairment and overall functioning. Specifically, these findings indicate that ADHD symptom severity was significantly associated with teachers rating children as exhibiting more problematic classroom behaviors (e.g., relationships with peers, difficulties organizing tasks and completing assignments, disrupting the classroom environment), and with clinicians rating children as having poorer overall global functioning. If WM was a core deficit in children with ADHD (Rapport et al., 2001), we would expect that WM ability would have also significantly contributed to teachers’ and clinicians’ ratings of these maladaptive behaviors. To the contrary, WM ability did not independently contribute to any measure of behavioral functioning. Thus, WM weaknesses do not appear to be contributing to or acting as a driver of ADHD-like behaviors. Rather, our findings indicate that WM ability, but not ADHD symptoms, is specifically related to academic functioning. This is consistent with findings from Alloway and colleagues (2010) who found that children with poor
WM (irrespective of ADHD), were more likely to perform worse on academic measures as compared to their peers with average WM.

While not of primary interest for this study, it is notable that among the children with ADHD in our sample, fewer than half had compromised WM ability even when based on a liberal-cut off criterion (i.e., 25th percentile). These findings are consistent with other reports (Nigg et al., 2005; Nikolas & Nigg, 2015), which suggest that only a minority of children with ADHD present with WM difficulties, again suggesting that WM is not a core underlying deficit of ADHD, but rather points to notable cognitive heterogeneity of the disorder (Castellanos & Tannock, 2002).

It is notable within our data that there were virtually no differences observed on academic, behavioral, and global functioning measures when the analyses were conducted using children’s auditory-verbal or visual-spatial WM ability. Prior studies have reported closer associations between reading skills and auditory-verbal as compared to visual-spatial WM (Brady, 1991; Jorm, 1983; Schuchardt et al., 2008), and less consistently between math ability and visual-spatial WM (McLean & Hitch, 1999; Schuchardt et al., 2008). Yet our data might suggest that academic achievement is more related to the ability set forth by the central executive component of WM as opposed to the modality-specific slave systems, although this speculation was not directly tested in our study.

Given the current findings linking WM to academic performance, but not ADHD, it is not surprising that WM training, which does improve WM in children with ADHD, seems to have little or no effect on ADHD symptoms (Chacko et al., 2014; Rapport, Orban, Kofler, & Friedman, 2013; van-Dongen-Boomsma, Vollebregt, Buitelaar, & Slaats-Willemse, 2014). We (Simone et al., 2016) previously suggested that cognitive heterogeneity in ADHD might account for the limited efficacy of WM training, and that greater benefits may be obtained if the treatment is
limited specifically to those children who have ADHD and poor WM. Our present data suggest that, while WM might improve the acquisition of academic skills in such children (given that WM significantly contributed to performance on academic achievement tests), it would likely have only limited effects on ADHD symptoms as WM did not significantly contribute to school behavioral performance or global functioning. Nevertheless, further research is needed to clarify the extent to which children with ADHD with low or intact WM would benefit from WM training in improving their acquisition and application of academic skills, as well as reducing the manifestation of ADHD symptoms and their impact in real-world settings.

Study 2 has several notable strengths. First, this is a well-characterized sample of children with and without ADHD who have been followed annually from preschool age through 8-years-old. Second, we used well-established diagnostic measures along with objective measures of auditory-verbal and visual-spatial WM to classify the children. We had a diversity of outcome measures including objective tests, teacher reports, and clinician impressions. Finally, by utilizing a regression approach, we were able to assess for significant and unique contributions of our independent variables on each outcome measure.

Nevertheless, there were some limitations to the current study, which must be considered. First, our sample was comprised of a narrow age range (only 8-year-old children). While this likely reduced variability in findings, caution is warranted when generalizing these results to older or younger children. Second, the scales used to assess teacher judgments of academic functioning, and to a lesser extent classroom behavioral functioning, were comprised of only three and five items, respectively. It is possible that there were too few items to make a valid estimate of each construct we proposed we were assessing. As the sample was originally recruited with strict exclusionary criteria for preschool Full Scale IQ, it likely limited the number of children with truly
impaired WM (i.e., ≥ 2 standard deviations below the mean) and may limit generalization of findings to some clinical settings. Also, we did not collect information from the children regarding their actual in-school academic performance (e.g., report cards), and therefore it remains open whether teacher-ratings of academic functioning in the classroom are reliable estimates of their actual school academic performance. Finally, it is important to note that moderate correlations were observed among the WM measures, academic achievement tests, and ADHD symptom domains. While this suggests there is some overlap among these variables, they are also relatively distinct from each other. Nevertheless, while WM was observed to be a significantly unique contributor to academic test achievement, it remains possible that shared aspects of WM and the ADHD symptom domains could be partially responsible for this as well.

