

INHIBITORY CONTROL, WORKING MEMORY, AND STATE  
REGULATION IN FAMILIES OF HYPERACTIVE AND INATTENTIVE  
PRESCHOOLERS

by

Amita Santra

A dissertation is submitted to the Graduate Faculty in Psychology in partial fulfillment of the  
requirements for the degree of Doctor of Philosophy,

The City University of New York

2008

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This manuscript has been read and accepted by the Graduate Faculty in Psychology in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

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## ABSTRACT

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Amita Santra

Advisor: Jeffrey M. Halperin, Ph.D.

**Objective:** To determine the extent to which inhibitory control, working memory, and state regulation serve as candidate endophenotypes for Attention-deficit/Hyperactivity Disorder (ADHD). **Method:** The above neurocognitive factors were assessed in preschool children with either high (HI) or low (NC) levels of hyperactivity/inattention, as well as in their parents. Performance of (1) these HI and NC preschoolers, and (2) the parents of these two groups of children, as well as (3) performance of children in relation to their parents on the computerized novel experimental measures were compared. **Results:** The findings suggest that preschool children with elevated levels of ADHD symptoms present with a global state regulation deficit that likely impacts functioning across a wide array of domains. Yet, when appropriate matched control conditions were utilized to control for lower-level processes, there was no evidence to suggest the presence of specific deficits in executive functioning. Although mothers of HI preschoolers did not display any neurocognitive deficits, fathers of these preschoolers exhibited specific deficiencies in response inhibition and state regulation after controlling for lower-level processes. **Conclusion:** The current findings support the notion that a global state regulatory

deficit may underlie the cognitive and behavioral deficits characteristic of ADHD. These data also point to familial aggregation of a response inhibition deficit, which children inherit from their parents; however, these traits may not be sufficiently developed during the preschool period to show any specific deficit. Response inhibition has been linked to top-down executive control, and may underlie the remission of the symptoms over time.

## ACKNOWLEDGEMENTS

This dissertation would have not been possible without the contribution of some wonderful people and I owe my sincere gratitude to them. My deepest gratitude is to my advisor, Dr. Jeffrey Halperin, whose guidance and encouragement not only helped me to overcome difficult milestones in my graduate career but also touched my personal life immensely. I am amazingly fortunate to have such an advisor who did not impose his beliefs on me, but allowed me to explore my ideas independently, patiently guiding me with his expertise. His constructive criticism and guidance have taught me how to think like a scientist, how to conceptualize data, and how to give scientific presentations at major conferences. I am also thankful to him for helping me improving my writing style and for carefully reading and commenting on countless revisions of this manuscript. I will always cherish his mentorship. In addition, I thank Dr. Halperin and the National Institute of Health for providing financial assistance for this dissertation thorough Minority Supplement grant # 41516-01-04-8800.

I am also privileged to have such a dedicated, caring, flexible, and cohesive dissertation committee. The members were readily available for meetings and valuable advice via e-mail or phone. I cannot thank my committee members enough for allowing me to defend my dissertation with short notice. Dr. Hillary Gomes' insightful comments on this manuscript provoked thoughts and scientific reasoning that helped me shape and organize my dissertation. I am grateful to her for carefully reading and providing me with detailed editorial comments on the manuscript. My deepest gratitude to Dr. Veronica Hinton not only for her valuable constructive criticism on the research aspect of the dissertation but also for her support and encouragement that was necessary to keep me sane right before defending the dissertation. I greatly appreciate Dr. Edward Greenblatt for his consistent support, encouragement, and

guidance. Frequent informal valuable discussions based on his expertise on childhood psychological disorders influenced my conceptualization of this dissertation. My greatest appreciation to Dr. Janine Flory for her practical advice and statistical expertise that was invaluable to this manuscript.

I am indebted to the members of the Queens College Preschool Project (Agnieszka Mlodnicka, Bella Grossman, Beth Rabinovitz, Bipasha Basu, Burt Hatch, Chaya Gopin, Dione Healey, Elizabeth Kera, Ekaterina Staikova, Katia Castelli, Michelle Bubnik, Olga Berwid, Olga Nikelshpur, Suzanne Locascio, Taneka Wellington, and others), who played an important role in data collection and data management, and served as a great source of emotional support. I treasure their friendship and support that helped me prevail over numerous personal crises and enabled me to remain focused on my academic growth.

Most importantly, I would not be able to accomplish my academic goal without the love and support from my family. I express my heartfelt gratitude to my generous brother, Goutam Santra, for his financial support and devotion throughout my graduate school experience. I am grateful to my brother, Soutam Santra, my sister, Mamata Das and her husband, Shyamal Das for their constant encouragement and enthusiasm in maintaining my perspective. I thank my long-term friend and husband, Dr. David Marks for his endless faith in me. His constant encouragement, tolerance of my 'dissertation mood', and support at every level were undeniably the bedrock upon which my success in graduate school has been built. Finally, a very special thanks to those two individuals whom I owe everything that I am today, my parents, Mrs. Pramila Santra and Mr. Radhagobinda Santra. Their life-long encouragement to strive for the best and their unwavering confidence in my abilities has shaped me to be the ambitious person I am today. Hence, I dedicate this dissertation with my heartfelt love and gratitude to my parents,

who endured so much hardship and instilled within me a commitment to achieve academically.

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## **SPECIFIC AIMS**

Attention Deficit Hyperactivity Disorder (ADHD), characterized by inattention, hyperactivity and impulsivity, is among the most commonly diagnosed childhood psychiatric disorders. ADHD is diagnosed when age-inappropriate behavioral difficulties in these domains are present in more than one setting and have a negative functional impact, usually on academic performance, psychosocial interactions, and/or other areas of life. Although the core underlying deficit is not clear, impairment in cognitive functions and self regulation are observed among children with ADHD.

Findings from behavioral genetic studies indicate that ADHD is, to a substantial extent, genetically mediated. High prevalence rates of the disorder are observed among first degree relatives of individuals with ADHD and monozygotic twins show a higher concordance rate for the disorder than dizygotic twins. Yet, the question as to what precisely is transmitted genetically, the behavior or cognitive deficits that underlie the complex phenotypes, remains unanswered. The heterogeneity in the behavioral expression of the disorder indicates that perhaps numerous genes with small effect sizes interact in creating the complex clinical presentation. Molecular genetic approaches have identified a few genes that seem to be associated with ADHD, but they account for very little of the variance of the disorder, and researchers are still far from being able to identify the specific mode of genetic transmission. These difficulties point to the need for using more narrowly defined, directly identified, and objectively measured characteristics that might be more closely associated with the genetic underpinnings of the disorder. Such narrowly defined measures or latent traits, that are presumed to be more closely related to genes than the complex behavioral disorders defined in

Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) and ICD-10, are referred to as endophenotypes.

An endophenotype is conceptualized as any heritable characteristic (e.g., neurophysiological, endocrinological, cognitive, neuropsychological, etc.) that is normally associated with a condition but is not a direct symptom of that psychological condition (Gottesman, 2003). The endophenotype has become an important concept in the etiological exploration of complex disorders as it is presumed to provide a closer and simpler association with the genetic underpinning of the disorder than the overt phenotype itself. This allows for the decomposition of disease symptomatology into narrowly, well-defined measures that may be extremely helpful in searching for genes. The rationale is that, if the identified characteristic (or endophenotype) is specific and involves elementary phenomena, the number of genes required to produce variations in such an elementary trait would be fewer than those involved in producing the more complex diagnostic entity (Gottesman, 2003).

Searching for endophenotypes for a heterogeneous condition like ADHD can narrow-down the search for a specific set of genes by focusing on what is presumably being inherited that make these children susceptible to ADHD. For example, if “Characteristic A” serves as a candidate endophenotype for ADHD, individuals who are genetically vulnerable to ADHD should exhibit Characteristic A irrespective of their behavioral symptomatology. Thus, children, who are susceptible to ADHD but do not express behavioral symptoms, could be identified by the presence of Characteristic A. Similarly, Characteristic A should be present in family members of children with ADHD. Thus, if endophenotypes are successfully identified in family members it can assist in monitoring, diagnosis, treatment, as well as bring us closer to successfully identifying the genetic basis of ADHD.

Investigators (Doyle et al., 2005) have identified characteristics that should be inherent in an endophenotype to make it most useful in research: 1) it should co-occur with the behavior of interest, 2) it should be able to be measured in a psychometrically sound way, 3) it should be heritable, and 4) it should show genetic overlap with the disorder of interest. Endophenotypes composed of cognitive profiles are valuable in the search for genetic correlates of ADHD because: (1) specific neurocognitive deficits are associated with ADHD but are not direct symptoms of ADHD, (2) in contrast to behavioral rating scales, cognitive measures provide objectively-defined scores, and (3) cognitive measures seem to show some degrees of heritability.

The present study was designed to evaluate specific neurocognitive traits (i.e., inhibitory control, state regulation, and working memory) that might serve as potential candidate endophenotypes for ADHD by determining the extent to which they run in families of children with ADHD. These domains of functioning were selected because they have frequently been found to be impaired in individuals with ADHD (Castellanos et al., 2005; Castellanos & Tannock, 2002; Kuntsi et al., 2006) and seem to meet the required criteria for candidate endophenotypes as described above (Doyle et al., 2005).

The primary aim of this dissertation is to measure aspects of these traits in preschool children with high or low levels of hyperactivity/inattention (the core symptoms of ADHD) and their parents. Children with high levels of hyperactivity/inattention reported by teachers *or* parents were grouped as 'hyperactive/inattentive' (HI) and children with low or no hyperactivity/inattention reported by teachers *and* parents were categorized as 'normal control' (NC). By comparing (1) the parents of these two groups of children as well as (2) performance of children in relation to their biological parents on measures of potential endophenotypes, we hope to gain insight regarding transmission of neurocognitive characteristics associated with

ADHD. If these measures are appropriate endophenotypes of ADHD, parents of HI children should perform more poorly than parents of controls irrespective of the presence of their own ADHD symptoms.

The following hypotheses were proposed:

1. Children from the HI group will perform significantly more poorly on measures of inhibitory control, working memory, and state regulation compared to children from the NC group.
2. Parents of HI preschoolers will perform significantly more poorly on these same measures as compared to parents of NC preschool children. Further, parents of children in the HI group who do not exhibit ADHD symptoms on behavioral rating scales will perform in between the parents of NC children and symptomatic parents of the HI group.
3. Consistent with the notion that neurocognitive performance is at least in part genetically mediated, performance of parents and their offspring on measures of inhibitory control, working memory, and state regulation will be significantly correlated.

## INTRODUCTION

### Overview

ADHD is among the most commonly diagnosed childhood psychiatric condition with prevalence estimates of 5 – 10% (Faraone et al., 2003). It is currently defined as a multidimensional developmental disorder (DSM-IV, American Psychiatric Association, 1994) characterized by persistent, age inappropriate levels of inattention, hyperactivity, and impulsivity.

### Subtypes

Three subtypes of ADHD have been identified: 1) Predominantly Inattentive Type, 2) Predominantly Hyperactive/Impulsive Type, and 3) Combined Type. If six or more symptoms from either the inattentive or hyperactivity-impulsivity domains persist for at least six months in a developmentally inappropriate manner and cause clinically significant psychosocial impairment (e.g., disruptive in social situations, peer rejection, difficulty getting along with others, etc.) in multiple settings (e.g., home, school), the individual receives a diagnosis of that corresponding subtype (e.g., ADHD, Predominantly Inattentive Type or ADHD, Predominantly Hyperactive-Impulsive Type). If an individual exhibits six or more symptoms from both domains in developmentally inappropriate and impairing manner, he/she receives the diagnosis of 'ADHD, Combined Type. To date, it is not clear whether these subtypes of ADHD are etiologically related, or alternatively, reflect covariations in symptoms with different etiologies, as the findings have been inconsistent (discussed in the 'etiology' section under the twin paradigm).

### Gender Differences

Historically the prevalence of ADHD has been documented to be higher in boys than in girls; the male to female ratio in clinics is about 9 to 1 and in the community it is about 4 to 1 (Faraone et al., 2001). The difference between clinically-referred and community-based gender ratios suggests that girls with ADHD are less likely to be referred for treatment. Thus, girls are believed to be under-reported and under-treated. Conversely, relative to girls, boys more often exhibit symptoms of hyperactivity and impulsivity which are more likely to be disruptive in psychosocial interactions and are more often referred for treatment.

### Comorbidity

It is well-known that the symptomatology of ADHD usually does not exist in isolation; rather, other comorbid behavioral and psychological difficulties are oftentimes present. ADHD frequently co-occurs with other childhood psychiatric disorders such as Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and mood and anxiety disorders. As many as 70 – 80% of children with ADHD have at least one comorbid psychiatric disorder (Biederman et al., 1987; Biederman et al., 1991; Smalley, 2000; Sprich et al., 2000). In addition, these children oftentimes have other developmental disorders such as language and cognitive/reading disabilities (Willcutt et al., 2000b).

### Stability

Although ADHD is a disorder with childhood onset, symptoms frequently persist into adolescence and adulthood (Biederman et al., 1996; Cunningham & Boyle, 2002; Hechtman et al., 1984; Mannuzza et al., 1991). Among individuals with a childhood diagnoses of ADHD, the symptoms manifest and remit differentially with age. Severe hyperactivity is more common among young children. However, the hyperactivity symptoms that are prominent in childhood

substantially diminish by adolescence, whereas symptoms of inattention, and perhaps impulsivity, more often persist well into adolescence and adulthood (Brown & Gammon, 1995; Achenbach et al., 1995; Hart et al., 1995). Additionally, developmental variations exist with regard to the specific phenotypic manifestations of hyperactivity symptoms. For adults, the perceived persistence of ADHD symptoms may hinge on the extent to which the behaviors are compatible with certain situational demands. For instance, an adult who works in an office which requires attending regular meetings may fidget, need multiple breaks, etc. On the other hand, that same adult, if employed in a less structured job (e.g., small business owner, salesman, theatrical performer, etc.), might not experience difficulties to the same degree due to the lack of situational demands even though the problems are objectively still present. Moreover, adolescents and adults with developed social skills may be better able to conceal the inappropriate hyperactivity. Hence, adolescents or adults with childhood ADHD may no longer manifest overt symptoms or meet clinical diagnostic criteria for hyperactivity/impulsivity, yet when required by situational demands to remain still and/or seated for extended periods of time, may experience discomfort and/or the desire to move.

#### Structural and Functional Brain Anomalies

Based in part on the early onset and chronicity of the disorder, brain anomalies have been posited to play a central role in the etiology of ADHD. This assumption has been supported by findings from brain imaging studies indicating anomalies in the fronto-subcortical (Castellanos et al., 2002) and fronto-striatal (Schneider et al., 2006) circuitry in ADHD probands. A meta-analysis conducted by Valera and colleagues (2006) suggested reduction in size in all four lobes of the cerebral cortex (Castellanos et al., 2002), caudate (Castellanos et al., 2002), and corpus callosum (Hill et al., 2003) in ADHD probands compared to normal controls. Similar findings

were also reported by Seidman and colleagues (2006), who reported decreased overall cortical gray matter and anterior cingulate cortex in ADHD adults compared to normal controls. Moreover, dysregulation in neuronal activity in the prefrontal cortex, cerebellum, dorsal part of the anterior cingulate, as well as basal ganglia and midbrain dopamine systems have been most frequently implicated in the pathophysiology of ADHD (Castellanos, 2001; Schneider et al., 2006; Zang, 2006; Zang, 2007). In sum, although neuroimaging studies have not yielded consistent findings, and have implicated anomalies throughout the brain, the primary focus of attention has been on fronto-striatal circuits that are believed to be involved in motor regulation and a wide array of higher-order cognitive functions (Schneider, 2006; Todd, 2001). Irregularity in neuronal activity in these circuits is assumed to mediate inattention and poor motor inhibition in ADHD probands (Faraone, 1998; Konrad et al., 2006; Todd & Botteron, 2001). A recent theoretical review by Halperin and Schulz (2006) further suggested that plasticity in these neuronal circuits is closely associated with recovery of ADHD-related symptomatology throughout neurodevelopment.

### Neurocognitive Deficits

Consistent with the neuroimaging data, a wide array of neurocognitive deficits, particularly impairments in inhibition, working memory, and state regulation, have been reported in individuals with ADHD as compared to normal controls (Castellanos et al., 2005; Castellanos & Tannock, 2002; Kuntsi et al., 2006). These impairments are usually measured by latency and accuracy on neuropsychological measures, and have been posited to be the core deficits of ADHD (Barkley, 1997; Castellanos & Tannock, 2002; Pennington et al., 1996; Schachar et al., 1995).

A meta-analysis conducted by Willcutt and colleagues (2005) reported significant group differences in neurocognitive functioning (i.e., response inhibition, working memory, set-shifting, and interference control) between ADHD probands and normal controls on 109 out of 168 (65%) comparisons, where probands performed significantly more poorly than normal controls. Effect sizes (the quantifiable magnitude of group effects) for all measures fell within the range considered to be medium in size (.43-.69). These authors reported the strongest and most consistent effects for measures of response inhibition, spatial working memory, and planning.

Response inhibition, which has been assessed using a variety of different measures, has been found to be deficient in children with ADHD (Casey et al., 1997; Durston et al 2006; Nigg 2001; Oosterlaan et al., 2005; Schachar et al., 2000; Vaidya et al., 1998). In particular, deficient response inhibition seems to be relatively specific to the children with ADHD as children with other disorders (e.g., CD, ODD, Learning Disabilities) did not differ significantly from normal controls on such measures (Pennington & Ozonoff, 1996; Schachar and Logan, 1990; Schachar et al., 2000; Schachar et al., 1995).

Despite some inconsistencies, children with ADHD also tend to show impairments in working memory, particularly spatial working memory, with an average effect size of 1.34 (Cohen et al., 2000; Martinussen & Tannock, 2006; McInnes, 2003; Westerberg et al., 2004; Williams et al., 2000). Although there are exceptions, some researchers have suggested that the working memory deficit is associated with ADHD and not comorbid ODD or CD (Oosterlaan et al., 2005).

