

Moderator Effects of Working Memory on Symptom Stability in Attention-Deficit/Hyperactivity
Disorder by Dopamine D1 and D2 Receptor Polymorphisms during Development

By

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Abstract

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Advisor: Jeffrey M. Halperin, Ph.D.

Background: Developmental changes in dopaminergic pathways in the prefrontal cortex (PFC) that are important for working memory have been hypothesized to play a central role in the trajectory of attention-deficit/hyperactivity disorder (ADHD), but not the initial onset of the disorder. This dissertation research examines whether dopamine receptor D1 (DRD1) and dopamine receptor D2 (DRD2) gene polymorphisms moderate the association between improvements in working memory and declines in attention problems in ADHD from childhood to adolescence/young adulthood. Methods: Participants were 76 racially/ethnically diverse youth diagnosed with ADHD in childhood and followed prospectively for almost 10 years. Stability of ADHD symptomatology was measured as a quantitative trait using the Attention Problems scale from the Child Behavior Checklist collected both in childhood and adolescence/young adulthood. Digit Span Forward and Digit Span Backward were administered at both time points to assess working memory maintenance and manipulation, respectively. Genotype and age were moderator variables. Results: DRD1 and DRD2 polymorphisms were associated with the stability of attention problems in adolescence/young adulthood, but not childhood. DRD1 polymorphisms, but not DRD2, significantly moderated the association between working memory and attention problems, with the strongest effects evidenced during adolescence/young adulthood. Notably, DRD1 moderation of working memory on attention

problems was specific to manipulation performance. Conclusions: Attention problems decreased over the course of almost 10 years if manipulation concomitantly improved during this period of development in a subgroup of individuals with childhood-diagnosed ADHD depending on their genetic makeup.

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Specific Aims

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood and is characterized by symptoms of inattention and/or hyperactivity-impulsivity. There is a strong genetic disposition to developing ADHD as evidenced by heritability estimates of approximately 75% based on twin studies (Faraone, et al., 2005). Several genetic polymorphisms that increase the risk for developing ADHD have been identified but none of the associations have been consistently replicated (Asherson, 2004; Faraone, et al., 2005; Gizer, Ficks, & Waldman, 2009).

Longitudinal studies have demonstrated that a large proportion of individuals diagnosed with ADHD in childhood symptomatically improve as they grow older, while in others, ADHD persists into adulthood with varying degrees of impairment (Mannuzza & Klein, 2000). It has been suggested that the persistence of ADHD into adolescence and adulthood is genetically mediated, perhaps more so than childhood-diagnosed ADHD (Faraone, 2004; Kuntsi, Rijdsdijk, Ronald, Asherson, & Plomin, 2005b). However, research on genetic factors influencing the developmental course of ADHD is limited.

The phenotypic heterogeneity across individuals and development raises questions regarding the validity of ADHD as a unitary psychiatric condition (Levy, Hay, McStephen, Wood, & Waldman, 1997). It has been suggested that “ADHD” is better conceptualized as falling at the extreme tail-end of a cluster of normally distributed quantitative traits rather than a categorical classification (Fergusson & Horwood, 1995; Levy, et al., 1997). Unfortunately, dimensional approaches have not been widely employed despite twin studies showing that genetic liability for ADHD is continuously distributed throughout the general population (Asherson, 2004; Chen, et al., 2008). The

attention problems subscale from the Child Behavior Checklist (CBCL-AP) is a popular dimensional measure of ADHD-like behaviors that correlates well with the clinical DSM-IV assessment of ADHD (Derks, Hudziak, Dolan, Ferdinand, & Boomsma, 2006) and effectively discriminates ADHD cases from their typically developing siblings and peers (Hudziak, Copeland, Stanger, & Wadsworth, 2004). Further, the CBCL-AP is highly heritable and genetically stable over time such that genetic effects explain approximately 75% of the heritability during development (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2004). Thus, the CBCL-AP appears to be a useful but underutilized measure of intermediate ADHD-related traits.

Endophenotypes are heritable, intermediate traits that confer risk for developing a disorder and share genetic variance with a disorder, yet are assumed to be less genetically complex than the clinically-defined disorder (Castellanos & Tannock, 2002; Doyle, et al., 2005a; Doyle, et al., 2005b; Gottesman & Gould, 2003). Evidence is emerging that impairments in working memory might be a core feature of ADHD (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), and working memory has been proposed as a putative ADHD endophenotype (Castellanos & Tannock, 2002). While variations of the digit span task have been used for over a century as a way to assess “short-term memory” (Richardson, 2007), the term “working memory” was not introduced until 50 years ago (Miller, Galanter, & Pribram, 1960). Two key components of working memory are *maintenance* and *manipulation*, and the ability to manipulate information in working memory seems to be differentially weaker in individuals with ADHD relative to pure maintenance of information (Hale, Hoepfner, & Fiorello, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Manipulation is also weaker in non-affected siblings of

children diagnosed with ADHD relative to typically developing controls with no immediate family history of ADHD (Rommelse, et al., 2008b) , which is one of the criteria of a valid endophenotype (Doyle, et al., 2005b).

Optimal working memory performance functions within a narrow range of dopaminergic transmission (i.e., inverted U-shaped curve) in PFC microcircuitry (Williams & Castner, 2006). Dopamine D1 receptors are crucial for modulating the persistent neuronal activity that is essential for continuous updating (Paspalas & Goldman-Rakic, 2005). The dopamine D2 receptor also modulates various components of working memory (Wang, Vijayraghavan, & Goldman-Rakic, 2004). Three functional polymorphisms were identified recently that were linked with differences in dopamine D2 expression and neural and behavioral differences during working memory paradigms (Zhang, et al., 2007). Thus, both D1 and D2 receptors seem prominently involved in the fractionation of working memory (Wang, et al., 2004; Williams & Castner, 2006; Zhang, et al., 2007). However, recent *in vivo* neuroimaging documented a direct dynamic association between working memory training and changes in D1 density in PFC but not with D2 density changes in the striatum, which suggests that D1 is a driving force of working memory plasticity (McNab, et al., 2009).

The brain develops from a predetermined and organized dynamic blueprint during development (Andersen, 2003). Skills that rely heavily on PFC are among the last to develop since PFC maturation is more delayed and variable relative to other areas of the brain (Andersen, 2003; Gogtay, et al., 2004). For example, working memory improves over the course of childhood until early adulthood (~19 years) when stable adult level skills are attained (Gathercole, 1998). Developmental improvements in manipulation

relative to maintenance are associated with increased recruitment of dorsolateral PFC and superior parietal cortex (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). D1 receptor density and second messenger activity similarly changes dynamically during development in PFC, with D1 density peaking during adolescence then decreasing in adulthood (Andersen, Thompson, Rutstein, Hostetter, & Teicher, 2000; Brenhouse, Sonntag, & Andersen, 2008). Our lab recently reported that working memory deficits were present in adolescents/young adults, who had childhood ADHD, but only in individuals who continued to have persistent ADHD from childhood; ADHD remitters did not differ from controls in terms of working memory (Halperin, Trampush, Miller, Marks, & Newcorn, 2008). Adaptations in working memory may thus underlie symptom heterogeneity in ADHD over time and be a viable endophenotype that is particularly sensitive to dopamine receptor function and developmental factors. In fact, it has been hypothesized that developmental changes in dopaminergic systems in PFC may play a central role in the trajectory of ADHD (Andersen, 2002; Halperin & Schulz, 2006) but not in the initial onset of symptoms in early childhood (Halperin & Schulz, 2006).

The primary aim of this dissertation is to examine the potential moderator effects of maintenance and manipulation on the stability of attention problems by dopamine D1 and D2 receptor gene polymorphisms (DRD1 and DRD2, respectively), and the degree to which any such associations change as a function of development. It was hypothesized that improvements in manipulation over time would be more robustly linked with a diminution of attention problems, but that the relationship would vary by genetic makeup, and that, within a prospectively followed sample of children diagnosed with ADHD, these interactions would be stronger at later developmental stages. To date, no study has

examined the interactive contributions of maintenance and manipulation, DRD1 and DRD2, and development on symptom stability in ADHD.

General Introduction

Clinical Features of ADHD

Clinical Characteristics of the Core Symptoms

ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity that usually emerge during early childhood. Impairments from these symptoms must be present in two or more settings (e.g., home, school, or work) and evidence of clinically significant difficulties in social, academic, or occupational functioning are required to meet current diagnostic criteria as defined by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994). Additionally, symptoms must be chronic (present for at least six months) and the onset of some symptoms must occur before the age of 7 years within at least one of two domains.

The 18 symptoms that comprise ADHD as defined in DSM-IV load on two independent yet overlapping behavioral constructs: nine symptoms reflect inattentiveness, and nine reflect a combination of hyperactivity and impulsivity. The inattentive dimension and the hyperactivity/impulsivity dimension are expressed to different degrees among children and adults with ADHD, which is reflected in the current DSM-IV classifications of ADHD Predominately Inattentive Type, ADHD Predominantly Hyperactive/Impulsive Type, and ADHD Combined Type. At least 6 of 9 positively endorsed symptoms are required for an individual to be diagnosed with ADHD Inattentive Type, and 6 of 9 are required for a diagnosis of ADHD Hyperactive/Impulsive Type. However, the majority of school-age children are diagnosed with ADHD Combined Type. The predominately Inattentive Type is the second most common

diagnosis, followed by the predominantly Hyperactive/Impulsive Type. Refer to Table 1 for additional details regarding the specific symptoms and current diagnostic criteria.

Psychosocial Impact

ADHD is a chronic condition that results in considerable cost and distress to individuals, families, educational systems and society. In the 2006 National Health Interview Survey conducted by the U.S. Center for Disease Control, 4.5 million children between ages 3-17 (7% of the childhood population in the United States) were recognized as having been diagnosed with ADHD at some point in time, making ADHD the most prevalent psychiatric disorder of childhood and adolescence in the U.S. (Bloom & Cohen, 2007). ADHD affects an estimated 5-10% of the worldwide population (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The total cost associated with ADHD (e.g., treatment, labor losses, healthcare costs) in the U.S. in 2000 was estimated at \$31.6 billion (Birnbaum, et al., 2005). Furthermore, the past 10 to 20 years have seen a dramatic increase in the use of psychostimulants for the treatment of ADHD, and it has been estimated that almost three quarters of children with a diagnosis of ADHD receive stimulant medications at some point (Swanson, et al., 2007). The scientific investigation of the complex etiology of ADHD is therefore imperative given such widespread public health implications.

Table 1. ADHD Symptoms and Diagnostic Criteria from DSM-IV

<p>A. Either (1) or (2)</p> <p>(1) <i>Inattention: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.</i></p> <p>a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities</p> <p>b) often has difficulty sustaining attention in tasks or play activities</p> <p>c) often does not seem to listen when spoken to directly</p> <p>d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)</p> <p>e) often has difficulty organizing tasks and activities</p> <p>f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)</p> <p>g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)</p> <p>h) is often easily distracted by extraneous stimuli</p> <p>i) is often forgetful in daily activities</p> <p>(2) <i>Hyperactivity-impulsivity: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.</i></p> <p><i>Hyperactivity</i></p> <p>a) often fidgets with hands or feet or squirms in seat</p> <p>b) often leaves seat in classroom or in other situations in which remaining seated is expected</p> <p>c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)</p> <p>d) often has difficulty playing or engaging in leisure activities quietly</p> <p>e) is often "on the go" or often acts as if "driven by a motor"</p> <p>f) often talks excessively</p> <p><i>Impulsivity</i></p> <p>g) often blurts out answers before questions have been completed</p> <p>h) often has difficulty awaiting turn</p> <p>i) often interrupts or intrudes on others (e.g., butts into conversations or games)</p> <p><i>Other criteria for diagnosis:</i></p> <p>(B) Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.</p> <p>(C) Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).</p> <p>(D) There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.</p> <p>(E) The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).</p>
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Stability of Symptoms across the Lifespan

A salient feature of ADHD is the marked phenotypic heterogeneity seen over development. Studies on the longitudinal course of ADHD have demonstrated that a significant proportion of individuals diagnosed in childhood symptomatically improve as they grow older (Barkley, Fischer, Smallish, & Fletcher, 2002; Weiss, 1985). For example, longitudinal studies of community-based and clinically-referred samples have shown that nearly half of preschool-aged children with severe ADHD-like symptoms do not continue to exhibit these behaviors as they transition into elementary school and middle school (Campbell, 1995; Lahey, Miller, Gordon, & Riley, 1999; Lavigne, et al., 1998). In older children diagnosed with ADHD for the first time, symptomatic improvement occurs in 30% to 60% of cases as they move into late adolescence and early adulthood (Halperin, et al., 2008; Lahey, et al., 1999).

Nevertheless, ADHD symptoms do persist across development in many individuals (Kuntsi, et al., 2005b) and it is not uncommon for severe difficulties associated with ADHD to continue well into adulthood and across the lifespan (Mannuzza & Klein, 2000). A recent meta-analysis reported that rates of “persistent ADHD” from childhood, defined as meeting full DSM-IV criteria at age 25 years, are approximately 15%; however, when DSM-IV ‘partial remission’ criteria are used, the rates leap to approximately 65% (Faraone, Biederman, & Mick, 2006a). While supporting an age-related decline in symptoms, this meta-analysis highlights the continuity of moderate to severe symptoms into adulthood for many individuals. As such, ADHD is no longer considered a childhood-only disorder, as it often continues into adulthood in many cases (Faraone, et al., 2006a). Data from the National Center for

Health Statistics on patterns of adult ADHD reported a 4.4% prevalence rate in the general U.S. adult population, and adult ADHD-related treatment rates have been estimated at 24% for men and 28% for women (Birnbaum, et al., 2005).

The natural trajectory of the symptom domains that characterize ADHD change over development as well (Hart, Lahey, Loeber, Applegate, & Frick, 1995). In early childhood, the externalizing symptoms of hyperactivity and impulsivity are most apparent, with inattention typically a less common concern. Then, over development, it has been shown that hyperactivity tends to decrease, while inattention, disorganization, and forgetfulness become increasingly more prominent later in development (Halperin, et al., 2008; Hart, et al., 1995).

Such marked heterogeneity *within individuals* and *across development* raises questions regarding the validity of ADHD as a distinct psychiatric condition (Levy, et al., 1997). It has been argued that ADHD is better conceptualized as representing the extreme tail-end of a normal and continuously distributed cluster of dimensional traits that occur naturally in the general population (Fergusson & Horwood, 1995; Levy, et al., 1997). An advantage of this dimensional approach of conceptualizing ADHD is that it avoids conflict as to what diagnostic algorithms are most appropriate for diagnosing ADHD at various developmental stages (Faraone, et al., 2006b) and reduces clinical referral bias (Rutter, et al., 1990). Further, it is problematic that at the present time, the same 18 items/symptoms are used to diagnose ADHD in children and adults as defined in DSM-IV. Finally, taking a dimensional approach increases power for molecular genetics studies of ADHD relative to a categorically phenotyped case-control association study (Neale, Eaves, & Kendler, 1994).

Neuropsychological Studies

Initially conceptualized as a disorder confined to boys who were hyperactive or hyperkinetic, the notion of attentional dysfunction was introduced by Virginia Douglas in the early 1970's based on her examination of vigilance deficits (Douglas, 1972). This work ignited an international field of research dedicated to characterizing the precise nature of attentional dysfunction, as well as cognitive correlates of hyperactivity and impulsivity, thereafter (Seidman, 2006). Since then, neuropsychological research of ADHD has informed modern clinical practice and treatment development for patients with ADHD (Klingberg, et al., 2005; Klingberg, Forssberg, & Westerberg, 2002); driven contemporary theoretical models of the underlying pathophysiological correlates in ADHD (Barkley, 1997; Halperin & Schulz, 2006; Sonuga-Barke & Castellanos, 2007); and guided modern neuroimaging research (Schulz, et al., 2004; Schulz, Newcorn, Fan, Tang, & Halperin, 2005a; Schulz, et al., 2005b; Seidman, Valera, & Makris, 2005b).

Profiles of Preschool Children

Despite the onset of ADHD often occurring between 3 and 5 years of age, most neuropsychological studies have been conducted with school-age children. The limited literature examining preschoolers with ADHD has yielded inconsistent results regarding the presence/absence of neurocognitive impairments. A handful of these studies are highlighted below.

Sonuga-Barke and colleagues examined aspects of planning, working memory, and inhibition in preschoolers with and without elevated ADHD symptom counts (Sonuga-Barke, Dalen, Daley, & Remington, 2002). They reported that only inhibition was associated with severity of ADHD in their sample. Other groups have reported that

ADHD preschoolers perform worse than typically developing preschoolers on tests of vigilance, motor control, and working memory (Mariani & Barkley, 1997), and on tasks of early academic skills such as memory, reasoning, and conceptual development (DuPaul, McGoey, Eckert, & VanBrakle, 2001).

Sonuga-Barke and colleagues conducted another study of ADHD in preschoolers to test their “dual-pathway model” of executive dysfunction and delay aversion (Sonuga-Barke, Dalen, & Remington, 2003). They used tests of working memory, set shifting, planning, delay of gratification, and preference for delayed rewards to generate latent factors of executive dysfunction and delay aversion, and reported that both factors made significant and independent contributions to predictions of ADHD symptoms but only the executive dysfunction factor correlated significantly with age. They suggested that executive dysfunction may just be emerging during early childhood and that delay aversion might be a more fixed characteristic (Sonuga-Barke, et al., 2003).

Newer research supports the Sonuga-Barke hypothesis that executive function deficits are subtle in hyperactive preschoolers but then emerge across development, whereas lower-order deficits (e.g., state regulation) are more prominent in hyperactive preschoolers and remain relatively stable across development. For example, Marks and colleagues demonstrated that despite evidence of poor performance on measures of working memory and inhibitory control in preschoolers at-risk for ADHD, weaknesses could not be specifically attributed to executive function impairments above and beyond lower-order deficits (Marks, et al., 2005). Similarly, Berwid and colleagues showed that preschoolers at-risk for ADHD did not exhibit specific deficits in inhibitory control or sustained attention (Berwid, et al., 2005). The most consistent effect related to risk status

across tasks was the greater number of errors, and longer and more variable reaction times of children at-risk for ADHD (Berwid, et al., 2005). These studies suggest that ADHD-associated decrements in performance on executive function tasks in preschool children are likely related to generalized behavioral dysregulation (e.g., impaired state regulation or delay aversion) rather than to insufficiently developed executive function systems (Berwid, et al., 2005; Marks, et al., 2005; Sonuga-Barke, et al., 2003).

Profiles of School-Age Children

Neuropsychological functioning in children age 7 to 12 with ADHD has been studied extensively, especially executive functioning (Pennington & Ozonoff, 1996; Schachar, Mota, Logan, Tannock, & Klim, 2000; Shallice, et al., 2002). Executive functions broadly encompass a constellation of neurocognitive processes such as attentional control, working memory, inhibitory control, cognitive flexibility and shifting, planning and organization (Pennington & Ozonoff, 1996; Willcutt, et al., 2005). Others have focused their research efforts on examination of lower-order cognitive processes (Sergeant, Geurts, & Oosterlaan, 2002; Sergeant, Oosterlaan, & van der Meere, 1999). This comprehensive body of research has facilitated the use of meta-analytic techniques to assist in characterizing the nature and severity of specific executive and non-executive dysfunction in school-age children diagnosed with ADHD. The most recent and comprehensive meta-analyses will thus be the focus here since it is difficult to draw reliable conclusions from single studies (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005b).

Broad Executive Functions. A meta-analysis of 83 studies identified consistent executive function deficits in children with ADHD (N = 3734) compared to non-ADHD controls (N = 2969), with the most pronounced ADHD-related weaknesses noted on

measures of response inhibition, vigilance/sustained attention, working memory, and planning (Willcutt, et al., 2005). A comprehensive analysis of 123 studies analyzed intellectual, academic, executive and non-executive measures in ADHD (Frazier, Demaree, & Youngstrom, 2004). ADHD groups scored significantly lower than controls on general intelligence tests, academic measures, and an array of executive and non-executive function measures. When comparing ADHD to non-ADHD controls, effect sizes for full-scale IQ (FSIQ) were larger than those found for several execution function measures (e.g., Wisconsin Card Sorting Test and Rey Complex Figure Test), and effect sizes for measures of academic achievement and accuracy on variations of the continuous performance test (CPT) were significantly larger than those for FSIQ (Frazier, et al., 2004). (Note that while the majority of the studies used in this meta-analysis comprised children aged 10-12 years, the authors also included studies of adult samples [8% of the total number of studies]). A selective analysis of working memory showed strong effects for differences between ADHD children and controls in spatial storage ($d = .85$) and spatial central executive ($d = 1.06$) (Martinussen, et al., 2005). Smaller effects in the working memory domains of verbal storage ($d = .47$) and verbal central executive ($d = .43$) were reported (Martinussen, et al., 2005).

Inhibition. Recently, five meta-analytic reviews have included the Stroop Color Word Test to delineate the nature of inhibition deficits in ADHD (Frazier, et al., 2004; Homack & Riccio, 2004; Lansbergen, Kenemans, & van Engeland, 2007; Schwartz & Verhaeghen, 2008; van Mourik, Oosterlaan, & Sergeant, 2005). Two studies reported relatively small to null differences for Stroop interference performance across different developmental periods (Schwartz & Verhaeghen, 2008; van Mourik, et al., 2005). The

others reported more pronounced interference deficits in ADHD probands relative to controls (Frazier, et al., 2004; Homack & Riccio, 2004; Lansbergen, et al., 2007). Computational differences in extracting interference scores have been attributed to these mixed findings (Lansbergen, et al., 2007). Two recent meta-analyses have been conducted on Stop-Signal Task performance to index response inhibition deficits, or lack thereof, in children with ADHD (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). Both studies reported that children with ADHD exhibited slower and more variable reaction times to primary task stimuli (i.e., go-stimuli), as well as slower stop signal reaction times, with moderate effects sizes noted across analyses (Alderson, et al., 2007; Lijffijt, et al., 2005).

Response Variability. Variability in reaction times, as noted above on measures of response inhibition (Alderson, et al., 2007; Lijffijt, et al., 2005), has received a great deal of attention from researchers in recent years (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Castellanos, et al., 2005; Halperin, et al., 2008; Russell, et al., 2006). In a review of 18 studies of the CPT in both children and adults with ADHD compared to non-ADHD controls, 16 studies reported significantly greater reaction time variability (as measured by the standard deviation of reaction time; RTSD) in ADHD relative to controls (Klein, Wendling, Huettner, Ruder, & Peper, 2006). The authors noted that increased RTSD was frequently reported along with normal mean reaction time latency, suggesting that increased RTSD is not secondary to overall slower or faster responding. And in almost all of these studies, RTSD yielded the strongest effect sizes (Klein, et al., 2006). Increased response variability continues to be one of the most consistent cognitive phenotypes reported in children with ADHD (Albrecht, et al., 2008; Uebel, et al., 2010).