Overall, our findings indicate that WM ability is specifically associated with academic achievement across a wide array of skills in children with and without ADHD and not with the presence or severity of ADHD symptoms. Further, severity of ADHD symptoms is unrelated to academic achievement, although symptoms of inattention may have an impact on classroom performance.
STUDY 3:

The Chicken or the Egg, Which Came First?

A Longitudinal Examination of Working Memory and ADHD

Study 3 examined the predictive and longitudinal relations between ADHD and WM ability. As previously noted, Rapport and colleagues have postulated that WM is the core underlying neurocognitive deficit that is responsible for the manifestation of ADHD symptomatology. Additionally, WM training interventions have been utilized for this population, which operate under the premise that improving WM will lead to a reduction of the core ADHD symptoms (Klingberg, 2002). However, implementation of such interventions may be premature when we do not yet understand the cause-and-effect relations (if one exists) between WM and ADHD symptomatology.

If WM weaknesses were to represent the core deficit of ADHD, onset of WM difficulties should precede the emergence of ADHD symptomatology. Yet, it is well-established that ADHD, especially hyperactive/impulsive behaviors, can be detected quite early in development, as early as 3-4 years old (Campbell, Shaw, & Gilliom, 2000; Egger, Kondo, & Angold, 2006; Lahey et al., 2004; Lahey et al., 1998). With regards to the development of WM, the brain undergoes rapid, non-linear growth (Simmonds et al., 2014) which starts prenatally and continues through early adulthood, with development of anterior brain regions (i.e., the prefrontal cortex) occurring later in maturational development. The progressive neuronal growth and myelination of the cerebral cortex, especially the prefrontal cortex, has been strongly associated with the development of cognitive processes (Casey, Giedd, & Thomas, 2000; Nagy, Westerberg, & Klingberg, 2004), such as WM. While some data suggest that basic WM maintenance (i.e., repeating short amounts of information) can be detected in preschool children (Roman, Pisoni, & Kronenberger, 2014),
development of WM manipulation does not typically begin until later in development (i.e., 7-9 years old; Wechsler, 2003; Kaplan et al., 2004), which coincides with neuroimaging data displaying greater gains in cortical maturation during this period (Shaw et al., 2007). Thus, as ADHD can be detected in many children in early preschool years (Campbell, Shaw, & Gilliom, 2000; Egger, Kondo, & Angold, 2006; Lahey et al., 2004; Lahey et al., 1998), and potentially before development and emergence of overall WM processes, it is worthwhile to investigate whether early ADHD exists/predicts later WM symptoms in addition to whether early WM predicts later school-aged ADHD symptoms.

At this point, very few studies have systematically examined the longitudinal/predictive relations between ADHD and WM. While Gau and Chiang (2013) found that early inattentive symptoms were significantly related to WM in early adolescence, their study was conducted by obtaining reports of childhood ADHD symptoms retrospectively from parents, and as we know, retrospective reports have been shown to be particularly suspect (Miller, Newcorn, & Halperin, 2010). Longitudinal studies utilizing prospective data of preschoolers (Brocki et al., 2007; Schoemaker et al., 2014) have found somewhat divergent results. Schoemaker and colleagues (2014) found evidence for WM deficits in ADHD over time (including during the preschool years), whereas Brocki and colleagues (2007) found no longitudinal relations between ADHD and WM; and importantly, they did not find any relation between early WM scores and ADHD symptom severity in early childhood either. This could be due to the lack of sensitivity in their measures. To date, no study has longitudinally examined the extent to which early WM predicts change in ADHD severity over time and vice versa, the extent to which early ADHD predicts change in WM ability.
Therefore, the final study investigated if preschool WM ability significantly predicted later school-aged ADHD, as well as the alternative hypothesis that preschool ADHD symptoms would significantly predict later school-aged WM ability. To the best of our knowledge, the latter has yet to be systematically studied with prospective data in any context. Therefore, it was hypothesized that preschool inattentive symptoms would significantly predict later WM performance in school-aged children, above-and-beyond baseline WM functioning in the preschool years, but early WM would not predict later ADHD symptomatology, above-and-beyond baseline inattentive and hyperactive/impulsive symptoms.