State regulation, hypothesized by some investigators (Borger & van der Meere 2000) to be the key or core deficit in ADHD, is usually assessed by variability in latency to responding on

reaction time tasks (RT variability). Significantly greater variability in reaction times among ADHD children is suggestive of a lack of consistent effort in regulating one's cognitive energetic state to an optimal level to counteract a performance decrement (Oosterlaan and Sergeant 1996). In fact, deficiencies in state regulation may be among the most promising neurocognitive characteristics of ADHD, as measures of RT variability have been found to consistently and uniquely differentiate ADHD probands. In particular, ADHD probands have been shown to demonstrate slower and more variable reaction times as compared to normal control children and those with other disorders (Borger & van der Meere 2000; Castellanos et al., 2005; Kuntsi et al., 2001; Wiersema et al., 2005).

In summary, findings from the extant literature suggest that children with ADHD are quite heterogeneous and present with a wide array of neuropsychological deficits. While the literature has focused to a large degree on executive functions, recent meta analyses suggest that effect sizes for these deficits are mostly in the moderate range and are probably insufficient to account for all or even most of the variance in ADHD. However, some more narrowly defined areas - in particular, deficits in inhibitory control, working memory, and state regulation - appear to be among the most consistently reported differences. Hence, neurocognitive probes comprised of measures that assess these cognitive functions may enable specification of the clinical utility.

### **Etiology of ADHD**

Although the precise cause remains unknown, as discussed above, variable phenotypic expression and comorbidity with other psychological conditions suggest that the etiology of ADHD is likely multi-factorial. Data from behavioral genetic studies indicate high prevalence

rates of the disorder among biological first-degree relatives of individuals with ADHD and higher concordance for the disorder among monozygotic vs. dizygotic twins. These findings suggest that ADHD is, to a substantial degree, genetically mediated (see below); however, such data do not indicate which specific trait(s) is/are genetically transmitted. Although, high heritability of the disorder has prompted investigators to search for genes that are associated with ADHD (see below), the field is still far away from clearly identifying the responsible genes. Data from behavioral and molecular genetic studies are discussed below.

### **Behavioral Genetics**

The behavioral genetic approach studies the determinants of a particular behavior/phenotype by investigating the extent to which it is attributable to a set of common genetic material. This method typically involves comparing the concordance rate of the behavior of interest between the child and family members, between adopted and biological family members, and/or between twin pairs. If the concordance rate is high among individuals who share more genetic material (e.g., monozygotic twins or biological relatives) compared to individuals who share less genes (e.g., dizygotic twins or adoptive relatives), it can be inferred that the behavior of interest is genetically linked. Behavior genetic approaches quantify three major factors that influence behavior (Hay et al., 2001):

- 1) Genetic effects - genetic influence can be due to either additive or dominance genetic factors. When several alleles at different gene loci act in an additive manner to influence the behavior it is known as additive genetic influence. On the other hand, behavior influenced by either a single gene or set of dominant genes is referred to as a dominance genetic effect. Usually, the behavior genetic approach is used to examine complex

genetic phenotypes which are presumed to be determined at least in part via additive genetic effects.

- 2) Shared environmental effects- environmental factors such as parenting style, family stress, social status, and/or conflict that influences everybody in a family in a similar manner are known as shared environmental factors. Influence of these factors makes the experience of members of one family different from the members of another family.
- 3) Non-shared environmental effects - environmental factors such as prenatal events and psychosocial interactions outside of the home and family environments are considered to be non-shared environmental factors. Non-shared environmental factors are unique to an individual and make the experience of that individual different from other members of the same family.

The role of genetic influences in the etiology of ADHD, as indicated by family (Biederman et al., 1992; Biederman et al., 1995; Biederman et al., 2002; Gothelf et al., 2004; Smalley, 2000), twin (Eaves et al., 1997; Goodman & Stevenson, 1989; Hudziak et al., 2000; Martin et al., 2002; Nadder et al., 1998; Price et al., 2005; Rietveld et al., 2003a; Rietveld et al., 2004; Sherman et al., 1997; Thapar et al., 2000; Todd et al., 2001; Willcutt et al., 2000a), adoption (Cantwell, 1975; Morrison & Stewart 1973; Alberts-Corush et al., 1986; Sprich et al., 2000), and segregation studies (Morrison & Stewart, 1974; Faraone et al., 1992), as well as the genome project, have gained enormous attention in recent years because of the high prevalence of the disorder among family members of children with ADHD.

### Family Studies

This approach examines the reoccurrence of disorders among family members. Members of a family share genetic materials with each other to varying degrees depending on their relationships. The closer the relation, the more genetic material shared. For example, first degree relatives (i.e., parents and offspring or siblings) share, on average, 50% of their genetic material. The more distant the relation, the less genetic material shared. Hence, frequent recurrence of a disorder or phenotype among close vs. distant relatives may be attributable to the genes.

*Findings from Family Studies:* As compared to controls, elevated rates of the Attention Deficit Disorder (ADD) (25% - 31%) and ADHD (16%) have been documented in relatives of children with ADD (Biederman et al., 1986 & 1990) and ADHD (Biederman et al., 1992), respectively. Biederman and colleagues (1995) found that, in a sample of 84 parents with clinically diagnosed childhood-onset ADHD, 57% of their biological children met criteria for the disorder. These investigators (Biederman et al., 2002) further showed that parental ADHD served as a risk factor for their children regardless of whether the parent's ADHD symptoms persisted or remitted later in life. There was a significant increase in prevalence of ADHD among children of persisted-ADHD parents (38%) and remitted-ADHD parents (40%) compared to that of non-ADHD parents (11%). There was no significant difference in the prevalence rate of ADHD among children of persisted-ADHD and remitted-ADHD parents. These findings indicate that it is not active ADHD symptoms in the parents, but rather whether they ever had the disorder that affects risk in their offspring.

Gender Differences and Genetics     While the reason for gender differences in the prevalence of ADHD remains unknown, it has been hypothesized that the disorder has different

threshold levels for boys and girls. Some investigators reported that the threshold (or loading) for girls to manifest the disorder is higher than that is required for boys (Rhee et al., 1999; Rhee & Waldman, 2004). Hence, according to this hypothesis, the disorder is less prevalent in girls compared to boys but should be comparatively more prevalent in relatives of girls with ADHD. Some investigators (e.g., Pauls et al., 1983; Smalley, 2000) have provided support for this hypothesis, but others (e.g., Faraone et al., 2000; James and Taylor, 1990; Kuntsi et al., 2005; Rietveld et al., 2003a) have not. Smalley (2000), comparing affected sibling pairs (ASP) with their parents, reported that the frequency of ADHD in parents was higher in families with at least one girl ADHD proband than in families with all boy probands (63% vs. 45%). The author defined ASP as at least one sibling in a pair having met full DSM-IV criteria for ADHD and the other one either meeting full criteria or falling one symptom short of diagnostic criteria. Based on this finding it was suggested that girls require a greater loading of familial influence to develop the disorder relative to boys. However, the frequency of the disorder did not vary based on parent's gender, which suggests that ADHD is not mediated by an X-linked recessive gene. Conversely, Faraone and colleagues (2000) reported no such differences in the prevalence of the disorder. They found a significantly higher prevalence of ADHD and other comorbid disorders (e.g., mood, anxiety, substance use) among the relatives of ADHD probands than among relatives of normal controls regardless of the probands' gender. Based on these data the authors suggested that proband gender does not influence the prevalence of ADHD among relatives.

Comorbidity and Genetics Notably, significantly higher rates of ODD, CD (Biederman, 1986; Smalley, 2000), reading disability (Willcutt et al, 2000), and affective disorders (Biederman et al., 1987; Smalley, 2000; Sprich, 2000) have been evident in biological relatives of ADHD probands compared to relative of normal controls. Smalley (2000) reported

high rates of comorbid disruptive behavior disorders (ODD without CD = 40%; ODD + CD = 20%) among family members of ASP (defined above). She found a significant increase in the prevalence of CD or antisocial personality disorder among fathers of ASP with CD (36%) (only 5% mothers had CD) as compared to fathers of ASP without CD (13%). In addition, among ADHD+CD ASP, 73% of their fathers had ADHD+CD/Antisocial Personality Disorder and 10% had only CD/Antisocial Personality Disorder.

Similar findings were reported in a sample of patients with Velocardiofacial syndrome (VCFS), a neurodevelopmental disorder caused by microdeletion of 22q11 (Gothelf et al., 2004). The most common comorbid condition in patients with VCFS is ADHD, with a prevalence rate of 35-55% (Gothelf et al., 2003). These investigators (Gothelf et al., 2004) showed that patients with VCFS + ADHD had significantly higher rates of ADHD in first degree relatives irrespective of their perinatal and/or developmental history and psychiatric comorbidity, compared to patients without ADHD comorbidity (12% vs. 2.2%). This high degree of associated disorders in ADHD probands and their families further suggests that similar sets of genes that are associated with ADHD may also influence comorbid disorders.

### Summary of Family Study Findings

Table 1 below summarizes the results of family studies of ADHD. Although, findings from family studies suggest that ADHD is highly concordant between children and first degree relatives, it is difficult to conclude whether the familial resemblances are due to genetic or environmental factors as they share both. To disentangle genetic and environmental effects, twin and adoption paradigms are necessary.

Table 1  
Summary of Family Study

Authors	Prevalence assessed in	Prevalence Rate		Measures
		Proband	vs. Control	
Biederman et al., 1986	Relatives of ADD children and controls	31.5%	5.7%	DICA-P
Biederman et al., 1992	Relatives of ADHD children and controls	16%	3%	K-SADS-E, CTRS
Biederman et al., 1995	Children of parents with childhood-onset ADHD	57%	18%	K-SADS-PL
Smalley, 2000	Affected Sibling Pairs and their parents	55%	n/a	K-SADS-PL
Biederman et al., 2002	Children of parents with remitted/persisted ADHD	40% / 38%	11%	K-SADS-E
Gothelf et al., 2004	Relatives of children with VCFS + ADHD	12%	2.2%	K-SADS-PL, CTRS

### *Twin Studies*

Among behavioral genetic approaches, the most powerful and frequently embraced approach is the twin paradigm, in which the behaviors/phenotypes of monozygotic (MZ) twins are compared with those of dizygotic (DZ) twins. MZ twins develop when, soon after fertilization, the egg splits into two halves; hence, the resulting twins are exactly same in their genetic makeup (100% similar genetically). On the other hand, DZ twins are developed when two separate eggs are fertilized by two separate sperm; hence, genetically they are no more similar than any two singleton siblings (on average 50% similar genetically). The correlation of a behavior of interest between a given twin and their co-twin is known as the concordance rate, which is expected to be higher in MZ than in DZ twins for a genetically influenced trait. Although the twin paradigm has many advantages, the biggest pitfall of this approach is that MZ twins may be perceived and treated by parents, teachers, and other informants as more similar than DZ twins based on their physical similarities rather than genetic similarities. When rating MZ twins, mothers tend to exhibit rater bias effects (e.g., contrast effect) more often than

teachers (Sherman et al., 1997). Contrast effects occur when parents [presumably] subconsciously set one twin as the standard by which they rate the behavior of the co-twin on a rating scale. As a result, differences are accentuated. Another important limitation is that, while it is erroneously assumed that the only difference between MZ and DZ twins is the degree of genetic overlap, they may differ in other aspects (e.g., environmental influence, individual difference, gender difference, etc.).

*Assessment of genetic effect:* Since twin pairs, irrespective of zygosity, generally share similar environments but different degrees of genetic similarity (MZ share 100%; DZ share 50%); the basic assumption in twin paradigms is that the environment is equivalent for both MZ and DZ twin pairs (Plomin, 1994). Hence, any difference in the inter-twin concordance (MZ versus DZ) on the behavior of interest can be attributed to the difference in genetic influence. The proportion of phenotypic variability accounted for by genetic influence is known as “heritability” (Plomin, 1994). Heritability can be estimated by doubling the difference between MZ and DZ concordance rate. Since MZ and DZ share 100% and 50% genetic similarity, respectively, the difference between their correlation (MZ and DZ) represents only half of the genetic variance (Plomin, 1994). Therefore, to estimate the complete variance (heritability), this difference in concordance needs to be doubled. For example, if the concordance between MZ twin pairs is .65 and the concordance between DZ twin pairs is .35 for a phenotype, then the heritability of that phenotype is  $(.65 - .35) \times 2 = .60$ . A heritability of .60 means that 60% of the observed variability for that particular phenotype among individuals is due to genetic factors, whereas the rest of the variability (40% of the variance in this example) is due to non-genetic influences plus measurement error.

*Assessment of shared environmental effect:* In twin studies, the shared environmental effect is estimated by taking the difference between the MZ correlation and the heritability of a phenotype (Plomin, 1994; 2000). The assumption here is that since MZ twins are 100% alike genetically and live in the same environment, the phenotypic variance that cannot be accounted by genetic variance must be due to the shared environment. For example, if the MZ correlation of a phenotype is .60 and the heritability is .50 (i.e., the DZ correlation was .35), the difference between genotype and heritability, which is .10, is inferred to be due to shared environmental effect.

*Assessment of non-shared environmental effect:* The estimate of non-shared environmental effects is the variance that cannot be explained by genetic or shared environmental variance. In twin studies, it is estimated by subtracting the MZ correlation from 1. Since MZ twins are genetically identical and live in the same environment, any difference between the MZ pairs is assumed to be due to non-shared environmental effects plus measurement error (Plomin, 1994). For example, if the MZ correlation for a phenotype is .60, the estimate of non-shared environmental effect plus measurement error is  $1 - .60 = .40$ . Measurement error in assessing non-shared environmental effect entails the individual variability and questionable reliability of used measures. Since behavior genetic methods oftentimes rely on rating scales, which are highly subjective and susceptible to bias (e.g., viewing MZ twins as more phenotypically similar than they actually are or subconsciously treating adoptive siblings differently due to lack of familial resemblance), the reliability of these measures is oftentimes far from perfect.

*Findings from Twin Studies:* Even though concordance rates vary from study to study, twin paradigms have generally concluded that approximately 60 to 85% of the variance of ADHD is

accounted for by genes (Coolidge et al., 2000; Eaves et al., 1997; Edelbrock et al., 1995; Gjone et al., 1996; Nadder et al., 1998; Price et al., 2005; Rhee et al., 1999; Rietveld et al., 2003a; Rietveld et al., 2003b; Rutter et al., 1999). Using both categorical diagnostic (Gillis et al., 1992; Stevenson, 1992) and dimensional approaches (Coolidge et al., 2000; Gjone et al., 1996; Price et al., 2005; Rietveld et al., 2003a; Sherman et al., 1997; Thapar et al., 2000) based on questionnaire-derived symptom scores, investigators have consistently found higher concordance rates between MZ vs. DZ twin pairs, and higher variance among DZ relatives to MZ twin pairs.

Rietveld and colleagues (2003a), using a cross-sectional paradigm, investigated the heritability of overactivity (OA) in three-year-old twin pairs, and attention problems (AP) in seven, ten, and twelve-year-old twin pairs. They obtained maternal ratings on the Child Behavior Checklist (CBCL) and used a T-score of 67 as a diagnostic cut-off. Overall, the concordance rate for MZ twins was higher (.63 - .75) than for DZ twins (.07-.31). Furthermore, at each age the concordance rate between MZ twins was much higher than that for DZ twins with respect to OA and AP. The concordance rate between MZ twin pairs was .63 at age 3; .68 to .70 at age 7; .70 at age 10; .75 to .70 at age 12. In contrast, the concordance rate between DZ twin pairs was .08 to .07 at age 3; .15 to .23 at age 7; .20 to .30 at age 10; and .25 to .31 at age 12. Since twin pairs are presumed to share the same environment, but MZ twins share more genetic influence than DZ twins, the investigators concluded that the increased familial resemblance between MZ twin pairs was more likely to be due to genetic influence (68% - 76%) than shared environmental influence. Furthermore, the concordance between DZ twins was less than half of that for MZ twins, which suggests the presence of a contrast effect. Data from this study indicated that the contrast effect decreased with age, as evident by increases in correlational strength among DZ twin pairs.

The remaining variance that could not be explained by genetic influence and shared environmental effects (which were negligible) was assumed to be due to the non-shared environmental effects and measurement error (e.g., contrast effect, reliability of the measure). As discussed earlier, this is calculated by subtracting the MZ correlation from 1. Using this calculation, the investigators estimated that approximately one third of the total variance for OA and AP is accounted for by non-shared environmental effects.

Gender Difference and Genetics In the above study (Reitveld et al., 2003a) the authors did not find significant differences in the concordance rate of the disorder between males and females and suggested no gender difference in the heritability of the disorder. Similarly, Kuntsi and colleagues (2005), using a twin paradigm, reported no gender difference in the heritability of ADHD, as the correlation of heritability estimate for boy and girl twin pairs was similar even when the same-sex DZ and opposite-sex DZ twin pairs were compared.

Symptom Stability and Heritability Rietveld and colleagues (2003a), investigating the heritability of overactivity in three-year-old twin pairs, and attention problems in seven, ten, and twelve-year-old twin pairs, found higher concordance rates between MZ twin pairs at each age compared to that for DZ twin pairs. Based on this finding, the authors inferred that genetic influences are important for the stability of these phenotypes. However, due to the cross-sectional nature of this study, this conclusion must be viewed cautiously.

Later, analyzing the same data in a longitudinal fashion, Rietveld and colleagues (2004) again found substantially higher concordance rates among MZ vs. DZ twins at all ages and genders. The concordance rates between MZ twin pairs and DZ twin pairs were .66 (MZ) and .13 (DZ) at age 3, .71 (MZ) and .28 (DZ) at age 7, .72 (MZ) and .28 (DZ) at age 10, and .72 (MZ) and .26 (DZ) at age 12. Their conclusions were similar to that derived from cross-sectional

analyses, in that genetic influence was deemed important (heritability = 70 %-75%) for the development, manifestation, and stability of OA and AP. They further emphasized that, although dominance genetic influence is important for etiology, the additive genetic influence may contribute more to the stability of OA and AP. In this longitudinal analysis, the contrast effect decreased with age, raising the speculation that, as parents are exposed to behavior of other children over time, they increase their frame of reference and are less likely to compare one twin with his/her co-twin, and instead rate each twin independently relative to norms.