Overall, no specific neurocognitive deficit has been definitively linked with ADHD. Rather, these studies indicate that school-age children with ADHD typically evidence a broad array of moderately reliable and generalized neuropsychological weaknesses across domains of small to modest magnitude relative to their typically developing peers without ADHD.

Profiles of Adolescents

Relative to the extensive neuropsychological research in school-age children and similar to the modest literature of preschoolers, neuropsychological research of adolescents within the 13 – 17 age range with ADHD is still in its infancy. The lack of research is unfortunate for several reasons: substance abuse, personality disorders, psychotic disorders, and bipolar disorder most often emerge during adolescence; patterns of emotional and behavioral dysregulation may become more difficult to alter once an individual passes through adolescence; and this is arguably the final time that neural connectivity strengthens in the brain (Steinberg, et al., 2006). Therefore, it seems crucial to know whether adolescents with ADHD, a group already greatly at risk for increased comorbid psychopathology, exhibit a similar pattern(s) of non-specific neurocognitive impairment during this final period of childhood development.

Small to moderate executive function weaknesses in adolescents diagnosed with ADHD have been reported that were independent of age, IQ, comorbidity, and sex; and weaker executive functions were related to symptoms of inattention but not hyperactivity-impulsivity (Martel, Nikolas, & Nigg, 2007). Data from a large Finnish population cohort study recently reported that adolescents with ADHD performed worse on measures of reading fluency, working memory, inhibition, response variability, and

set-shifting relative to those with subthreshold ADHD and typically developing controls (Loo, et al., 2007). Using a principal components analysis, they reported that approximately half (52%) of the ADHD cohort was classified as having a categorically-derived executive function deficit (either working memory, response inhibition, or both) relative to 29% of the subthreshold ADHD group and 10% of the control group (Loo, et al., 2007). Conclusions suggest that higher-order executive deficits do exist in adolescents with ADHD (Loo, et al., 2007; Martel, et al., 2007). However, effect sizes were noted to be somewhat diminished relative to the effect sizes typically reported in the school-age ADHD studies (Alderson, et al., 2007; Martel, et al., 2007); a view that has been challenged by others (Lijffijt, et al., 2005). Clearly, more work needs to be done in this area.

Profiles of Adults

A small literature has profiled the extent to which neuropsychological deficits underlie the clinical presentation of ADHD in adults. Because ADHD was for many years considered to be a “childhood only” disorder, there has been limited research available on neuropsychological functioning in adult ADHD although enough data has been collected for a few initial meta-analyses. A 2004 meta-analysis reported that adults diagnosed with ADHD performed worse than adult controls with no history of ADHD across multiple neuropsychological domains (Hervey, Epstein, & Curry, 2004). Adults with ADHD evidenced consistently weaker performance on various CPT parameters, whereas the Stroop Color-Word Test, Wisconsin Card Sorting Test, and Trail-Making Test only differentiated adults with and without ADHD moderately well, if at all (Hervey, et al., 2004; Nigg, et al., 2005a; Seidman, 2006). A 2005 meta-analysis

compared 13 studies of at least one neuropsychological measure of executive functioning along with any other measures in adults with and without ADHD (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005). This study reported medium effect sizes both in executive functioning areas such as verbal fluency ($d = .62$), inhibition ($d = .64 - .89$), and set shifting ($d = .65$) and in non-executive functioning domains such as consistency of response ($d = .57$), word reading ($d = .60$) and color naming ($d = .62$) (Boonstra, et al., 2005). A meta-analysis of intellectual functioning in adults with ADHD reported that, on average, adults with ADHD perform below normal controls on measures of intelligence by an average of 2.94 FSIQ points, which is essentially not clinically meaningful and suggests that adults with ADHD may be similar, higher, or lower on intellectual ability relative to nonclinical comparison groups (Bridgett & Walker, 2006).

Neuropsychological functioning in adult with ADHD continues to be an emerging area of research that is in need of more data to help clarify the contribution that neuropsychological dysfunction makes to adult ADHD. The studies highlighted above suggest that adults with ADHD have cognitive deficits that are broadly similar to children and adolescents with the disorder in that their difficulties are not confined to executive functioning (Boonstra, et al., 2005; Bridgett & Walker, 2006; Hervey, et al., 2004; Nigg, et al., 2005a; Seidman, 2006). Also similar to children, MRI data has shown that adults with ADHD have volume differences in brain regions in areas involved in attention and executive control (Seidman, et al., 2006). Overall, these studies are largely consistent with studies of children and support the idea that adults with ADHD have a valid disorder with pervasive neurocognitive features (Boonstra, et al., 2005; Hervey, et al., 2004; Nigg, et al., 2005a; Seidman, 2006; Seidman, et al., 2006).

Summary of Neuropsychological Studies

School-age children diagnosed with ADHD evidence reliable impairments in executive functioning that are consistently moderate in magnitude (i.e., effect size). This suggests that executive dysfunction is prominent in many ADHD cases, but is neither necessary nor sufficient to cause ADHD (Nigg, et al., 2005b; Willcutt, et al., 2005).

Neuroanatomically, PFC is presumed to exert control over the various cortical-subcortical substrates of executive functioning (Arnsten & Li, 2005; Halperin & Schulz, 2006). Several investigators have proposed that the primary symptoms of ADHD do in fact arise from deficits in core executive functions (Barkley, 1997; Castellanos & Tannock, 2002; Pennington & Ozonoff, 1996).

However, attributing ADHD symptomatology solely to impaired executive functioning may be unwarranted. Regarding above meta-analysis of Willcutt and colleagues noted above, effect size differences between groups with and without ADHD, as measured by Cohen's d , fell in the medium range on average ($d = .46 - .69$) (Willcutt, et al., 2005). Others have reported that fewer than half of children with ADHD evidence "deficient" executive functioning (operationally defined as scores falling below the 10th percentile) (Nigg, et al., 2005b). Also, as noted above, cognitive deficits in ADHD are not specific to executive function: effect size differences for FSIQ, academic achievement measures, and the control conditions of the Stroop Color-Word task are of similar magnitude as the effect sizes for executive function measures (Frazier, et al., 2004; van Mourik, et al., 2005). Deficits in non-executive domains such as sensorimotor timing (Rommelse, et al., 2008c), visual-perception (Banaschewski, et al., 2006; Sergeant, et al., 2002; Sergeant, et al., 1999), arousal and state regulation (Aston-Jones &

Cohen, 2005; Aston-Jones & Gold, 2009; Halperin & Schulz, 2006; Sergeant, et al., 2002; Sergeant, et al., 1999) and increased intra-individual response variability (Albrecht, et al., 2008; Halperin, et al., 2008; Klein, et al., 2006) are similarly as prominent in ADHD as executive function deficits.

These discoveries have led other investigators to hypothesize that executive dysfunction in ADHD may in fact be due to deficiencies in less effortful, lower-order cognitive systems rather than higher-order, multimodal association areas (Castellanos, et al., 2006; Castellanos, et al., 2005; Halperin & Schulz, 2006; Sergeant, et al., 1999). As such, solely characterizing ADHD as an “executive dysfunction” disorder or as a “regulatory dysfunction” disorder is unsubstantiated given that many individuals diagnosed with ADHD perform poorly on both higher-order and lower-order neuropsychological measures (Castellanos, et al., 2006; Halperin & Schulz, 2006; Halperin, et al., 2008; Nigg, et al., 2005b; Rommelse, et al., 2007).

Neuroimaging Studies

Neuropsychological research has provided the framework within which neuroimaging studies have burgeoned in recent years. Prior to the availability of neuroimaging data, “frontal lobe dysfunction” was presumed to be the neural substrate of ADHD given the resemblance between patients with frontal lobe lesions and the ADHD phenotype (e.g., poor impulse control and inattention) (Stuss & Benson, 1984). The frontal lobes receive information from diverse regions of the brain and integrates multisensory input from the temporal, parietal and occipital lobes, as well as subcortical limbic and motor structures (Averbeck & Seo, 2008). While neuroimaging research has supported frontal lobe pathology in ADHD to a large extent, the research has also provided support for more diffuse and dynamic neurologic dysfunction (Castellanos, et al., 2006; Halperin & Schulz, 2006). Both structural and functional correlates of ADHD are presented in the following sections.

Structural Magnetic Resonance Imaging (sMRI)

Cortex and Frontal Lobes. Using the Talairach coordinate system to delineate the four cerebral lobes (frontal, parietal, temporal and occipital), Mostofsky and colleagues reported significant lobar volume discrepancies only in the frontal lobes (controls > ADHD) (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). They then further subdivided the frontal lobe into five regions (motor, premotor, prefrontal, anterior cingulate, and deep white matter) to examine gray matter, white matter and lateral volumetric differences, and found that controls had significantly larger prefrontal, premotor and deep white matter volume; larger gray matter volume in both frontal hemispheres; and larger left premotor white matter volume relative to children with

ADHD. No volumetric differences were found in the anterior cingulate and motor regions (Mostofsky, et al., 2002). Abnormal morphology was noted in the frontal cortices of children and adolescents with ADHD in an independent study, with reduced regional brain size localized mainly to inferior portions of dorsal prefrontal cortices bilaterally (Sowell, et al., 2003). Conversely, from 1991 to 2001, 152 children with ADHD and 139 age-matched controls (age range 4.5 – 19 years for both groups) contributed a total of 544 MR images to researchers at the National Institute of Mental Health (NIMH) to study brain volume trajectories during development (Castellanos, et al., 2002). At baseline, non-ADHD controls had significantly greater total cerebral volume and larger frontal gray matter and white matter volume than children with ADHD. However, once they adjusted for significant group differences in total cerebral volume, no differences in frontal gray matter or white matter volume remained between the two groups. Notably, an analysis of the follow-up scans ten years later showed no differences in frontal lobe morphometry in ADHD; rather, the frontal lobes had the smallest effect size of any anatomical region (Castellanos, et al., 2002). A region of interest (ROI) survey of two sMRI studies reported evidence of large, significant differences between ADHD and control groups in prefrontal and other frontal lobe ROIs, as well as deep frontal white matter (Valera, Faraone, Murray, & Seidman, 2007).

Subcortical Regions and Limbic System. The subcortical structures of the limbic system regulate emotions and drives, olfaction, memory, and homeostatic functions including autonomic and neuroendocrine control (Blumenfeld, 2002). Limbic structures lie deep within medial and ventral regions of diverse cortical and subcortical loci. The main components of the limbic system include the limbic cortex (parahippocampal gyrus,

cingulate gyrus, medial orbitofrontal cortex, temporal pole, and anterior insula), hippocampal formation, amygdala, olfactory cortex, diencephalon, basal ganglia, basal forebrain, septal nuclei, and brainstem (Blumenfeld, 2002). Limbic system dysfunction has been implicated in the pathophysiology of ADHD on the basis that emotional dysregulation, impulsivity, reward insensitivity and motivational deficits are present in a subgroup of individuals with ADHD (Cardinal, Winstanley, Robbins, & Everitt, 2004; Nigg & Casey, 2005).

In children and adolescents diagnosed with ADHD, larger bilateral hippocampal volume and reduced bilateral amygdala volume over the area of the basolateral complex has been reported (Plessen, et al., 2006). In contrast, others have reported no significant differences in hippocampal and amygdala volume between adults with and without ADHD (Perlov, et al., 2008). This conflict might reflect developmentally linked changes in hippocampal and amygdala volume in ADHD. Recently, a study using “cytoarchitectonic mapping” of the thalamus to delineate volume abnormalities reported marked volume loss in the region of the pulvinar nuclei bilaterally in youth with ADHD (Ivanov, et al., 2010). The lateral portions of the pulvinar, where the morphological anomalies were most prominent, support circuitry that detects salient somatosensory stimuli (Ivanov, et al., 2010; Shaw, 2010).

Basal Ganglia. The basal ganglia are a collection of ventral telencephalic gray matter nuclei that interact with the cerebral cortex to control important motor, cognitive and emotional functions (Middleton & Strick, 2000). The basal ganglia comprise three input nuclei (caudate and putamen [known as the striatum], and the subthalamic nucleus), and two output nuclei (globus pallidus and substantia nigra). Virtually all afferent

projections to the basal ganglia arrive at the striatum, and efferent projections leave the basal ganglia via the internal segment of the globus pallidus and the substantia nigra pars reticulata (Blumenfeld, 2002; Cohen & Frank, 2009; Middleton & Strick, 2000). There are intrinsic excitatory and inhibitory connections within the basal ganglia that facilitate movement and learning. The *direct pathway* travels from the striatum directly to the internal segment of the globus pallidus or substantia nigra pars reticulata and facilitates “go” learning via dopamine D1 receptors (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007a). Conversely, information along the *indirect pathway* travels from the striatum to the external segment of the globus pallidus and then to the subthalamic nucleus before ultimately reaching the internal segment of the globus pallidus or substantia nigra pars reticulata; the indirect pathway facilitates “no-go” learning via D2 receptors (Frank, et al., 2007a).

Basal ganglia dysfunction has long been implicated in the pathophysiology of ADHD (Dougherty, et al., 1999). The size and symmetry of the caudate nucleus received a lot of the early attention in neuroimaging studies of children with ADHD with mixed results. The inconsistent findings are in part due to disagreement of what constitutes “normal” caudate symmetry (Castellanos, et al., 2002; Filipek, et al., 1997). Of the groups that define normal caudate asymmetry as left greater than right, Filipek and colleagues reported that children with ADHD had “reverse” asymmetry (i.e., right greater than left), which they ascribed to significantly smaller left caudate volume overall and smaller volume of the head of the caudate in ADHD (Filipek, et al., 1997). Conversely, another study reported that left caudate volume was significantly larger than right caudate volume across all of their groups (ADHD-Combined Type, ADHD-Inattentive Type, and

controls) (Pineda, et al., 2002). Neither ADHD group, when combined or analyzed separately, differed from controls when the volume of the caudate nucleus head of each side were compared; in other words, all three groups had left caudate nucleus head volumes significantly higher than right, although there were no between-group differences (Pineda, et al., 2002). Recently, large deformation diffeomorphic metric mapping (LDDMM) was used to examine basal ganglia volume and shape in boys and girls with and without ADHD (Qiu, et al., 2009). The statistical power of LDDMM mapped signals is significantly increased over conventional Talairach–Tournoux averaging. Boys with ADHD showed significant volume compression bilaterally in the caudate head and body, anterior putamen, left anterior globus pallidus, and right ventral putamen; volume expansion was most pronounced in the posterior putamen. No volume or shape differences were identified in girls with ADHD (Qiu, et al., 2009).

Developmentally, the aforementioned longitudinal study of Castellanos reported that, upon initial scans, the control group had significantly larger total caudate volume than the ADHD group (Castellanos, et al., 2002). However, this difference disappeared over time as the ADHD subjects “normalized” to an average size that was equal to controls. They suggested that the caudate nucleus is likely to reach its maximum volume around 10 years of age and then gradually decline over time in both ADHD and typically developing children (Castellanos, et al., 2002). Notably, it has been hypothesized that the normalization of caudate volume by late adolescence is potentially related to the reduction in ADHD motor symptoms that are seen with increasing age (Frank, Scheres, & Sherman, 2007c).

Corpus Callosum. The corpus callosum is the largest interhemispheric commissure connecting the right and left cerebral hemispheres. Reductions in corpus callosum size may lead to a decrease in the amount of fibers that normally traverse the hemispheres and henceforth reduced intercerebral communication of information (Giedd, et al., 1994). Anterior (rostrum, genu, and rostral body) and posterior (splenium) regions of the corpus callosum have been reported to be reduced in ADHD (Giedd, et al., 1994; Valera, et al., 2007). However, differences in total corpus callosum area have not been consistently found in ADHD, which has led to speculation that the relationship between ADHD and corpus callosum reductions may be site specific (Giedd, et al., 1994). Interestingly, a comparison of the corpus callosum of children diagnosed with ADHD to their non-affected siblings demonstrated no differences in corpus callosum morphometry between siblings with and without ADHD, irrespective of whether local anatomy or total structure was examined (Overmeyer, et al., 2000). These investigators speculated that corpus callosum abnormalities may be more environmentally sensitive than genetic mediated in ADHD (Overmeyer, et al., 2000).

Cerebellum. Differentiation in cerebellar morphometry between children with ADHD and typically developing controls is arguably the most consistent neuroanatomic substrate reported in ADHD to date (Valera, et al., 2007). An early quantitative examination of cerebellar and vermal volumes reported that overall vermal volume was significantly lower in 46 boys with ADHD relative to 47 age-matched controls (Berquin, et al., 1998). Diminished volume was localized to the posterior-inferior lobule (lobules VIII to X) and remained significant after adjusting for total cerebral volume and IQ. An independent group of researchers who similarly adjusted for overall brain size and IQ

found identical discrepancies in the posterior-inferior cerebellar vermis (i.e., ADHD < controls), which they too attributed to a smaller posterior-inferior lobe (lobules VIII-X), without any significant differences in the posterior-superior lobe (lobules VI to VII) (Mostofsky, Reiss, Lockhart, & Denckla, 1998). In 2001, cerebellar vermis morphometry was examined in a group of 50 girls diagnosed with ADHD and compared to 50 typically developing girls. Similar to boys with ADHD, girls with ADHD had significantly smaller volumes of the posterior-inferior cerebellar vermis (lobules VIII to X), which remained significant after adjusting for total cerebral volume (Castellanos, et al., 2001). Finally, smaller cerebellum in ADHD was the only significant difference that remained following adjustment for total cerebral volume as reported by Castellanos and colleagues in their larger study (Castellanos, et al., 2002). At baseline, cerebellar volume was 3.5% smaller in the ADHD group than in the control group. Final follow-up scans showed that both groups continued to exhibit an exponential increase in total cerebellar volume; however, the smaller ADHD cerebellum held, with a non-significant trend for the difference to increase as the two cohorts aged (Castellanos, et al., 2002).

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI measures the hemodynamic response (i.e., change in blood flow and blood oxygenation) related to neural activity in the brain (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). fMRI studies have implicated the prefrontal cortex, basal ganglia, thalamus and cerebellum in the pathophysiology of ADHD (Arnsten & Li, 2005; Casey, et al., 1997; Casey & Durston, 2006; Casey, et al., 2007; Durston, et al., 2007; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Durston, et al., 2003; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Rubia, et al., 2000; Rubia, et al.,

1999; Rubia, Smith, Brammer, & Taylor, 2007; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Scheres, Milham, Knutson, & Castellanos, 2007; Schulz, et al., 2004; Schulz, et al., 2005a; Schulz, et al., 2005b). Yet, specific and reliable neural substrates have not been identified, as both hypoactivation and hyperactivation within these regions have been observed in ADHD. Despite the lack of consistent replication, insufficient processing in these cortical-subcortical regions seems to be at least partially involved in the pathophysiology of ADHD. Most of the fMRI research on the neural correlates of ADHD has been conducted using response inhibition paradigms, a handful of which will be discussed below.

Response Inhibition and Cortical-Subcortical Networks. Several studies have attempted to uncover the neural underpinnings of response inhibition in ADHD. A study led by Kurt Schulz and colleagues from our lab have examined response inhibition in our longitudinal sample of adolescents diagnosed with ADHD during childhood, and compared them to adolescents with no history of ADHD on performance parameters of a go/no-go task with fMRI (Schulz, et al., 2004). Adolescents with childhood ADHD exhibited markedly greater activation of the inferior frontal gyrus and frontopolar regions of the middle frontal gyrus bilaterally, right dorsolateral middle frontal gyrus, left anterior cingulate gyrus, and left medial frontal gyrus during inhibition of prepotent responses relative to controls. Controls exhibited greater activation of the left precentral gyrus, right lingual gyrus, right inferior temporal gyrus, left hippocampus and bilateral cerebellum relative to the ADHD group. Notably, activation of the anterior cingulate gyrus was inversely related to performance such that greater activation was associated with more difficulty inhibiting the prepotent response (Schulz, et al., 2004).

Rubia and colleagues (2005) examined inhibition and error processing in adolescents with and without ADHD. In controls, successful inhibition was characterized by increased neural activation in a network comprised of the right inferior and mesial prefrontal cortex, left dorsolateral prefrontal cortex, anterior cingulate gyrus, left parietal cortex, bilateral precentral cortex, and right hemisphere and vermis of the cerebellum; adolescents with ADHD showed no significant activations within this network. Activation patterns during error processing were similar in ADHD and control adolescents overall, and comprised the rostromesial prefrontal cortex, bilateral temporal lobes, and posterior cingulate gyrus; however, controls showed significantly greater activation of the posterior cingulate and precuneus relative to ADHD (Rubia, et al., 2005). Finally, reduced activation patterns in ADHD in the rostral mesial prefrontal cortex during motor inhibition; and in right inferior prefrontal, temporal, and parietal cortices during task switching has also been demonstrated (Smith, Taylor, Brammer, Toone, & Rubia, 2006). These studies implicate frontal-striatal dysfunction in ADHD, though there is conflicting evidence in terms of the direction of the neural effects i.e., hyper-activation versus hypo-activation (Rubia, et al., 2005; Schulz, et al., 2004; Smith, et al., 2006).

An atypical activation pattern in prefrontal-subcortical pathways during successful response inhibition in ADHD was reported to be heritable (Durstun, et al., 2006). These investigators compared a group of children and adolescents diagnosed with ADHD, a group of their unaffected siblings, and a group of typically developing controls. It was reported that controls activated a network that included the bilateral inferior frontal gyrus, anterior cingulate gyrus, regions in the middle and superior frontal gyri, and the

left inferior parietal lobe when successfully exerting inhibitory control. Siblings with no history of ADHD showed increased activation in right inferior frontal gyrus, bilateral anterior cingulate gyrus, right inferior parietal lobule, and right superior temporal gyrus during successful inhibition, although their relative activation pattern was weaker than controls. In contrast, siblings diagnosed with ADHD showed increased activation in right middle frontal gyrus and right inferior parietal lobule during successful inhibition, but did not activate the inferior frontal gyrus or anterior cingulate gyrus (Durston, et al., 2006). This study suggests that inhibition deficits in ADHD are genetically linked.

Response Variability. A few studies have examined the neural mechanisms underlying increased intra-individual response variability in ADHD in the context of attentional control paradigms. A study that employed event-related fMRI and the Attention Network Test (ANT) reported that during alerting, which is thought to underlie response variability, controls activated the right anterior cingulate significantly more than children with ADHD (Konrad, et al., 2006). By contrast, the ADHD group showed significantly greater activity in the brainstem/locus coeruleus during alerting (Konrad, et al., 2006). During conflict resolution, children with ADHD demonstrated increased parietal activity compared to controls, which they hypothesized as possibly representing a “compensatory” mechanism in ADHD in order to overcome underactivation of the frontal-striatal network that typically developing controls used (Konrad, et al., 2006). In another study, Rubia and colleagues reported that youth with ADHD showed decreased activation patterns in regions of the superior and middle temporal gyri, striato-thalamic area, and cingulate during an attention task (Rubia, et al., 2007). Regions of underactivation correlated with response variability and with age in controls but not in

ADHD participants (Rubia, et al., 2007). Thus, developmentally anomalous functional activation patterns within the brainstem, temporal lobes, thalamus, and cingulate might underlie increased intra-individual response variability in ADHD (Konrad, et al., 2006; Rubia, et al., 2007).