Method

Participants

For Study 3, at their initial evaluation (Time 1; T1), parents/caregivers and teachers rated all children using the ADHD-Rating Scale-IV (ADHD-RS-IV; DuPaul, Power, Anastopoulos, & Reid, 1998). Of the 216 children assessed at T1, 155 had complete, usable data from the 8-year-old evaluation (Time 2; T2). At T2, children’s parents and/or caregivers completed a semi-structured clinical interview and were supplemented by teacher ratings and clinician impressions of the child’s behavior to determine the children’s diagnostic status. See Table 7 for key demographic characteristics of the sample at T2.
Table 7: Descriptive characteristics of sample (N = 155)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD*</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>4.26</td>
<td>0.48</td>
<td>3.05 – 4.99</td>
</tr>
<tr>
<td>Socioeconomic Status (SES)</td>
<td>63.78</td>
<td>17.83</td>
<td>20 – 97</td>
</tr>
<tr>
<td>KSADS Inattentive Symptom Severity</td>
<td>7.87</td>
<td>6.05</td>
<td>0 – 18</td>
</tr>
<tr>
<td>KSADS Hyperactive/Impulsive Symptom Severity</td>
<td>9.48</td>
<td>6.47</td>
<td>0 – 18</td>
</tr>
<tr>
<td>NEPSY Sentence Repetition Scaled Score</td>
<td>11.21</td>
<td>2.41</td>
<td>6 – 19</td>
</tr>
<tr>
<td>NEPSY Comprehension of Instructions Scaled Score</td>
<td>9.55</td>
<td>2.42</td>
<td>1 – 14</td>
</tr>
<tr>
<td>NEPSY Averaged Scaled Score</td>
<td>10.38</td>
<td>2.10</td>
<td>5.00 – 16.50</td>
</tr>
<tr>
<td><strong>Time 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>8.56</td>
<td>0.31</td>
<td>7.92 – 9.33</td>
</tr>
<tr>
<td>KSADS Inattentive Symptom Severity</td>
<td>9.48</td>
<td>6.57</td>
<td>0 – 18</td>
</tr>
<tr>
<td>KSADS Hyperactive/Impulsive Symptom Severity</td>
<td>8.29</td>
<td>6.07</td>
<td>0 – 18</td>
</tr>
<tr>
<td>Working Memory Index (WMI) Standard Score</td>
<td>99.72</td>
<td>14.03</td>
<td>65-135</td>
</tr>
</tbody>
</table>

*SD = Standard Deviation

Materials

**Diagnostic Measures**


**Working Memory Measures**

A Developmental Neuropsychological Assessment (NEPSY; Korkman, Kirk, & Kemp, 1998). At T1, preschool WM was assessed using two subtests (Sentence Repetition and Comprehension of Instructions) from the NEPSY. Scaled scores for each subtest were calculated and the mean of these two scaled scores was used in the final analyses to capture an overall depiction of preschool WM ability. These two NEPSY subtests are moderately correlated ($r = 0.51$, $p = 0.001$).

The Sentence Repetition subtest requires children to listen to a series of phrases and are asked to repeat back as much of the phrase as possible. Phrases grow in length as the test progresses. This task was chosen as it requires the use of WM maintenance to accurately retain
and reproduce information. This task has been used by others as a measure of WM ability in young children (Breaux, Griffith, & Harvey, 2016).

Comprehension of Instructions requires participants to listen to a series of orally-presented prompts and select an appropriate target from an array of pictures which matches the single- or multi-step commands they previously heard. Items grow in complexity as the task progresses. While this subtest is largely deemed a language measure, successful completion requires the child to hold several bits of information in short-term store in order to correctly execute the single- or multi-step commands they previously heard. As such, performance on listening comprehension tasks has been shown to be highly correlated with measures of both verbal and visuospatial WM (McInnes, Humphries, Hogg-Johnson, & Tannock, 2003).