Further exploring the genetic influence in the stability and change in ADHD symptomatology, Gjone and colleagues (1996), investigating a sample of Norwegian same-sex twin pairs, reported higher correlations among 5-9 year-old MZ twins (male = .72, female = .76) than 5-9 year-old DZ twins (male = .21, female = .23) with respect to attention problems as measured by the CBCL. These investigators also reported a similar pattern of correlations among 12 to 15-year-old twin pairs (MZ male = .78, female = .73; DZ male = .45, female = .33). The estimated heritability for 5-9-year-olds was .73 in boys and .76 in girls with no significant gender difference. They also found that this heritability estimate remained irrespective of symptom severity. In addition, the correlations among MZ twins were stable and higher than those of DZ twins independent of age, which suggests that the symptoms are stable and genetically mediated. Similar to the finding of Rietveld and colleagues (2003a; 2004), in this study the correlation among DZ pairs also increased with age, which suggests a decrease in the dominance genetic effect and/or contrast effect.

Kuntsi and colleagues (2005), in a longitudinal twin study (ages 2, 3, 4, 7, and 8 years), concluded that genes (72%) as well as shared (14%) and non-shared (14%) environmental influences are important to the manifestations of ADHD. In addition, they assessed genetic and

environmental contributions to the stability of the disorder. These authors compared the behavior of one twin at one age with the behavior of their co-twin at another age and suggested that, if this phenotypic correlation across age remains higher among MZ twins than that of DZ twins, such a pattern would indicate that the stability of the phenotype is genetically mediated. The investigators found the symptoms were moderately stable in MZ twins (phenotypic correlation across age: range = .27-.58) from 2 to 8 years-old. They concluded that the stability of symptoms was mainly due to genetic contributions (59-96%) and non-shared environmental influence (4-41%). Similar to other investigators (Gjone et al., 1996; Rietveld et al., 2003a; Rietveld et al., 2004) these authors also found that contrast effects decrease with age as parents increase their frame of reference.

In a 5-year longitudinal twin study incorporating 8-9 year old Swedish children, Larsson and colleagues (2004) showed that the majority of children continued to meet DSM-III-R criteria at a 5-year follow-up. They found that, at follow-up, the intra-twin correlation remained stable and higher among MZ vs. DZ twins. In addition, there was an equally robust correlation for both boys ( $r=.51$ ;  $p<.001$ ) and girls ( $r=.51$ ;  $p<.001$ ) between baseline and follow-up symptoms. These findings suggest that ADHD is stable and that this stability is mostly due to genetic influences (higher and stable correlation among MZ vs. DZ). Using structural equation modeling, the authors showed that genes, and to a lesser extent, non-shared environmental influences, accounted for stability of the disorder. Although the analysis seemed to indicate that shared-environmental factors play an important role in childhood, the authors indicated that this might be a chance finding, or that the effect of shared environment might decrease with age due to developmental changes. Similarly, Price and colleagues (2005), in a longitudinal study of preschoolers (ages 2, 3, and 4), showed that ADHD symptoms were moderately stable over time

and that this stability was 91% genetically mediated. Further, in studying genetic and environmental contributions to the stability of ADHD and comorbid conditions (ODD/CD), Nadder and colleagues (2002) showed that the covariation of ADHD and ODD/CD across informants and over time was mainly due to genetic factors and not environmental factors. Hence, the overlapping genetic factors seem to contribute to the comorbidity of ADHD and ODD/CD.

Heritability of ADHD Subtypes Several investigators have explored the heritability of ADHD subtypes (Inattentive, Hyperactive-Impulsive, and Combined). Sherman and colleagues (1997) found Inattentive and Hyperactive-Impulsive subtypes were highly heritable in 11 to 12 year-old twin boys by both mother and teacher report. Nonetheless, in this study, the heritability estimate was higher based on mother report (Inattention .69; Impulsivity-Hyperactivity = .91) than by teacher report (Inattention .39; Impulsivity-Hyperactivity = .69). This was perhaps due to the rater bias and contrast effect, as the correlation among MZ twins (.70-.92) was 2 ½ to 3 times higher than that for DZ twins (.30-.32) twin pairs on mother reports. Conversely, rater bias was not observed in teacher ratings as no significant systematic difference was found between twin pairs rated by the same teacher and by different teachers.

Environmental contributions to the heritability of ADHD subtypes in this study were inconsistent, and the data did not provide support for non-shared environmental effects except for teacher reports on the Predominantly Inattentive Type (.39). These authors further investigated cross-twin correlations on inattention and hyperactivity/impulsivity dimensions. The rating of inattention for one twin was compared with the ratings of hyperactivity-impulsivity of the co-twin and was found to be more robustly correlated among MZ (.50 - .53) vs DZ twins (.22-.40). The higher concordance among MZ vs. DZ twins indicates that inattention and

impulsivity-hyperactivity may be mediated by common genetic factors. High heritability for hyperactive/impulsive (89%) and inattentive dimensions (90%) were also found in a sample of female twin pairs (Hudziak et al., 1998). Levy and colleagues (1997) suggested that the Predominantly Hyperactive-Impulsive Type, but not the Predominantly Inattentive Type, "breeds true." Although the findings are still inconsistent regarding which subtype is more heritable, unlike the findings from family studies, data from twin studies indicate major genetic contributions to the transmission of subtypes.

To resolve the question of whether ADHD subtypes cluster exclusively in families, Todd and colleagues (2001) used latent class analysis on adolescent (13-23 years-old) female twins and assessed the heritability of ADHD subtypes. This approach categorized groups of symptoms into 'classes' based on discrete symptom profiles. The authors generated nine classes (e.g., mild inattentive, severe inattentive etc.). The authors separately assessed the concordance rate of DSM-IV ADHD subtypes and latent class ADHD subtypes between MZ and DZ twin pairs. For DSM-IV ADHD subtypes, the concordance for same subtype among MZ twin pairs was 75%. That is, 75% of the time the co-twin of an affected MZ twin had the same subtype. For instance, in MZ twin pairs if one twin had the Predominantly Inattentive Type the co-twins were significantly more likely to have the Predominantly Inattentive or Combined subtypes but not the Predominantly Hyperactive-Impulsive Type. The co-twins of MZ twins with Combined subtypes were significantly more likely to have Combined and Predominantly Inattentive subtypes but not the Predominantly Hyperactive-Impulsive subtype. Conversely, if MZ twins had the Predominantly Hyperactive/Impulsive subtype, the co-twins were significantly more likely to have the Predominantly Hyperactive-Impulsive Type than any other subtypes. DZ twins did not tend to have same subtype except for the Predominantly Inattentive Type. These

results suggest a lack of familial specificity in ADHD subtypes for Predominantly Inattentive and Combined subtypes and indicate that only the Predominantly Hyperactive/Impulsive DSM-IV subtype breeds true.

When Todd and colleagues compared twin pairs in same and cross-latent class ADHD subtypes, they found the prevalence of being in the same class was high for both MZ (63-90%) and DZ (12-72%) twin pairs. In addition, there was no significant association of twins being in cross-class. These findings suggest high familial specificity in latent class ADHD subtypes.

To further investigate the extent of genetic contribution to the difference in familial specificity in subtypes between DSM-IV and latent class approaches, the authors compared the frequency of MZ vs. DZ twin pairs in all possible same- and cross-DSM-IV and latent classes. The results indicated that all latent classes were purely genetic subtypes, as a high frequency of MZ appeared in the same classes but not across classes. However, Predominantly Inattentive and Combined DSM-IV subtypes did not seem to be purely genetic as there was a large frequency of cross subtypes for twin pairs.

Symptom Pervasiveness and Heritability Thapar and colleagues (2000) used a twin design to investigate whether greater cross-situationality of symptoms was associated with increased heritability of ADHD. Using the DuPaul ADHD Rating Scale (DuPaul, 1998), school-age children were classified as meeting ADHD criteria based on parent ratings only, teacher ratings only, or by both (pervasive) informants. Heritability estimates were higher for parent-rated ADHD probands (.80) than for teacher-rated ADHD probands (.50). However, the heritability estimate for pervasive probands (.79) was not any greater than that for parent-rated probands. This finding suggests that the genetic contribution does not vary as a function of the pervasiveness of the disorder. However, similar to Sherman and colleagues (1997), these

investigators found that, based upon teacher ratings, shared environmental effects (.36) were more important than non-shared environmental effects (.14). The non-shared environmental influence accounted for most of the environmental contribution in parent-rated probands (.20) and pervasive probands (.21).

Similarly, Martin and colleagues (2002) reported high heritability (70-81%) of ADHD symptoms in 5-16 year-old twins for both parent and teacher ratings; however, the parent rating estimated higher heritability due to a possible contrast effect. Consistent with the abovementioned studies, here the authors also found the shared environmental influence was important in teacher ratings.

Summary of Twin Study Findings Consistently higher concordance rates among MZ vs. DZ twin pairs indicate that ADHD is genetically mediated; however, the results do not deny the importance of environmental influences. Table 2 below summarizes the results of twin studies of ADHD.

Table 2  
Summary of Twin Study

Authors	Concordance	Heritability	Shared-env	Non-shared	Measures
Gjone et al., 1996	MZ = .73 DZ = .22	73- 76%	negligible	27%	CBCL
Levy et al., 1997	MZ = .82-.88 DZ = .37-.48	75-91%	13%	18-12%	ADHD-RS- DSM-III, DISC
Sherman et al., 1997	MZ = .69-.92 DZ = .30-.57	39-91%	0-39%	.9 – 31%	TRF, DICA- R
Hudziak et al., 2000	MZ = .66-.69 DZ = .20-.26	60-76%	n/a	31-40	CBCL
Thapar et al., 2000	MZ = .52-.69 DZ = .28-.52	50-80%	0-36%	14-21%	DuPaul ADHD-RS
Todd et al., 2001	MZ = .68 DZ = .22	n/a	n/a	n/a	Latent class, ADHD-RS
Martin et al., 2002	MZ = .55-.81 DZ = -.04-.38	70-81%	0-63%	40-59%	Conners, SDQ
Nadder et al., 2002	Time1: MZ = .21-.62 DZ = 0-.37 Time 2: MZ = .05-.63 DZ = .03-.36	Time1: 46-73% Time 2: 27-95%	n/a	Time 1: 19.2-62% Time 2: 4.4-72.6%	CAPA, Conner's
Rietveld et al., 2003a	MZ = .69 DZ = .17	68 - 76%	negligible	30%	CBCL
Rietveld et al., 2004	MZ = DZ =	70-75%	negligible	25%	CBCL
Larsson et al., 2004	Baseline: MZ =.73-.80 DZ =.44-.57 F-up: MZ =.63-.74 DZ =.26 -.39	Baseline: 35-68% F-up: 61-74%	Baseline: 12-40% F-up: negligible	Baseline: 19-25% F-up: 26-39%	ADHD-RS
Price et al., 2005	MZ = .54-.69 DZ = .03-.21	78-81%	n/a	.19-.22	RPSPC-R,
Kuntsi et al., 2005	MZ = .86 DZ = .47-.49	72%	14%	14%	RPSPC-R, CPRS-R

### Adoption Studies

This paradigm studies behaviors of children who were separated from their biological parents at birth and adopted by another family. Here the behaviors/phenotypes of interest in

adopted children are compared with those of their biological parents (or siblings) as well as in adoptive parents (or siblings). The assumption is that if the determinants of the behaviors have a genetic component, then the adopted child would resemble his/her biological parents (or siblings) more so than the adoptive parents (or siblings). On the other hand, if the determinants of the behaviors have little or no genetic component, the adoptive child would resemble his/her adoptive parents (or siblings), as the adopted child shares the environment but not genes with their adoptive parents (or siblings).

*Assessment of genetic effects:* Since children share genes with their biological parents (or siblings) and share an environment with their adoptive parents (or siblings), adoption study paradigms allow for an excellent means by which to isolate genetic effects from environmental effects. In adoption studies, heritability can be estimated by doubling the correlation of biological first degree relatives because they share 50% of the genetic influence, but no shared environmental influence (Plomin, 1994).

*Assessment of shared environmental effects:* In adoption studies, the estimate of shared environmental effect is assessed by examining the correlation between biologically unrelated adoptive siblings. The adoptive siblings are genetically unrelated so the familial resemblance between them must be due to the shared environment. For example, if the correlation of a phenotype between adopted siblings is .10, the shared environmental effect is 10%.

*Assessment of non-shared environmental effects:* As is the case with twin studies, non-shared environmental effects are estimated by subtracting the sum of heritability and shared environmental effects from 1.0. However, this value represents both non-shared environmental effects as well as error.

*Findings from Adoption Studies:* Evidence derived from the relatively few adoption studies conducted show elevated rates of ADHD among the biological parents of ADHD probands but not their adopted parents (Alberts-Corush et al., 1986; Cantwell, 1975; Morrison & Stewart 1973; Van den Oord et al., 1994; Sprich et al., 2000). Morrison & Stewart (1973) and Cantwell (1975) found higher rates of hyperactivity in biological relatives of hyperactive probands than in the adoptive relatives of hyperactive probands. These investigators also found a higher prevalence of hyperactivity among the biological relatives of hyperactive probands than in biological relatives of normal controls. Similarly, biological parents of hyperactive children were found to exhibit more attentional difficulties than parents of normal children (Alberts-Corush et al., 1986). These data suggest a strong familial association between hyperactivity and inattention of children and attention problems in their biological parents. Significantly high concordance between adoptive children and their biological parents was also observed on the Attention Problem Index of the Children Behavior Checklist (van den Oord et al., 1994).

Sprich and colleagues (2000) compared the prevalence of ADHD in (adoptive) families of adopted ADHD probands, non-adoptive ADHD probands, and normal controls. The adopted children in this sample were adopted within the first year of their life by families of the same ethnicity. The investigators assessed the rate of behavior disorders (i.e., ADHD and ODD) and affective disorders in the first-degree adoptive relatives of adopted probands with ADHD. The authors compared this prevalence rate with those of first-degree biological relatives of non-adopted ADHD probands. Further they compared the prevalence rate of ADHD in first-degree relatives of non-adopted controls. They found the rate of ADHD in adoptive families of adopted probands was low and did not differ from the rate of ADHD in the biological parents of normal control children. However, there was a significantly increased rate of ADHD in the biological

parents of non-adopted probands, which suggests a genetic pattern of the disorder. These authors also found a higher frequency of affective and comorbid behavioral disorders in biological relatives of non-adopted ADHD probands compared to that of adopted relatives of adoptee probands and biological relatives of normal controls. These findings indicate that the comorbid psychiatric conditions among biological relatives of ADHD probands are genetically mediated. Based on these findings the authors concluded that psychiatric disorders among relatives in a family with an ADHD proband is not caused by the environmental and psychological adversity of raising a child with ADHD; rather it is likely attributable to the variable manifestations of the genes that influence ADHD. They also speculated that some non-genetic factors in the biological parents of adoptees such as impulsivity, which could conceivably give rise to early pregnancy or maternal smoking during pregnancy, may constitute increased risk factors.

Summary of Adoption Study Findings Significantly higher rates of ADHD among family members where genetic material is shared (biological parents) as compared to those where genetic material is not shared (adoptive parents) indicates that ADHD is genetically mediated.

#### Summary of Behavioral Genetics Findings

Despite a number of methodological limitations (e.g., inconsistency in the definition of the disorder, use of subjective rating scales), the findings from behavioral genetic studies, using family, twin, and adoption paradigms, provide compelling evidence for a genetic contribution to the development, manifestation, and stability of ADHD (diagnosis and symptoms) across age, gender, and geographical locations. However, less than 100% concordance between MZ twins indicates reduced penetrance or etiological heterogeneity of the disorder. As such, these findings not only suggest that genes play an important role in mediating the susceptibility to ADHD, but

also provide the strongest evidence for environmental roles in this psychopathology (Plomin, 1994; 2001). It is possible that genes influence the susceptibility to the disorder, while the expression of the phenotype perhaps depends, at least in part, on shared and non-shared environmental risk factors.

### Shared Environmental Effects

Data derived from correlational research suggests that a large number of adverse environmental factors such as family dysfunction, stress, family conflict (DuPaul et al., 2001; Biederman et al., 1995), disrupted parent-child interactions, parental misattributions about childhood behavior, and poor parenting practices (Shelton et al., 1998) are seen more in families of children with ADHD compared to families of children without ADHD. Increased family conflicts and stressful environments are reported in families with ADHD children compared to families of non-ADHD children (DuPaul et al., 2001; Gadow et al., 2000). Parents of children with ADHD seem to have increased marital conflict compared to parents of non-ADHD children (Murphy & Barkley, 1996; Shelton et al., 1998). Poor parenting style (Shelton et al., 1998), especially use of less authoritative style (Hinshaw et al., 1997), was more frequently observed in parents of children with ADHD relative to parents of normal control children. DuPaul and colleagues (2001) indicated that parents of children with ADHD tend to use more punitive punishments and fewer reinforcements. Lack of parental involvement such as maternal non-responsiveness seems to predict ADHD characteristics in young children (Carlson et al., 1995).

Taken together these correlational findings suggest an association between psychosocial adversity and ADHD. However, the direction of the cause-and-effect as to whether the family dysfunction leads to ADHD or having ADHD children causes family dysfunction, or whether some other factors (e.g., genes) cause both remains unresolved. Nonetheless, replication of these

correlational findings with more genetically sensitive paradigms (i.e., adoption or twin studies), which allow for a better separation between gene and environment, show little or no significant relationship between psychosocial adversity that is shared among children in a family and manifestation of the disorder. Alternatively findings from twin and adoption studies, as described earlier, suggest that the etiology of ADHD is mostly accounted for by genes and the non-shared environmental effect; the shared environmental effect is considered to be negligible. Hence, though correlational studies provide strong associations between shared psychosocial adversities and ADHD, these factors are perhaps crucial for general psychological development of children and not specific to ADHD per se.