To help better determine whether hypo- or hyper-activation is more characteristic of ADHD, Dickstein and colleagues employed the recently developed activation likelihood estimation (ALE) technique to carry out a quantitative voxel-wise meta-analysis of published fMRI studies (Dickstein, Bannon, Castellanos, & Milham, 2006). Controls demonstrated significantly greater probability of activation in a variety of regions relative to ADHD including areas of left ventral and dorsolateral prefrontal cortex, anterior cingulate cortex, bilateral parietal lobe, right thalamus, left middle occipital gyrus, and an area centered at the right claustrum extending from the insula to the striatum. In contrast, regions of greater probability of activation that were associated with ADHD included the left frontal lobe, insular cortex, portions of middle frontal gyrus, left thalamus and the right paracentral lobule. When analyses were limited to studies of response inhibition, a more restricted pattern of increased likelihood of activations for controls compared to ADHD was indicated in the bilateral prefrontal cortex, cingulate cortex, left parietal lobe, and right caudate; in contrast, ADHD subjects were more likely to activate the medial frontal gyrus and the right paracentral lobule relative to controls during response inhibition (Dickstein, et al., 2006).

Resting State fMRI. Recently, the idea that individuals with ADHD have abnormal patterns of spontaneous neural activity and connectivity in the “default-mode network” has been explored with the use of resting-state fMRI maps (Sonuga-Barke &

Castellanos, 2007). The default-mode network is characterized by recruitment of a discrete network of brain regions that can be measured with fMRI when the mind is at rest that includes the medial posterior cingulate (Brodmann area's [BA] 30 and 31); precuneus (BA 7); paracentral lobule (BA 5); inferior parietal regions (BAs 40, 39, and 7); angular gyri (BAs 19 and 39); inferior frontal cortices (BAs 10, 47); superior and middle frontal gyri (BAs 8, 9, and 10); and a cluster of dorsal medial frontal regions (BAs 8, 9, 10, and 32) (Raichle, et al., 2001). Default-mode network activity is high at baseline then decreases during attention-demanding cognitive tasks (Raichle, et al., 2001). Because resting-state scans require no cognitive task, this approach provides detailed information about spontaneous inter-regional connectivity in the brain by bypassing potentially confounding issues related to task performance (Sonuga-Barke & Castellanos, 2007).

A study that used a regional homogeneity (ReHo) analysis to measure temporal synchrony of the resting-state in adolescent boys with and without ADHD reported decreased ReHo associated with ADHD in frontal-striatal-cerebellar circuits including the inferior frontal gyrus bilaterally, right anterior cingulate cortex, left caudate, bilateral pyramis and left precuneus; and significantly increased ReHo in bilateral lingual gyrus, bilateral cuneus, right culmen, and left parahippocampal gyrus in ADHD (Cao, et al., 2006). ReHo mapping was recently reported to discriminate between ADHD and controls diagnostically, with abnormal patterns of activity in regions of the prefrontal cortex, anterior cingulate cortex and thalamus able to correctly classify as much as 85% of ADHD cases (Zhu, et al., 2008).

Our view of ADHD has been unmistakably shaped by the evolution and sophistication of modern neuroimaging techniques. The early anatomical studies provided the first evidence of frontal-striatal-cerebellar dysfunction in ADHD, which were followed up by functional studies implicating these same pathways. Then, with the advances in imaging techniques that allowed for longitudinal mapping of cortical growth trajectories, it became fairly clear that the patterns of dysfunction in ADHD were far from static and that they change dynamically in important ways during development. Importantly, it seems to be the case that a proportion of children who are diagnosed with ADHD early in childhood will eventually “outgrow” the disorder and “catch up” to their peers depending on their neural and cognitive development. Furthermore, there is the new evidence that the brains of youth with ADHD differ from their non-ADHD peers not only while performing a cognitive task, but also while they are at rest. That said, many of these associations have not been consistently replicated in independent samples and there is no shortage of conflicting findings. Nonetheless, this body of research will continue to grow at a rapid pace and there will no doubt be much knowledge to gain in the future to improve the developmental trajectory of ADHD.

Dopamine

Dopamine is a neuroactive substance classified under the category of a “classical” neurotransmitter. Classical neurotransmitters are made presynaptically, released into the postsynaptic cleft and modulate post-synaptic action. See Table 2 for detailed criteria of a classical neurotransmitter. Dopamine is one of the most thoroughly investigated neurotransmitter systems in the central nervous system due to its critical involvement in multiple homeostatic, cognitive and motor functions (Aizman, et al., 2000; Arnsten & Li, 2005; Bellgrove & Mattingley, 2008; Brozoski, Brown, Rosvold, & Goldman, 1979; Cichon, Nothen, Erdmann, & Propping, 1994; Cook, et al., 1995; Dahlstrom & Fuxe, 1964; Dal Toso, et al., 1989; Durstewitz, 2006; Girault & Greengard, 2004).

A “dopamine deficit” hypothesis of ADHD was initially proposed over 30 years ago (Glick & Milloy, 1973; Levy & Swanson, 2001; Reimherr, Wood, & Wender, 1980; Wender, 1972; Wender, Epstein, Kopin, & Gordon, 1971). Contemporary theories of the pathophysiology of ADHD continue to implicate dopaminergic dysfunction (Andersen & Teicher, 2000; Barkley, 1997; Halperin & Schulz, 2006; Sagvolden, Johansen, Aase, & Russell, 2005; Sonuga-Barke, 2003). Modern neuroimaging has since demonstrated that dopamine is one of the two primary neurotransmitters (norepinephrine being the other) that is manipulated by psychostimulants such as methylphenidate (Ritalin) and amphetamine (Adderall), which for a half century have provided the primary pharmacological treatment for ADHD (Volkow, Wang, Fowler, & Ding, 2005). In patients with ADHD, low doses of a stimulant reduce excess motor activity and enhance arousal and concentration (Fan & Hess, 2007). Finally, dopamine receptors and the dopamine transporter are functionally expressed in cortical-subcortical networks such as

the prefronto-striatal pathway that underlie neurocognitive functions implicated in the pathophysiology of ADHD (Aizman, et al., 2000; Andersen, 2002; Arnsten & Li, 2005; Bellgrove, et al., 2005a; Bellgrove, et al., 2009; Castellanos & Tannock, 2002).

Table 2. Classical Neurotransmitter (NT) Criteria

1) NT is localized to presynaptic neurons
2) Enzymes needed to make NT localized to presynaptic neuron
3) Must be a mechanism to stop NT action
4) When NT is synthetically placed on postsynaptic neuron, get the same effect as if the presynaptic neuron fired
5) When presynaptic cell fires, NT should be found in the synaptic cleft
6) Drugs that interfere with the postsynaptic action of the NT must block the effect of presynaptic firing
7) Drugs that interfere with the stopping mechanism will prolong NT action

Neurobiology

Neurochemistry. Dopamine belongs to a larger class of *catecholamine* neurotransmitters that includes *norepinephrine* and *epinephrine*. The catecholamines and the *indoleamine serotonin (5-HT)* fall under an even broader neurochemical class of *monoamines*. Dopamine is estimated to account for as much as 80% of the total brain catecholamine content despite a rather modest number of dopamine cells in the entire human brain (approximately 1 million in the entire human brain, as compared to 10 billion cells in the cortex alone) (Feldman, Meyer, & Quenzer, 1997).

The catecholamines serve as precursors for one another. The biosynthetic process of catecholamine production starts with the amino acid *tyrosine*, which is converted in to *L-DOPA* by *tyrosine hydroxylase*. *L-DOPA* is then converted to dopamine by *aromatic L-amino acid decarboxylase (AADC)*. Once dopamine is synthesized it can be converted into norepinephrine by *dopamine-beta hydroxylase (DBH)*. Finally, norepinephrine can be converted into epinephrine by *phenylthanolamine N-methyltransferase (PNMT)*.

Dopamine synthesis occurs at the synaptic terminal button of neurons once tyrosine hydroxylase is transported from the cell body. Once dopamine is released into the synaptic cleft, most of it binds to the post-synaptic cell. A small percentage of extrasynaptic dopamine is recycled into the terminal by via reuptake by the dopamine and/or norepinephrine transporter; and an even smaller percentage of extrasynaptic dopamine is degraded by *monoamine oxidase* (MAO-A and MAO-B) or *catechol-O-methyltransferase* (COMT).

Neuroanatomy. There are several dopaminergic systems in the brain.

Dopaminergic cell groups were originally mapped in the 1960's by Dahlstrom and Fuxe (1964) and categorized as A8-A15. Two of the most important dopaminergic systems that have been implicated in several psychiatric (e.g., schizophrenia) and neurologic (e.g., Parkinson's disease) disorders originate in the substantia nigra (SN) and ventral tegmental area (VTA) of the mesencephalon. The *nigrostriatal tract* (NS) originates from cells in the substantia nigra pars compacta (A9 cell group) that project to the dorsal striatum (caudate nucleus and putamen). The NS is vital to motor control. The *mesocorticolimbic system* (MCL) projects from the VTA (A10 cell group) to the limbic striatum (hypothalamus, amygdala, septum, hippocampus, and nucleus accumbens) and to the frontal lobe/prefrontal cortex. The MCL is involved in a broad array of behavioral functions including reward, motivation, cognition and working memory, and drug abuse. The NS and MCL pathways partially overlap as a small portion of nigrostriatal neurons come from the VTA, and a small portion of mesocorticolimbic neurons come from the SN (Feldman, et al., 1997).

Neurophysiology. Midbrain transmission of dopamine to the cortex via the MCL pathway is regulated by *tonic* and *phasic* dopamine neuron firing at multiple synaptic junctures (Floresco, West, Ash, Moore, & Grace, 2003; Grace, 1991; Grace, Floresco, Goto, & Lodge, 2007). Animal models demonstrate that extrasynaptic tonic dopamine release is initiated by slow, spontaneous spike activity of dopaminergic neurons in the VTA at single cell and network levels (Floresco, et al., 2003; Grace, et al., 2007). Tonic dopamine then propagates rostrally to the striatum and cortex. Tonic dopamine release supplies the baseline level of extracellular dopamine in the MCL via D1 receptor activation. Tonic dopamine is reciprocally regulated by glutamatergic and γ -aminobutyric acid (GABA) afferents from the striatum and cortex (Floresco, et al., 2003; Grace, et al., 2007).

In contrast, high amplitude phasic dopamine release results from ‘burst’ firing of VTA and striatal dopamine neurons in response to behaviorally relevant stimuli. Phasic dopamine firing is hypothesized to be the functionally relevant signal sent to postsynaptic D2 receptor sites along the MCL to modulate goal-directed behavior (Grace, et al., 2007).

Alterations of tonic and phasic MCL dopaminergic transmission occur on very different temporal scales; seconds to minutes for tonic dopamine turnover versus milliseconds for phasic dopamine firing (Grace, et al., 2007). Synaptic dopamine released by burst firing is restricted by the high-affinity and rapid reuptake dopamine transporter system, whereas change in tonic dopamine is regulated by the overall stable activity of MCL dopamine neurons (Floresco, et al., 2003; Grace, 1991; Grace, et al., 2007). Finally, only dopamine neurons that are tonically active are capable of burst

firing; thus tonic dopamine serves to suppress the responsivity of the phasic dopamine system (Floresco, et al., 2003; Grace, et al., 2007).

Dopamine Receptor Subtypes

The five known dopamine receptors, designated D1 through D5, belong to the G protein-coupled receptor (GPCR) superfamily (Feldman, et al., 1997; Missale, Nash, Robinson, Jaber, & Caron, 1998). D1 and D5 are part of the D1-like receptor subfamily and D2, D3 and D4 are part of the D2-like receptor subfamily. The main biochemical mechanism that differentiates the two subfamilies is that D1 and D5 induce adenylyl cyclase activity, whereas D2, D3 and D4 either inhibit adenylyl cyclase activity or have no effect on its activation (Diaz Heijtz & Castellanos, 2006).

Dopamine D1 receptor distribution. The gene that codes the D1 receptor is DRD1. DRD1 is located at chromosome 5q35.1 and contains two exons separated by a small intron in the 5' untranslated region (UTR). Three independent labs have cloned the gene for D1, DRD1, which encodes a protein of 446 amino acids with a structure of seven membrane-spanning domains (Dearry, et al., 1990; Feldman, et al., 1997; Gingrich, et al., 1991). The D1 receptor is more abundant than D2 in most areas of the brain (Hurd, Suzuki, & Sedvall, 2001). However, comparative studies of humans and other species have reported similar concentrations of D1 and D2 receptors in the neostriatum (Camps, Kelly, & Palacios, 1990; Feldman, et al., 1997; Hurd, et al., 2001), which suggests that the distribution of D1 and D2 has been well preserved in the basal ganglia—namely the neostriatum (caudate, putamen and nucleus accumbens)—during evolution and among species, with evidence of less preservation outside of the basal ganglia/striatum (Camps, et al., 1990).

The greatest distribution of D1 density in rats is in the termination areas of the caudate nucleus, putamen, nucleus accumbens, olfactory tubercle, and substantia nigra; intermediate levels of D1 receptor binding are reported in the ventral pallidum, entopeduncular nucleus, and some of the nuclei of the amygdala; and low D1 levels have been reported in rat neocortex, thalamus, cerebellum, hippocampus, septum, and most areas of the hypothalamus (Feldman, et al., 1997). In humans, the highest density of D1 is in the caudate nucleus, putamen and nucleus accumbens (De Keyser, et al., 1988). In the globus pallidus, the pars medialis contains a three-fold higher concentration of D1 receptors than the pars lateralis (De Keyser, et al., 1988). D1 receptors are present in the amygdala and substantia nigra; are present in low concentrations in the thalamus; and absent in the cerebellum.

The entire cerebral cortex is also rich in D1 receptor expression (De Keyser, et al., 1988; Hurd, et al., 2001). D1 receptors have both pre- and post-synaptic localization on individual pyramidal cells in PFC; with the postsynaptic receptor more frequently observed (Missale, et al., 1998). Notably, D1 receptors outnumber D2 receptors by 20 to 1 in DLPFC of nonhuman primates, a region important for working memory (Castner & Williams, 2007; Lidow, Goldman-Rakic, Gallager, & Rakic, 1991). Finally, it has even been suggested that the greatest development of the dopamine system in evolution has been the dramatic elevation of D1 receptor abundance in PFC in primates relative to rodents (Castner & Williams, 2007).

Dopamine D2 receptor. D2 is the main autoreceptor of the dopaminergic system, though it also has important postsynaptic functions (Lindgren, et al., 2003). Two isoforms of the D2 receptor exist in both rats (Giros, et al., 1989) and humans (Dal Toso,

et al., 1989). The two isoforms are produced by the same gene by alternative mRNA splicing of exon 6; a long isoform (D2L) consisting of 443 amino acids in humans is mostly expressed postsynaptically; and a short isoform (D2S) of 414 amino acids that is mainly expressed at presynaptic terminals (Bertolino, et al., 2009; Feldman, et al., 1997; Lindgren, et al., 2003). The two isoforms differ by an insertion of 29 amino acids in the third intracellular loop of D2L (Dal Toso, et al., 1989). The ratio of D2S/D2L differentially modulates dopaminergic signaling within the cortico-striato-thalamo-cortical network (Bertolino, et al., 2009).

D2 receptors evidence a widespread and heterogeneous distribution of expression in the brain (Hurd, et al., 2001). D2 is most abundant in the caudate nucleus, putamen, core of the nucleus accumbens, olfactory tubercle, substantia nigra pars compacta, and glomerular layer of the olfactory bulbs (Feldman, et al., 1997; Hurd, et al., 1997; Hurd, et al., 2001; Missale, et al., 1998). D2 expression is equal in the pars medialis and pars lateralis of the globus pallidus. D2 receptors are also present in the amygdala, substantia nigra, and the anterior lobe of the pituitary gland but are absent in the cerebellum and thalamus (Missale, et al., 1998). Finally, D2 receptors are in relatively low concentrations in PFC and temporal lobe, confined primarily to the entorhinal area, granule cells of the hippocampal formation, and cingulate cortex (De Keyser, et al., 1988).

Dopamine Dysfunction in ADHD

As noted above, abnormal dopaminergic function has long been implicated in the pathophysiology of ADHD (Glick & Milloy, 1973; Levy & Swanson, 2001; Reimherr, et al., 1980; Wender, 1972, 1973; Wender, et al., 1971), with particular interest in whether

disrupted tonic and/or phasic dopamine transmission is involved. Recently, it was hypothesized that low tonic dopamine in individuals with ADHD causes a relative ‘up-regulation’ of phasic dopamine responsivity, leading to hypersensitivity to environmental stimuli (Sikstrom & Soderlund, 2007). Depending on the nature of the environmental stimulation, phasic dopamine neuron firing may lead to low, well-adapted, or high dopamine levels and subsequently to appropriate behavior (or lack thereof) (Sikstrom & Soderlund, 2007). Yet others (Frank, Santamaria, O’Reilly, & Willcutt, 2007b; Madras, Miller, & Fischman, 2005; Sagvolden, et al., 2005) have rejected the enhanced phasic/reduced tonic dopamine hypothesis of ADHD, arguing that reduced levels of tonic and phasic dopamine are associated with ADHD since both extracellular tonic dopamine (Volkow, et al., 2001) and synaptic phasic dopamine (Schiffer, et al., 2006) levels are increased in the MCL with stimulant medications (Frank, et al., 2007b). Nonetheless, few would argue that dopamine dysfunction is at least partially involved in the pathophysiology of ADHD.

Evidence of an association between D1 receptors and treatment in ADHD comes from a recent study in rodents which showed that a D1 antagonist reversed the beneficial effect of oral doses of methylphenidate, suggesting that D1 stimulation contributes to the cognitive-enhancing effects of methylphenidate (Arnsten & Dudley, 2005). However, these findings are at odds with those from a different group of investigators who examined dopaminergic neurotransmission in the hyperactive and inattentive mouse mutant *coloboma* to identify pre- and postsynaptic elements essential for the effects of amphetamine in these mice (Fan & Hess, 2007; Fan, Xu, & Hess, 2010). This latter group of researchers demonstrated that activation of D2-like, but not D1-like dopamine

receptors was necessary for an amphetamine-induced reduction in locomotor activity (Fan & Hess, 2007; Fan, et al., 2010). Thus, the degree to which D1 and/or D2 receptors are important therapeutic mechanism in ADHD is unclear, as is our understanding of the degree to which tonic and/or phasic dopamine transmission is involved.

Working Memory

The term “working memory” was introduced 50 years ago as an important psychological construct involved in the regulation of behavior (Miller, et al., 1960). Working memory is typically conceptualized as the brain’s ability to temporarily maintain information in a limited-capacity yet highly accessible system for the purpose of manipulating the information in order to execute a purposeful behavior or perform a mental operation (Karatekin, 2004). Working memory processes have been shown to underlie a wide range of cognitive functions; from briefly remembering a series of informational bits such as a phone number; to planning, educational learning, reasoning and comprehension (Crone, et al., 2006).

One of the most comprehensive models of working memory is the Baddeley and Hitch model, originally published over 35 years ago (Baddeley & Hitch, 1974). The model was revised by Baddeley in 1986 (Baddeley, 1986) and again in 2000 (Baddeley, 2000). According to the model, working memory can be divided into limited-capacity subsystems (the phonological loop, the visuospatial scratchpad, and the episodic buffer), with an overarching control system (the central executive) (Baddeley, 1996, 2000; Baddeley, 1986; Baddeley & Hitch, 1974). Data from cognitive neuroscience and neuropsychology generally supports the validity of the model (Alderson, Rapport, Hudec, Sarver, & Kofler, 2010; Rapport, et al., 2008; Rudner & Ronnberg, 2008; Siegert, Weatherall, Taylor, & Abernethy, 2008), although it is not without critics (Nairne, 2002).

Neural Substrates

The seminal work of Joaquin Fuster (1973) was the first to demonstrate that cells in PFC show patterns of sustained and elevated discharge during the delay period

between the onset and offset of a stimulus. Modern neuroimaging has confirmed that PFC is crucial to working memory (Crone, et al., 2006; D'Esposito, Postle, Ballard, & Lease, 1999; Owen, Evans, & Petrides, 1996; Smith & Jonides, 1999). For basic working memory storage/maintenance tasks, neuroimaging studies have revealed fairly reliable patterns of hemispheric dominance for verbal (i.e., left hemisphere) and nonverbal (i.e., right hemisphere) material in ventrolateral (VL) PFC and premotor cortex (Reuter-Lorenz, et al., 2001). Conversely, there is little evidence for DLPFC activation for cognitive loads less than five units, with several indications that DLPFC is only recruited for higher loads and/or longer delays (Reuter-Lorenz, et al., 2001). The evidence for mid-DLPFC activation is highly consistent for tasks that include additional processing and manipulation of stored items (i.e., executive demands), with a tendency toward bilateral activation under such conditions (Drew & Vogel, 2009; Reuter-Lorenz, et al., 2001; Smith & Jonides, 1999).

Posterior and subcortical areas of the brain are also being shown to be important in working memory. For example, it has been shown that neurons in the basal ganglia interact with PFC to “gate” working memory by enhancing the “signal-to-noise ratio” by filtering irrelevant information (Durstewitz, Seamans, & Sejnowski, 2000; Vogel, McCollough, & Machizawa, 2005a).

Dopamine and Working Memory

More than three decades worth of work by Patricia Goldman-Rakic and colleagues has demonstrated that dopamine mechanisms in PFC are critically involved in working memory (Brozoski, et al., 1979; Sawaguchi & Goldman-Rakic, 1991, 1994). Dopamine cells in DLPFC are especially engaged in tasks with a delay component

between the presentation of a stimulus and a behavioral response (Durstewitz, et al., 2000; Janssen & Shadlen, 2005; Sawaguchi & Goldman-Rakic, 1991, 1994; Williams & Castner, 2006; Williams & Goldman-Rakic, 1995). While DLPFC is also important in response inhibition and cognitive flexibility (Janssen & Shadlen, 2005), working memory is particularly reliant on dopamine transmission in DLPFC.

Within PFC, endogenous, extracellular dopamine levels are regulated by catechol-*O*-methyltransferase (COMT) due to a lack of dopamine transporter proteins outside the striatum (Janssen & Shadlen, 2005). Dopamine methylation by COMT accounts for upwards of 60% of dopamine inactivation in PFC/DLPFC (Karoum, Chrapusta, & Egan, 1994; Miner, Schroeter, Blakely, & Sesack, 2003). However, COMT degradation of dopamine in PFC is much slower than DAT reuptake in the striatum and only occurs outside the synaptic cleft. This biases PFC to be in a tonically-mediated state at baseline and stable for holding information in working memory (Bilder, Volavka, Lachman, & Grace, 2004).

Experimental studies have demonstrated that dopamine catabolism in PFC is much slower than DA turnover in the striatum (Frank, et al., 2007b; Lapish, Kroener, Durstewitz, Lavin, & Seamans, 2007), making it imperative that dopamine signals in PFC are temporally precise. If dopamine signaling in PFC is slow in onset and protracted, PFC neurons cannot accurately map the constantly changing stimulus-response associations needed to guide moment-to-moment behavior (Lapish, et al., 2007) nor stabilize information in working memory (Durstewitz, et al., 2000).