Wechsler Intelligence Scale for Children – Fourth Edition – Integrated (WISC-IV-Integrated; Kaplan et al., 2004). WM at 8-years-old was assessed using the WMI of the WISC-IV Integrated. See above.

See Table 8 for bivariate correlations of preschool and 8-years-old WM and symptom severity at preschool and 8-years-old.
Table 8: Pearson Bivariate Correlations for WM, symptom severity scores, and NEPSY scores

<table>
<thead>
<tr>
<th></th>
<th>K-SADS Inattentive Severity Score 8-years-old</th>
<th>K-SADS Hyp/Imp Severity Score 8-years-old</th>
<th>K-SADS Inattentive Severity Score 3-4 years-old</th>
<th>K-SADS Hyp/Imp Severity Score 3-4 years-old</th>
<th>NEPSY Sentence Repetition Scaled Score</th>
<th>NEPSY Comprehension of Instructions Scaled Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMI</td>
<td>-.377**</td>
<td>-.246**</td>
<td>-.435**</td>
<td>-.295**</td>
<td>.413**</td>
<td>.351**</td>
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<tr>
<td>K-SADS Inattentive</td>
<td>1</td>
<td>.765**</td>
<td>.659**</td>
<td>.629**</td>
<td>-.223**</td>
<td>-.053</td>
</tr>
<tr>
<td>Hyp/Imp Severity</td>
<td>1</td>
<td>.640**</td>
<td>.725**</td>
<td>-.218**</td>
<td>-.089</td>
<td></td>
</tr>
<tr>
<td>Score 8-years-old</td>
<td>1</td>
<td>.832**</td>
<td>-.294**</td>
<td>-.287**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-SADS Inattentive</td>
<td>1</td>
<td>-.227**</td>
<td>-.232**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyp/Imp Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 3-4 years-old</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEPSY Sentence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetition Scaled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

Procedure

At T1, preschoolers completed the two subtests from the NEPSY (Korkman, Kirk, & Kemp, 1998) which required WM involvement. At T2, children completed the WMI from the WISC-IV Integrated (Kaplan et al., 2004). At both evaluations to determine the children’s ADHD diagnostic status, parents/caregivers completed a comprehensive psychiatric evaluation about their child which consisted of a semi-structured interview via the KSADS-PL, and was supplemented with several parent and teacher rating scales.

At both evaluations, the children were assessed by a member of the research team while the parents were interviewed in a separate room. For the 8-year-old evaluation, examiners were blind to the children’s diagnostic status at study-entry. Parents/caregivers provided informed
consent for study involvement at T1 and T2. At T2, children also provided verbal assent. This study was approved by the Institutional Review Board at the City University of New York.

Statistical Analyses

Four separate linear regressions were conducted to determine whether ADHD symptoms and WM were longitudinally related. Two regressions determined if preschool WM predicted school-aged inattentive symptoms, above-and-beyond preschool inattentive symptom severity, and if preschool WM predicted school-aged hyperactive/impulsive symptoms, above-and-beyond preschool hyperactive-impulsive symptom severity. To test the alternate hypothesis that early ADHD symptoms predict later WM ability, we again conducted separate linear regressions; one to determine if preschool inattentive symptoms predicted school-aged WM, above and beyond preschool WM, and a second to test if hyperactive/impulsive symptoms predicted school-aged WM, above and beyond preschool WM.

For each model, step 1 included the time between T1 and T2. As SES has been shown to be highly correlated with health disparities in childhood (Bradley & Corwyn, 2002) it was added into each model on step 2 prior to the variables of interest (i.e., ADHD and WM) to determine if the relations between ADHD and WM would be significant above and beyond contributions made by SES.

Steps 3 and 4 varied across models. When examining whether early WM predicted later ADHD symptoms, T1 KSADS scores of ADHD inattentive or hyperactive/impulsive symptoms were entered into Step 3, and T1 WM scores were entered into Step 4. T2 Inattentive or Hyperactive/impulsive scores served as the dependent variable. This allowed us to determine whether preschool WM predicts later ADHD inattentive or hyperactive/impulsive symptoms (outcome variable) above and beyond contributions already made by preschool ADHD scores.
When examining whether early ADHD symptoms predicted later WM ability (outcome variable), T1 WM was entered into the model in Step 3 and T1 inattentive or hyperactive/impulsive symptoms were entered into Step 4. T2 WM score served as the dependent measure.