#### *Non-Shared Environmental Effects*

Several researchers (Plomin, 1994; Rutter, 1997; Rietveld, 2003b) have expressed more interest in what makes children from the same family different from each other than what makes them similar. These investigators believe the unique environmental experiences (e.g., differential parental affection, pre- and perinatal factors, friends/peer relationships) that they do not necessarily share with the rest of the family members are relatively more crucial in the manifestation of ADHD than shared environmental factors. According to Plomin (1994), shared environmental factors can have different effects on different children in a family because of the individual differences that exists between siblings. As discussed above, this assumption has been supported by many twin studies where, after accounting for genetic influences, the remaining variability was assumed to be accounted for largely by non-shared environmental factors (Coolidge et al., 2000; Gjone et al., 1996; Rietveld et al., 2003a; Sherman et al., 1997). Further, the effects of shared environmental factors seem to decline with age, and non-shared environmental factors seem to have a larger influence during adolescence than in childhood

(Larsson et al., 2004). This is true perhaps because adolescents tend to extend their social interactions beyond what is defined and influenced by parents and become more influenced by these unique environmental factors.

#### Gene-Environment Interaction Effects

Many researchers have speculated that genes influence susceptibility to the disorder, but expression of the phenotype perhaps depends on environmental risk factors. Therefore, it is neither genes alone nor environmental risk factors alone that exert their effects independently; rather they function in conjunction with each other. Season of birth, one such environmental factor (though unspecific) seems to interact with genetic predisposition. Children with the DRD4 7R allele, a candidate gene for ADHD, who were born in the spring and summer, seemed to have a 2.8 fold increased risk of hyperkinetic disorder (HD) (Seeger et al., 2004). Conversely, children with the DRD4 7R and born in autumn and winter, had a 5.4 fold decreased risk (Seeger et al., 2004). These authors found that neither the season of birth alone nor the presence of the DRD4 7R allele posed a risk, but the combination of the two increased the risk. It is possible that the genetic predisposition perhaps makes the child vulnerable to the disorder and the environmental factors provide a means for expressing the difficulties.

Rietveld and colleagues (2004) speculated that, in school, where there are more distractions and disciplinary rules, children with ADHD traits fail to meet such demands, which escalates their behavioral difficulties. They supported their speculation by showing increases in attentional problems in boys at 7 to 10-years of age. Nevertheless, in some extreme cases, harsh environmental factors can play a major role in the expression of the disorder even in the absence of the genetic predisposition, or the genetic predisposition can down regulate the optimum environmental effect and allow the expression of the disorder.

## **Molecular Genetics**

Behavioral genetic data provide compelling evidence that ADHD is genetically mediated, but the precise genetic transmission that influences development of ADHD still remains unknown. To identify the suspected gene(s), and find associated markers for susceptibility requires investigation at the molecular level. Hence findings from behavioral genetic studies actually set the stage for molecular genetic research.

In an attempt to localize the chromosomal region that might harbor ADHD susceptible genes, genome-wide linkage scans have been conducted; however, the findings are inconclusive. Conversely, research involving several dopamine- and serotonin-related candidate genes provides substantial evidence for a contribution of these genes to the etiology of ADHD. In particular, the following genes have been well-replicated, and based on pooled odd ratios (OR) ranging from 1.2 to 1.5, are suggested to be associated with ADHD: DAT, DRD4, DRD5, DBH, 5-HT, and ADRA2A (Faraone, et al., 2005; Waldman et al., 2006).

Dopaminergic genes have been primarily targeted because methylphenidate, an efficacious pharmacological treatment for ADHD, binds to the dopamine transporter and inhibits dopamine reuptake to achieve its therapeutic effect (Krause et al., 2000; Spencer et al., 2000). Results from family-based association studies show a small but significant OR (1.13), which suggests dopamine transporter (DAT) genes are worth investing more (Faraone et al., 2005). DRD4 is prevalent in frontal-subcortical networks, and the 7-repeat allele of DRD4 is associated with ADHD pathology, particularly inattention (Kustanovich et al., 2004). Although findings based on dinucleotide repeat of DRD5 genes are mostly non-significant, a meta-analysis found significant association between DRD5 and ADHD (Maher et al., 2002). The Taq1

polymorphism of Dopamine Beta Hydroxylase (DBH) gene, the main enzyme that facilitates the conversion of dopamine to norepinephrine, was found to be significantly (OR = 1.33) associated with the prevalence of ADHD (Kopeckova et al., 2006). Furthermore, Bellgrove and colleagues (2006) showed that ADHD children with two copies of the Taq1 polymorphism of the DBH allele had significantly poorer sustained attention compared to ADHD children without those alleles and non-genotyped control children. Serotonergic and adrenergic system genes have also been studied extensively. Among the serotonergic genes, 5HT1B receptor gene indicates some positive association with ADHD (Faraone et al., 2005). Among adrenergic genes, the alpha2A receptor gene has been implicated in ADHD etiopathogenesis especially the Predominantly Inattentive Type (Deupree et al., 2006; Waldman et al., 2006).

Although the findings from molecular genetic studies have been replicated, the results are still inconclusive and do not account for a substantial proportion of the biological basis of the disorder. Perhaps the inconsistent findings are a consequence of small sample sizes, low statistical power to detect small effect sizes, and the heterogeneity of ADHD itself. Thus, while molecular genetic approaches are beginning to add to the knowledge in the field of ADHD etiology, they are still far from being able to identify the specific mode of genetic transmission.

### **Genetics of Neurocognitive Deficits**

As discussed earlier, ADHD is a highly heritable disorder with a wide array of associated neurocognitive deficits, with deficits in response inhibition, working memory, and state regulation especially prominent (Castellanos et al., 2005; Castellanos & Tannock, 2002; Kuntsi et al., 2006). The extant literature also suggests that these deficits seem to have a familial pattern because children with ADHD and their family members tend to have difficulties in similar

cognitive areas regardless of their behavioral expression of the disorder (Nigg et al., 2004; Seidman et al., 2000; Slaats-Willems et al., 2003). For example, using an adoption paradigm, researchers found biological relatives of adopted ADHD children performed poorer on tasks involving visual attention, response inhibition, and visuospatial skills than their adoptive relatives (Alberts-Corush et al., 1986; Nigg et al., 1997). In another study, investigators (Crosbie & Schachar, 2001) reported a higher prevalence of the disorder among family members of ADHD children with poor inhibitory control (48.1%) compared to family members of ADHD children with relatively good inhibitory control (18.5%) and family members of normal control participants (7.7%). Thus, a deficit in inhibitory control appeared to be associated with ADHD and perhaps serves as a possible genetic marker for the disorder among first degree relatives. Investigating self-reported behavior and neurocognitive deficits, Kera and colleagues (2004) reported that biological parents of hyperactive children performed more poorly (longer reaction time and increased errors) on a continuous performance task (CPT) than parents of children without behavioral difficulties. However, the parents of these groups did not differ on self-report ratings.

Familial patterns of working memory and state regulation deficits have not been studied extensively; however, limited data suggest a familial pattern of these neurocognitive traits. For instance, a higher correlation in the pattern of task performance (i.e., number of errors, reaction time) on working memory measures among monozygotic vs. dizygotic twins has been reported (Stins et al., 2005). A high heritability estimate (.64) was also reported for reaction time, which is often used to measure state regulation (Kuntsi & Stevenson, 2001). Together these findings not only indicate that neurocognitive deficits are associated with ADHD, but also suggest that the pattern of these deficits is perhaps heritable.

### Summary of Etiology

Findings for behavioral genetic studies leave no doubt that ADHD is highly heritable. Molecular genetics have identified and implicated a few dopaminergic and serotonergic candidate genes; however the findings are still inconclusive. In addition, the cognitive deficits that are associated with ADHD seem to run in families. Thus, evidence suggests that the neurocognitive deficits in ADHD probands are perhaps genetically mediated, and the specific cognitive traits that these children inherit may make them more susceptible to ADHD-like behavioral symptoms.

### **Challenges to the Existing Field**

Although molecular genetics have identified a few associated genes, to date the field is a long way from clearly identifying the specific genes that account for most of the variance in ADHD. A number of factors obscure the identification, localization, as well as the precise contribution of certain genes to manifestations of ADHD:

- 1) The question as to what precisely is transmitted genetically, the behavioral symptomatology or cognitive deficits that underlie the phenotypes, remains unanswered. Hence, it is not clear whether investigators should search for genes associated with behavioral symptoms or cognitive deficits.
- 2) The mode of specific genetic transmission is unknown. Heterogeneity in phenotypic expression of the disorder indicates that perhaps numerous genes with small effect sizes interact to varying degrees in creating the complex clinical presentation of the disorder. Low statistical power makes it difficult to detect genes with small effect

- sizes. In addition, heterogeneity makes the search for possible genes even more difficult, as it is hard to know the nature of such interactions between genes in the expression of the disorder.
- 3) Comorbid conditions associated with ADHD (e.g., Oppositional Defiant Disorder, Conduct Disorder, Learning Disability, etc.) make the search for responsible genes even more difficult as the genetic liability of ADHD overlaps with several comorbid psychiatric conditions, which are difficult to disentangle (Nadder et al., 2002). If a set of genes is responsible for the condition of interest as well as the comorbid condition, it becomes difficult to precisely attribute the gene's effect on one or the other condition.
  - 4) Subtypes based on phenomenology that have distinct clinical correlates further hamper the identification and localization of the responsible genes. The reason is that it is not clear whether these subtypes share the same genetic risk factors and the degree of possible genetic overlap.

### **Endophenotypes**

ADHD is a highly heritable heterogeneous condition, which involves multiple characteristics that are likely mediated by multiple genes. For complex conditions such as ADHD, biologically-based, narrowly-defined, directly identified, and objectively measured phenotypes that lie in between the overt behaviors and underpinning genes may constitute more promising tools in identifying particular genes than the disorder as a whole. These narrowly defined traits are known as endophenotypes. Although this is a relatively new term for the field of ADHD research, it has been fruitful in understanding the etiology of other biological and

psychological disorders. The term endophenotype was first used by John and Lewis (1966) while studying the evolutionary biology of insects. They described the overt external features of insects as ‘exophenotypes’ and internal microscopic features as ‘endophenotypes.’ This term (endophenotype) was later adopted by psychiatry as it seemed to fill the gap between phenotypes and elusive genotypes.

An endophenotype is conceptualized as a heritable phenotype (e.g., neurophysiological, endocrinological, cognitive, neuropsychological, etc.) that is normally associated with a condition but is not a direct symptom of that psychological condition and that is more proximal to the biological basis of the clinical disorder than its symptoms (Gottesman, 2003). In addition, the disorder and its endophenotypes are influenced by one or more of the same susceptibility genes (Doyle et al., 2005). The assumption here is that an endophenotype is genetically less complex than the underlying disorder as it involves one of the several possible pathophysiologies that combine to produce the overall diagnosis. Therefore, in theory, searching for genes for an endophenotype will result in greater statistical power to detect individual genes of small effect size and bring us one step closer to identifying susceptible genes for the diagnostic entity (Doyle et al., 2005). Another assumption is that an endophenotype is associated with the disorder but is not a direct symptom of the disorder; hence an individual with the trait (endophenotype) can be identified even in the absence of disease symptomatology. Thus, if potential endophenotypes are successfully identified in family members they may serve as a powerful predictive tool in monitoring, diagnosis, and intervention.

### *Criteria for Endophenotypes*

Investigators (Doyle et al., 2005) have identified characteristics that should be inherent in an endophenotype to make it most useful in research: 1) it should co-occur with the behavior of interest, 2) it should be measurable in a psychometrically sound way, 3) it should be heritable, 4) it should show genetic overlap with the disorder of interest, meaning that the disorder of interest and the candidate endophenotype both should run in first degree relatives in a consistent pattern.

#### *Possible Candidate Endophenotypes for ADHD*

The quest for ADHD endophenotypes is at a preliminary stage; however, endophenotypes defined by neurocognitive measures (e.g., response inhibition, working memory, state regulation, etc.) seem to be promising in the search for genetic correlates of ADHD as they tend to fulfill the candidacy requirements (discussed later in detail). It has long been speculated that response inhibition and working memory are among the few cognitive functions that attain the required characteristics of endophenotypes as they can be measured in a psychometrically sound way, fairly consistently distinguish ADHD patients from control participants, show neural bases, and show evidence of heritability. Therefore, measures of these constructs have emerged as important paradigms for studying ADHD. Although, initially ignored, recent investigators suggest that state regulation, as assessed by individual reaction time variability on an array of cognitive measures may represent a ubiquitous cognitive trait for ADHD that may serve as a candidate endophenotype (Castellaos & Tannock, 2002). Since the pathophysiology of ADHD is highly heterogeneous and cognitive functions are interrelated, these candidate endophenotypes are not mutually exclusive. Each candidate endophenotype may play a significant role in different aspects of ADHD.

*Response Inhibition* Response inhibition has been described by Barkley (1997) as the central deficit of ADHD and that behavioral abnormalities such as hyperactivity and impulsivity in ADHD probands are secondary to this core deficiency.

*Response Inhibition Deficit Co-occurs with ADHD and is Measured in a Psychometrically Valid Way:* Numerous studies have documented deficient response inhibition as measured by various tasks in ADHD probands (Casey et al., 1997; Durston et al., 2004; Nigg 2001; Vaidya et al., 1998). ADHD probands tend to make significantly more commission errors and have slower reaction times on response inhibition tasks compared to normal controls. Schachar and colleagues (2000) reported that, compared to normal controls, children with ADHD were approximately 70 milliseconds slower to stop an ongoing action. A meta-analysis conducted by Oosterlaan and colleagues (1998) reported that children with ADHD were 103 milliseconds slower than normal controls on a response inhibition measure with an effect size of .64.

*Response Inhibition has a Neural Basis:* Tasks measuring response inhibition implicate a neural basis for this function, as it activates specific brain regions (e.g., right prefrontal cortex) during the task, and damage to those regions results in deficient response inhibition (Durston et al., 2004; Sowell et al., 2003). In general, the structural neuroimaging data indicate volumetric reduction in the prefrontal cortex, especially in the right hemisphere, among ADHD probands (Sowell et al., 2003). Parallel reduction was reported in unaffected siblings (siblings who do not exhibit ADHD symptomatology) of ADHD probands (Durston et al., 2004).

Meta analysis of functional neuroimaging studies showed that the frontal cortex (especially the right inferior frontal cortex) and striatum (caudate and putamen) are activated in healthy adults during inhibition of a prepotent response tendency (Aron & Poldrack, 2005). The

right inferior frontal cortex is further implicated by a neuroimaging lesion study where patients with a right frontal lesion had significantly slower reaction time on a response inhibition task than both patients with left frontal lesion and normal controls. Moreover, the extent of damage in only the right inferior frontal cortex positively correlated with slowing in reaction time. Patients with left frontal lesions did not differ from normal controls in terms of slowing in reaction time (Aron et al., 2003). Additionally, using fMRI, Durston and colleagues (2006) reported that, although children with ADHD and their unaffected siblings did not differ significantly with respect to task performance, they both had decreased activation in ventral prefrontal and inferior parietal cortex during the response inhibition task compared to normal controls.

*Response Inhibition is Heritable:* Crosbie and Schachar (2001) investigated whether deficient inhibitory control delineates a familial subgroup of ADHD. These researchers categorized the children with ADHD into two groups based on their performance on a response inhibition task (Stop Task); those ADHD children with long stop-signal reaction times (RT) were defined as having poor inhibition while those with short stop-signal RT were defined as having relatively good inhibition. The authors then compared the prevalence rate of ADHD among family members of these two groups and family members of normal control children. The investigators found a higher prevalence of the disorder among family members of ADHD children with poor inhibitory control (48.1%) than in the families of probands with good inhibitory control (18.5%) and in families of normal controls (7.7%). Moreover, among children with ADHD, those with poor inhibition were significantly more likely to have a first degree relative with ADHD than children with relatively good inhibition even after accounting for relevant variables (e.g., severity or type of ADHD symptoms, comorbidity, age, sex, IQ).

Therefore, deficient inhibitory control seems to identify a subgroup of children with ADHD that have a greater risk for familial ADHD.

These findings lead to the question, if poor inhibition indicates a genetic risk for ADHD then what accounts for the disorder in the relatively intact inhibition group? The authors addressed this issue by showing that, while the group difference was non-significant; compared to normal controls, ADHD probands with relatively good inhibition had more family history of ADHD. Therefore, the children with relatively good inhibition as well as those with poor inhibition were likely affected by genetic risk factors. However, they speculated that the children with relatively good inhibition may have been affected by genetic susceptibility factors that are less penetrant than those that affected the children with poor inhibition. The other speculation made by the authors was that there may be non-genetic factors that caused a phenocopy of ADHD through alternative pathways or through an interaction with genetic susceptibility (Crosbie & Schachar, 2001).

Slaats-Willemse and colleagues (2003) also investigated whether deficient response inhibition is a cognitive endophenotype for ADHD by comparing ADHD probands with a family history of ADHD with their non-affected siblings (siblings without behavioral symptoms of ADHD), and normal controls (Ages 6-17 years) using multiple response inhibition and attention tasks. The authors found that ADHD probands differed significantly from normal controls on all dependent measures (e.g., false alarm, accuracy score, interference score, etc); however, non-affected siblings did not differ significantly from ADHD probands or normal controls. Their performance was poorer than normal controls but better than probands. For example, ADHD probands made 44% errors, non-affected siblings made 32% errors, and normal controls made 6.4% errors on a sustained attention task. The findings from all the measures indicate that non-

affected siblings of probands had deficient response inhibition and attention difficulty, which did not significantly differ from probands or normal controls, supporting their intermediate position between probands and normal control. Their finding is consistent with others and strengthens the evidence that deficient response inhibition is a candidate cognitive endophenotype of ADHD.

In this latter study the authors further investigated whether the findings were influenced by comorbid psychopathology and found that most of the probands had at least one comorbid disorder such as ODD, anxiety, or mood disorders; however, only a few of their siblings had these disorders. Therefore, they concluded that if deficient response inhibition could be accounted for by comorbid disorders, then that should affect only probands. However, deficient response inhibition was seen in probands as well as non-affected siblings. Therefore, they concluded that deficient inhibition is not an artifact of comorbid conditions; rather it is suggested to be due to ADHD per se.

Investigators further attempted to show the association between response inhibition and genes that are already implicated in ADHD. Groot and colleagues (2004) reported significantly higher correlations between the reaction times of MZ normal control twin pairs compared to those of DZ twin pairs. Based on this finding the authors suggested that response inhibition may be genetically mediated. Additionally, in a genetic study of ADHD children, it was found that probands with the 7-repeat allele for the DRD4 gene had significantly poorer response inhibition compared to probands without 7-repeat allele (Langley and Marshall, 2004). In a similar study, Loo and colleagues (2003) reported that ADHD probands with a 10-repeat dopamine transporter (DAT) allele made significantly more commission errors on a response inhibition measure than probands with a 9-repeat DAT allele.