Role of Dopamine D1 and D2 Receptors

Dopamine D1 receptors are crucial for working memory functions since either excessive or insufficient D1 stimulation impairs working memory performance (Sawaguchi & Goldman-Rakic, 1991, 1994; Williams & Castner, 2006). In other words, optimal working memory follows “inverted U-shaped curve” of D1 signaling in PFC (Williams & Goldman-Rakic, 1995). Repeated, intermittent D1 stimulation with a D1 agonist has been shown to restore cognitive function in animals rendered D1-deficient in PFC as a result of chronic and continuing haloperidol treatment (Castner, Williams, & Goldman-Rakic, 2000). Notably, intermittent D1 agonist stimulation ameliorated spatial working memory deficits during the treatment period and this cognitive restoration persisted for more than one year following cessation of D1 therapy despite ongoing haloperidol administration (Castner, et al., 2000). Recently, computerized training of working memory has been linked with changes in the density of cortical D1 receptors, as measured by D1 binding potential (bp) in PFC and parietal cortex (McNab, et al., 2009). These findings were specific to D1, as D2 receptor binding in bilateral caudate and putamen did not show any relation to working memory changes (McNab, et al., 2009). Thus, plasticity of D1 receptors in PFC appears to be a neurophysiological marker of variation and change in working memory.

Recent studies have suggested that D2 receptors are important in working memory as well (Wang, et al., 2004). For example, functional polymorphisms in the dopamine D2 receptor gene (DRD2) have been linked to performance and neural activation patterns during working memory paradigms (Bertolino, et al., 2009; Zhang, et al., 2007). Allelic variation at these polymorphisms has been associated with differential D2 receptor expression and differences in D2S/D2L ratios (Zhang, et al., 2007). Another

DRD2 marker, the DRD2/Taq1A polymorphism, which reportedly affects DRD2 mRNA translation and stability, and postsynaptic D2 receptor density in the striatum (Ritchie & Noble, 2003) has been reported to interact with COMT polymorphisms to affect working memory (Stelzel, Basten, Montag, Reuter, & Fiebach, 2009). Taken together, dopamine D1 receptors are clearly important in working memory, and emerging evidence suggests that D2 receptors are also important to some degree.

Durstewitz and Seamans (2008) have proposed a biophysical model of working memory dynamics in PFC that details D1 and D2 receptors as key modulators of working memory network homeostasis. Their model, based on neurocomputational simulation methods, posits that at baseline, a D2-dominated activity state ('D2-state') is associated with a reduced energy barrier across the cell membrane, allowing for easier access to PFC networks and faster cognitive switching. A disadvantage of being in the D2-state is that the network is less stable. In contrast, a 'D1-state' is characterized by a high energy barrier among different PFC network states, leading to active working memory representations that become highly resistant to distraction and noise. A disadvantage of being in the D1-state is decreased access to PFC networks for updating working memory traces, putatively leading to more rigidity at the cognitive-behavioral level (Durstewitz & Seamans, 2008). The underlying assumption is that the D1- and D2-states are differentially regulated by the level of endogenous dopamine in the MCL and controlled by PFC (Bilder, et al., 2004; Durstewitz & Seamans, 2008).

Finally, the basal ganglia is also linked with working memory performance in healthy individuals (Frank & Hutchison, 2009). For example, working memory impairments in Parkinson's disease have been linked with decreased basal ganglia

activation (Lewis, Dove, Robbins, Barker, & Owen, 2003). Given that both D1 and D2 receptors are expressed most abundantly in the basal ganglia, it is plausible that these receptors modulate working memory through both cortical and subcortical mechanisms.

Developmental Sensitivity

A study that examined post-mortem levels of COMT across the lifespan revealed that COMT enzyme activity increases linearly with age in DLPFC (Tunbridge, et al., 2007). Further, COMT enzyme activity reportedly peaked in middle adulthood and was significantly greater than in adolescence/young adulthood (Tunbridge, et al., 2007). The relevance of this study lies in the fact that working memory improves over the course of childhood until late adolescence (approximately age 19 years) when adult level skills are attained (Gathercole, 1998; Luna, Garver, Urban, Lazar, & Sweeney, 2004). Crone and colleagues reported that developmental improvements in working memory manipulation relative to pure maintenance are associated with increased recruitment of DLPFC and superior parietal cortex but not VLPFC (Crone, et al., 2006). Taken together, these studies suggest that developmental improvements in working memory and specifically higher-order manipulation are associated with the developmental changes in dopamine mechanisms and neural substrates in PFC.

Working Memory in ADHD

There have been a number of demonstrations of a strong relationship between performance on various attentional control tasks and working memory capacity (Awh, Vogel, & Oh, 2006; D'Esposito, et al., 1999; Vogel, et al., 2005a; Vogel, Woodman, & Luck, 2005b). Impairments in working memory are considered by some to be a core feature of ADHD (Barkley, 1997; Castellanos & Tannock, 2002). Deficits in working

memory manipulation as measured by digit span backward are robust in ADHD probands (Willcutt, et al., 2005), and are also present to a moderate degree in their non-affected siblings (Rommelse, et al., 2008b). A recent fMRI study of adolescent girls showed that those diagnosed with ADHD had less efficient neural response patterns than age-matched female peers without ADHD in DLPFC and VLPFC on a delayed match-to-sample task (Sheridan, Hinshaw, & D'Esposito, 2007). Klingberg and colleagues have shown that working memory skills can improve following targeted computerized training in children with ADHD (Klingberg, et al., 2005; Klingberg, et al., 2002). Their training program also improved response inhibition and reasoning skills, and reduced symptoms of inattention (Klingberg, et al., 2005; Klingberg, et al., 2002).

Recently, we reported that deficits in working memory were associated with ADHD in adolescence/young adulthood, but only in those individuals who continued to have persistent ADHD from childhood. ADHD remitters were no different than age-matched controls on a comprehensive index of working memory (Halperin, et al., 2008). The current study further delves into the genetic and developmental nature of this interesting finding. That is, how do changes in working memory during development influence symptom stability in ADHD, and does this relationship vary by differences in dopamine receptor gene polymorphisms?

Genetic Studies

The etiology of ADHD is considered to be multifactorial, with genetic and environmental risk factors, and the interaction of genes with the environmental (G×E) all contributing to varying degrees to the risk of developing ADHD (Faraone, et al., 2005; Thapar, et al., 2003; Thapar, Langley, Asherson, & Gill, 2007; Thapar, et al., 2005a; Thapar, O'Donovan, & Owen, 2005b; Waldman & Gizer, 2006). While the empirical evidence for these assumptions has generally been supported, no single causal mechanism has been consistently pinpointed. Nonetheless, the past decade of research has shown that ADHD has a strong genetic etiology, as evidenced by consistently high heritability rates that range from 60-90% and average approximately 75% (Faraone, et al., 2005; Neale, et al., 2008; Waldman & Gizer, 2006). Consistently high heritability rates have made ADHD an important neuropsychiatric disorder for the purpose of conducting molecular genetic studies (Faraone, et al., 2005; Neale, et al., 2008). In fact, more than 1,800 publications dealing with the genetics of ADHD have been published to date (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010).

Dopamine System Genes

Since the mid-1990's, subsequent to two seminal papers (Cook, et al., 1995; LaHoste, et al., 1996) the majority of molecular genetic studies of ADHD have focused on examining dopamine system genes (Gizer, et al., 2009; Swanson, et al., 2000a; Waldman & Gizer, 2006). Many of the reported neuropsychological deficits and abnormal neuroimaging findings in ADHD are believed to emanate in part from dopamine dysfunction (Berwid, et al., 2005; Rubia, et al., 1999; Schachar, et al., 2000; Scheres, et al., 2007; Schulz, et al., 2004; Schulz, et al., 2005a; Schulz, et al., 2005b;

Seidman, 2006; Seidman, Biederman, Faraone, Weber, & Ouellette, 1997; Seidman, et al., 2005b; Seidman, et al., 2006; Shallice, et al., 2002; Shaw, et al., 2006).

Several studies have now identified environmental risk factors that interact with dopamine genes to increase risk of developing ADHD including psychosocial adversity (Laucht, et al., 2007), prenatal exposure to cigarette smoke (Becker, El-Faddagh, Schmidt, Esser, & Laucht, 2008) and maternal alcohol use (Brookes, et al., 2006a).

While the complex etiology etiological of ADHD renders it unlikely that a single cause of ADHD will ever come about, dopamine dysfunction of some sort, whether rooted in genes, the environment, or a G×E interaction is almost certain (Frank, et al., 2007c).

Case-control studies have identified polymorphisms in a few dopamine genes that are associated with ADHD (Brookes, et al., 2006b; Cook, et al., 1995; LaHoste, et al., 1996; Thapar, et al., 2005a). Yet, while some associations have been replicated in independent samples, many have not (for reviews see Faraone, et al., 2005; Waldman & Gizer, 2006). Further, only a few of the candidate gene associations have been supported by meta-analysis (Mick & Faraone, 2008).

A 2005 meta-analysis conducted by Faraone and colleagues (2005) identified polymorphisms in seven genes as being significantly associated with ADHD. Four of the seven genes are involved in dopamine transmission: the dopamine transporter (SLC6A3/DAT1); the dopamine D4 receptor (DRD4); the dopamine D5 receptor (DRD5); and dopamine beta hydroxylase (DBH). The serotonin transporter (SLC6A4/5-HTTLPR); the serotonin 5-HT_{1B} receptor (5-HT1B); and synaptosomal-associated protein 25kDa (SNAP-25) were also significantly associated with ADHD (Faraone, et al., 2005). In 2006, the International Multi-Center ADHD Genetics (IMAGE) project, a

large-scale European study with 674 ADHD Combined-Type cases and 102 affected siblings examined 1,038 single-nucleotide polymorphisms (SNPs) spanning 51 candidate genes for association and linkage with ADHD (Brookes, et al., 2006b). This study confirmed the association of DRD4 and DAT1 to ADHD, providing additional evidence that dopamine gene polymorphisms are associated with ADHD. However, similar to the meta-analysis of Faraone, this study also identified polymorphisms in 17 other non-dopamine related genes that were significantly associated with ADHD (Brookes, et al., 2006b). Thus, while dopamine system genes have been implicated in the etiology of ADHD with a certain degree of consistency, the genetic effects of individual gene variants is small (e.g., pooled odds ratios in the meta-analysis ranged from 1.18 to 1.46) which suggests that none of these genes individually accounts for an overwhelming proportion of the variance in genetic risk for ADHD (Faraone, et al., 2005).

Polymorphisms within DRD1 and DRD2 have garnered less attention than DRD4 and DAT. A few studies have reported associations between DRD1 variants and ADHD, particularly with inattentive symptoms (Bobb, et al., 2005; Luca, et al., 2007; Misener, et al., 2004). However, results have been inconsistent (Kirley, et al., 2002; Nyman, et al., 2007). Notably, no DRD1 polymorphisms have been associated with working memory in ADHD per se (Luca, et al., 2007). The DRD2/Taq1A polymorphism has been associated with ADHD-related phenotypes in some studies (Nyman, et al., 2007) but not others (Rowe, et al., 1999). Recently, it was reported that D2 receptor availability is reduced in adults with ADHD in the left ventral striatum, left midbrain, and left hypothalamus (Volkow, et al., 2009). These studies provide mixed evidence for the involvement of D1 and D2 receptors in the etiology of ADHD.

Intermediate Phenotypes

While ADHD as a categorical diagnosis/phenotype is an obvious first choice for candidate gene, linkage, and genome-wide association analyses, such an approach is complicated and is unlikely to yield consistently replicable results for a complex genetic disorder such as ADHD (Chen, et al., 2008). Additional complications arise from issues such as small sample sizes, population stratification, and small effect sizes for individual gene polymorphisms, phenotype heterogeneity, diagnostic heterogeneity, developmental factors, and comorbidity (Asherson, 2004; Chen, et al., 2008; Neale, et al., 2008). The phenotypic heterogeneity of ADHD with individuals and across development raises additional questions regarding the validity of ADHD as a distinct, unitary psychiatric condition (Asherson, 2004; Fergusson & Horwood, 1995; Levy, et al., 1997).

This issue is not unique to ADHD. Other genetically complex neurobehavioral disorders such as autism spectrum disorders (Anderson, et al., 2007; Lord, et al., 2006; Starr, Szatmari, Bryson, & Zwaigenbaum, 2003), mood and depressive disorders (Luby, Si, Belden, Tandon, & Spitznagel, 2009; Najman, et al., 2008), and anxiety disorders (Carballo, et al., 2010; Oh, et al., 2008) show similarly unstable patterns of phenotypic and diagnostic instability during development. Phenotypic heterogeneity is partially responsible for the lack of consistent replication of linkage and association studies of ADHD (Chen, et al., 2008; Neale, et al., 2008) and other complex psychiatric disorders (Deo, Costa, DeLisi, DeSalle, & Haghghi, 2010). As such, researchers have increasingly turned to intermediate phenotype approaches to study both the clinical symptoms that define ADHD and the cognitive mechanisms thought to underlie ADHD. Two of these

approaches, quantitative trait mapping and neurocognitive endophenotypes, are highlighted below.

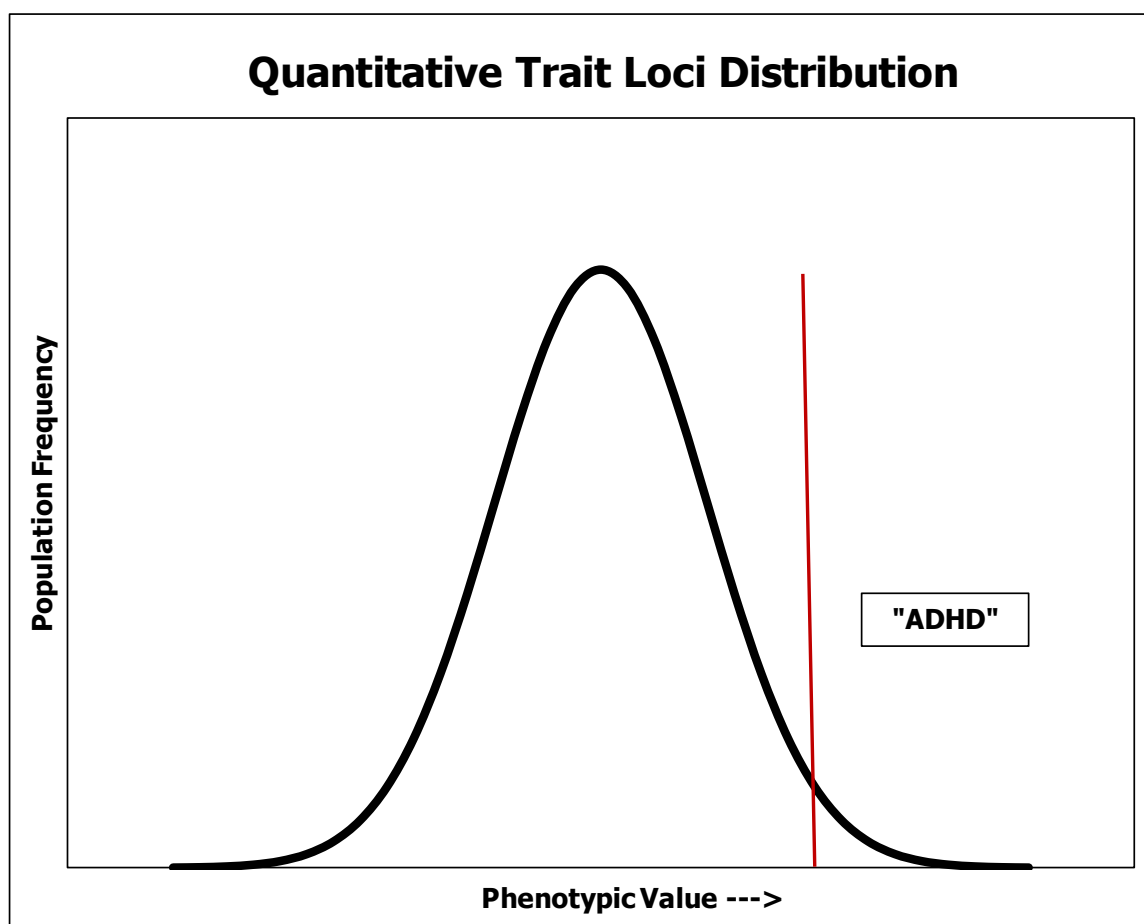
Quantitative trait loci (QTL) mapping. An alternative approach, for which there is emerging evidence of usefulness in genetics studies, is to consider ADHD as representing the extreme of continuously and normally distributed dimensional traits that are present in the general population rather than a categorical classification (Asherson, 2004; Curran, Purcell, Craig, Asherson, & Sham, 2005; Fergusson & Horwood, 1995; Lasky-Su, et al., 2007; Levy, et al., 1997). See Figure 1 for a theoretical QTL model.

QTL genetic mapping studies can be conducted either with clinical samples or epidemiological samples and operate under the assumption that a) multiple susceptibility genes of small magnitude contribute to ADHD, b) there is greater power to detect these small genetic effects if the ADHD phenotype is dimensional instead of categorical, and c) that the quantitative ADHD trait(s) are normally distributed throughout the general population (Curran, et al., 2005; Kuntsi, Andreou, Ma, Borger, & van der Meere, 2005a). Still, quantitative approaches to association and linkage mapping in ADHD have not been widely employed despite twin studies investigating individual differences in symptoms indicating that genetic liability for ADHD is continuously distributed throughout the population (Chen, et al., 2008).

To give an empirical example of the advantage of QTL mapping, the IMAGE project recently completed the first genome-wide association scan (GWAS) of DSM-IV defined ADHD using a large sample of 909 complete proband-parent trios and reported that no SNP achieved genome-wide significance (Neale, et al., 2008). The IMAGE investigators followed-up with a second GWAS study that used six quantitative

phenotypes derived from the 18 DSM-IV ADHD symptoms and found that 2 SNPs achieved genome-wide significance (Lasky-Su, et al., 2008). Thus, there appears to be a clear advantage of QTL mapping over categorical phenotyping in ADHD.

Figure 1. Theoretical Distribution of ADHD as a Quantitative Trait. ADHD is at the tail end of normally distributed cluster dimensional traits that exist in the general population. “ADHD” would thus represent individuals who fall to the far right end of the distribution.



Endophenotypes. A complimentary methodological approach to QTL mapping to better detect genetic risk for ADHD that has been used recently is the study of endophenotypes (Doyle, et al., 2005a; Doyle, et al., 2005b; Gottesman & Gould, 2003; Risch & Merikangas, 1996; Rommelse, et al., 2008a). Endophenotypes are heritable

traits that confer risk for developing a disorder and share genetic variance with a disorder, yet are assumed to be less genetically complex than the clinical phenotype of the disorder (Gottesman & Gould, 2003). Table 3 outlines more detailed criteria of a psychiatric endophenotype.

The use of neuropsychological measures to study processes such as working memory, response inhibition and motor control has been encouraged to help discover neurocognitive endophenotypes that are relevant to ADHD (Castellanos & Tannock, 2002; Doyle, et al., 2005a; Fan, Wu, Fossella, & Posner, 2001). This idea stems from the fact that many cognitive constructs are heritable in the general population. For example, individual differences in executive function have been reported to be almost entirely genetic (i.e., 99% heritable) (Friedman, et al., 2008). Individual differences in working memory show moderately high heritability estimates of 43-49%, and a large part of the genetic variance in the storage and central executive components of working memory is due to a common genetic factor that accounts for 11-43% of the variance (Ando, Ono, & Wright, 2001).

Table 3. Neurocognitive Endophenotype Criteria (adapted from Doyle et al, 2005)

1) Associated with ADHD
2) Good psychometric properties
3) Evidence of heritability and association with specific genes in the general population
4) Familial/genetic overlap of the neurocognitive function and ADHD
5) Grounded in neuroscience

In the first published study of neurocognitive endophenotypes in ADHD, Swanson and colleagues (2000b) demonstrated that, contrary to expectations, the absence of the 7-repeat allele of the dopamine D4 receptor (DRD4-7R) in children diagnosed with

ADHD was associated with impaired performance on measures of attention and inhibitory control; ADHD children with the DRD4-7R allele performed similar to control children. Similar work has replicated this initial association: Two independent groups that used computerized choice reaction time (RT) tasks of sustained attention reported that the ADHD subgroups with the DRD4-7R made significantly fewer errors of commission and had significantly lower RTSD scores than the DRD4-7R absent ADHD subgroups (Bellgrove, et al., 2005c; Manor, et al., 2002).

Subsequently, Kollins and colleagues (2008) reported that two SNPs in DRD2 were significantly associated with commission errors on a CPT task in children with ADHD, even after applying the false-discovery rate (FDR) correction which makes an association that much more difficult to detect. Others have shown that allelic variation in DAT1 can differentially affect aspects of cognitive functioning in ADHD (Bellgrove, et al., 2005a; Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005b; Bellgrove, et al., 2009). Thus, genetic factors associated with both normal cognitive functions and ADHD such as dopamine system genes may help identify subgroups of children with ADHD who are at an increased risk for impairment due to cognitive dysfunction relative to youth with ADHD with similar behavioral excesses but without neurocognitive deficits (Swanson, et al., 2000b).

Genes and Neurocognition in ADHD: A Developmental Perspective

Only in recent times have investigators begun to acknowledge the limitations of a single “snapshot” of neuropsychological functioning in ADHD and appreciate the importance of developmental factors (e.g. age, symptom stability, environmental changes) that have the potential to confound estimates of neurocognitive dysfunction in youth with ADHD. Further, as noted previously, a salient feature of childhood ADHD is that the disorder tends to improve with age, with symptomatic improvement occurring in 30% to 60% of children as they move into late adolescence and up to 85% by early adulthood (Faraone, et al., 2006a; Halperin & Schulz, 2006; Lahey, et al., 1999). Unfortunately, the ADHD literature currently lacks sufficient data on the stability of neuropsychological functioning over development. More importantly, however, is a lack of research on whether neuropsychological functions covary with and/or predict symptom stability during development.

Developmental Stability of Neuropsychological Function

The first follow-up neuropsychological study of ADHD reported that hyperactive children were significantly slower, more variable, and made more errors than controls on the Stroop test at their young adult outcome evaluation (Hopkins, Perlman, Hechtman, & Weiss, 1979). A later study reported stable impairments in academic skills and on measures of attention and impulsivity from childhood to older adolescence (Fischer, Barkley, Edelbrock, & Smallish, 1990). Seidman and colleagues demonstrated evidence of persistent executive function deficits in ADHD children relative to controls from early childhood to late adolescence in a cross-sectional cohort study of boys and girls with and without ADHD spanning ages 6-20 years, (Seidman, et al., 1997; Seidman, et al., 2005a).