To control for the use of four regression analyses, an alpha level of 0.01 was used to determine significance.

Results

Does early WM predict later ADHD symptoms?

As displayed in Figure 5, time between evaluations ($\beta = 0.06, t(151) = -1.02, p = 0.31$) and SES ($\beta = -0.04, t(151) = -0.67, p = 0.51$) did not predict 8-year-old inattentive symptoms, but as expected, preschool inattentive symptoms significantly predicted 8-year-old inattentive symptom severity ($\beta = 0.67, t(151) = 10.18, p < 0.001$), accounting for 39.1% of the variance. Preschool WM did not predict 8-year-old inattentive symptom severity ($\beta = 0.07, t(151) = 1.12, p = 0.26$), above-and-beyond what was already accounted for by time between evaluations, SES, and preschool inattentive symptoms.

Figure 5. Linear regression of preschool WM on 8-year-old ADHD inattentive symptoms

$\beta =$ Standardized Beta Coefficients.
Similarly, as displayed in Figure 6, time between evaluations ($\beta = -0.07$, t(151) = -1.20, p = 0.23) and SES ($\beta = 0.09$, t(151) = -1.53, p = 0.13) did not predict 8-year-old hyperactive/impulsive symptoms; while preschool hyperactive/impulsive symptoms significantly predicted 8-year-old hyperactive/impulsive symptom severity ($\beta = 0.71$, t(151) = 12.02, p < 0.001), accounting for 44.8% of the variance. Again, preschool WM did not significantly predict 8-year-old hyperactive/impulsive symptom severity ($\beta = 0.03$, t(151) = 0.53, p = 0.59) above-and-beyond what was already accounted for by the other variables.

Figure 6. Linear regression of preschool WM on 8-year-old ADHD hyperactive/impulsive symptoms
$\beta$ = Standardized Beta Coefficients.

Do early ADHD symptoms predict later WM?

As shown in Figure 7, time between evaluations ($\beta = -0.13$, t(150) = -1.97, p = 0.05) and SES ($\beta = 0.15$, t(150) = 2.08, p = 0.04) did not significantly predict 8-year-old WM ability. Beyond that, preschool WM significantly predicted 8-year-old WM ($\beta = 0.30$, t(150) = 4.11, p < 0.001) accounting for an additional 13.6% of the variance. Further, above-and-beyond time between evaluations, SES, and preschool WM, preschool inattentive symptom severity significantly predicted 8-year-old WM ability ($\beta = -0.30$, t(150) = -4.12, p < 0.001), explaining an additional 7.4% of the variance of 8-year-old WM ability ($R^2 = 0.32$, F(4, 150) = 17.37, p < 0.001).
Time between evaluations ($\beta = -0.14$, $t(150) = -1.94$, $p = 0.05$) and SES ($\beta = 0.17$, $t(150) = 2.23$, $p = 0.03$) did not predict 8-year-old WM, but again preschool WM significantly predicted 8-year-old WM ability ($\beta = 0.35$, $t(150) = 4.75$, $p < 0.001$) accounting for 13.6% of the variance (see Figure 8). However, preschool hyperactive/impulsive symptom severity did not significantly predict 8-year-old WM ability, above-and-beyond time between evaluations, SES, and preschool WM ability ($\beta = -0.16$, $t(150) = -2.16$, $p = 0.03$).

Figure 7. Linear regression of preschool ADHD inattentive symptoms on 8-year-old WM
\( \beta = \) Standardized Beta Coefficients.