Evidence from the above studies suggests that response inhibition is a good candidate endophenotype as it consistently differentiates probands from normal controls on experimental measures, shows evidence of heritability, and implicates activation of specific brain regions during response inhibition tasks in healthy adults and functional and structural changes to those regions in ADHD probands. Furthermore, association with specific genes and performance on response inhibition task argues in favor of response inhibition as a cognitive endophenotype.

Working Memory Working memory involves the ability to hold, process, and monitor information simultaneously (Baddeley, 1996). It is an important aspect of executive functioning as it is necessary to comprehend, maintain, and manipulate task-related information to successfully complete many tasks.

*Working Memory Deficits Co-occur with ADHD & Can be Measured in a Psychometrically Valid Way:* Although impairment in working memory is associated with ADHD, the findings are equivocal as some investigators reported working memory deficit in ADHD probands (Cohen et al., 2000; Martinussen & Hayden, 2005; Martinussen & Tannock, 2006; McInnes, 2003; Pasini et al., 2007; Williams et al., 2000) and others failed to document such deficits (Pennington & Ozonoff, 1996; Wu, 2006). Perhaps the disparity is partially due to the fact that different investigators have examined different aspects and/or modalities of working memory tasks (i.e., auditory/verbal and visual/spatial). ADHD probands tend to have significantly more difficulty with visual-spatial working memory relative to verbal working memory.

McInnes (2003), using a verbal and spatial sequencing task, showed that children with ADHD performed significantly poorer relative to normal controls on both verbal and spatial working memory tasks after controlling for basic language abilities. In this study, verbal span

was assessed by a forward number sequence task and verbal working memory was assessed by a backward number sequence task. The spatial span was assessed by a task in which the examiner inserted a pencil into holes on a board that gradually increased in length from sets of two to sets of six windows in forward sequence; participants were required to follow the same forward sequence, inserting his/her finger into the holes. Spatial working memory was assessed by gauging the child's ability to reproduce the sequence in reverse direction. ADHD probands had comparable performance to normal controls on the verbal span task and deficient performance on the spatial span task. The fact that the deficit was more pronounced on the spatial vs. verbal span task indicated that ADHD probands have significantly more difficulty with visual-spatial vs. verbal working memory skills. This finding suggests that deficit in visual-spatial working memory is a more consistent correlate of ADHD than verbal working memory and may worth investigating its candidacy for endophenotype of ADHD.

Oosterlaan and colleagues (2005) used the Self-Ordered Pointing Task (SOPT; Milner 1982) to assess spatial working memory in 6 - 12-year-old children with ADHD, children with ADHD and comorbid ODD/CD, and normal controls. The SOPT task was originally adopted by Petrides and Milner (1982) and requires children to constantly compare the present design with previous designs and the remaining choices. In the study by Oosterlaan et al. (2005), a series of cards were presented and participants instructed to point to the designs in any order but without pointing to any particular design more than once. The authors reported that children with ADHD committed significantly more errors with increased level of task difficulty compared to controls, a pattern that did not appear to be accounted for by comorbid ODD/CD.

*Working Memory has a Neural Basis:* Evidence from human and animal neuroimaging studies have demonstrated that working memory (especially visual spatial working memory) is

mediated by neural circuits involving the prefrontal cortex (Braver et al., 1997; Carlson et al., 1998; Desimone, 1996) and modulated by dopaminergic and noradrenergic neurotransmitters. Petrides and colleagues (1993) also reported mid-dorsolateral frontal cortex activation during working memory task performance.

*Working Memory is Heritable:* Stins and colleagues (2005) reported that an increase in memory load led to an increase in reaction time and errors on a working memory task. In this study, 5-year-old MZ and DZ normal control twin pairs were required to memorize one animal (load 1) or two animals (load 2) and respond to the presence of an animal from the memory set. As expected by the authors, reaction time and errors were higher for load 2 as compared to load 1. The genetic analysis revealed that the twin correlation for overall reaction time on the memory task was higher for MZ (.52-.64) than for DZ (.02 - .2). Concordance for the increase in 'search time' with increasing memory load was also higher for MZ (.33- .40) than for DZ (-.15-.15). A similar pattern of correlations was observed for overall accuracy (MZ = .26- .54; DZ = .11 - .44). Higher correlations among MZ vs. DZ pairs indicated a possible influence of genes and shared environmental effects on task performance. This pattern of performance indicates familial influence.

In sum, the abovementioned findings indicate that working memory has a neural basis and that the construct can be measured in a psychometrically valid way. Performance on visuo-spatial working memory tasks tends to discriminate normal controls from ADHD probands and the pattern of performance also shows some heritability. Thus, data suggest that deficient visuo-spatial working memory may be a good candidate endophenotype.

State Regulation Although, it is natural to see some degree of fluctuation in performance from moment to moment, as compared to controls, ADHD probands have

consistently been shown to have significantly greater levels of reaction time (RT) variability. Such observations led to the recent suggestion that intra-individual variability, which purportedly measures cognitive state regulation, may be etiologically associated with the pathophysiology of ADHD (Sergeant, 2000). State regulation is defined as the ability of an individual to change from a non-optimal cognitive activation state to an optimal state to meet particular task demands (Sergeant, 2000). Although initially ignored, this is perhaps the most ubiquitous finding in the recent literature, as children with ADHD tend to differ on state regulation measures (e.g., RT variability, signal detection ( $d$ )) even when they do not differ on other neurocognitive measures (e.g., response inhibition, working memory) (Borger & van der Meere 2000; Castellanos et al., 2005; Nigg, 2005; Wiersema et al., 2005). Hence, the cognitive deficits in ADHD have been posited to stem from bottom-up regulatory impairments rather than top-down executive functioning difficulties (Sergeant, 2000).

*State Regulation Deficits Co-occur with ADHD & Can be Measured in a Psychometrically Valid Way:* Investigators have reported that children with ADHD are significantly slower, commit more errors, and are more variable in their speed of responding to the Stop Task vs. normal controls (Castellanos et al., 2005; Kuntsi et al., 2001; Pasini et al., 2007).

Borger and van der Meere (2000) compared ADHD probands and normal controls on a reaction time task and cardiac measures, reflecting arousal, motor activation, motor inhibition, and effort allocation. The reaction time task had two conditions: (1) fast presentation rate of stimuli (2 second inter stimulus interval (ISI)) and (2) slow presentation rate of stimuli (6 second ISI). There was no group difference in response inhibition, which was measured by rates of commission errors, on the either conditions of the reaction time task. Additionally, no group

differences were observed for any of the abovementioned measures in the condition with fast presentation rate of stimuli. However, in the slow condition, ADHD probands had slower reaction times to the 'go signal' than normal controls, which according to these authors, indicates poor motor activation. The heart rate deceleration before the onset of the 'go signal', which is thought to measure motor preparation, was significantly slower in those with ADHD, suggesting poor motor preparation. After a response to a 'go signal' the cardiac shift from deceleration to acceleration was delayed in those with ADHD, which was interpreted as delayed response initiation. Further, greater heart rate variability in children with ADHD vs. normal controls during the task indicated less effort was allocated among ADHD children. The authors concluded that the slow presentation of stimuli set the ADHD children in a non-optimal cognitive activation state which led to poor motor preparation and response initiation. Based on these data, they posited that poor state regulation, rather than response inhibition deficits, is the key deficit in ADHD.

This finding was further supported by Wiersema and colleagues (2005), who compared ADHD probands, early and continuously treated phenylketonuria (PKU), and normal controls on a reaction time task with an ISI of either 2 seconds (fast condition) and 8 seconds (slow condition). On the fast condition, children with ADHD responded equally fast as normal controls but significantly faster than PKU treated children. However, on the slow condition, ADHD children responded significantly slower than both normal controls and PKU treated children. With regard to state regulation, measured by variability in RT, children with ADHD responded more variably than normal controls and PKU treated children and this effect was most pronounced during the slow condition. In addition, P3 amplitude, a measure of effort allocation (higher P3 amplitude indicates more effort allocation), on the event-related potential indicated

lower P3 amplitude in ADHD probands than normal controls and PKU treated children suggesting that children with ADHD allocated less effort to regulate their under activated cognitive state. Based on these findings, the authors argued that children with ADHD have deficient state regulation and not response inhibition impairments.

Similarly, Sonuga-Barke (2002) reported that children with ADHD underutilize the processing time on very short or very long ISI trials, as they had difficulty modulating their cognitive state to meet the changing task demands. In another study, Klein and colleagues (2006) compared fifty two 7-to-14-year-old children with ADHD and 48 age-matched controls on reaction time tasks. The authors reported that intra-subject variability was the best group discriminator between controls and probands across all measures. This robust finding was also reported by Kalff and colleagues (2005) in a sample of 5-6-year-old children with ADHD, 'at risk' for ADHD, and normal controls in The Netherlands, where the groups significantly differed on response speed variability. These findings provide support for the etiologic relevance of state regulation in ADHD.

*State Regulation has a Neural Basis:* Converging lines of evidence from animal and human studies suggests that fluctuations in RT variability are probably associated with a catecholaminergic deficit in basal ganglia neuronal activity (Castellanos, et al., 2005; Walter et al., 2001). Castellanos and colleagues (2005) showed that variability in RT oscillation was significantly higher (frequency = .05 Hz) in ADHD probands than age-matched controls on the electroencephalogram, Eriksen Flanker task. Walters and colleagues (2001) showed synchronized phase-locked fluctuations in basal ganglion neurons of locally anesthetized rats. This fluctuation in neural activity was modulated by low doses of dopaminergic agonists and uptake blockers (i.e., methylphenidate and dextroamphetamine) (Ruskin et al., 2001a, 2001b;

Ruskin et al., 2003). Thus it is speculated that a catecholaminergic deficiency in the ability to appropriately modulate low-frequency fluctuations in neuronal activities may underlie attentional lapses and hence reaction time variability (Castellanos, et al., 2005).

*State Regulation is Heritable:* Although the heritability of RT variability has not been studied widely, limited data suggest heritability of RT variability. Kuntsi & Stevenson (2001) compared 46 hyperactive twin pairs (7-11-years-old), in which at least one twin was hyperactive, with 47 control twin pairs on multiple psychological measures. They found the highest heritability estimate (.64) for the standard deviation of a reaction time task, which assessed individual RT variability. Since RT variability is believed to be indicative of non-optimal activation, they concluded that state regulation is both genetically influenced and genetically related to hyperactivity. Thus, while research in this area remains at a preliminary stage, RT variability seems to meet criteria as a candidate ADHD endophenotype.

### **Purpose and Hypotheses for This Dissertation**

The extant literature suggests that ADHD is highly heritable and often associated with deficiencies in inhibitory control, working memory, and state regulation. In addition, performance on measures of these neurocognitive processes tends to show a familial pattern. These neurocognitive functions have been, to a certain extent, investigated for their candidacy as ADHD endophenotypes. Most researchers have demonstrated performance differences between ADHD probands and normal controls on measures in these cognitive domains (Casey et al., 1997; Durston et al., 2004; Nigg 2001; Vaidya et al., 1998). Several studies have assessed the relationship between cognitive impairments in ADHD probands and the prevalence of ADHD among their first degree relatives (Crosbie & Schachar, 2001). Other investigators reported

cognitive deficits, even in the absence of behavioral symptoms, in first degree relatives of ADHD probands (Nigg et al., 2004; Kera et al., 2004; Seidman et al., 2000; Slaats-Willemse et al., 2003). However, there are virtually no studies that have investigated the pattern of neurocognitive profiles in children with ADHD and their biological parents compared to normal control children and their parents employing similar age-appropriate cognitive measures. Such an investigation will allow one to compare the neurocognitive profiles of parents and their offspring not only at group level but also at individual level, which could further strengthen the support for the familial pattern of these deficits.

Although different investigators and studies tend to provide support for different neurocognitive functions to be central to ADHD, the literature points to multiple neural pathways, multiple genes, and modest effect sizes that suggest that one particular deficit may not be adequate to explain a complex multi-structured condition like ADHD. Hence, the present study was designed to examine inhibitory control, working memory, and state regulation to determine the extent to which they may serve as ADHD endophenotypes that will facilitate research into the etiology of the disorder. Using analogous experimental measures, each of these processes were assessed in preschool children with ADHD symptomatology (Hyperactive/Inattentive (HI) group) and normally developing preschoolers (Normal Control (NC) group), as well as in their parents (HI parents (HI-P) and NC parents (NC-P)), respectively. By comparing these two groups of parents' performance and their children's performance on analogous measures, we hoped to acquire additional insight into the transmission of specific neurocognitive characteristics. The following hypotheses were proposed:

1. Preschoolers in the HI group will perform significantly more poorly on measures of inhibitory control, working memory, and state regulation compared to NC participants.

2. Parents of HI preschoolers will perform more poorly on these same measures as compared to parents of NC preschool children. Further, parents of children in the HI group who do not exhibit ADHD symptoms on behavioral rating scales will perform in between the parents of NC children and symptomatic parents of the HI group.
3. Consistent with the notion that neurocognitive performance is at least in part genetically mediated; the performance of parents and their offspring on measures of inhibitory control, working memory, and state regulation will be significantly correlated.

## METHODS

### Recruitment

#### *Recruitment of Child Participants:*

As part of a larger study designed to assess symptoms of ADHD in preschoolers, packets consisting of an explanatory cover letter, consent form, and behavior rating scale (ADHD-RS; DuPaul et al., 1998) were sent home with 3 to 4-year-old children in public and private preschools in Long Island and New York City, New York. Participants were also recruited via clinical referrals from school psychologists, social workers, and other health professionals, as well as responses to flyers and advertisements in local news papers. Once parental consent and the completed rating scales were received by mail, teachers of those children were requested to complete an identical rating scale. Potential participants were pre-screened based on these rating scales and a phone conversation with the parents, and were excluded if they: (i) did not meet the grouping criteria (described below in the “Procedure” section), (ii) had a history of a major chronic physical illness, (iii) were receiving systemic treatment with medication including treatment with psychotropic medication, (iv) had a diagnosis of autism or pervasive developmental disorder, or (v) were non-English speaking. Children who met all of the pre-screening criteria were further screened during the on-campus assessment (described below in the “Procedure” section) and excluded if they received a Full Scale IQ score less than 80 on the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002).

#### *Recruitment of Parent Participants:*

As parents brought their children for the second phase of the ongoing study and waited for the completion of their child’s assessment, mothers and fathers were introduced to the current

project. Parents were ensured that their decision to agree or decline participation in this study did not impact their involvement with the ongoing project. Separate consent forms were signed if they agreed to participate in this dissertation project. The second phase of the ongoing project was comprised of two sessions; hence, different parents (e.g., mother in the first session and father in the second session) were encouraged to be present for the two sessions so that data could be collected from both parents. Parent participants were classified according to their child's initial categorization based on behavior ratings on the ADHD-RS completed by parents and teachers in the ongoing study; that is, parents of Normal Control (NC) children were grouped as NC parents (i.e., NC-M = NC mother; NC-F = NC father) and parents of Hyperactive/Inattentive (HI) children were categorized as HI parents (i.e., HI-M = HI - mother; HI-F = HI - father). Parents were excluded if they had a history of a neurological disorder (e.g., epilepsy), estimated FSIQ score less than 80, or were non-English speaking.

This study as well as the larger project were reviewed and approved by the Queens College, CUNY Institutional Review Board. Parents were compensated \$20 per hour for their involvement in the main project. However, they did not receive additional compensation for their participation in the current study since it did not require additional time above and beyond the time required for the child assessment.

## Measures

### *Child Measures:*

#### 1. *Standardized Tests*

Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III;  
Wechsler, 2002): The WPPSI-III is an individually administered measure of intelligence that

generates a Full Scale IQ (FSIQ) score, which provides an index of overall intellectual functioning, and is comprised of two broad areas: Verbal IQ (VIQ), which represents an individual's verbal ability, and Performance IQ (PIQ), which entails non-verbal, perceptual-motor abilities. In addition, it provides a measure of Processing Speed (ages 4 and above), which estimates the efficiency with which information is processed; a General Language Composite Score is also generated, which provides a rough indication of basic receptive and expressive language abilities. The WPPSI-III was used in this dissertation to estimate child intellectual functioning, which is a critical factor when assessing neurocognitive deficits in ADHD probands as it rules out other relevant variables (e.g., low intellectual ability).

## 2. *Rating Scales*

Attention Deficit/Hyperactivity Disorder (ADHD) Rating Scale –IV (ADHD-RS; DuPaul et al., 1998): The two versions of the ADHD-RS-IV (ADHD-RS: Home and ADHD-RS: School) consist of the eighteen (9 inattentive, 9 hyperactive/impulsive) DSM-IV behavioral descriptors for ADHD. They have both been found to have adequate reliability and validity in assessing the presence of ADHD symptoms in young children (Havey et al., 2005; Kaplan et al., 2004; Michanie et al., 2007). In addition, moderate levels of agreement have been identified between parent and teacher ratings on the ADHD-RS-IV ( $r = .55$ ; Healey et al., 2007). Both versions were administered in the current study to assess the presence of symptoms associated with ADHD at home and at school and used to categorize children into two groups (i.e., 'normal control' and 'hyperactive/inattentive').

A. The ADHD-RS-IV: Home – is an eighteen item questionnaire that is rated by parents on a 4-point Likert scale (0 = never or rarely, 1 = sometimes, 2 = often, and 3 = very often) describing the child's behavior at home.

B. The ADHD-IV –RS: School is a similar questionnaire to the Home version; however, the school version is completed by teachers describing the child’s behavior at school.