Finally, a study of alertness and inhibitory control in children with ADHD and controls (mean age = 11.0 years at baseline) who were examined three times over 2.6 years reported no group differences on these measures by the final assessment; however, 61% of their ADHD cohort no longer met criteria for the disorder by the final follow-up assessment (Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005).

Neuropsychological Stability Relative to Symptom Stability

None of the above studies examined whether neuropsychological functioning paralleled ADHD symptom stability over development. This is critical to understanding whether neuropsychological dysfunction is core to ADHD or perhaps an epiphenomenon (Carr, Nigg, & Henderson, 2006; Halperin, et al., 2008). One of the few studies addressing this issue examined neurocognitive performance of 5- and 6-year-old children who were diagnosed as either having ADHD or subthreshold ADHD 18 months later, along with typically developing children without significant ADHD symptoms (Kalff, et al., 2002). Poorer performance on measures of visuomotor integration, verbal working memory, and visual attention at baseline were predicative of ADHD 18 months later; and visual closure, number recall, and verbal fluency measures were not. Further, neurocognitive performance of subthreshold ADHD children 18 months prior was generally in between that of ADHD children and controls (Kalff, et al., 2002).

Fischer and colleagues reported that executive and non-execute skills correlated with the presence or absence of childhood ADHD at early adult follow-up in a prospectively followed group with ADHD (Fischer, Barkley, Smallish, & Fletcher, 2005). Those with persistent ADHD had weaker executive skills than controls, while those with ADHD in childhood but not in early adulthood (i.e., remitters) had relatively

intact executive skills. In contrast, both persisters and remitters demonstrated slower processing speed at outcome (Fischer, et al., 2005).

Similar cognitive patterns have been reported recently in girls diagnosed with ADHD in childhood and followed through adolescence (Hinshaw, Carte, Fan, Jassy, & Owens, 2007). Girls who continued to meet criteria for ADHD at follow-up (i.e., persisters) demonstrated significantly more executive function deficits than girls who no longer met criteria in adolescence (i.e., remitters), which were independent of IQ, comorbidities and demographic factors (Hinshaw, et al., 2007).

Our group has reported similar findings in our longitudinal sample of adolescents/young adults with and without childhood ADHD (Halperin, et al., 2008). Specifically, when divided into subgroups of ADHD persisters and remitters, performance on putative measures of executive or effortful processes closely paralleled adolescent/young adult clinical status, with remitters performing more similarly to controls than persisters; persisters evidenced continued executive function deficits. In contrast, performance on tasks of less effortful, perhaps bottom-up processes generally differentiated those with childhood ADHD from controls irrespective of adolescent/young adult clinical status (Halperin, et al., 2008).

Overall, these studies suggest that components of the neurocognitive symptom profile of ADHD are stable traits marking liability to develop the disorder such as lower order processes, while other neurocognitive functions are possibly unstable epiphenomena or even compensatory such as higher order executive processes (Carr, et al., 2006; Halperin & Schulz, 2006; Halperin, et al., 2008; Sonuga-Barke, et al., 2003).

Developing versus Mature Neural Systems

Recent longitudinal sMRI studies have demonstrated significant neuroanatomical differences in child and adolescent ADHD that fluctuate dynamically during development. The first study to examine structural changes over time followed a large sample of ADHD youth and age-matched healthy controls (age range of 4.5-19 years) using a mixture of longitudinal and cross-sectional MRI analytical methods (Castellanos, et al., 2002). At baseline, healthy controls had significantly greater total cerebral volume than ADHD patients, as well as larger frontal gray and white matter. However, after adjustment for total cerebral volume, no significant difference in frontal total volume, white matter or gray matter remained between the two groups. Further, analysis of a subset of follow-up scans 2-3 years later demonstrated no disparity in frontal morphometry between the two groups; rather, the frontal lobes had the smallest effect sizes of any anatomical region. Baseline differences in cerebellar volume persisted, and final follow-up scans showed both groups continued to exhibit exponential increases in total cerebellar volume. However, the smaller ADHD cerebellum held, with a non-significant trend for the difference between ADHD and controls to increase as both groups aged (Castellanos, et al., 2002). Longitudinal cerebellar growth has been linked recently to different clinical outcomes in ADHD: the growth trajectory of total cerebellar volume in children with ADHD with a better clinical outcome a few years later paralleled the growth trajectory of normally developing controls, whereas cerebellar growth in ADHD probands with worse clinical outcome exhibited a progressive decrease in total cerebellar volume that fell further away from the normal trajectory over time (Mackie, et al., 2007).

Automated measures of cortical thickness across the entire cerebrum have been used recently and found to be useful in detecting an association between rates of cortical thinning and symptom improvement in ADHD (Shaw, et al., 2006). As a group, children with ADHD had significantly reduced cortical thickness which was most prominent in PFC and anterior temporal cortices relative to typically developing controls. On baseline scans examined retrospectively, ADHD children with worse clinical outcomes had a thinner cortex in medial and superior prefrontal regions and cingulate cortex bilaterally compared to ADHD children with better clinical outcomes, which remained significant after adjustment for IQ and overall cortical thickness. The “good” outcome ADHD patients evidenced minimal differences in cortical thickness from controls except for a small region of cortical thinning in left DLPFC and showed normalization of right parietal cortical thickness over time. Thickness of the left mesial and dorsolateral PFC accounted for approximately 15% of the variance in ratings of global function at follow-up (Shaw, et al., 2006).

Functionally, an association between neural activation gradients in VLPFC and the remission of ADHD symptoms in adolescent boys diagnosed with ADHD in childhood has been reported by our group (Schulz, et al., 2005a). Greater bilateral activation of the ventrolateral convexity of the inferior frontal gyrus and left inferior parietal lobule was found in ADHD persisters relative to remitters, who in turn had greater activation than controls during successful response inhibition (Schulz, et al., 2005a).

Subsequent work by Shaw and colleagues has suggested that ADHD is characterized by a *delay* rather than a *deficiency* in regional cortical maturation (Shaw, et

al., 2007a). In their longitudinal study, cortical maturation progressed in a similar manner regionally in both children with and without ADHD, with primary sensory areas attaining peak cortical thickness before polymodal, high-order association areas. However, there was a marked delay in attaining peak thickness throughout most of the cerebrum in ADHD: the median age by which 50% of the cortical points attained peak thickness for the ADHD group was 10.5 years, which was significantly later than the median age of 7.5 years for typically developing controls. The delay was most prominent in lateral PFC and in the posterior portions of the middle and superior temporal gyri bilaterally (Shaw, et al., 2007a). Taken together, these studies have improved our understanding of the developmental course of ADHD in terms of how it is influenced by structural and functional development of the brain.

Genetic Factors and the Developmental Trajectory of ADHD

It has been suggested that longitudinal data that enable the examination of moderating influences of genes on environmental events (and vice versa) needs to be investigated in a methodologically sound manner to better understand the developmental course of early psychopathology (Munafo, 2006). And while there is strong evidence that childhood-onset ADHD is highly heritable (Faraone, et al., 2005), there is less data to support the hypothesis that the persistence of ADHD into adolescence and adulthood is perhaps more so genetically mediated than childhood-onset ADHD (Faraone, 2004). The work that has been done is promising nonetheless in terms of both behavioral and molecular genetics research.

For example, a study of 4,000 twin pairs demonstrated that symptom stability in ADHD from early-to-mid childhood was mainly due to shared genetic influences with

minimal environmental influence (Kuntsi, et al., 2005b). Others have reported similar findings (Larsson, Larsson, & Lichtenstein, 2004). At the molecular genetic level, the DRD4-7R allele has been associated with normalization of cortical thickness in parietal and prefrontal cortices and with better clinical outcome in adolescence in individuals diagnosed with ADHD in childhood (Shaw, et al., 2007b). Children with ADHD who possessed at least one copy of the DRD4-7R allele had a distinct trajectory of cortical development characterized by normalized cortical thinning, were less likely to maintain a diagnosis of ADHD at follow-up, had higher IQ's, and evidenced better global functioning than their childhood-diagnosed ADHD counterparts without the DRD4-7R allele despite no differences in ADHD severity at baseline between those with and without the DRD4-7R allele (Shaw, et al., 2007b).

While these initial studies are pioneering, research on other possible genetic factors that influence the developmental course of ADHD is still rather limited.

Current Study

Working memory is strongly mediated by top-down control from PFC, where maturation occurs at a delayed and variable rate throughout development relative to other areas of the brain, and is not complete until at least early adulthood (Andersen, 2003; Gogtay, et al., 2004). The functional significance of this developmental phenomenon was first demonstrated in a seminal study over four decades ago in which lesions to DLPFC impaired working memory in adult monkeys but not in younger adolescent monkeys (Goldman, 1971). Newer research has further shown that prefrontal-striatal networks implicated in the development of working memory skills continue to mature and strengthen into early adulthood (Heijtz, Kolb, & Forssberg, 2007). Assuming that these models are correct, impairments in working memory in ADHD should be much more prominent later in development. In fact, it has been hypothesized that PFC development plays a central role in the trajectory of ADHD (Andersen, 2002; Halperin & Schulz, 2006) but not in the initial onset/emergence of ADHD in early childhood (Halperin & Schulz, 2006).

Dopamine D1 and D2 receptor expression and function also changes dynamically during development. For example, D1 receptor density and second messenger activity peaks during adolescence and then decreases in adulthood in PFC (Andersen, et al., 2000; Brenhouse, et al., 2008). In rodents, genetically-induced overexpression of D2 receptors in the striatum can lead to impairments in working memory, deficits which persist even after D2 overexpression is turned off (Kellendonk, et al., 2006). This latter finding has been hypothesized to suggest that working memory deficits partially result from

developmental but not concurrent functioning of upregulated D2 receptors (Kellendonk, et al., 2006).

Finally, computerized working memory training improves ADHD symptomatology (Klingberg, et al., 2005; Klingberg, et al., 2002) and improvements in working memory capacity are associated with changes in D1 receptor binding in PFC but not with changes in D2 receptor binding in the striatum (McNab, et al., 2009). To our knowledge, no studies have examined whether working memory and ADHD symptomatology are associated in the same individuals at different developmental stages, whether development changes the association, and whether the association varies by dopamine receptor gene polymorphisms. A non-longitudinal examination may hide the emergence of prominence (i.e., penetrance) of genetic polymorphisms involved in ADHD and neurocognitive status during new developmental phases (Kuntsi, et al., 2005b). Therefore, this dissertation examines whether the naturalistic course of change in working memory over developmental is perhaps also associated with dopamine receptor function and the behavioral trajectory of ADHD in a longitudinal cohort of adolescents and young adults with childhood-diagnosed ADHD.

Primary Aims

1. To assess moderator effects of working memory maintenance and manipulation on attention problems by allelic variation in DRD1 and DRD2.
2. To assess whether moderator effects vary during development in a prospectively followed ADHD cohort.

Primary Hypotheses

1. Working memory manipulation will be more strongly linked with attention problems than pure working memory maintenance.
2. Dopamine D1 receptor gene variants will evidence stronger moderator effects than dopamine D2 receptor gene variants.
3. Moderator effects will be of greater magnitude later in development when working memory skills reach mature adult levels and are more prominent in the disorder.

Methods and Materials

Sample

Included in the current study were 76 adolescents and young adults (Mean age of 18 years) who were initially diagnosed with ADHD in childhood and subsequently re-evaluated and genotyped at follow-up. This sample of 76 was drawn from a larger cohort of 98 ADHD probands who were successfully recruited for a longitudinal study and evaluated on average 9.8 years (SD = 1.8 years) after initially being diagnosed with ADHD in childhood. First recruited in the early-to-mid 1990s, this predominantly inner-city cohort was racially and ethnically diverse (75% classified as racial/ethnic minorities) and of low to lower-middle socioeconomic status (SES) (Halperin, et al., 1997; Halperin, et al., 1994).

Childhood Evaluation (“Baseline”). Initial screening in childhood included teacher reports on the Inattention/Overactivity scale of the IOWA Conners’ Rating Scale (Loney & Milich, 1982; Pelham, Milich, Murphy, & Murphy, 1989) and structured interview of a parent using the Diagnostic Interview Schedule for Children (DISC) version 2.1 (Fisher, et al., 1993) or 2.3 (Shaffer, et al., 1996). Those recruited prior to 1994 were diagnosed using DSM-III-R criteria for ADHD; those recruited after 1994 were evaluated using DSM-IV criteria. General cognitive functioning at baseline was assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R) (Wechsler, 1974) or Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (Wechsler, 1991). Psychosis, neurological disorders, or IQ below 70 was exclusionary at baseline.

Adolescence/Young Adulthood Evaluation (“Follow-up”). At the follow-up evaluation when youth were in the late adolescent and early adult age range, participants and their parent(s) were interviewed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime (K-SADS-PL) to evaluate ADHD and other Axis I psychiatric disorders (Kaufman, et al., 1997). A comprehensive neuropsychological battery (Halperin, et al., 2008) including the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997) was also administered. Table 4 provides descriptive characteristics of the sample at baseline and follow-up.

Table 4. Demographic and Descriptive Characteristics

	Baseline	Follow-up
	(<i>n</i> = 76)	(<i>n</i> = 76)
Age, mean (SD), y	9.0 (1.3)	18.4 (1.7)
Male, No (%)	67 (88)	-
Racial/ethnic minority, No (%)	57 (75)	-
SES, mean (SD)	31.8 (14.9)	41.9 (17.8)
Wechsler FSIQ, mean (SD)	94.0 (15.0)	92.9 (14.8)
CBCL Externalizing, mean (SD)	69.7 (11.2)	60.7 (12.9)
CBCL Internalizing, mean (SD)	65.1 (12.0)	56.8 (13.4)
CBCL Attention Problems, mean (SD)	72.1 (10.2)	60.6 (09.0)

Note: SD, standard deviation; SES, socioeconomic status; FSIQ, Full-Scale IQ; CBCL, Child Behavior Checklist

Written informed consent was obtained from a parent/legal guardian of those under the age of 18 years, and assent was obtained from these adolescents. Informed consent was obtained from participants 18 years of age or older. Participants were compensated for their time and travel. The Institutional Review Boards of Queens College of the City University of New York and the Mount Sinai School of Medicine approved all procedures.

Behavioral and Neurocognitive Measures

Working Memory: Maintenance and Manipulation

Digit Span Forward. At baseline, the WISC-R/WISC-III included the digit span (DS) subtest. The longest digit span forward (LDSF) component of the WISC-R/WISC-III DS subtest is widely used clinically to assess *maintenance* of information in working memory. LDSF is administered by orally presenting a series of numbers that the examinee has to verbally repeat verbatim. The WISC-R digits forward (DF) section included 7 items (3-9 digits in length). The WISC-III DF retained all 7 WISC-R DF items; however, a two-digit series was added as the beginning item of the WISC-III to provide a downward extension of DF to include a total of 8 items (2-9 digits in length) (Wechsler, 1991). See Table 5 for a comparison of the stimuli used for the digits forward subtest from the WISC-R, WISC-III, and WAIS-III.

Digit Span Backward. The longest digit span backward (LDSB) component of the WISC-R/WISC-III DS subtest is a simple yet robust measure of *manipulation*, testing how many orally-presented number series an individual can attend to at once, store and then repeat verbally in reverse order (Hale, et al., 2002). The WISC-III retained all 7 WISC-R digit span backward items (2-8 digits in length) (Wechsler, 1991). See Table 6 for a comparison of the stimuli used for the digits backward subtest from the WISC-R, WISC-III, and WAIS-III.

Table 5. Digit Span Forward Stimuli from the WISC-R, WISC-III and WAIS-III

<i>digit length</i>	Digits Forward					
	Trial 1			Trial 2		
	WISC-R	WISC-III	WAIS-III	WISC-R	WISC-III	WAIS-III
2	--	2	1	--	4	6
	--	9	7	--	6	3
3	3	3	5	6	6	6
	8	8	8	1	1	9
	6	6	2	2	2	4
4	3	3	6	6	6	7
	4	4	4	1	1	2
	1	1	3	5	5	8
	7	7	9	8	8	6
5	8	8	4	5	5	7
	4	4	2	2	2	5
	2	2	7	1	1	8
	3	3	3	8	8	3
	9	9	1	6	6	6
6	3	3	6	7	7	3
	8	8	1	9	9	9
	9	9	9	6	6	2
	1	1	4	4	4	4
	7	7	7	8	8	8
7	4	4	3	3	3	7
	5	5	5	9	9	4
	1	1	9	8	8	1
	7	7	1	5	5	7
	4	4	7	2	2	9
	2	2	4	1	1	3
8	3	3	2	6	6	8
	8	8	8	3	3	6
	1	1	5	2	2	3
	6	6	8	9	9	8
	4	4	1	7	7	2
9	5	5	9	6	6	9
	9	9	2	3	3	5
	7	7	6	1	1	1
	6	6	4	5	5	7
	3	3	7	4	4	4
	5	5	2	4	4	7
	3	3	7	2	2	1
	8	8	5	6	6	3
9	7	7	8	9	9	9
	1	1	6	1	1	4
	2	2	2	7	7	2
	4	4	5	8	8	5
	6	6	8	3	3	6
	9	9	4	5	5	8

Table 6. Digit Span Backward Stimuli from the WISC-R, WISC-III and WAIS-III

<i>digit length</i>	Digits Backward					
	Trial 1			Trial 2		
	WISC-R	WISC-III	WAIS-III	WISC-R	WISC-III	WAIS-III
2	2	2	2	6	6	5
	5	5	4	3	3	7
3	5	5	6	2	2	4
	7	7	2	5	5	1
	4	4	9	9	9	5
	7	7	3	8	8	4
4	2	2	2	4	4	9
	9	9	7	9	9	6
	6	6	9	3	3	8
	4	4	1	9	9	6
5	1	1	5	7	7	1
	3	3	2	8	8	8
	5	5	8	5	5	4
	7	7	6	2	2	3
	1	1	5	3	3	7
6	6	6	3	6	6	2
	5	5	9	7	7	4
	2	2	4	1	1	8
	9	9	1	9	9	5
	8	8	8	4	4	6
	8	8	8	4	4	4
7	5	5	1	5	5	7
	9	9	2	7	7	3
	2	2	9	9	9	9
	3	3	3	2	2	1
	4	4	6	8	8	2
	2	2	5	1	1	8
	6	6	9	3	3	7
8	9	9	4	1	1	2
	1	1	3	7	7	8
	6	6	7	9	9	1
	3	3	6	5	5	9
	2	2	2	4	4	6
	5	5	5	8	8	5
	8	8	8	2	2	3

At follow-up, participants were administered the DS subtest from the WAIS-III [note that with the exception of the actual digits used, LDSF and LDSB from the WISC-R/III and WAIS-III are identical in administration and scoring procedures]. The WISC-III and WAIS-III test manuals provided normative data for LDSF and LDSB from the

respective standardization samples stratified by age (Wechsler, 1991, 1997). These data were used to generate age-corrected z-scores for each participant's respective LDSF and LDSB score at baseline and follow-up.

ADHD Symptomatology

Child Behavior Checklist-Attention Problems (CBCL-AP). The CBCL, a widely used broad band behavior rating scale was completed by parents at baseline (Achenbach, 1991) and follow-up (Achenbach & Rescorla, 2001). Parents rated the frequency of each item on a three point scale ("never," "sometimes," or "often/always"). Raw scores on the CBCL are standardized to T-scores by age for several different subscales.

The attention problems subscale (CBCL-AP) consists of 11 items reflecting attention (*e.g., can't concentrate; can't pay attention for too long; confused or seems to be in a fog; daydreams or gets lost in own thoughts; and stares blankly*), motor activity (*e.g., can't sit still, restless, or hyperactive; nervous movements or twitching; poorly coordinated or clumsy*), impulsivity (*e.g., impulsive or acts without thinking*) and other ADHD-related behaviors (*e.g., acts too young for age; nervous, high-strung, or tense; and poor school work*). The CBCL-AP was used as dimensional measure of ADHD because it effectively discriminates ADHD cases from non-cases (Hudziak, et al., 2004) and correlates well with the clinical DSM-IV assessment of ADHD (Derks, et al., 2006). Importantly, scores on the CBCL-AP have proven to be highly heritable and genetically stable over time such that genetic effects explain approximately 75% of heritability developmentally from age 7 and beyond (Rietveld, et al., 2004).

LDSF, LDSB, and CBCL-AP were selected for use in the current study because they were collected at baseline and follow-up, allowing for the examination of whether

basic working memory maintenance (i.e., LDSF) and/or complex manipulation (i.e., LDSB) processes are differentially associated with attention problems during development.

Genetic Marker Selection

Four DRD1 and four DRD2 SNPs were selected and genotyped. All of the SNPs were either functional polymorphisms, in strong LD with functional polymorphism, or were previously associated with ADHD-related phenotypes or working memory.

DRD1 Markers

rs4532. rs4532 is an A > G transition in the 5' UTR of DRD1. rs4532 was initially identified by single-strand conformational analysis (Cichon, et al., 1994). rs4532 may affect D1 expression either directly or indirectly via LD with rs686, a known functional SNP in the 3' UTR of DRD1 that affects D1 expression levels (Huang, et al., 2008). Specifically, the common rs4532/T allele is in perfect LD with the common rs686/A allele which increases D1 expression by 27% relative to the rare rs686/G allele (and hence rare rs4532/C allele) (Huang, et al., 2008). Notably, the rs4532/C allele has been previously associated with an increased risk of ADHD (Bobb, et al., 2005) inattention (Luca, et al., 2007; Misener, et al., 2004), nicotine dependence (Comings, et al., 1997; Huang, et al., 2008), and impulsivity (Bobb, et al., 2005).

rs265978. rs265978 is located 3.7 kilo base pairs (kb) downstream from the 3' UTR of DRD1. rs265978 is in strong LD ($D' = .96$) with rs686 in Haploview and was used as a Tag SNP for rs686. To our knowledge, no previous studies have examined the association between rs265978 and ADHD-related phenotypes.

rs265975. *rs265975* is located 5.5 kb downstream from the 3' UTR region of *DRD1*. *rs265975* has been linked to nicotine dependence itself in a large sample (N = 2037) of African-American and Caucasian smokers in the Mid-South region of the United States, as part of a *DRD1* haplotype that included *rs265973* and *rs686*, and as part of another haplotype formed by *rs265975*, *rs686*, and *rs4532* (Huang, et al., 2008). On the other hand, Nyman and colleagues (2007) failed to find an association between *rs265975* and ADHD.

rs265973. *rs265973* is located 7 kb downstream from the 3' UTR region of *DRD1*. *rs265973* has been associated with nicotine dependence itself and as part of the above noted 3-SNP *DRD1* haplotype (Huang, et al., 2008). Again, however, it has not been associated with ADHD (Nyman, et al., 2007). Table 7 gives details of the four *DRD1* SNPs under examination.