Figure 8. Linear regression of preschool ADHD hyperactive/impulsive symptoms on 8-year-old WM.
\( \beta = \) Standardized Beta Coefficients.
Discussion

To the best of our knowledge, this was the first study to prospectively examine whether preschool WM predicted later school-aged ADHD symptoms and/or whether preschool ADHD symptoms predicted later school-aged WM ability. Our findings indicate that a longitudinal association between WM and ADHD does exist, however, in the alternate direction than what has been previously postulated by other researchers (e.g., Rapport and colleagues). Preschool inattentive symptom severity significantly predicted later WM ability at school-age above-and-beyond other factors, namely SES and preschool WM ability; whereas, preschool WM ability did not significantly predict school-aged inattentive and hyperactive/impulsive symptoms above baseline estimates of these symptom domains. As inattention symptoms predicted later WM ability (and not the other way around), one could reasonably assume that the development of inattentive symptoms precedes the manifestation of WM problems. This is relatively consistent with the behavioral trajectory of ADHD in which symptoms emerge in the preschool years, but cognitive difficulties, such as WM, are not present until later in the progression of the disorder. Thus, based on our findings it is unlikely that WM represents a core deficit in children with the disorder because in order for this to be the case one would reasonably assume that WM deficiencies would be present prior to the behavioral manifestation of ADHD symptoms.

Similar to other findings (Gau & Chiang, 2013), we found that inattentive symptoms, but not hyperactive/impulsive symptom severity, significantly predicted school-aged WM ability. Analogously, several concurrent studies have found correlations between inattention and WM (Martinussen & Tannock, 2006; Savage, Cornish, Manly, & Hollis, 2006; Thorell, 2007), but yet others have not been able to replicate these findings (Rucklidge & Tannock, 2002). Yet others have found associations between WM and hyperactivity/impulsivity (Rapport et al., 2009), which
we did not find. Based on our findings, it is possible that there are underlying shared neural pathways among WM and inattentiveness, but this will require further exploration.

Our findings have important clinical implications. Klingberg (2005; 2010) popularized the use of Cogmed Working Memory Training (CWMT) operating under the notion that improved WM would lead to a core reduction in the symptoms of ADHD, yet recent data (Chacko et al., 2014; van-Dongen-Boomsma et al., 2014), reviews (Rapport et al., 2013), and meta-analyses (Cortese et al., 2015) have suggested that CWMT may not yield real-world improvements in children with ADHD. Our study targeted the core assumption of CWMT by addressing whether WM is the core deficit of children with ADHD. In order for this to be supported, we would have needed to find that preschool WM predicted later school-aged ADHD symptom manifestation. Yet, our findings did not indicate this. Rather, since we found that inattention predicted later WM, but not that WM predicted later ADHD symptoms, it is unlikely that improvements in WM would lead to a reduction in ADHD symptom expression. Further, since there was no longitudinal association found between WM and hyperactive/impulsive symptoms (in either direction), it is highly unlikely that WM training would lead to improvements in hyperactive/impulsive symptom manifestation. Furthermore, these findings also suggest that it is important to pay attention to inattention in the early preschool years. As previously mentioned, inattentive symptoms largely go unnoticed by parents, teachers, and clinicians in the early childhood years, as hyperactive/impulsive symptoms are typically more prominent, easily observable, and lead to greater impairment during that time. However, based on our findings that early inattention, but not preschool hyperactivity/impulsivity predicted later WM ability, it would be useful to devise better strategies to particularly identify inattention in the early childhood years as inattention appears to uniquely impact the trajectory of future cognitive processes. By being able to identify children
with prominent inattentive symptoms early on, we would also be able to implement intervention strategies earlier, in hopes that this could improve future trajectories of cognitive processes, such as WM.

Study 3 has several notable strengths. First, this is a well-characterized sample of children with and without ADHD who have been followed annually from preschool age through 8-years-old. Second, we used reliable and valid measures to determine ADHD diagnosis and WM ability at various time points. Finally, by utilizing a regression approach, we were able to assess longitudinal associations between ADHD and WM ability.

There are also several limitations that must be considered. For this study, 8-year-old children were used for the final follow-up year. As such, we cannot generalize our findings to younger or older children with ADHD. Future research should extend these findings by following children through adolescence and possibly into adulthood. Additionally, while we utilized regression analyses to examine longitudinal associations between childhood ADHD and WM, more sophisticated analyses (e.g., structural equation modeling) would be highly worthwhile to determine bidirectional relations across multiple time points between ADHD and WM.

Nevertheless, these data strongly suggest that ADHD symptoms, and in particular inattention, precede and possibly lead to later WM weaknesses rather than the behavioral symptoms being the result of early weaknesses in WM.