### 3. *Objective Measures*

#### A. Novel Experimental Measures

1. **The Perceptual and Motor Conflict Task (PMCT)** (Nassauer and Halperin, 2003): This is a novel experimental computerized task with built-in control conditions to isolate perceptual and motor inhibition. This task was slightly modified by Marks and colleagues (2005) for use with preschool children. To keep the measure short and engaging, the modified children’s version of the PMCT involves bright colored stimuli, fewer conditions, and fewer stimuli (20) in each condition than the original version of the task. There was no additional difference between the original and the modified versions. The PMCT is comprised of two components:

i) **The Stimulus Conflict Task (SCT)** is designed to assess one’s ability to inhibit responses to incompatible stimuli. The task consists of three conditions: 1) non-conflict direction, 2) non-conflict location, and 3) direction-location conflict. It is designed to measure perceptual conflict and the capacity to screen-out visual interference. In the first condition (*direction*), successive centrally-located bright green colored arrows pointing to either the right (10 stimuli) or left (10 stimuli) side are presented in a randomized order, one arrow at a time, on a computer monitor. Participants need to press the left or right side of a large-button mouse corresponding to the side to which the arrow is pointing (i.e., respond to the stimulus direction). For the second condition (*location*), successive bright green rectangles are presented randomly on either the right (10 stimuli) or left (10 stimuli) side of the computer screen; participants are instructed to respond to the location of the stimulus using the same computer mouse. This

condition is designed to elicit prepotent response tendencies to respond to the location of the stimulus; data from this condition are not used in the analysis. Finally, on the third condition (*direction-location conflict*) participants are presented with 20 successive bright green arrows pointing randomly to the right or left (10 stimuli each), which appear either on the right (10 stimuli) or left (10 stimuli) side of the computer screen. The participants are instructed to disregard the location of the arrow and to press the button on the same side to which the arrow is pointing (respond to the stimulus direction). Thus, participants are required to inhibit their prepotent response to stimulus location, and instead respond to stimulus direction.

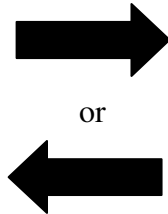
To assess the effect of stimulus-response compatibility, often referred to as the ‘Simon Effect,’ the *direction-location conflict* condition of the SCT is subdivided into two components: *conflict-congruent* (location of the stimulus and the direction of the arrow are compatible – i.e., to the same side) and *conflict-incongruent* (location of the stimulus and the direction of the arrow are incongruent – i.e., to opposite sides). The Simon Effect was named after J. R. Simon, who first described the phenomenon that responses are slower to the incongruent versus congruent stimuli, even if the stimulus location is task-irrelevant (Simon & Small, 1969). In the *conflict-congruent* context, the stimuli are spatially congruent with the response key: 5 arrows pointing to the left on the left side of the screen and the correct response requires pressing the left mouse button and 5 arrows pointing to the right appearing on the right and the correct response requires pressing the right mouse button. In the *conflict-incongruent* context, 5 arrows pointing to the left appear on the right and the correct response requires pressing the left mouse button; an additional 5 arrows pointing to the right appear on the left side, and the correct response requires pressing the right mouse button. The entire *direction-location conflict* condition is presented to the participants as one uninterrupted condition; however, data are analyzed separately from these

two contexts to assess the Simon Effect. Figure 1.a depicts the SCT stimuli and the task instructions.

Figure 1a. Stimuli and Instructions on the Stimulus Conflict Task

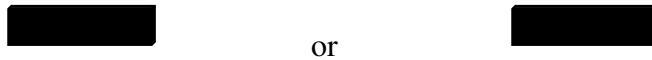
Condition 1 (Compatible):

“Press the mouse button on the same side where the arrow is pointing”



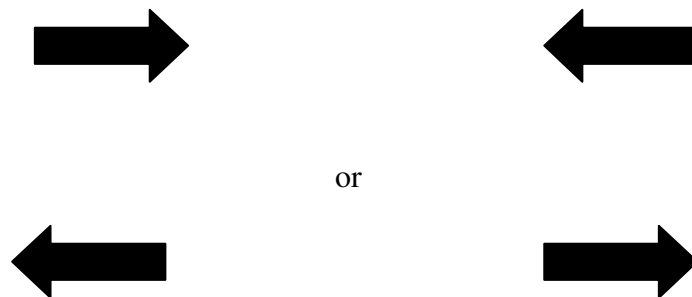
Condition 2 (Compatible):

“Press the mouse button on the same side where the block is located”



Condition 3 (Incompatible):

“Disregard the location and press the mouse button on the same side where the arrow is pointing”



ii) **Response Conflict Task (RCT)** is designed to assess one’s ability to override a prepotent motor response. The task consists of a control (*non-conflict direction*) and an experimental (*conflict direction*) condition. As in the SCT, the control (*non-conflict direction*) condition requires children to press the left or the right mouse button corresponding to the side to

which successive centrally located bright red colored arrow are pointing (10 right and 10 left, presented in a randomized order). For the conflict (*conflict direction*) condition, children are again shown centrally-located red arrows randomly pointing to the right (10) or left (10). However, in this condition, they are asked to press the mouse button on the side opposite to which the arrow is pointing. Thus, participants are required to inhibit prepotent tendencies and engage in a new response set. Figure 1.b depicts the RCT stimuli and the task instructions.

Figure 1b. Stimuli and Instructions on the Response Conflict Task

Control Condition (Compatible)

“Press the mouse button on the same side where the arrow is pointing”



or



Experimental Condition (Incompatible)

“Press mouse button on the opposite side where the arrow is pointing”



or



To assess latency to response (reaction time), the bright colored stimuli for both components of the PMCT are programmed to remain on the screen until a response is made. A one second inter-stimulus interval is introduced after a response is made. Accuracy, median reaction time (RT), and the standard deviation (SD) of reaction time (RT) were recorded for each condition and used as dependent measures of performance. Since median reaction time is less

likely to be affected by the outliers it was used as a dependent measure instead of mean reaction time.

## 2. **Delayed Non-Matching to Sample Test (DNMST; Marks et al., 2005):**

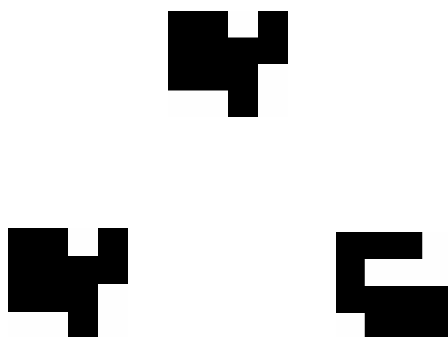
The DNMST is a computerized task designed to measure non-verbal visual working memory using a paradigm similar to that used by Goldman and her colleagues (1971) with non-human primates. The task consists of two conditions: control (*matching*) condition and experimental (*memory*) condition. During the control condition, participants are shown an array of stimuli on a computer screen, which consists of two horizontal rows of non-verbalizable visual images (see Figure 2 for example). In each trial, the bottom row contains one more stimulus than the top row, and all but the one additional randomly placed stimulus are identical to those in the top row (albeit sequenced differently). The participant's task is to identify the non-matching stimulus in the bottom row. This condition does not involve memory; rather it assesses the participant's ability to match stimuli, which is necessary to establish before proceeding to the experimental condition. During the experimental condition, participants are shown a row of similar, but not identical, non-verbalizable stimuli for four seconds and then the stimuli disappear. A one second inter-stimulus interval is introduced. Then a second row of stimuli consisting of all the initial stimuli they had just seen plus a new stimulus appear in a random order on the screen. Participants are required to identify the non-matching new stimulus. Therefore, the experimental condition involves nonverbal working memory, which is paired with the control condition that involves only matching-to-sample and no memory. For both conditions, the number of stimuli in both rows increases by one every three trials; however, in all instances, the participant's task remains the same (i.e., to identify the non-matching figural stimulus). The task terminates when

the participant responds incorrectly on at least two of three trials within a given task level or successfully completes all 4 task levels. Participants obtain one point for each correct response for a maximum of 12 points in each condition. The number of correct responses for each condition was tabulated and used as the measure of performance. Figure 2 illustrates the DNMST stimuli and instructions.

Figure 2. Stimuli and Instructions on the Delayed Non-Matching to Sample Task

#### Control Condition

Identify the non-matching stimulus – “Which one is new in the bottom row?”



#### Experimental Condition

Remember displayed stimulus (i)



---Stimulus(i) disappears and is followed by a one second interstimulus interval---

Stimulus(i) reappears with one extra stimulus

Recognize the previously viewed stimulus(i)- “Which one is new?”



## B. Actigraph

The actigraph (model number WAM-7164) is a small (5 cm x 4 cm) solid-state electronic device used to objectively measure physical activity level. These actigraphs were obtained from ActiGraph, LLC, of Pensacola, Florida (formerly known as Computer Sciences and Applications, Inc. of Shalimar, Florida), and utilize internal accelerometers (acceleration magnitude, 0.05–2.00 G; frequency response, 0.25–2.50 Hz) to store data on the number of movements per unit time. Data collected using actigraphs have been shown to effectively differentiate children with ADHD from controls (Porrino et al., 1983) and to significantly correlate with parent and teacher ratings of hyperactivity (Reichenbach et al., 1992).

At the beginning of the second phase of the assessment, both actigraphs were initialized using a reader interface unit and programmed to obtain movement counts in 60s epochs. Participants wore one actigraph around their waist and one around their non-dominant ankle throughout the entire assessment session. After the evaluation, the actigraphs were returned to the reader interface unit, and the data were downloaded into Microsoft Excel spreadsheets. The median activity level of the ankle and waist actigraph measures were calculated separately for each participant and used as the dependent measure.

### *Parent Measures:*

#### 1. *Standardized Tests*

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999): This individually administered scale of intelligence is an abbreviated measure of intelligence. It was developed in 1999 to provide a quick and efficient screening measure of intelligence. The WASI is comprised of four subtests (Vocabulary, Block Design, Similarities, and Matrix Reasoning) that are similar

to those subtests respectively in the WAIS–III. Due to time constraints and feasibility, only the Vocabulary and Matrix Reasoning subtests were selected to estimate general intellectual ability of participants. The estimated Full Scale IQ (FSIQ) based on these two subtests of the WASI has been shown to correlate well ( $r = .87$ , Wechsler, 1999) with the FSIQ score of the WAIS-III. The Vocabulary subtest, is comprised of 42 items, and requires participants to define words that are verbally as well as visually presented to them. It measures expressive verbal knowledge, vocabulary, and fund of linguistic information. The Matrix Reasoning subtest consists of a series of 35 incomplete patterns and requires participants to identify a stimulus from a group of stimuli in order to complete a series of incomplete patterns. This subtest measures non-verbal fluid reasoning and general intellectual ability.

Estimated IQ is particularly important to rule out other relevant variables (e.g., low cognitive functioning) that could contribute to the participant's performance. Thus, WASI was adopted here to ensure that the participants were at least functioning within the Low Average range of intelligence and that their poor performance on the cognitive measures could not be attributed to their compromised intellectual functioning.

## *2. Rating Scales*

The Conners' Adult ADHD Rating Scale: Two versions of the Conners' Adult ADHD Rating Scale (Conners et al., 1999) (CAARS- S:L and CAARS- O:L) were used in this study to assess the parents' current level of ADHD symptoms. Both are frequently-used rating scales that have been shown to distinguish adults with and without ADHD (LaMalfa et al., 2007; Murphy & Adler, 2004).

A. The Conners' Adult ADHD Rating Scale - Self Report: Long (CAARS- S:L) is a 66-item self-report rating scale that contains nine empirically derived scales that assess a broad range of problem behaviors in adults. Included are four factor-derived subscales (Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, Problems with Self Concept), three DSM-IV ADHD symptom subscales (Inattentive Symptoms, Hyperactive-Impulsive Symptoms, Total ADHD Symptoms), a 12-item ADHD Index, and a validity scale to capture careless response patterns. On this scale participants rate their own behaviors on a 4-point Likert scale (0 = not at all, never; 1 = just a little, once in a while; 2 = pretty much, often; 3 = very much, very frequently). For the present study, the 'ADHD Index' was used as a measure of adult ADHD severity.

B. Conners' Adult ADHD Rating Scale – Observer Report: Long (CAARS-O:L) is designed similarly to the CAARS-S:L. However, this scale is completed by an informant familiar with the participant well (e.g., spouse, significant other, parent, etc). As with the CAARS-S:L, ratings on the 'ADHD Index' was used to gauge the severity of ADHD symptoms among adult participants.

### 3. *Objective Measures*

#### A. Novel Experimental Measures

1. **The Perceptual and Motor Conflict Task (PMCT)** (Nassauer and Halperin, 2003): Parents were administered the original version of the PMCT, which is analogous to the child version described above. However, the parent version includes black and white stimuli, additional conditions, and more stimuli than the child version. The two components (SCT and RCT) of the task are described below.

i) **Stimulus Conflict task (SCT)** is a computerized task that consists of three conditions: 1) non-conflict direction, 2) non-conflict location, and 3) direction-location conflict. It is designed to measure perceptual conflict and the capacity to screen-out visual interference. For the first condition (*direction*), successive centrally-located arrows pointing to either the right (20 stimuli) or left (20 stimuli) side are presented in a randomized order, one arrow at a time, on a computer monitor. Participants need to press the left or right side of a standard mouse button corresponding to the side to which the arrow is pointing (i.e., respond to the stimulus direction). For the second condition (*location*), successive rectangles are presented randomly on either the right (20 stimuli) or left (20 stimuli) side of the computer screen; participants are instructed to respond to the location of the stimulus using the same computer mouse. This condition is designed to elicit prepotent response tendencies to respond to the location of the stimulus; data from this condition are not used in the analysis. Finally, on the third condition (*direction-location conflict*) participants are presented with 80 successive arrows pointing randomly to the right or left (40 stimuli each), which appear either on the right (40 stimuli) or left (40 stimuli) side of the computer screen. The participants are instructed to disregard the location of the arrow and to press the button on the same side as where the arrow is pointing (respond to the stimulus direction). Thus, participants are required to inhibit their prepotent response to stimulus location, and instead respond to stimulus direction.

Similar to the child version, to assess the Simon Effect the *direction-location conflict* condition is subdivided into two contexts: *conflict-congruent* (location of the stimulus and the direction of the arrow are on the same side) and *conflict-incongruent* (location of the stimulus and the direction of the arrow are on the opposite side). In the *conflict-congruent* context, the stimuli are spatially congruent with the response key: 20 arrows pointing to the left on the left

side of the screen and the correct response requires pressing the left mouse button, 20 arrows pointing to the right appearing on the right and the correct response requires pressing the right mouse button. In the *conflict-incongruent* context, 20 arrows pointing to the left appeared on the right and the correct response requires pressing the left mouse button; and finally 20 arrows pointing to the right appeared on the left and the correct response requires pressing the right mouse button. The entire *direction-location conflict* condition is presented to the participants as one uninterrupted condition; however, data are analyzed separately from these two contexts to assess the Simon Effect. Figure 1.a in the “Child Measures” section depicts the SCT stimuli and the task instructions.

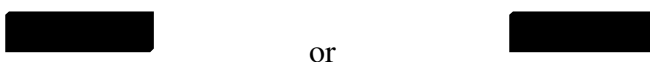
ii) **The Response Conflict task (RCT)** is a computerized task that consists of a series of two compatible (i.e., *non-conflict location, non-conflict direction*) and three incompatible (i.e., *conflict location, conflict direction, direction-location conflict*) conditions. The conflict and the non-conflict conditions are presented as pairs in the following manner: the location non-conflict is followed by the location-conflict; the direction non-conflict is followed by the direction conflict; and the direction-location conflict is presented at the end. This task is designed to assess the participant’s ability to override a prepotent motor response. As in the SCT, the *non-conflict location* condition requires participants to press a mouse button corresponding to the side to which a rectangle appears (20 stimuli at the right side and 20 stimuli at the left side) in random order. In the *conflict location* condition similar rectangles appear in a random order (20 stimuli on the right side and 20 stimuli on the left side); however, for this condition participants are instructed to respond using the mouse button on the opposite side to which the rectangle appears. In the *non-conflict direction* condition centrally located arrows pointing right (20 stimuli) or left (20 stimuli) are presented in a randomized order; similar to the first condition in the SCT,

participants are required to press the mouse button on the side to which the arrows are pointing. For the *conflict direction* condition, participants are again shown centrally-located arrows randomly pointing to the right (20 stimuli) or left (20 stimuli). However, in this condition, they are asked to press the mouse button on the side opposite to which the arrow is pointing. Finally in the *direction-location conflict* condition, participants are presented in a randomized order 20 arrows pointing left, located on the right side of the computer screen, and required to press the right mouse button; 20 arrows pointing right, located on the left, and required to press the left mouse button; 20 arrows pointing left, located on the left, and required to press the right mouse button; and 20 arrows pointing right, located on the right, and required to press the left mouse button. In this condition participants are instructed to disregard location of the stimuli and respond to direction; however, they are instructed to press the button opposite to the direction in which the arrow is pointing. Thus, this final condition combines both perceptual and motor conflict characteristics. Figure 3 depicts the RCT stimuli and the task instructions.

Figure 3. Stimuli and Instructions on the Parent vs. of the Response Conflict Task

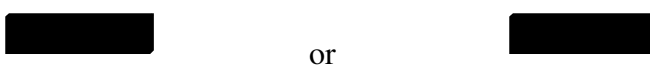
Condition 1 (Compatible)

“Press the mouse button on the same side as the block”



Condition 2 (Incompatible)

“Press the mouse button on the opposite side of where the block is”



Condition 3 (Compatible)

“Press the mouse button on the same side as where the arrow is pointing”



or



Condition 4 (Incompatible)

“Press mouse button on the opposite side of where the arrow is pointing”



or



Condition 5 (Incompatible)

“Disregard the location and press the mouse button on the opposite side of where the arrow is pointing”



or



For both components of the PMCT, the stimuli remain on the screen until a response is made, after which there is a 1-second inter-stimulus interval. Accuracy, median reaction time, and the standard deviation of reaction times were recorded for each condition, and used as the dependent measures of performance.

2. **Delayed Non-Matching to Sample Test (DNMST; Marks et al., 2005)** – The adult version of the DNMST was exactly the same as the child version of the DNMST that is described above in the “Child Measures” section. The number of correct responses were calculated for both conditions of the DNMST and used as the dependent measure.

## B. Actigraph

The same actigraphs used for child participants were also employed to objectively measure parents' activity level during the assessment period. Parents wore one actigraph around their waist and another one around their non-dominant ankle. The median activity level obtained over an hour long evaluation session from the ankle and waist actigraph measures were calculated using the same procedure described earlier and used as the dependent measure.