Table 7. *DRD1* Polymorphisms

SNP	Location	Alleles	Minor (Freq.)	Function
<i>rs4532</i>	Exon 1 (5'UTR)	T/C	C (0.24)	D1 expression (direct or LD)
<i>rs265978</i>	3.7 kb downstream	T/C	C (0.32)	Tag SNP for <i>rs686</i>
<i>rs265975</i>	5.5 kb downstream	C/T	T (0.37)	Associated with ND
<i>rs265973</i>	7 kb downstream	C/T	T (0.48)	Associated with ND

Note. SNP, single nucleotide polymorphism; UTR, untranslated region; LD, linkage disequilibrium; kb, kilo base pairs; ND, nicotine dependence

DRD2 Markers

rs12364283. *rs12364283* is a rare polymorphism within the promoter region 844 base-pairs upstream of the transcription start site of *DRD2*. *rs12364283* is associated with enhanced D2 expression in PFC and striatum, with the minor C allele significantly enhancing promoter activity over the major T allele (Zhang, et al., 2007). This group of

investigators subsequently reported an interaction between rs1236428 and schizophrenia that affected neural activity patterns on fMRI during the N-back working memory paradigm: in patients with schizophrenia, the T/C genotype was associated with significantly less prefrontal and striatal BOLD activity relative to schizophrenic patients with the T/T genotype; and no such interaction was evident in comparison health controls (Bertolino, et al., 2009).

rs2283265. rs2283265 is a G > T SNP in intron 5 of DRD2 (Zhang, et al., 2007). The minor rs2283265/T allele shifts splicing from D2S to D2L in PFC and striatum (expressed postsynaptically) and is associated with less efficient neural activity in the caudate, left claustrum, inferior frontal gyrus, left superior temporal gyrus, and right posterior cingulate during working memory performance (Zhang, et al., 2007). This group of investigators also reported that rs2283265 interacts with working memory load on the N-Back task such that heterozygote subjects have significantly reduced performance at 2-back but not 1-back compared with homozygotes. Similarly, on an attentional control task, heterozygote subjects demonstrated reduced performance at the highest load of attentional control compared with homozygote subjects (Zhang, et al., 2007).

rs1076560. rs1076560 is an infrequent intron 6 SNP in DRD2 that is highly linked with rs2283265 ($D' = 1.0$) and of which the minor T allele also reduces formation of D2S in favor of D2L (Zhang, et al., 2007). Carriers of the rs1076560/T allele also evidence reduced neural activation in the head of the caudate nucleus, left middle frontal gyrus, left precentral gyrus, left anterior cingulate, left thalamus, left superior frontal gyrus, and left caudate tail during the working memory, suggesting greater energy

expenditures for similar task performance (Zhang, et al., 2007). rs1076560/T allele carriers demonstrated worse performance on a measure of attentional control (Zhang, et al., 2007)

The location of rs2283265 and rs1076560 in introns 5 and 6 suggests that exon 6 is involved in DRD2 splicing. Although rs2283265 and rs1076560 are tightly linked to each other, minigene experiments by Zhang indicated that both SNPs individually affect DRD2 splicing (Zhang, et al., 2007). Notably, the minor alleles which shift DRD2 splicing from D2S to D2L are also associated with greater activity in PFC and striatum during working memory, even when accuracy and reaction time are not different, suggesting greater energy expenditures during working memory for similar task performance based on the ratio of D2S to D2L (Bertolino, et al., 2009; Zhang, et al., 2007).

rs1800497. rs1800497 is located in the ankyrin repeat and kinase domain containing 1 (ANKK1) gene (Neville, Johnstone, & Walton, 2004) on chromosome 11 at q22–q23 located 10 kb downstream of the 3' UTR of DRD2 (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997; Reuter, et al., 2005). As such, it is sometimes referred to as the DRD2/ANKK1-TaqIA polymorphism. rs1800497 can affect DRD2 mRNA translation and stability as well as postsynaptic D2 receptor density in the striatum (Laakso, et al., 2005; Noble, Blum, Ritchie, Montgomery, & Sheridan, 1991), and has been associated with differences in glucose metabolism in the striatum and ventral- and medial PFC (Noble, et al., 1997). However, the direct impact of rs1800497 on D2 receptor density has been questioned (Lucht & Roskopf, 2008) given that it is located in the ANKK1 gene (Neville, et al., 2004). Zhang and colleagues have proposed an alternative

mechanistic view based on their finding that rs1800497 is in very strong LD with rs2283265 and rs1076560 (Bertolino, et al., 2009; Zhang, et al., 2007). Associations with ADHD have been mixed; Comings and colleagues found the A1 allele of rs1800497 to be more prevalent in patients with ADHD relative to controls (Comings, et al., 1991), whereas Rowe and colleagues did not find significant linkage or association with ADHD (Rowe, et al., 1999). Table 8 gives details of the four DRD2 SNPs under investigation.

Table 8. DRD2 Polymorphisms

SNP	Location	Alleles	Minor (Freq.)	Function
rs12364283	Promoter	A/G	G (0.07)	>D2 activity in PFC & striatum
rs2283265	Intron 5	C/A	A (0.13)	D2 splicing SNP; A = >D2L
rs1076560	Intron 6	C/A	A (0.15)	D2 splicing SNP; A = >D2L
rs1800497	DRD2/ANKK1	G/A	A (0.29)	High/low extrastriatal D2 binding

Note. PFC, prefrontal cortex; SNP, single nucleotide polymorphism; D2L, dopamine D2 receptor long isoform

Genotyping

Buccal swabs were obtained from study participants as a source of tissue to extract DNA. All genotyping was performed using TaqMan SNP genotyping assays available from Applied Biosystems. Briefly, a polymerase chain reaction (PCR) reaction was performed with genomic DNA (10ng/μl) and a TaqMan primer/probe set specific to each polymorphism. TaqMan probes incorporate minor groove binder technology at the 3' end which allows the probe to bind to the minor groove of the DNA helix to improve hybridization. Detection is achieved with exonuclease cleavage of a 5' allele-specific dye label, which generates the permanent assay signal. All probes also include a nonfluorescent quencher to eliminate all background fluorescence associated with

traditional quenchers. Results were read using an ABI Prism 7900HT instrument available in the Mount Sinai Quantitative PCR Shared Resource Facility.

Analytical Strategy

PLINK version 1.06 [<http://pngu.mgh.harvard.edu/purcell/plink/>] (Purcell, et al., 2007) was used to verify data quality, test for departure from Hardy-Weinberg equilibrium (HWE), and to test individual SNPs for association. Pairwise LD was evaluated with Haploview version 4.1 [<http://www.broadinstitute.org/haploview/>] (Barrett, Fry, Maller, & Daly, 2005). Haploblocks were determined according to published criteria (Gabriel, et al., 2002) and expressed as D' . HAPSTAT version 3.0 [<http://www.bios.unc.edu/~lin/hapstat/>] (Lin, Zeng, & Millikan, 2005) was used to test moderator effects of DRD1 and DRD2 haplotypes.

Hierarchical linear regression was used to test for moderator effects of maintenance and manipulation (i.e., independent variable) on attention problems (i.e., dependent variable) by genotype (i.e., moderator variable). A statistical moderator affects the direction and/or strength of the independent variation relation on the dependent variable, and is supported if the genotype \times working memory interaction term is significant. Each regression equation included the three main effects (i.e., genotype, LDSF, and LDSB) and the two interaction terms (i.e., genotype \times LDSF and genotype \times LDSB), plus any covariates. A joint 2-degrees of freedom (df) test was also included in the model as an omnibus test of genotype \times “working memory” and if significant, then the individual maintenance and manipulation interactions were interpreted. It is important to note that the significance of the main effects for the predictor and the

moderator are not directly relevant conceptually to testing the moderator hypothesis (Baron & Kenny, 1986).

Three separate models were examined: Baseline (i.e., data from the childhood evaluation); Developmental Change; and Follow-up (i.e., data from the adolescent/young adulthood evaluation). The Developmental Change model tested whether changes in working memory maintenance and manipulation were associated with changes in attention problems from childhood to adolescence/adulthood over the same period, and whether these associations were moderated by DRD1 and/or DRD2 polymorphisms. Three quantitative Developmental Change variables (i.e., change scores for LDSF, LDSB, and CBCL-AP) were extracted as residualized z-scores obtained by predicting the follow-up score from the baseline score. This method of quantifying change over time negates the correlation between change scores and baseline performance because the correlation of the residual score (i.e., least squares error term) with baseline performance is always zero. The Developmental Change and Follow-up models were adjusted for the number of years that had elapsed between the baseline and follow-up evaluations.

A limited number of haplotype-based moderation analyses were also executed. Only SNPs belonging to the haploblocks identified with Haploview were included in the haplotype moderator analyses to limit multiple testing. *P*-values < .05 were interpreted as significant for all analyses. Post-hoc probing of significant moderator effects required plotting and testing the simple slopes of the relation between attention problems (*y*-axis) and working memory (*x*-axis) by genotype (*z*-axis) (Holmbeck, 2002).

Results

Stability (Pearson r statistic) from baseline to follow-up was 0.34 ($P = .004$) for CBCL-AP, 0.52 ($P < .001$) for LDSF, and 0.37 ($P = .002$) for LDSB. Thus, each of these measures reflects a trait with moderate stability over development, but also a fair degree of variability over time. This is broadly consistent with the published literature on the stability of attention problems (Biederman, et al., 2001) and working memory (Biederman, et al., 2008; Biederman, et al., 2007) in ADHD.

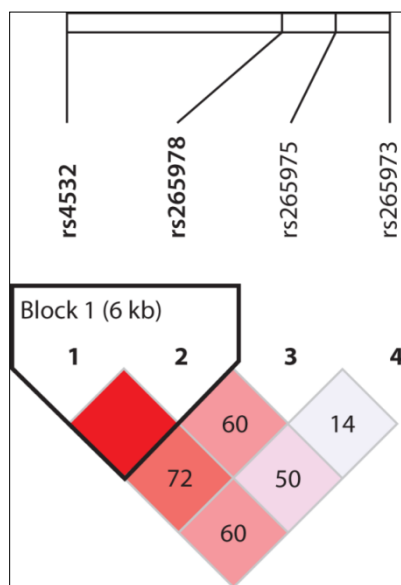
No SNP deviated significantly from HWE. Pairwise evaluation of LD detected a haploblock in strong LD within each gene. In DRD1 (Figure 2A), the SNPs belonging to the same haploblock were rs4532 and rs265978 ($D' = 1.0$) with haplotype frequencies of 67.6% for T-T, 23.8% for C-C, and 8.6% for T-C. In DRD2 (Figure 2B), rs2283265, rs1076560 and rs1800497 ($D' = 1.0$) comprised the haploblock with haplotype frequencies of 71.7% for C-C-G, 13.8% for C-C-A, 13.2% for A-A-A, and 1.4% for C-A-A.

Baseline Results

Baseline results are presented in Table 9. There were no significant main effects of genotype on attention problems. There were sporadic main effects of LDSF and LDSB such that better scores were associated with fewer attention problems, though the vast majority of these analyses were not significant. There were no significant genotype \times working memory joint interaction terms (average P -value = .557, range = .219 - .856). No haplotype main effects were significant, and no haplotype \times working memory interactions were significant (data not shown). Thus, the baseline model was not confirmed in childhood.

Figure 2. Haploview-generated Linkage Disequilibrium (LD) Patterns. D' value (x100) are noted at the intersection of each SNP pair. Shades of red in each box represent decreasing LD values.

A. DRD1 Haploplot



B. DRD2 Haploplot

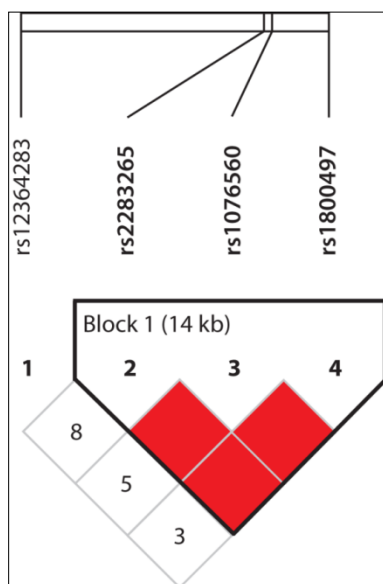


Table 9. Baseline Results

DRD1				DRD2			
<i>Parameter</i>	B	P	$R^2\Delta$	<i>Parameter</i>	B	P	$R^2\Delta$
rs4532	2.89	0.24	0.03	rs12364283	6.02	0.13	0.01
LDSF	2.53	0.10	0.10	LDSF	2.18	0.07	0.11
LDSB	-4.71	0.01		LDSB	-2.65	0.06	
rs4532×WM	NA	0.28	0.04	rs12364283×WM	NA	0.40	0.03
rs4532×LDSF	-1.90	0.42		rs12364283×LDSF	6.06	0.22	
rs4532×LDSB	4.06	0.12		rs12364283×LDSB	-3.45	0.37	
rs265978	2.55	0.29		0.02	rs2283265	-1.47	
LDSF	3.45	0.05	0.10	LDSF	2.90	0.04	0.10
LDSB	-5.34	0.01		LDSB	-3.01	0.04	
rs265978×WM	NA	0.22	0.04	rs2283265×WM	NA	0.77	0.01
rs265978×LDSF	-2.32	0.31		rs2283265×LDSF	-1.75	0.50	
rs265978×LDSB	4.23	0.10		rs2283265×LDSB	0.17	0.96	
rs265975	2.11	0.44		0.00	rs1076560	-1.32	
LDSF	1.20	0.59	0.13	LDSF	2.91	0.04	0.10
LDSB	-1.07	0.62		LDSB	-3.12	0.03	
rs265975×WM	NA	0.36	0.03	rs1076560×WM	NA	0.72	0.01
rs265975×LDSF	1.76	0.50		rs1076560×LDSF	-2.06	0.42	
rs265975×LDSB	-3.72	0.16		rs1076560×LDSB	0.77	0.83	
rs265973	1.86	0.46		0.01	rs1800497	-2.86	
LDSF	2.80	0.14	0.10	LDSF	2.62	0.11	0.10
LDSB	-3.86	0.08		LDSB	-3.90	0.05	
rs265973×WM	NA	0.86	0.01	rs1800497×WM	NA	0.84	0.01
rs265973×LDSF	-1.03	0.67		rs1800497×LDSF	-0.81	0.73	
rs265973×LDSB	1.27	0.64		rs1800497×LDSB	1.54	0.57	

Note: The reference allele is the minor allele (i.e., a positive regression coefficient means that having either 1 or 2 copies of the minor allele increases scores relative to having no copies of the minor allele). WM, working memory; LDSF, longest digit span forward; LDSB, longest digit span backward; B, regression coefficient; P, P-value; $R^2\Delta$, change in variance accounted for in regression model.

Developmental Change Results

Results from the models of Developmental Change are presented in Table 10. The main effect of rs1800497 was significant, with the minor A allele associated with greater improvements in attention problems over time. Similar to the Baseline models, most of the LDSF and LDSB main effects were not significant. However, there were three significant genotype \times joint working memory interaction terms (P -value range = .02 - .045), which were driven by three DRD1 \times LDSB individual interaction terms. Probing of the simple slopes revealed that greater improvements in the ability to manipulate information in working memory during development were associated with greater improvements in attention problems in individuals who were homozygous for the major alleles of rs4532, rs265978, and rs265973. By contrast, the manipulation-attention problems link was decoupled in individuals who carried 1 or 2 copies of the minor allele of these three DRD1 SNPs. See Figures 3A-C for more details.

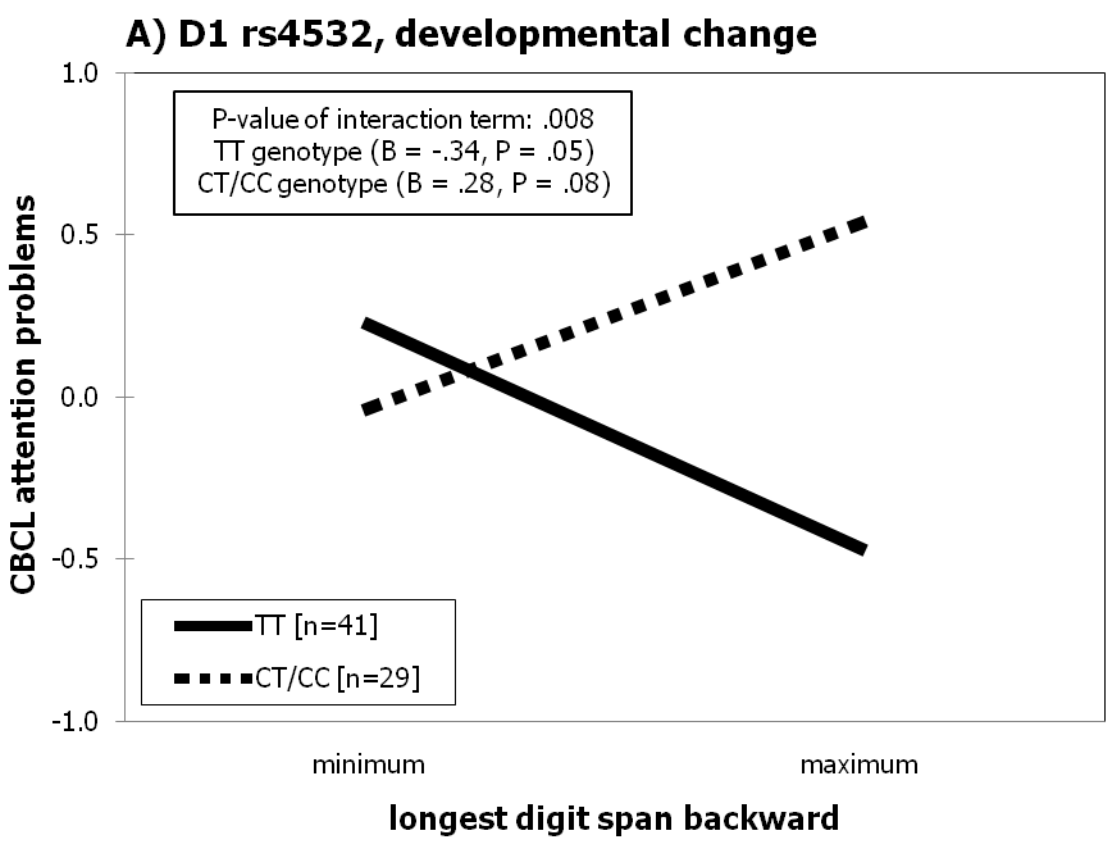
No DRD2 \times working memory interactions were significant.

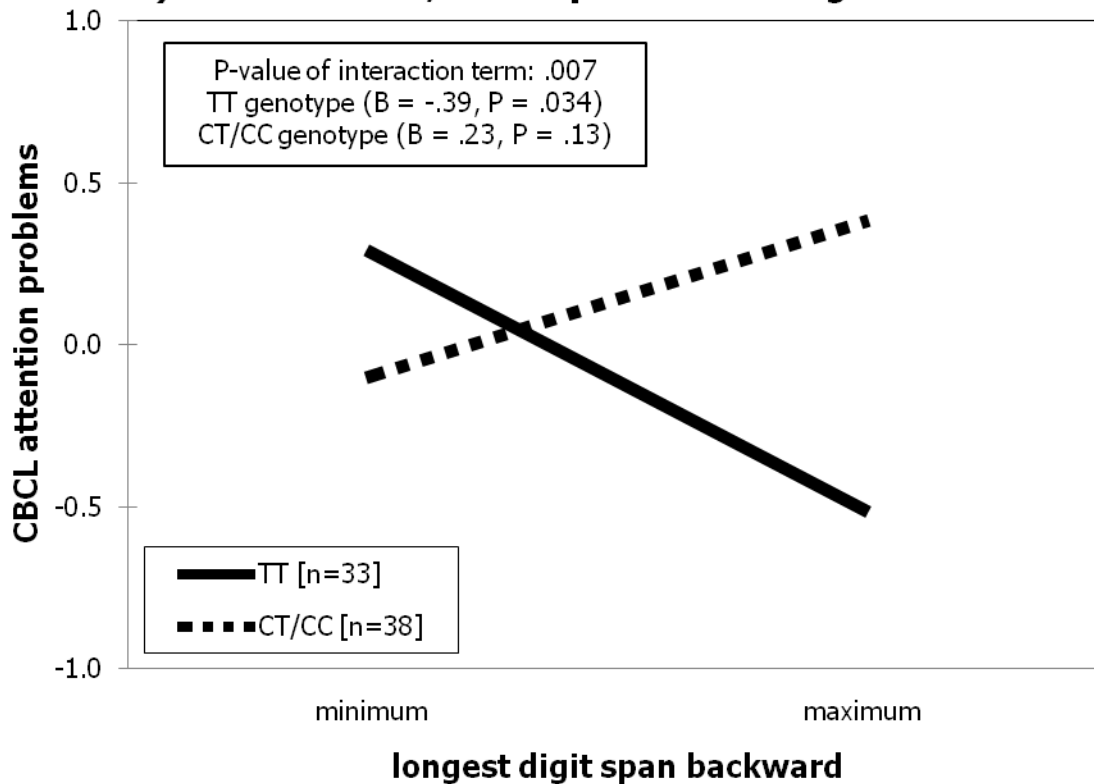
Table 10. Developmental Change Results

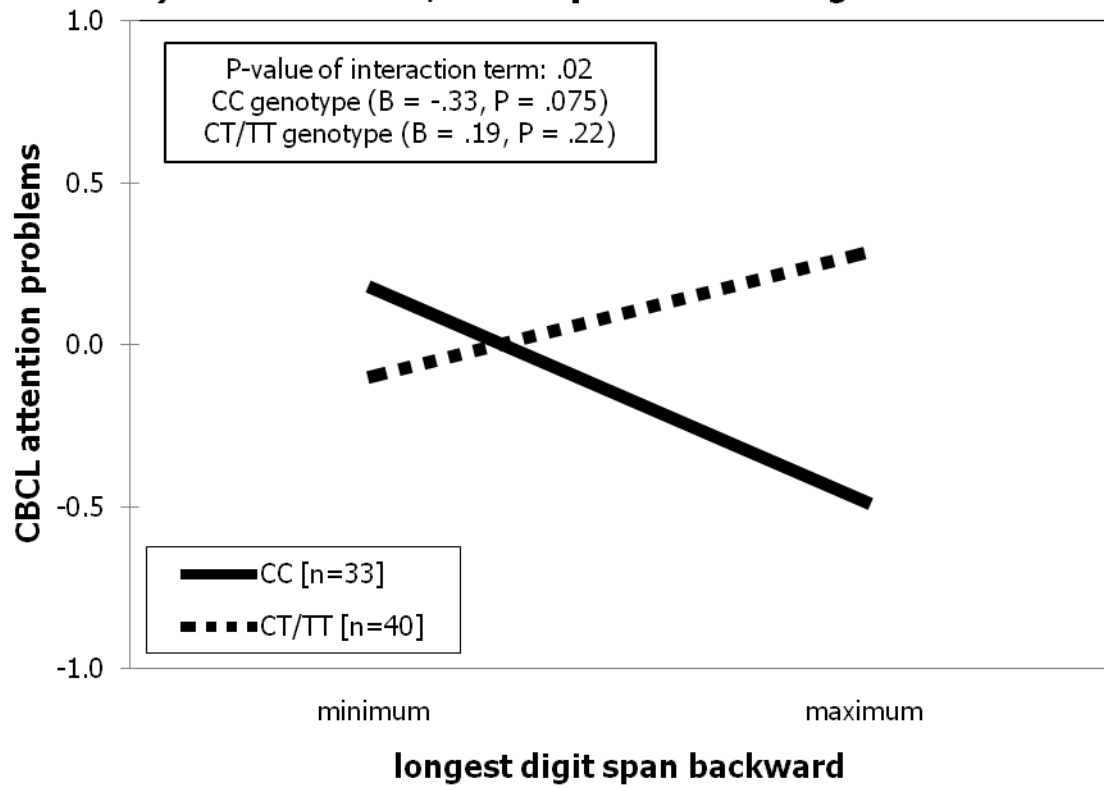
DRD1				DRD2			
<i>Parameter</i>	B	P	$R^2\Delta$	<i>Parameter</i>	B	P	$R^2\Delta$
rs4532	0.41	0.10	0.03	rs12364283	-0.23	0.52	0.01
LDSF	-0.04	0.79	0.00	LDSF	-0.04	0.74	0.00
LDSB	-0.34	0.05		LDSB	-0.07	0.60	
rs4532×WM	NA	0.02		rs12364283×WM	NA	0.62	
rs4532×LDSF	-0.13	0.61	0.10	rs12364283×LDSF	-0.22	0.62	0.01
rs4532×LDSB	0.65	0.01		rs12364283×LDSB	0.37	0.34	
rs265978	0.29	0.23	0.02	rs2283265	-0.06	0.83	0.00
LDSF	-0.05	0.74	0.00	LDSF	-0.15	0.28	0.00
LDSB	-0.39	0.03		LDSB	-0.01	0.93	
rs265978×WM	NA	0.02		rs2283265×WM	NA	1.00	
rs265978×LDSF	-0.13	0.59	0.11	rs2283265×LDSF	0.42	0.15	0.03
rs265978×LDSB	0.67	0.01		rs2283265×LDSB	-0.02	0.94	
rs265975	-0.20	0.49	0.01	rs1076560	-0.14	0.63	0.01
LDSF	0.16	0.49	0.00	LDSF	-0.15	0.30	0.00
LDSB	-0.07	0.75		LDSB	0.03	0.84	
rs265975×WM	NA	0.92		rs1076560×WM	NA	0.87	
rs265975×LDSF	-0.31	0.26	0.02	rs1076560×LDSF	0.37	0.20	0.02
rs265975×LDSB	0.10	0.69		rs1076560×LDSB	-0.15	0.60	
rs265973	0.26	0.28	0.01	rs1800497	-0.49	0.04	0.06
LDSF	-0.01	0.95	0.00	LDSF	-0.35	0.05	0.00
LDSB	-0.34	0.07		LDSB	0.21	0.23	
rs265973×WM	NA	0.045		rs1800497×WM	NA	0.36	
rs265973×LDSF	-0.30	0.24	0.09	rs1800497×LDSF	0.56	0.20	0.09
rs265973×LDSB	0.61	0.02		rs1800497×LDSB	-0.33	0.16	

Note: The reference allele is the minor allele (i.e. a positive regression coefficient means that having either 1 or 2 copies of the minor allele increases scores relative to having no copies of the minor allele). WM, working memory; LDSF, longest digit span forward; LDSB, longest digit span backward; B, regression coefficient; P, P-value; $R^2\Delta$, change in variance accounted for in regression model.