GENERAL DISCUSSION

Taken together, findings from these three studies suggest that while on a group-level children with ADHD demonstrate a pattern of WM difficulties, characterized by differentially greater weaknesses in manipulation relative to maintenance of information and in visual-spatial relative to auditory-verbal WM, these difficulties may not be evident in all children with the
disorder. Additionally, while WM ability is strongly linked to academic outcomes in children with and without ADHD, WM does not appear to be driving the manifestation of behavioral symptoms of the disorder. These findings lend support to Castellanos and Tannock’s model (2002) regarding the vast cognitive heterogeneity of ADHD, and reduce the likelihood that WM represents the core deficit of ADHD as postulated by Rapport and colleagues (2001). It still remains unclear what is accounting for the neurocognitive heterogeneity of the disorder, such that why some individuals with ADHD would exhibit this pattern of weaknesses (i.e., in WM), whereas others have intact WM and/or show deficits in other executive functions (such as inhibitory control) or have potentially no executive deficits.

Based on our findings, WM and ADHD (inattention in particular) are related, and thus dysfunction in these areas could be due to disruptions in similar underlying brain networks. Neuroimaging data would suggest that weaknesses in WM are due to disrupted activation in parietal areas for maintenance tasks (Courtney et al., 1996; Crosson et al., 1999; Zurowski et al., 2002) and disrupted activation of frontally-mediated networks for manipulation processes (Collette & Van der Linden, 2002), with mixed findings regarding neural activation differences for the visual-spatial and auditory-verbal modalities (Goldman-Rakic, 1995; Meyer et al., 2011; Desposito et al., 1998; Wager & Smith, 2003). Overall, across our studies it appears that children with ADHD (as a group) are exhibiting exceptionally poorer WM manipulation which likely means they are unable to recruit the necessary executive resources to complete more effortful cognitive tasks. Not surprisingly then, the biological bases of ADHD can be traced to disruptions in the catecholamine-rich cortico-striato-thalamo-cortical loop, which is largely modulated by dopamine and norepinephrine transmission from cortical to subcortical brain regions (Clark & Noudoost, 2014). It could be that delayed maturation of key cortical areas, which is evident in
children with ADHD (Shaw et al., 2007), and less efficient dopaminergic and noradrenergic transmission in such areas are contributing to the poor top-down control required to adequately complete more complicated/effortful cognitive tasks, such as WM.

As the prefrontal cortex and these key cortical areas do begin to mature, and for some children/adolescents with ADHD they do begin to “catch-up” to their typically-developing peers, this appears to contribute to the diminution of ADHD symptoms that some individuals with childhood ADHD experience in adolescence/adulthood (Halperin & Schulz, 2006; Giedd et al. 2010; Shaw et al., 2013). Consistent with this hypothesis, recent investigations have shown that children who have persistence of ADHD symptoms from childhood through adolescence, but not those who display a remission in ADHD symptoms over this period, continue to exhibit significant weaknesses in executive tasks (such as WM) compared to their typically-developing peers (Halperin et al., 2008).

As previously indicated, these three studies had numerous strengths which included a well-characterized sample of children who were followed yearly since preschool age; the use of reliable and valid cognitive and diagnostic measures; and utilization of sophisticated analyses to address pertinent gaps in the field. Despite these strengths, the aforementioned studies also had limitations which must be considered. Most notably, 8-year-old children were used in all of the conducted studies. While utilizing this narrow age range likely reduced the variability in our findings, it also reduces our generalizability of our findings to younger and older children with ADHD.

Future directions should include examining these various associations between WM and ADHD in samples of older children in order to determine if our findings extend to later school-age, adolescence, and adulthood. Also, even though we used unique statistical approaches to address our research questions, more sophisticated analyses (e.g., structural equation modeling)
would likely provide greater insight into the cause-and-effect relations between these variables and can be conducted using multiple time points across various ages of the lifespan.

In summary, findings from these three studies suggest that ADHD and WM are, to some extent, concurrently and predictively related. It is likely that ADHD, especially inattentiveness, and WM may have shared underlying brain networks that are responsible for the manifestation of both of these entities. Yet, contrary to what other researchers have postulated, it appears that deficient WM is not a primary contributor to the development of ADHD.
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