### Procedure

#### *Child Assessment:*

Based on the ADHD-RS, rated by parents and teachers, children were categorized into two groups; "hyperactive/inattentive" (HI) and "normal control" (NC). Those children whose parents or teachers endorsed 6 or more items within a single domain (i.e., Inattentive or Hyperactive/Impulsive) as '2' (often) or '3' (very often) were grouped as HI, and those children whose parents and teachers endorsed fewer than 3 such items in a given domain were grouped as NC. After categorization, if participants met all the exclusionary criteria the children and their parents were invited to the Developmental Neuropsychology laboratory at Queens College for the second phase of this study. The second phase consisted of two sessions which were held on two days in close proximity.

During the first session, a full description of the study was presented to parents, who then signed IRB-approved consent forms. During the first and second sessions, children were administered an array of cognitive measures as part of the larger study along with the WPPSI-III and the abovementioned novel computerized neuropsychological measures. Each computerized

measure was administered as paired control and experimental conditions to isolate the construct of interest. In all cases, the administration of the control condition preceded the experimental condition. To ensure that children comprehended task instructions, all participants completed practice trials in a booklet as well as on the computer. The computerized practice sessions (first three trials) were introduced in both the control and experimental conditions of all tasks. The practice session was programmed in such a way that if the child did not successfully complete 2 out of 3 trials, the practice session continued until it was clear that the child understood the task. Reinforcements (stickers) were given after each task regardless of accuracy to help maintain the children's interest and involvement in the task; breaks and snacks were used to prevent fatigue. Children were provided with a large two-button mouse that clearly differentiates the left from right button, therefore allowing the child to press the task-appropriate button with ease.

*Parent Assessment:*

While the parents were awaiting the completion of their child's assessment, they were approached to gauge their willingness to participate in the parent study. If interested, a separate informed consent procedure was used for each parent. The parent assessment was completed in a room adjacent to where their child was being evaluated. This provided a quiet and confidential setting with close proximity to their child. All assessments were completed by trained graduate students who were blind to the child and parents' group status at the time of the evaluation. After consenting to the current dissertation project, parents were provided with a pair of actigraphs to wear around their waist and non-dominant ankle. Then they were administered the two subtests of the WASI followed by the PMCT and DNMST in randomized order, which was generated using a table of random numbers. Within the PMCT, the SCT and RCT were

administered in a fixed order, with the SCT administered first. For the DNMST the control condition always preceded the experimental condition. Unlike the child version of the PMCT, the parent version of this task did not start with practice trials. In contrast, the DNMST included built-in computerized practice trials, which were administered to all respondents. Finally, parents were asked to complete a rating scale (CAARS-S:L) describing their own behavior. In addition, a similar questionnaire (CAARS-O:L) to be completed by their significant other (e.g., spouse, close friend, or family member). To maintain the confidentiality and independence of the ratings, parent participants were asked to return the scales in a business reply envelope, and were discouraged from sharing the completed rating scales with each other when both spouses participated in the study. The entire test battery took approximately 45-55 minutes to complete.

### Data Analysis

To ensure the validity of the child PMCT data, only accurate responses that occurred within a selected range of reaction time were included in the data analysis. The lower limit of the range (400 ms) was established because faster responses did not exceed a chance level of accuracy in this preschool sample. The upper limit of the range was established separately for each condition by selecting the 90<sup>th</sup> percentile reaction time for that condition.

To ensure the validity of the parent PMCT data, as the extant literature suggests (Krusch et al., 1996; Miller et al., 1999) only trials with reaction times between 200 ms to 2000 ms were included in the data analysis. Further, only participants who performed with 75% or more accuracy were included in the data analysis. This 75% accuracy criterion was not applied to the child data since a large proportion of children had less than 75% accuracy. The data from mothers and fathers were analyzed separately for each measure.

Data from children, fathers, and mothers were analyzed using separate two-way (Group x Condition) analyses of variance (ANOVA). Child's grouping status (i.e., NC and HI) based on the ADHD-RS served as the between-groups independent variable 'Group' for both child and parent data analyses. The paired control and experimental conditions of each computerized task served as the within-group independent variable, 'Condition'. Number of correct responses, median reaction time (RT), and SD of RT were used as the dependent variables.

For both the child and parent versions of the SCT, number of correct responses and median RT on the *non-conflict direction* condition (control) were compared with those on the *direction-location conflict* (i.e., *conflict-congruent* and *conflict-incongruent*) condition (experimental). For the child version of the RCT, number of correct responses and median RT on the *location no-conflict* condition were compared with those on the *location-conflict* condition. For the parent version of the RCT, number of correct responses and median RT on the following paired conditions were compared: *location no-conflict* with *location conflict* condition, *direction no-conflict* with *direction conflict* condition, and *direction no-conflict* with *direction-location conflict* condition. To assess group differences in RT variability, the RT SD from the SCT and RCT were compared separately for both parents and child using independent samples t-tests. For the DNMST, the number of correct responses on the *matching* (control) condition was compared with that of the *memory* (experimental) condition. Separate two-way (Group X Condition) mixed ANOVAs were used for child and parent participants to assess the performance difference as a function of group and condition on each neurocognitive construct measured by the computerized tasks.

For each dependent measure, a significant main effect of Group would indicate a performance difference between NC and HI groups. A significant main effect of Condition,

indicating superior performance on the control condition than the experimental condition, would provide support for the validity of the experimental manipulation. A significant Group X Condition interaction would be consistent with the notion that a performance difference between groups varied as a function of condition. According to the additive factors model (Sergeant, 1996; Sternberg, 1969), which assumes that the task performance is the sum of sequential and independent processes, a significant interaction between Group and Condition would be required to infer a specific deficit in the neurocognitive constructs of interest. In contrast, if the interaction terms are not significant, a specific deficit in the function of interest cannot be inferred.

To assess group differences with regard to objectively measured activity level, the ankle and waist median activity counts were compared separately for both child and parent participants using independent samples t-tests.

To assess the Simon Effect, SCT data were further analyzed using separate 2-way (Group X Condition) ANOVAs between the *conflict-congruent* and *conflict-incongruent* conditions. A significant main effect of Condition, indicating relatively poorer performance on the *conflict-incongruent* condition, by definition, would reveal the presence of Simon Effect. A significant Group X Condition interaction would indicate that those from the HI and NC group exhibit the Simon Effect differentially.

*Hypothesis 1:* Children from the HI group will perform significantly more poorly on measures of inhibitory control, working memory, and state regulation compared to children from the NC group. This hypothesis was tested using separate 2-way (Group X Condition) mixed ANOVAs to evaluate performance differences between the HI and NC children across control and experimental conditions of each dependent measure of inhibitory control, working memory,

and state regulation. The accuracy (number of correct responses) and median reaction time on the SCT and RCT were used as the dependent measures to assess distinct aspects of inhibitory control. The performance difference in working memory was assessed by differential performance on memory and matching conditions on the DNMST by the HI and NC children. The group difference on the state regulation was assessed by comparing the HI and NC groups on the reaction time variability on the SCT and RCT using independent samples t-tests.

*Hypothesis II:* Parents of HI preschoolers will perform more poorly on the inhibitory control, working memory, and state regulation measures as compared to parents of NC preschool children. Further, parents of children in the HI group who do not exhibit ADHD symptoms on behavioral rating scales will perform in between the parents of NC children and symptomatic parents of the HI group.

Similar to the child data, the first part of Hypothesis II was evaluated using separate 2-way (Group X Condition) ANOVAs for father and mother to assess the performance difference between the parents of HI and NC children on the dependent measures of inhibitory control and working memory as a function of group and condition. The group difference on the state regulation was assessed using the reaction time variability of the SCT and RCT using separate independent samples t-tests for father and mother.

In order to evaluate the second part of the Hypothesis 2, based on their ratings on the CAARS, parents were subdivided into three groups: i) parents of NC without current ADHD symptoms (NC-SX; Mother =69; Father = 31), ii) parents of HI without current ADHD symptoms (HI-SX; Mother =52; Father = 31), and iii) parents of HI with current ADHD symptoms (HI+SX; Mother = 13; Father = 7). Ratings above 60 on the ADHD Index of CAARS-Self and/or CAARS-Observer were used to indicate the presence of current ADHD

symptoms. Separate 2-way (Group X Condition) mixed ANOVAs were used to assess the difference between these three groups on measures of inhibitory control and working memory for fathers and mothers. Again, an independent samples t-test with reaction time variability on the SCT and RCT serving as the dependent variable was used to assess group differences regarding state regulation.

*Hypothesis III:* Consistent with the notion that neurocognitive performance is at least in part genetically mediated, performance of parents and their offspring on measures of inhibitory control, working memory, and state regulation will be significantly correlated. This hypothesis was evaluated using Pearson product moment correlations examining the relationship between the performance of children and their parents on the measures of the abovementioned neurocognitive constructs. For example, children's performances on the control conditions were expected to be positively correlated with that of the parents' performance. Similarly, children's performances on the experimental conditions were expected to be positively correlated with that of parents' performance.

## RESULTS

### Sample Characteristics

#### Characteristics of Child Participants:

A total of 175 ethnically diverse children with a mean (SD) age of 4.29 (.48) years were recruited for the on-going project. Significant ( $p < .001$ ) group differences were observed with respect to WPPSI-III Full Scale IQ (FSIQ), Socio Economic Status (SES), and by definition, behavioral ratings on the ADHD-RS. The SES was assessed using the method outlined by Nakao & Treas (1994). As has been typically reported in the ADHD literature, children from the HI group, relative to normal controls, had significantly lower FSIQ scores and came from lower SES families.

Preschoolers from the HI group were also rated as significantly more hyperactive and inattentive on the ADHD-RS by both parents and teachers. However, the groups did not differ with regard to age and gender. Table 3 reports the sample characteristics for child participants.

Table 3  
Sample Characteristics: Child Participants

	<b>HI</b> (n=106)	<b>NC</b> (n=69)	<i>P</i>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
Age	4.34 (.47)	4.22 (.48)	.10
% Boys	72.8	60.3	.08
FSIQ	102.16 (13.09)	113.26 (11.93)	<.001
SES	47.66 (18.37)	59.43 (14.20)	<.001
ADHD-RS by Parent	27.76 (10.44)	8.67 (4.80)	<.001
ADHD-RS by Teacher	30.40 (12.40)	4.69 (4.36)	<.001

### Characteristics of Parent Participants:

One-hundred and ninety parents of the children in this sample (118 mothers, mean age 36.6 years, and 72 fathers, mean age 38.3 years) participated in the current project. Among the NC-Parents, there were 47 mothers and 31 fathers. Among HI parents, 71 were mothers and 41 were fathers. The parents of HI and NC groups differed significantly on the ADHD index of the CAARS – Observer completed by each parent’s significant other (fathers:  $p < .05$ ; mothers:  $p < .05$ ). Specifically, both mothers and fathers of HI children received higher ratings on the ADHD index of the CAARS-Observer. The two parent groups (controls and HI parents) did not differ with respect to CAARS-Self ratings or age. Tables 4 and 5 provide descriptive statistics of the parent sample.

Table 4  
Sample Characteristics: Mother Participants

	<b>HI</b> (n=71)	<b>NC</b> (n=47)	<i>P</i>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
Age	35.98 (6.44)	37.48 (5.64)	.19
FSIQ	103.46 (12.72)	106.19 (12.47)	.25
CAARS – ADHD Index: Self	45.42 (9.97)	46.63 (7.96)	.48
CAARS – ADHD Index: Observer	51.36 (8.30)	47.91 (7.63)	.03

Table 5  
Sample Characteristics: Father Participants

	<b>HI</b> (n=41)	<b>NC</b> (n=32)	<i>p</i>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
Age	37.74 (5.42)	39.02 (6.70)	.38
FSIQ	102.8 (12.21)	107.32 (11.39)	.11
CAARS – ADHD Index: Self	48.90 (8.51)	46.74 (9.90)	.38
CAARS – ADHD Index: Observer	50.71 (11.76)	45.0 (8.28)	.03

### Possible Participation Bias

The likelihood of parental participation varied significantly as a function of child's grouping status, such that a significantly greater proportion of parents of NC vs. HI preschoolers took part in the current study. However, no significant group difference was observed with regard to SES or parent- or teacher-reported ADHD severity as a function of parental participation. Tables 6 and 7 depict these findings.

Table 6  
Parental Participation as a Function of Child Group Status

Child's group status	Parents participated	Parent <i>didn't</i> participate	$\chi^2$	<i>p</i>
NC	59 (85.5%)	10 (14.5%)	4.75	.03
ADHD	80 (71.4%)	32 (28.6%)		

Table 7  
Child SES and Behavioral Ratings as a Function of Parents' Participation Status

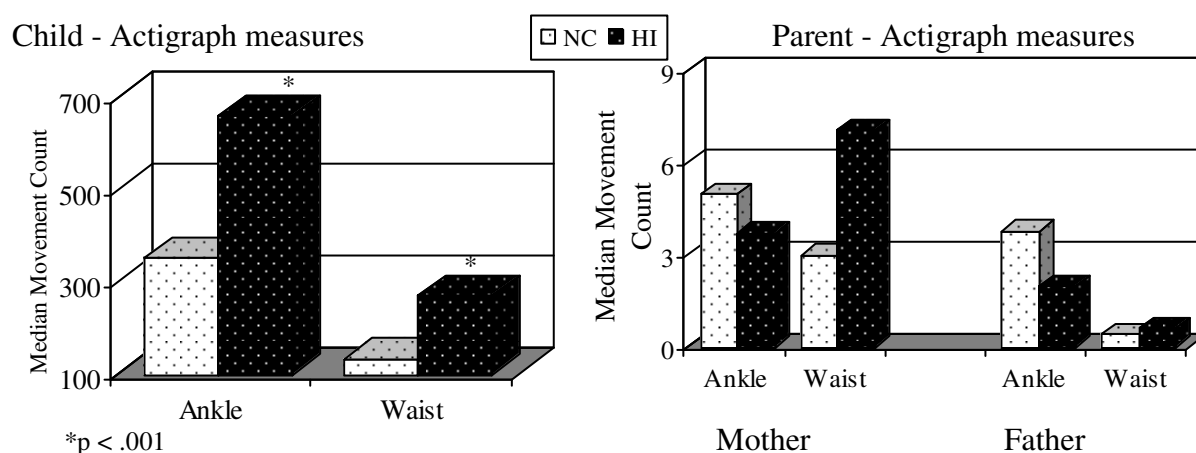
	Parent Participated (n=137)	Parent <i>Didn't</i> Participate (n=38)	<i>p</i>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	
SES	49.70 (16.24)	53.00 (17.79)	.50
ADHD ratings by Parents	21.60 (9.68)	19.77 (13.43)	.43
ADHD ratings by Teacher	22.65 (15.21)	19.53 (16.27)	.30

### Activity Level

In support of the child classifications based on parent and teacher ratings on the ADHD-RS, independent-sample t-tests revealed that children from HI and NC groups differed significantly with respect to ankle ( $t(156) = -3.50, p < .001$ ) and waist ( $t(155) = -4.03, p < .001$ ) median activity levels assessed by solid state actigraphs. HI preschoolers were significantly more active than controls as measured by both devices. Such group difference in activity level

was not observed among parents' ankle and waist actigraph measures. Figure 4 depicts the child and parent activity levels respectively.

Figure 4. Activity Levels as Measured by Actigraphs



## Hypothesis I: Children

### Response Inhibition

Two constructs of response inhibition; perceptual inhibition and motor inhibition were assessed by the SCT and RCT, respectively. For each task the number of correct responses (accuracy) and the median reaction time (latency to response) were used as dependent measures to compare the performance of the HI and NC children.

#### 1. Perceptual Inhibition (SCT)

*Number of correct responses:* A two-way (Group X Condition) mixed ANOVA for number of correct responses on the SCT was conducted between the paired control (*non-conflict direction*) and experimental (*conflict-congruent* and *conflict-incongruent*) conditions. The results yielded a significant main effect of Condition [ $F(2,159) = 711.77, p < .001$ ; partial  $\eta^2 = .90$ ] indicating that participants committed significantly more errors on the conflict conditions (i.e., *congruent conflict* and *non-congruent conflict* conditions) than the non-conflict condition.

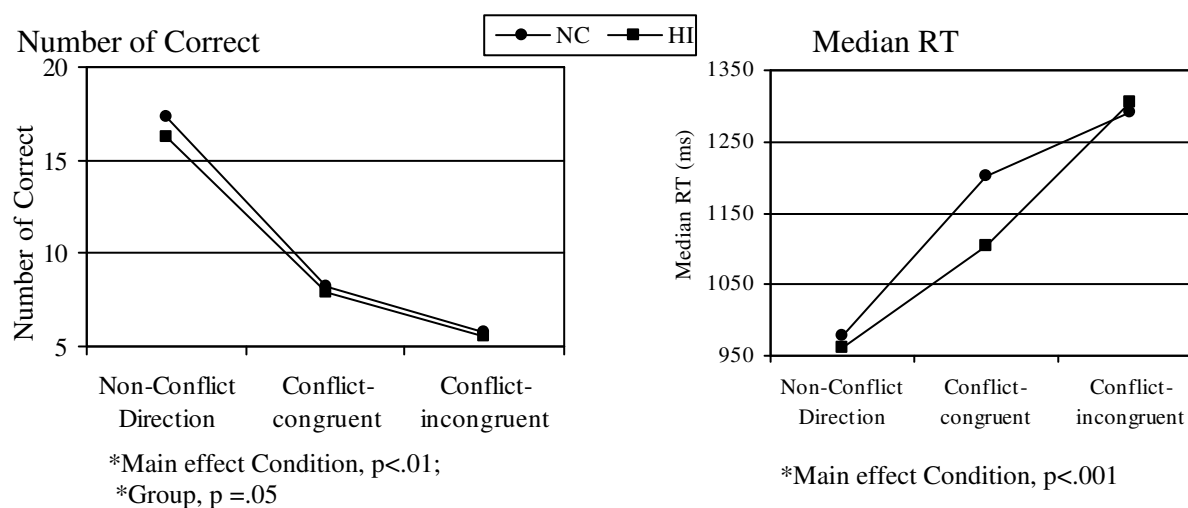
A significant main effect of Group also emerged [ $F(1,160) = 3.82, p = .05$ ; partial  $\eta^2 = .02$ ], indicating that HI children committed significantly more errors than NC participants irrespective of condition. However, there was no significant Group X Condition interaction ( $F(2, 159) = 1.39, p = .251$ ; partial  $\eta^2 = .02$ ), which suggests that although HI children committed significantly more errors than NC, their poorer performance was not due to a specific deficit in perceptual inhibition.