Figure 3. (A-C) Developmental Change Simple Slope Plots. The moderator effects of manipulation on attention problems by rs4532 (A), rs265978 (B) and rs265973 (C) during development are shown.



B) D1 rs265978, developmental change

C) D1 rs265973, developmental change

As shown in Table 11, there was a significant DRD1 haplotype main effect of the T-T haplotype on greater relative improvements in attention problems during development. Further, the DRD1 T-T haplotype significantly moderated the association between manipulation and attention problems during development relative to the combined T-C/C-C haplotype. See Figure 4 for details.

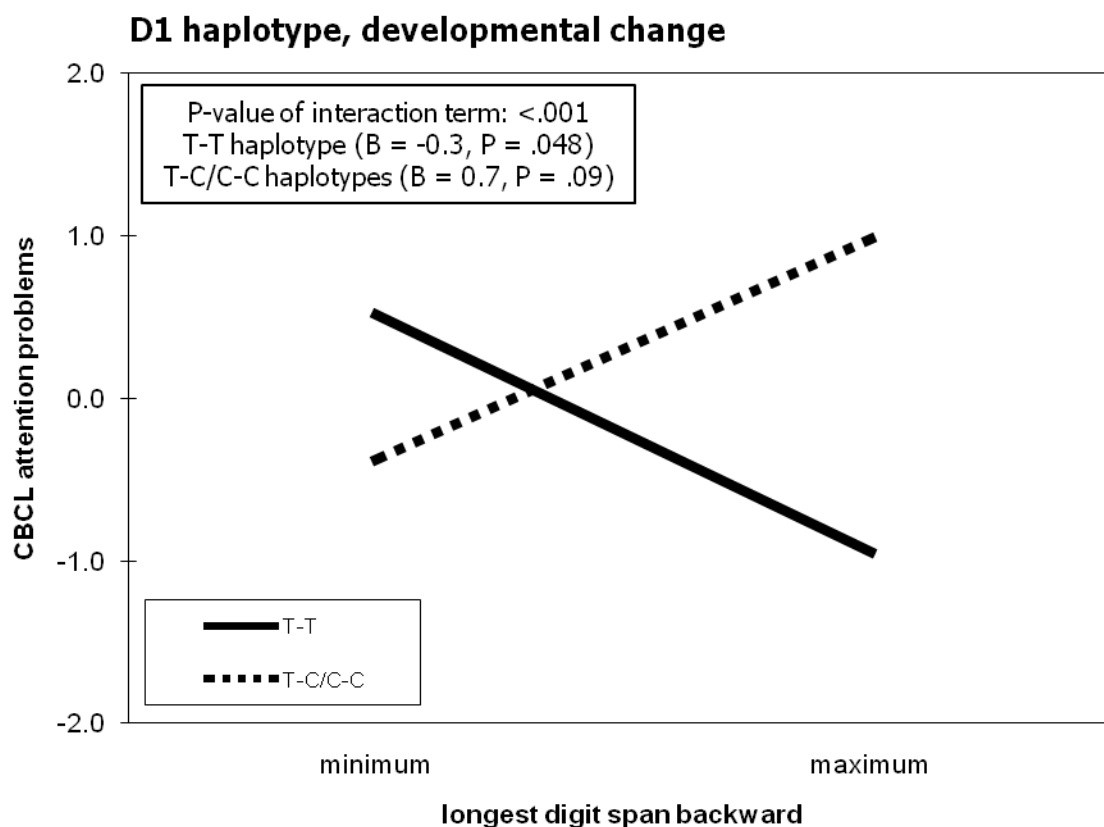
No DRD2 haplotype main effects and no DRD2 haplotype \times working memory interactions were significant (data not shown).

Table 11. DRD1 Haplotype Moderator Results. The haplotype consisted of SNPs rs4532 and rs265978. Only data from the Developmental Change and Follow-up analyses are shown.

<i>parameter</i>	Developmental Change				Follow-up			
	B	SE	Z	<i>P</i>	B	SE	Z	<i>P</i>
T-C/C-C haplotype	0.42	0.18	2.35	.02	4.58	1.65	2.78	.006
LDSB	-0.35	0.15	-2.34	.02	-3.15	1.48	-2.12	.03
LDSB \times T-C/C-C	0.64	0.19	3.45	<.001	6.53	1.88	3.47	<.001
T-C/C-C simple slope	0.72	0.42	1.72	.09	9.29	5.30	1.75	.08
T-T simple slope	-0.32	0.16	-1.98	.048	-3.28	1.57	-2.08	.037

Note. LDSB, longest digit span backward; B, regression coefficient; SE, standard error; Z, Z-statistic; *P*, P-value

Figure 4. Developmental Change Simple Slope Plots of the DRD1 Haplotype. The moderator effect of manipulation on attention problems by the DRD1 rs4532-rs265978 haplotype during development is shown.



Follow-up Results

Results from the adolescent/young adult evaluation are presented in Tables 12. A significant main effect of rs4532 emerged, with the minor C allele associated with greater attention problems. There was a significant main effect of rs1800497; the A allele was again associated with fewer attention problems. There were no significant LDSF main effects. There were significant LDSB main effects in most of the DRD1 models, but not in the DRD2 models. Again, three genotype \times working memory joint interaction terms were significant (P -value range = .009 - .031) due to three DRD1 \times LDSB individual

interaction terms. As shown in Figures 5 A-C, probing of the simple slopes revealed that greater improvements in the ability to manipulation information in working memory at follow-up were associated with fewer attention problems in individuals who were homozygous for the major alleles of rs4532, rs265978, and rs265973. Again, the manipulation-attention problems link was decoupled in individuals who carried 1 or 2 copies of the minor allele of these three DRD1 SNPs. Note that the genotype \times manipulation interactions accounted for 1-4% more variance relative to Developmental Change model interactions.

No DRD2 \times working memory interactions were significant.

As shown on the right most columns of Table 11 above, a DRD1 haplotype main effect was significant, with the T-T haplotype again associated with better attentional functioning. As shown in Figure 6, a DRD1 haplotype \times LDSB interaction was significant: for the T-T haplotype, manipulation was significantly inversely associated with attention problems in adolescence/young adulthood, whereas no association was detected for the T-C/C-C haplotype.

No DRD2 haplotype main effects or interactions were significant (data not shown).

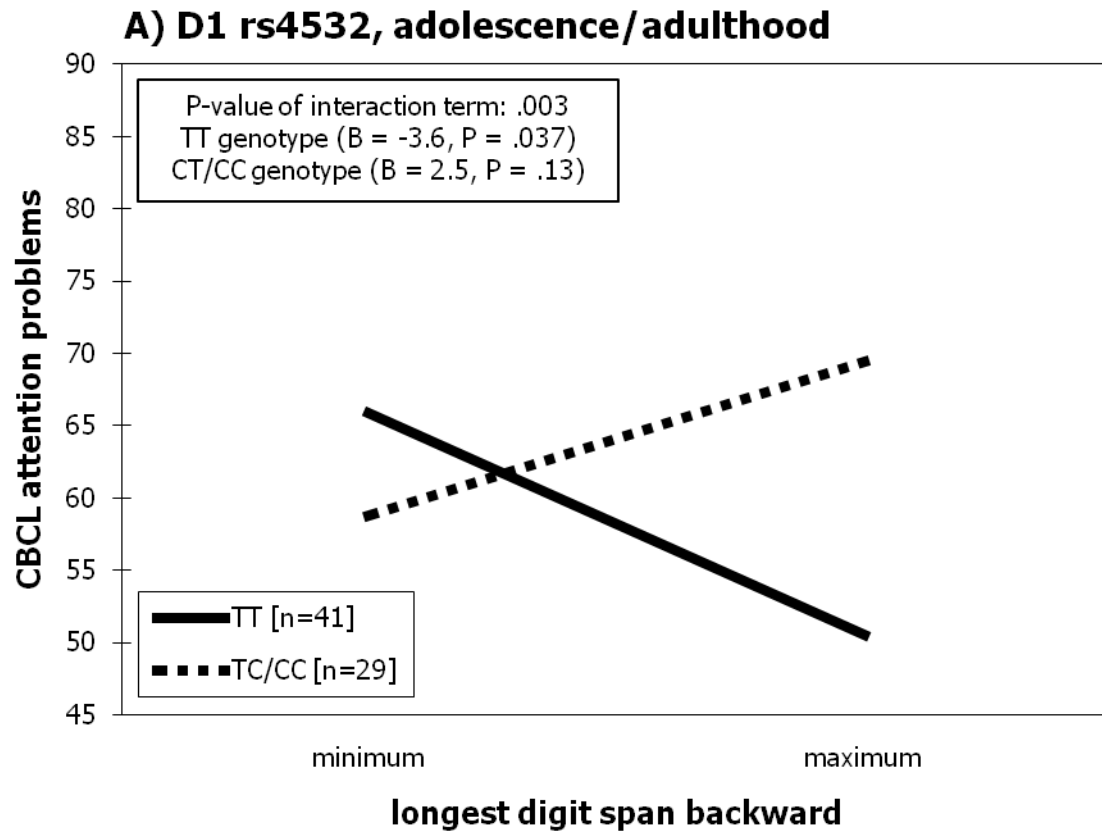
The Developmental Change and Follow-up models were re-analyzed adjusting for two potential confounding factors: history of psychostimulant treatment from childhood to adolescence/adulthood and racial/ethnic minority status. No changes in the results were detected after controlling for these two variables (data not shown).

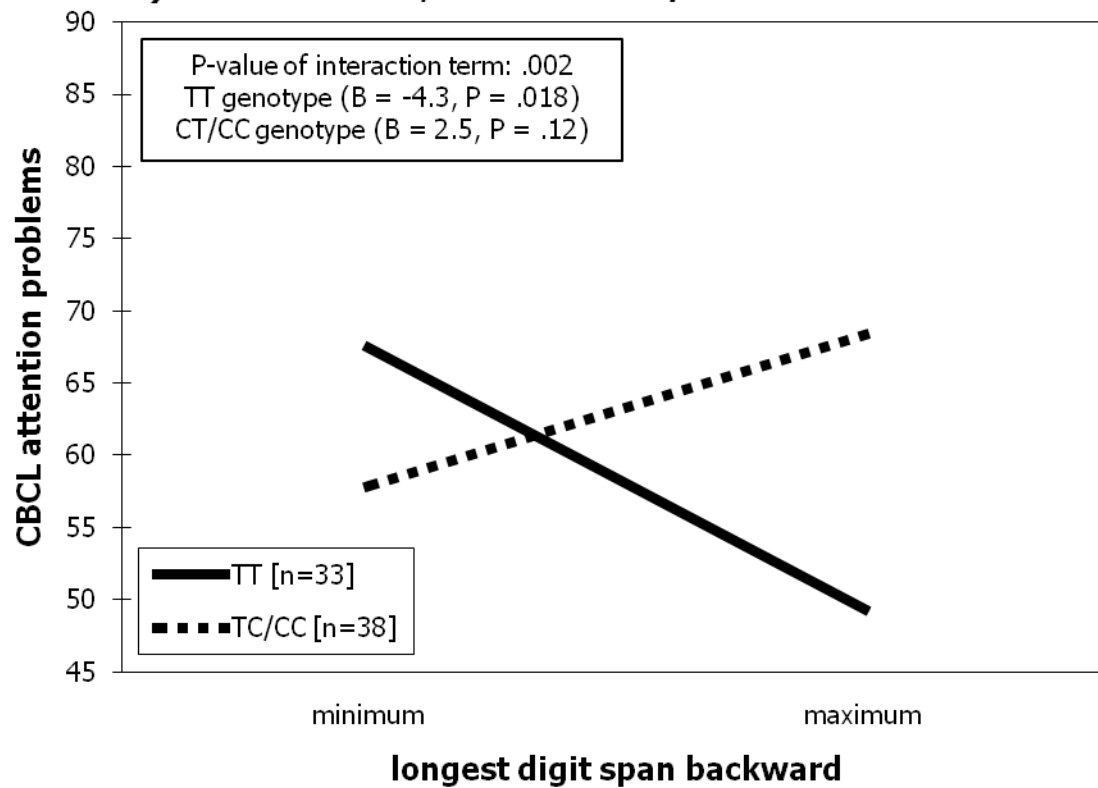
Table 12. Follow-up Results

DRD1				DRD2			
<i>Parameter</i>	B	P	R ² Δ	<i>Parameter</i>	B	P	R ² Δ
rs4532	4.75	.04	.04	rs12364283	1.37	.75	.00
LDSF	-0.74	.61	.03	LDSF	-1.08	.36	.02
LDSB	-3.44	.047		LDSB	-0.58	.65	
rs4532×WM	NA	.01		rs12364283×WM	NA	.58	
rs4532×LDSF	-2.72	.23	.13	rs12364283×LDSF	-1.82	.67	.02
rs4532×LDSB	7.44	.003		rs12364283×LDSB	6.41	.30	
rs265978	2.85	.20	.02	rs2283265	-1.45	.61	.01
LDSF	-0.53	.73	.02	LDSF	-1.57	.22	.02
LDSB	-4.18	.02		LDSB	-0.10	.95	
rs265978×WM	NA	.004		rs2283265×WM	NA	1.00	
rs265978×LDSF	-2.60	.25	.15	rs2283265×LDSF	1.88	.53	.01
rs265978×LDSB	7.97	.002		rs2283265×LDSB	-0.26	.94	
rs265975	-1.30	.63	.00	rs1076560	-2.08	.46	.01
LDSF	0.04	.99	.02	LDSF	-1.66	.21	.02
LDSB	-1.19	.60		LDSB	0.09	.96	
rs265975×WM	NA	.85		rs1076560×WM	NA	.98	
rs265975×LDSF	-1.57	.66	.01	rs1076560×LDSF	1.55	.60	.00
rs265975×LDSB	1.60	.56		rs1076560×LDSB	-0.65	.84	
rs265973	2.43	.26	.02	rs1800497	-5.55	.02	.09
LDSF	-0.60	.69	.02	LDSF	-2.04	.18	.02
LDSB	-3.55	.06		LDSB	2.52	.18	
rs265973×WM	NA	.03		rs1800497×WM	NA	.25	
rs265973×LDSF	-3.09	.18	.10	rs1800497×LDSF	1.86	.40	.04
rs265973×LDSB	6.65	.01		rs1800497×LDSB	-4.11	.10	

Note: The reference allele is the minor allele (i.e. a positive regression coefficient means that having either 1 or 2 copies of the minor allele increases scores relative to having no copies of the minor allele). WM, working memory; LDSF, longest digit span forward; LDSB, longest digit span backward; B, regression coefficient; P, P-value; R²Δ, change in variance accounted for in regression model.

Figure 5. (A-C) Follow-up Simple Slope Plots. The moderator effects of manipulation on attention problems by rs4532 (A), rs265978 (B) and rs265973 (C) are shown.



B) D1 rs265978, adolescence/adulthood

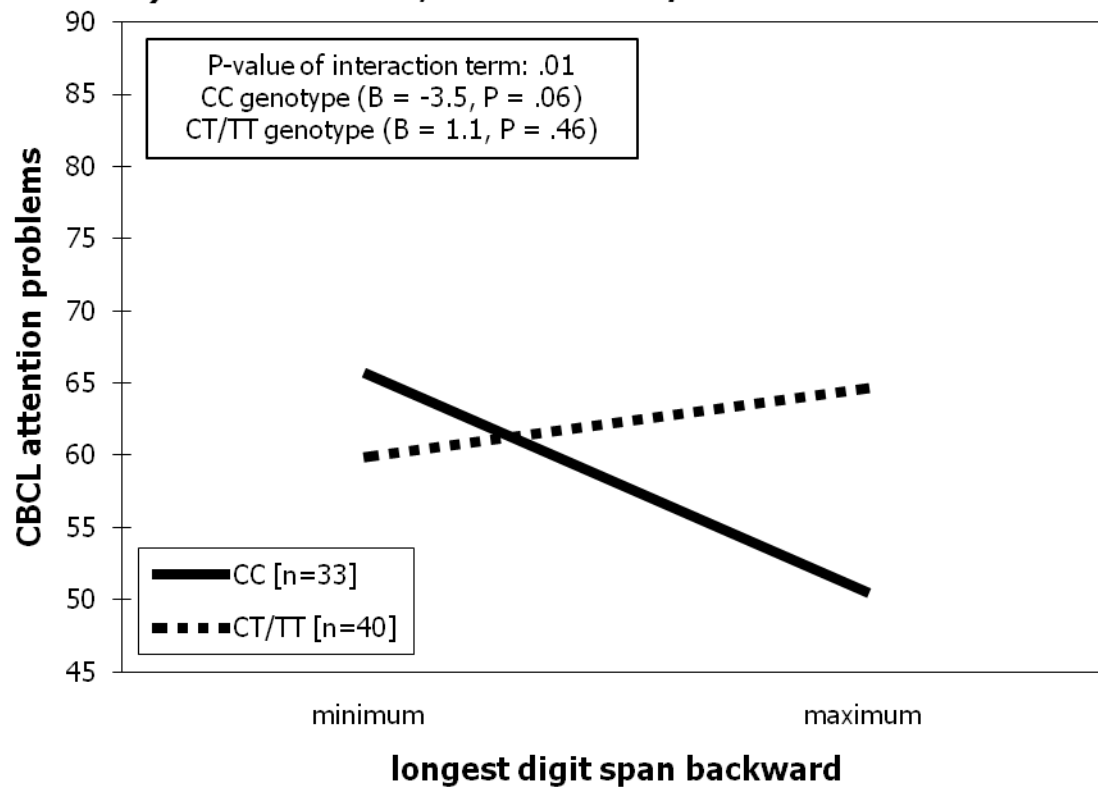
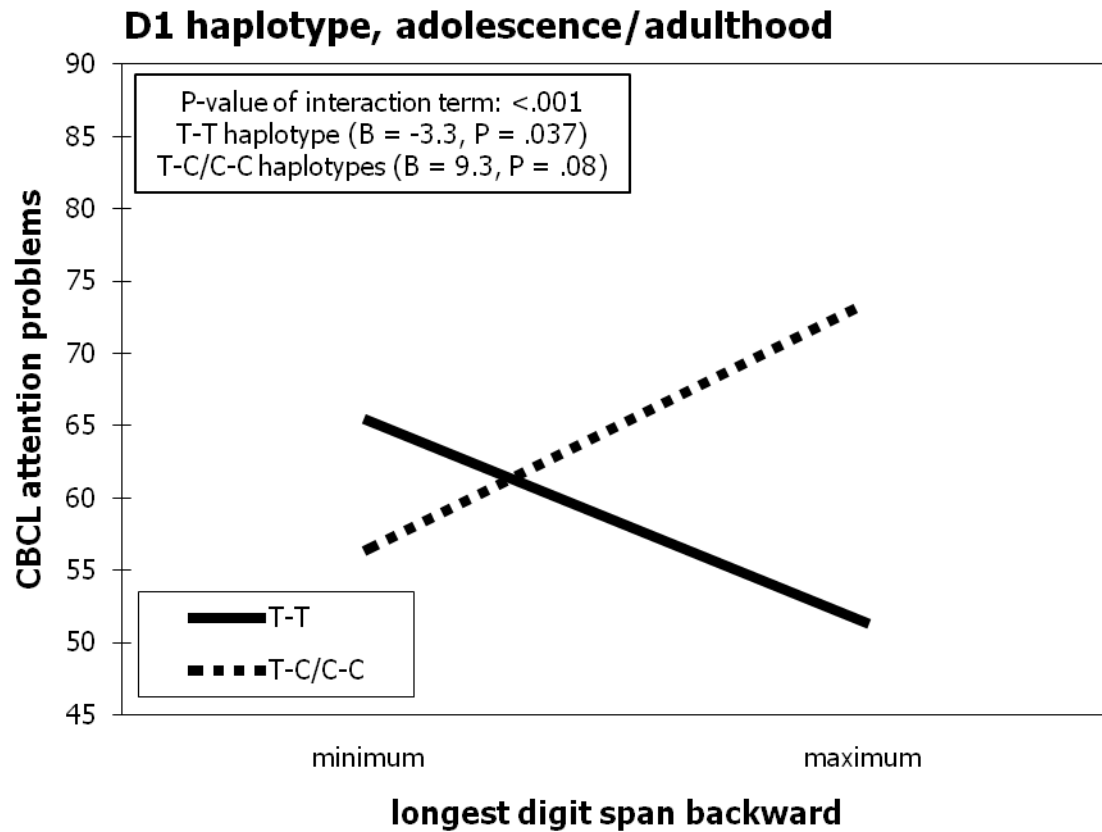
C) D1 rs265973, adolescence/adulthood

Figure 6. Follow-up Simple Slope Plots of the DRD1 Haplotype. The moderator effect of manipulation on attention problems by the DRD1 rs4532-rs265978 haplotype at follow-up is shown.



Discussion

The purpose of this dissertation research was to examine the effects of moderation between working memory maintenance and manipulation on attention problems by dopamine D1 and D2 receptor gene polymorphisms in a longitudinal cohort of youth with childhood-diagnosed ADHD. This unique ADHD sample was followed during development for almost 10 years and was comprised of mostly inner-city racial/ethnic minorities. By using this approach, it was possible to demonstrate that the direction and strength of the relation between working memory and attention problems was specific to manipulation, only moderated by DRD1 polymorphisms, and only detected during later developmental stages. By contrast, no significant moderator effects were detected at baseline, between DRD1 and maintenance, or by DRD2. Thus, several of the study hypotheses were confirmed.

No significant moderator effects in childhood. This cohort of youth with childhood-diagnosed ADHD was initially recruited when they were between the ages of 7 and 11 years. This is the approximate age range that the preponderance of molecular genetic studies of ADHD have likewise utilized (Bellgrove, et al., 2008; Bellgrove, et al., 2005a; Bellgrove, et al., 2009; Brookes, et al., 2006a; Faraone, et al., 2005; Gizer, et al., 2009; Kirley, et al., 2002; Kollins, et al., 2008; LaHoste, et al., 1996; Langley, et al., 2004; Mills, et al., 2004; Swanson, et al., 2000b; Swanson, et al., 1998; Taerk, et al., 2004). The dopaminergic system has been the most intensively analyzed neurotransmitter system in these genetic studies of ADHD (Banaschewski, et al., 2010; Faraone, et al., 2005; Swanson, et al., 2007). As has been emphasized in the current study, developmental change occurs within and between various levels (e.g.,

anatomically, functionally, and neurochemically) in the dopaminergic system (Andersen, 2003, 2005; Andersen, Dumont, & Teicher, 1997; Andersen & Navalta, 2004; Andersen & Teicher, 2000; Andersen, et al., 2000). The lack of consistent replication between dopamine system genes and ADHD is in part due to the developmental variability of the dopaminergic system per se. Nonetheless, it was important to examine whether these dopaminergic markers were associated with attention problems in our unique cohort at baseline.

As suspected, no main effects and no moderator effects were significant based on the phenotypic data collected in childhood. The hypothesis that the development of working memory ability affects the trajectory but not the emergence of ADHD was supported (Halperin & Schulz, 2006). However, there appears to be different pathways to symptom remission depending on genotype. It has been previously suggested that the genes and environmental factors that contribute to the emergence of ADHD in early childhood are not necessarily the same as those that contribute to its course and outcome during development (Thapar, et al., 2007). The current results support this assertion and implicate the dopamine D1 receptor as a potential genetic marker for this dissociation. Notably, had this study been limited to a childhood-only analysis, which is the age group that most published studies of genetics and ADHD have examined, it would have contributed yet another non-replication to the literature.

The direction and strength of the relation between manipulation and attention problems was moderated by the major alleles of 3 of the 4 DRD1 markers. As noted, PFC provides top-down control of working memory (Edin, et al., 2009). Working memory operates optimally within a limited range of dopamine transmission and D1

receptor signaling in PFC i.e., inverted U-shaped curve (Williams & Castner, 2006). Animal models of working memory have demonstrated that enhanced D1 receptor function can compensate for experimentally induced and naturally occurring changes/deficits in the dopaminergic system, and long-lasting recovery of cognitive and behavioral functions.

For example, repeated, intermittent treatment of a D1 agonist to rats with selective neonatal destruction of dopamine-containing neurons using 6-hydroxydopamine (6-OHDA) produced an enduring amplification of the ability of the acute D1 agonist challenge to ameliorate behavioral deficits (Criswell, Mueller, & Breese, 1989). Improvements lasted for at least six months and included a progressive increase in locomotor activity as well as several other behavioral enhancements (Criswell, et al., 1989). Work from the colleagues of Goldman-Rakic has similarly shown that repeated, intermittent D1 stimulation with D1 agonists can restore cognitive function in nonhuman primates rendered D1-deficient in PFC as a result of chronic haloperidol treatment (Castner, et al., 2000; Lidow, Elsworth, & Goldman-Rakic, 1997; Lidow & Goldman-Rakic, 1994; Williams & Castner, 2006). Notably, intermittent D1 agonist stimulation was shown to ameliorate spatial working memory deficits during the treatment period, and the cognitive “restoration” persisted for more than one year following cessation of D1 therapy despite ongoing haloperidol administration (Castner, et al., 2000; Lidow, et al., 1997; Lidow & Goldman-Rakic, 1994; Williams & Castner, 2006). This sensitizing regimen of repeated, intermittent D1 agonist treatment also produced profound and enduring enhancements of working memory performance in aged monkeys (Castner & Goldman-Rakic, 2004). Dopamine cell depletion in PFC is a naturally occurring process

in “elderly” monkeys which leads to a secondary decline in working memory. However, treatment with a D1 agonist restored working memory in these animals (Castner & Goldman-Rakic, 2004).

Both dorsal and ventral PFC regions have been implicated in the pathophysiology of ADHD (Dickstein, et al., 2006; Schulz, et al., 2005a; Schulz, et al., 2005b; Sheridan, et al., 2007). The most pronounced delay in cortical maturation in ADHD is reportedly in the lateral PFC (Shaw, et al., 2007a). While both dopamine D1 and D2 receptors are expressed in PFC, D1 dopamine receptors are far more abundant than D2, with a 20-fold increase in D1 receptor expression in primate DLPFC relative to D2 receptor expression (Lidow, et al., 1991). Thus, we hypothesize that rs4532, rs265978 and perhaps rs265973 are involved in the pathophysiology of ADHD based on their probable association with D1 receptor expression. There is indirect but strong evidence that the major and minor alleles of rs4532 and rs265978 shift D1 expression up or down by 27% (Huang & Li, 2009; Huang, et al., 2008). rs4532 is located in the 5' UTR of DRD1 and may affect D1 expression either directly or indirectly via LD with SNP rs686, a known functional polymorphism in the 3' UTR of the DRD1 gene that affects D1 receptor expression levels (Huang, et al., 2008). Here, greater D1 receptor expression due to allelic variation in rs4532 was not beneficial in terms of predicting attention problem severity from severity of cognitive dysfunction at baseline, whereas rs4532 strongly moderated the association later in development. Perhaps enhanced D1 expression positively facilitates the growth and development of cognitive functioning in PFC particularly as it relates to the development of working memory skill in youth with ADHD.

In the current study, the minor rs4532/C allele was associated with greater attention problems in adolescence/young adulthood. Previous studies of rs4532 and ADHD have been inconsistent. Two studies have reported no association between rs4532 and ADHD (Kirley, et al., 2002; Nyman, et al., 2007). Conversely, a trend towards overtransmission of the minor rs4532/C allele and significant overtransmission of a 4-SNP haplotype that included rs4532/C with inattentive symptoms in ADHD has been reported (Misener, et al., 2004). This group replicated the association with inattention in a family-based sample selected for reading problems (Luca, et al., 2007). Another study reported that ADHD probands were more likely than controls to have the rs4532/C allele and faster reaction times on a response inhibition task (Bobb, et al., 2005).

Our findings are consistent with prior studies of a weak association between rs4532 and childhood-onset symptoms of ADHD (Kirley, et al., 2002; Nyman, et al., 2007). Rather, rs4532 appears to be more strongly associated with several intermediate ADHD phenotypes. As an example, the minor rs4532/C allele is strongly associated with an increased risk of nicotine dependence (Huang, et al., 2008). Nicotine dependence is a phenotype that is linked with both ADHD (McClernon & Kollins, 2008) and with deficits in working memory in adolescent smokers (Jacobsen, et al., 2005; Jacobsen, Mencl, Constable, Westerveld, & Pugh, 2007). However, the current study is the first to demonstrate that the rs4532/C allele significantly predicts the persistence of attention problems into late adolescence and young adulthood, and that the rare rs4532/C allele decouples the relationship between improvements in manipulation and improvements in attention problems during development.

rs265978 is 3.7 kb downstream of the DRD1 gene and is in complete LD with rs4532 ($D' = 1.0$). rs265978 is used as a tag-SNP for the functional DRD1 rs686 polymorphism. Strong LD among these SNPs implicates this region of chromosome 5 as an important locus of D1 receptor expression. There were subtle differences between rs4532 and rs265978 in terms of association and moderation. Unlike rs4532, the rare rs265978/C allele was not directly associated with attention problems. However, a significant main effect of the DRD1 rs4532-rs265978 haplotype on attention problems was detected. Also, rs265978 was a slightly better moderator of the relationship between manipulation and attention problems, accounting for 1-2% more variance than rs4532 across the developmental change and follow-up analyses. The DRD1 rs4532-rs265978 haplotype also significantly moderated the relationship between manipulation and attention problems in the developmental change and follow-up analyses. Similar to rs4532, the significant moderator effects of rs265978 are presumed to be a function of differential D1 receptor expression.

Moderator effects increased in strength across development and were strongest in adolescence/adulthood. One of the most important aspects of the data presented herein is the developmental component as it allowed for the examination of change and variability in these intermediate ADHD phenotypes over time. That the significant associations detected in this study increased in magnitude over an approximately 10-year period from baseline to follow-up highlights this point. Further, these effects were accounted for by the interaction of genotype \times manipulation on attention problems *above and beyond* any independent effects. Such findings lend support to the idea that the persistence of ADHD

into adolescence and adulthood is genetically mediated to a greater degree than the emergence of ADHD in childhood (Faraone, 2004; Kuntsi, et al., 2005b).

Halperin and Schulz (2006) have postulated a neurodevelopmental model of PFC development that explains this phenomenon. To reiterate, we showed that developmental changes in attention problems from childhood to adolescence/early adulthood were largely influenced by three DRD1 polymorphisms and to some degree by the DRD2/ANKK1 Taq1A polymorphism. However, only the DRD1 polymorphisms moderated the simultaneous trajectory of improvements in manipulation on the diminution of attention problems across development with effect sizes shown to increase linearly during development. Thus, it is likely that the protracted maturation of a PFC-D1 receptor subsystem that is involved in the development of higher-order working memory skills and attentional functioning is mechanistically linked with the current findings. Further, as is discussed below in more detail, variability in D1 expression and possibly in D2/ANKK1 function appears to be a key moderator of this relationship (Huang, et al., 2008; Zhang, et al., 2007).

Working memory is a valid endophenotype in a subgroup of individuals with ADHD. It has been suggested that, “to date, progress with the investigation of endophenotypes for ADHD has been disappointing” (Stevenson, et al., 2005). It is argued here that the lack of progress in this area has to do with the fact that most studies have been conducted with children in their school-age years and that most candidate gene studies have focused on dopaminergic system genes. Further, most studies have employed tests of executive functioning to detect putative endophenotypes. It is not surprising then that the endophenotype studies have been “disappointing” (Stevenson, et

al., 2005) given that executive functions that rely on PFC and contributions from the dopaminergic system are not fully developed until late adolescence and early adulthood. For example, dopamine D1 receptors are slow to migrate to PFC during development (Andersen, et al., 2000; Brenhouse, et al., 2008). Germane to this point is that fact that inter-individual differences in working memory capacity are largely determined by the strength of prefrontal top-down control (Edin, et al., 2009).

In the current study, we used the oldest documented measure of “short-term memory” and found that a task that has been around for over 100 years (i.e., digit span) (Richardson, 2007) was an ideal measure for the purposes of detecting significant moderator effects during development. Previous studies have similarly demonstrated that the digit span task is superior to many other measures of executive functioning in terms of assessing whether working memory is a valid endophenotype of ADHD (Doyle, et al., 2008; Rommelse, et al., 2008b). In the current study, parent-rated attention problems were significantly correlated with this laboratory measure of manipulation ability, irrespective of directionality (i.e., fewer attention problems were related to better manipulation skills and vice versa), but *only* in those whose genotype has been associated with higher D1 expression, and only during later developmental stages. Similar to past research (Rietveld, et al., 2004), the CBCL-AP was suitable as a developmentally sensitive measure of ADHD. Attention problems and manipulation were unrelated to genotype in childhood in this group and unrelated at all points during development in carriers of the D1 allele that has been associated with lower D1 expression.

Such findings support the hypotheses that multiple pathways are involved in the development of ADHD (Sonuga-Barke, 2003) and that penetrance of genes that

contribute to the development of ADHD varies during development (Thapar, et al., 2007). These results also suggest that the ability to reliably correlate parent rated symptoms of ADHD with a child's performance on laboratory measures of neuropsychological functioning is possible if age and genetic background are taken into consideration. Importantly, if we can reliably predict parent-rated behavioral concerns from laboratory measures of cognitive functioning, we might be better able to predict how individuals will respond to specific treatments (e.g., computerized working memory training).

Having 1 or 2 copies of the minor allele of rs4532, rs265978 and rs265973 decoupled the relationship between manipulation and attention problems. We hypothesize that less dopamine D1 receptor expression is a risk factor for generalized behavioral dysregulation and phenotypes that are related to ADHD. As examples, the minor rs4532/C allele has been linked with acute smoking (Comings, et al., 1997) and nicotine dependence (Huang, et al., 2008); compulsive, addictive behaviors such as gambling, compulsive shopping, drug use, and compulsive eating (Comings, et al., 1997; Kim, et al., 2007; Limosin, Loze, Rouillon, Ades, & Gorwood, 2003); sensation seeking in alcoholic males (Limosin, et al., 2003); and faster response times (i.e., impulsivity) in ADHD (Bobb, et al., 2005). Less D1 expression by means of the rs4532/C allele might be the underlying cause of higher rates of dimensionally measured inattention that has been reported (Misener, et al., 2004) and replicated (Luca, et al., 2007) in two relatively large ADHD samples. We essentially found the same.

No significant moderator effects of working memory maintenance and attention problems by DRD1 markers. The demands on working memory during pure maintenance

are distinct from those involved in manipulation (Reynolds, 1997). From a theoretical perspective, the attentional control of working memory is maintained by the *central executive* component of the Baddeley and Hitch model of working memory (Baddeley, 1996, 2000; Baddeley, 1986; Baddeley & Hitch, 1974). The central executive is engaged by backward span tasks that require information to be manipulated. In contrast, the model's *phonological loop* is the system responsible for temporarily maintaining information in short-term auditory memory. DLPFC makes a greater contribution to manipulation than to maintenance. By contrast, VLPFC is implicated in pure maintenance (Smith & Jonides, 1999). We also view maintenance and manipulation as distinct processes with only partially overlapping neural substrates.

A recent event-related fMRI study demonstrated that developmental improvements from childhood to adolescence in manipulation relative to maintenance are associated with increased recruitment of DLPFC and superior parietal cortex but not VLPFC (Crone, et al., 2006). In this study, typically developing children were differentially worse at manipulation relative to maintenance in comparison to normally developing adolescents and adults. No age differences were observed in VLPFC during online maintenance; however, unlike the older participants, children failed to recruit right DLPFC and bilateral superior parietal cortex during the delay period for manipulation relative to maintenance. Across participants, DLPFC activation was correlated with performance on manipulation trials but VLPFC activation was not. Essentially, this study showed that children rely on maintenance networks during manipulation relative to adolescents and adults (Crone, et al., 2006).

A series of fMRI studies conducted by Schulz et al. (2004; 2005a; 2005b) using a subsample of individuals who also participated in the current study suggested that adolescents with childhood-diagnosed ADHD also tend to rely on VLPFC for “executive functioning” more so than non-ADHD adolescents. For example, our ADHD probands exhibited greater neural activation during response inhibition in VLPFC while performing a go/no-go task (Schulz, et al., 2004). Schulz (2005a) subsequently showed that VLPFC activation was associated with ADHD severity such that persisters made the most commission errors and showed the greatest VLPFC activation, remitters made fewer commission errors and had lower activity, and VLPFC activation was lowest in controls who made the fewest errors. Lastly, Schulz (2005b) showed that our ADHD probands demonstrated significantly greater activation of left VLPFC during interference control on a different task of response inhibition; as well as greater activation of the left anterior cingulate cortex, right VLPFC, and left basal ganglia during the dual task condition of interference control and response competition. Notably, controls demonstrated the least amount of VLPFC activation in these studies whereas ADHD probands with persistent symptomatology evidenced the greatest levels of VLPFC activation.

Thus, similar to the typically developing *children* in the Crone study, our *adolescents* with childhood-diagnosed ADHD essentially relied on lower-order maintenance networks during conditions with a high executive function load. On the other hand, the typically developing adolescents in both studies, as well as the adults in the Crone study relied upon and engaged more dorsal areas of PFC when they had to execute a task with added cognitive demands. Accordingly, as Shaw and colleagues have suggested, ADHD does appear to be characterized by some type of maturational delay in

cortical development, especially in multimodal association areas of PFC (Shaw, et al., 2007a). Children and adolescents with ADHD are therefore unable to engage the areas of the brain that would make it easier for them to exert cognitive control, which is perhaps one of the reasons why manipulation is more consistently impaired in ADHD than maintenance (Hale, et al., 2002; Willcutt, et al., 2005). It is suspected that variability in D1 receptor expression is contributory.

No significant moderator effects by DRD2. There is converging evidence that the DRD2 polymorphisms examined in this study are functional. rs12364283 is located in a conserved suppressor region of the gene and affects DRD2 expression in PFC and the striatum (Zhang, et al., 2007). rs2283265 and rs1076560 are two frequent intronic SNPs that alter the expression of D2S and D2L, and are associated with differential neural activity in PFC and striatum on fMRI during working memory. And despite being 10,000 bp downstream from DRD2, rs1800497 has been shown to affect DRD2 mRNA translation and stability and postsynaptic DRD2 receptor density in the striatum (Ritchie & Noble, 2003). rs1800497 is actually localized within a different gene downstream, the ankyrin repeat and kinase domain containing 1 gene [ANKK1] (Neville, et al., 2004). Recently, reduced D2 receptor binding was reported in adults with ADHD in the left ventral striatum, left midbrain, and left hypothalamus (Volkow, et al., 2009). Thus, it seemed plausible that these DRD2 SNPs would play a significant role in moderating working memory and attention problems.

However, that was not the case, as the only association that was detected was a main effect of rs1800497 on attention problems. The minor rs1800497/A allele was directly associated with *lower* attention problems in the developmental change analysis,

and an even stronger effect was detected at follow-up. This finding somewhat conflicts with another study that reported an association between the rs1800497/A allele and a categorical diagnosis of ADHD (i.e., the A allele increased risk for ADHD) (Nyman, et al., 2007). It is unclear why the rs1800497/A allele was advantageous in our ADHD cohort, although it is notable that the effect of rs1800497 was not present in childhood but significantly emerged over development. If genetic polymorphisms in the chromosomal region of DRD2/ANKK1 are truly involved in cognition and behavior in ADHD, then their influence is probably susceptible to developmental factors as well.

Limitations

This study has limitations that could have influenced the results. Despite considerable effort, it was not possible to follow all individuals from the childhood and adolescence/young adulthood studies, although available data suggest that this subsample was representative of the original cohort. The relatively modest sample size is thus potentially underpowered to detect genetic risk factors of small effect size for an etiologically complex disorder like ADHD. Nevertheless, our ability to detect significance with our limited sample size suggests that the findings may represent robust associations. Also, this study did not have a non-ADHD comparison group that was followed from childhood; thus it is not clear whether these results generalize beyond individuals with ADHD. Further, population structure limitations (ethnically/racially mixed population of inner-city individuals) makes the results susceptible to population stratification effects. However, as noted, all results were analyzed with and without minority status as a covariate, with no appreciable differences detected between the two sets of analyses. Because of these limitations, this study focused on several

polymorphisms for which there exists an expectation of association based on prior work, converging evidence supporting a role for these loci in ADHD, and clear predictions of the developmental and moderational effects based on theoretical models and empirical data. However, replication in larger independent samples of different racial/ethnic background is needed to fully refute these limitations. Nonetheless, this sample of predominantly racial/ethnic minorities is a population that has been mostly underrepresented in molecular genetic studies of ADHD to date.

Summary

Several theoretical models with underlying neurocognitive and pathophysiologic correlates have been proposed to account for the emergence of ADHD in childhood (Barkley, 1997; Sergeant, et al., 1999; Sonuga-Barke, 2003; Sonuga-Barke & Castellanos, 2007). Less has been written regarding possible mechanisms involved in regulating symptom persistence across the lifespan. An exception is the model of Halperin and Schulz (2006) who posited distinct neurocognitive mechanisms for the *etiology of and recovery from* ADHD during development. Of particular relevance to the current study is the view that prefrontally mediated, top-down dopaminergic mechanisms that are also important for executive functions are at least partially involved in reducing symptom severity in ADHD over development. Previous work from our lab has shown that symptom remission in ADHD is associated with better effortful cognitive control (including working memory) on neuropsychological measures (Halperin, et al., 2008), and that developmental changes in ADHD symptomatology are associated with functional changes in prefrontal-striatal activation patterns (Schulz, et al., 2005a; Schulz, et al., 2005b). This dissertation work attempted to build on these prior studies and

hypotheses by examining for potential moderator effects of working memory on symptom stability in ADHD by dopaminergic gene polymorphisms. Selection of behavioral phenotype (e.g., dimensional symptomatology), neuropsychological task (e.g., executive and non-executive components) and developmental factors (e.g., age) was vital to this attempt at deconstructing the complex ADHD phenotype.

No significant moderator effects were detected at baseline. There were modest main effects of rs1800497 and rs4532 on attention problems during development that were somewhat stronger at follow-up. Notably, the direction and strength of the relation between manipulation and attention problems was moderated by the major alleles of 3 of the 4 DRD1 markers. Further, moderator effects increased in strength across development and were strongest in adolescence/adulthood. Conversely, having 1 or 2 copies of the minor allele of rs4532, rs265978 and rs265973 decoupled the relationship between manipulation and attention problems. Also, there were no significant moderator effects between DRD1 markers and maintenance and no significant moderator effects by DRD2 at any time point. The key result, however, was demonstrating that attention problems got better over time if manipulation also improved during development in a subgroup of individuals with ADHD depending on their genetic makeup and age.

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