*Median reaction time (RT):* The 2-way (Group X Condition) mixed ANOVA for median RT on the SCT yielded a significant main effect of Condition [ $F(2,147) = 42.84, p < .001$ ; partial  $\eta^2 = .37$ ] but not Group [ $F(1,148) = .54, p = .46$ ; partial  $\eta^2 = .004$ ], indicating that, although participants were significantly slower on the conflict conditions as compared to the non-conflict conditions, RT did not differ as a function of group. In addition, there was no significant Group X Condition interaction [ $F(2,147) = 2.05, p = .13$ ; partial  $\eta^2 = .03$ ], suggesting that the groups did not perform differentially as a function of condition. The lack of a Group X Condition interaction indicates that the performance of HI preschoolers does not reflect a specific deficit in perceptual inhibition. Table 8 and Figure 5 depict children's performance on the SCT as indicated by the number of correct responses and median RT.

Table 8  
Mean (SD) of Dependent Measures of the Child SCT

	Number Correct		Median RT (ms)	
	Mean (SD)		Mean (SD)	
Condition	NC	HI	NC	HI
Non-Conflict Direction	17.37 (2.91)	16.23 (2.9)	979.11 (220.82)	960.40 (246.75)
Conflict-Congruent	8.24 (2.2)	7.86 (2.18)	1200.91 (370.61)	1104.52 (294.14)
Conflict-Incongruent	5.72 (2.85)	5.57 (2.7)	1291.64 (422.78)	1305.49 (504.42)

Figure 5. Child SCT



## 2. Motor Inhibition (RCT):

*Number of correct responses:* Similar to the findings on the SCT, 2-way (Group X Condition) mixed ANOVA for number of correct responses on the RCT yielded significant main effects of Condition [ $F(1,159) = 60.97, p < .001$ ; partial  $\eta^2 = .28$ ] and Group [ $F(1,159) = 5.76, p < .05$ ; partial  $\eta^2 = .04$ ], indicating that children were less accurate on the conflict condition and that the HI group performed, overall, less accurately than the NC group. However, there was no significant Group X Condition interaction for correct responses [ $F(1,159) = .97, p = .33$ ; partial  $\eta^2 = .006$ ], indicating that the groups did not perform differentially as a function of condition. Thus, poorer accuracy by HI group does not appear to be attributable to specific deficits in motor inhibition.

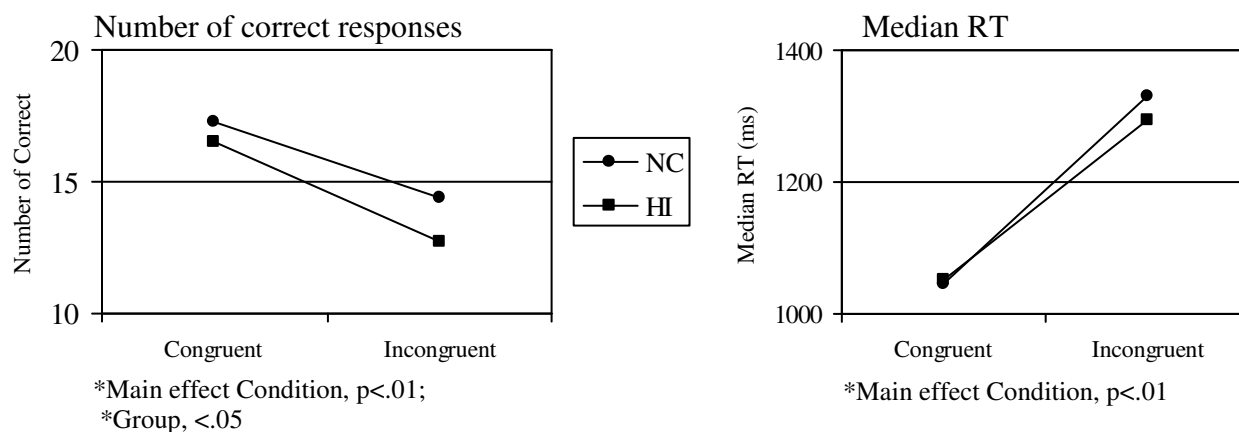
*Median RT:* Similar to the findings on the SCT, the 2-way (Group X Condition) mixed ANOVA for median RT on the RCT yielded a significant main effect of Condition [ $F(1,159) = 61.44, p < .001$ ; partial  $\eta^2 = .28$ ], indicating that participants were significantly slower on the conflict condition than the non-conflict condition. There was no significant main effect of Group

( $F(1,159) = .07, p = .80$ ; partial  $\eta^2 = .00$ ) or Group X Condition interaction ( $F(1,159) = .32, p = .57$ ; partial  $\eta^2 = .002$ ). Hence, again the findings do not provide support for a specific deficit in motor inhibition. Table 9 and Figure 6 depict the results of the RCT.

Table 9  
Mean (SD) of Dependent Measures of the Child RCT

Condition	Number Correct		Median RT (ms)	
	NC	HI	NC	HI
Congruent	17.31 (3.33)	16.48 (3.46)	1045.43 (289.29)	1050.23 (325.70)
Incongruent	14.37 (4.85)	12.69 (5.00)	1328.96 (435.31)	1295.40 (518.80)

Figure 6. Child RCT



### Working Memory

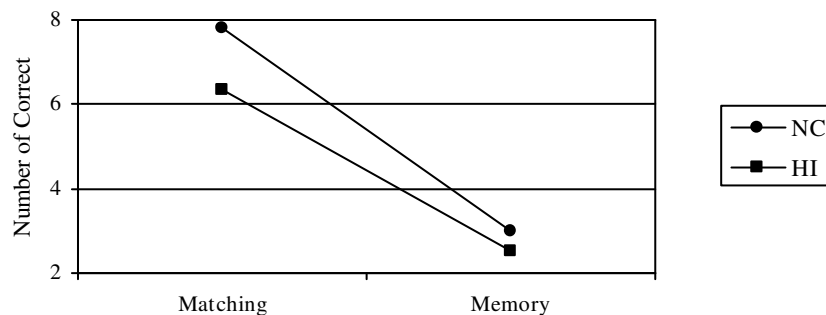
Working memory was assessed by the number of correct responses on the DNMST. The 2-way (Group X Condition) mixed ANOVA for DNMST yielded a significant main effect of Condition [ $F(1,162) = 272.22, p < .001$ ; partial  $\eta^2 = .63$ ] indicating that participants committed significantly more errors on the memory condition than the matching condition. There was a

significant main effect of Group ( $F(1,162) = 8.45, p < .05$  partial  $\eta^2 = .05$ ), indicating that HI children were significantly less accurate than NC irrespective of condition. Although not statistically significant, a marginally significant Group X Condition interaction emerged [ $F(1, 162) = 3.63, p = .058$ ; partial  $\eta^2 = .02$ ] such that the NC group had a somewhat steeper decline across conditions than the HI group (see Figure 7 and Table 10). Thus, the HI group did not demonstrate a specific visual working memory deficit as measured by this task; they performed more poorly irrespective of condition.

Table 10  
Mean (SD) of Dependent Measure of the Child DNMST

	Number Correct	
	Mean (SD)	
Condition	NC	HI
Congruent	7.82 (3.056)	6.33 (3.45)
Incongruent	3.00 (1.85)	2.52 (1.86)

Figure 7: Child DNMST



\*Main effect, Condition,  $p < .001$ ; \*Group,  $p < .05$ ; Group x Condition,  $p = .058$

### State Regulation

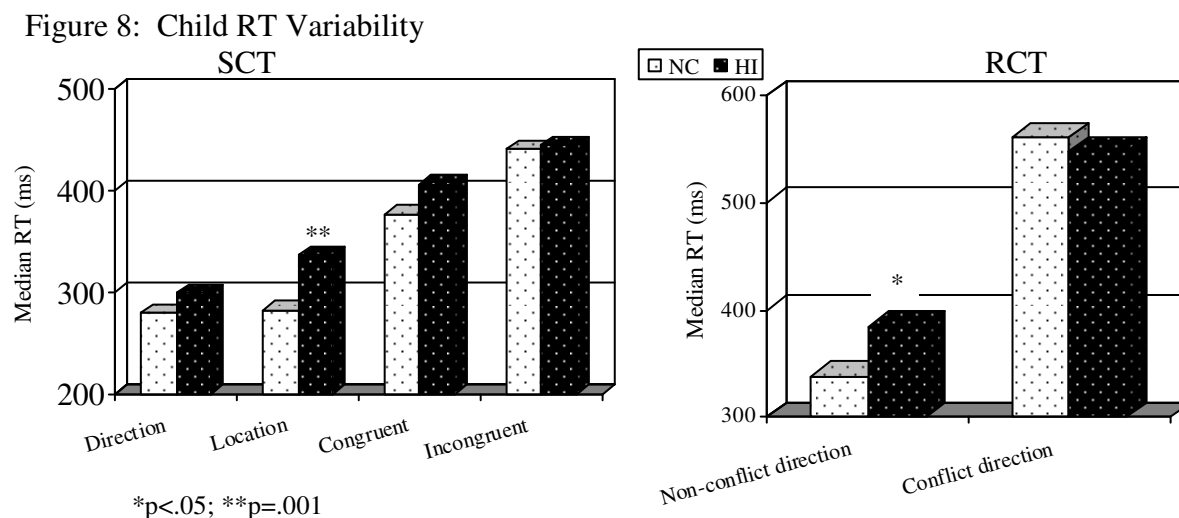
*RT variability (SCT)*: Independent samples t-tests using the RT standard deviation from the SCT yielded a significant ( $t(160) = -3.26; p = .001$ ) group difference on the non-conflict

location condition (not on non-conflict direction), but not on any conflict conditions (i.e., congruent conflict and incongruent conflict) of the SCT. Thus, as compared to NC, HI children have a greater variability in their reaction time for simple choice reaction time; however the group difference seems to diminish on the more challenging conflict conditions.

*RT variability (RCT):* Similar to the SCT, independent-samples t-tests yielded a significant group difference on the standard deviation of RT on the non-conflict condition ( $t(159) = -2.13; p < .05$ ) but not on the conflict condition of the RCT. Again, HI children had greater variability in reaction time than NC on the non-conflict condition but not the more complex conflict condition. Table 11 and Figure 8 depict the RT Variability on the SCT and RCT.

Table 11  
Mean (SD) of RT Variability of the Child SCT and RCT

Condition	Median RT (ms)	
	Mean (SD)	
	NC	HI
<b>SCT Non-Conflict Direction</b>	279.66 (91.50)	299.05 (93.23)
<b>SCT Non-Conflict Location</b>	282.55 (91.21)	335.98 (110.09)
<b>SCT Conflict-Congruent</b>	376.35 (165.72)	405.52 (177.25)
<b>SCT Conflict-Incongruent</b>	439.70 (223.38)	443.89 (305.91)



In sum, although HI children performed more poorly than NC across most measures, the lack of significant Group x Condition interactions does not support the hypotheses that their relatively poorer performance is due to a specific deficit in response inhibition or working memory. However, differences in RT variability are at least partially consistent with state regulation deficits in the HI group that might diminish under more challenging conditions.

## **Hypothesis II: Part 1**

### **Mothers:**

#### **1. Perceptual Inhibition (SCT)**

*Number of correct responses:* The two-way (Group X Condition) mixed ANOVA for number of correct responses was conducted between the paired control (*non-conflict direction*) and experimental (*conflict-congruent* and *conflict-incongruent*) conditions of the SCT. The results revealed that there was a significant main effect of Condition [ $F(2,115) = 37.42, p < .01$ ; partial  $\eta^2 = .394$ ] indicating that mothers committed significantly more errors on the conflict condition than the non-conflict condition. There was no significant main effect of Group [ $F(1,116) = 8.21, p = .367$ ; partial  $\eta^2 = .01$ ] or Group X Condition interaction [ $F(2,115) = .328, p =$

.721; partial  $\eta^2 = .01$ ] indicating that the HI-M and NC-M did not perform differentially as a function of condition.

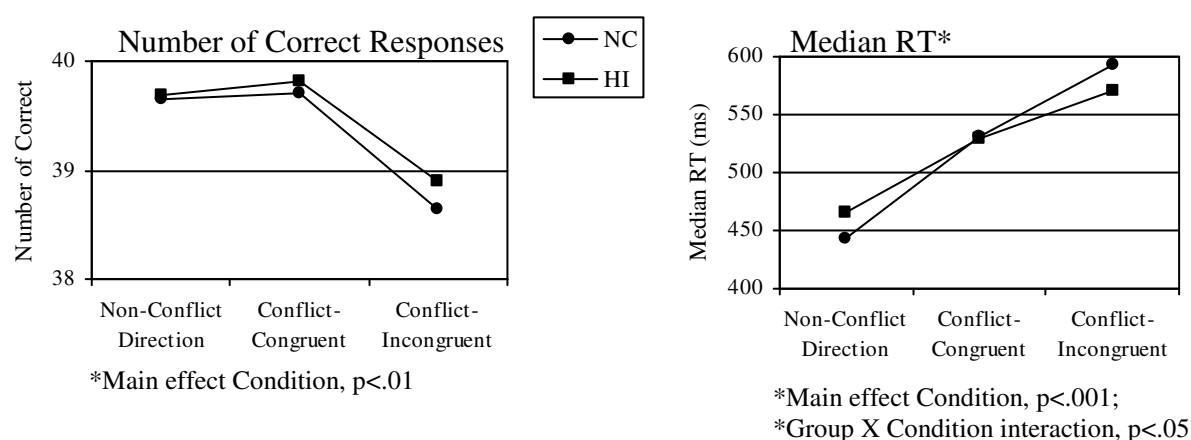
*Median RT:* The two-way (Group X Condition) mixed ANOVA for SCT median RT was conducted between the paired control (*non-conflict direction*) and experimental (*conflict-congruent* and *conflict-incongruent*) conditions. The results demonstrated that there was a significant main effect of Condition [ $F(2,115) = 190.62, p < .001$ ; partial  $\eta^2 = .77$ ] and Group X Condition interaction [ $F(2,115) = 6.19, p < .05$ ; partial  $\eta^2 = .10$ ] but no significant main effect of Group [ $F(1,116) = .007, p = .93$ ; partial  $\eta^2 = .001$ ]. These findings indicate that mothers had longer reaction times on the conflict conditions compared to non-conflict conditions. Although the groups did not perform differentially overall, the nature of Group X Condition interaction suggests that the mothers of NC group had a relatively shorter reaction time on the non-conflict condition and a longer reaction time on the incongruent-conflict condition than the mothers of HI participants. Hence, the interaction for median RT suggests that, as the complexity of the task condition increased, NC-M took a longer time to make a response than HI-M.

In sum, the significant main effects of condition for the number correct and median reaction time of the SCT suggest that, as the complexity of the task increased, mothers, irrespective of group status, struggled to maintain their accuracy and required a longer time to respond. Further, the significant Group X Condition interaction for SCT median RT quite interestingly suggests that this increased difficulty was more evident among NC-M vs. HI-M with increased complexity of the task. Table 12 and Figure 9 depict the findings based on the number of correct responses and median RT.

Table 12  
Mean (SD) of Dependent Measures of the Mother SCT

Condition	Number Correct Mean (SD)		Median RT (ms) Mean (SD)	
	NC-M (n=46)	HI-M (n=72)	NC-M (n=46)	HI-M (n=72)
Non-Conflict Direction	39.65 (.74)	39.68 (.58)	443.72 (83.88)	465.67 (100.62)
Conflict-Congruent	39.70 (.96)	39.82 (.48)	531.84 (83.92)	528.79 (86.47)
Conflict-Incongruent	38.65 (2.02)	38.90 (1.14)	593.18 (100.38)	570.13 (95.94)

Figure 9: Mother SCT



## 2. Motor Inhibition (RCT)

*Number of correct responses:* Separate two-way (Group X Condition) mixed ANOVAs for number of correct responses were conducted for each pair of control and experimental condition of the RCT: i) *location no-conflict* and *location conflict* condition, ii) *direction no-conflict* and *direction conflict* condition, and iii) *direction no-conflict* and *direction-location conflict* condition (i.e., *conflict-congruent* and *conflict-incongruent*). The results demonstrated that there were significant main effects of Condition for each paired analysis, indicating that participants committed significantly more errors during the conflict conditions than the non-

conflict conditions on every paired comparison. There were no significant main effects of Group for any of the abovementioned ANOVAs. There was a significant Group X Condition interaction [ $F(1,122) = 3.92, p = .05; \text{partial } \eta^2 = .03$ ] for only the comparison between *location no-conflict* and *location conflict* conditions. The nature of the interaction suggests that NC-M committed comparable errors to the HI-M on the non-conflict condition and significantly more errors on the conflict condition than the HI-M. There were no other interactions for other ANOVAs. Tables 13 and 14, and Figures 10a, 10b, and 10c depict the F-values and results respectively.

Table 13  
Mean (SD) of Number Correct of the Mother RCT

Condition	Number Correct Mean (SD)	
	NC-M (n=50)	HI-M (n=74)
Non-Conflict Location	39.92 (.34)	39.92 (.32)
Conflict Location	39.46 (.95)	39.74 (.64)
Non-conflict Direction	39.58 (.70)	39.65 (.56)
Conflict Direction	39.18 (1.9)	39.38 (1.1)
Conflict-Congruent	37.70 (3.96)	36.73 (7.9)
Conflict-Incongruent	38.26 (2.9)	38.27 (5.1)

Table 14  
Mother RCT: Number of Correct Responses

Paired Conditions	Main Effect of Condition	Main Effect of Group	Interaction
Non-conflict Location & Conflict Location	$F(1,122) = 19.58$ , $p < .001$ ; partial $\eta^2 = .14$	$F(1,122) = 2.89$ , $p = .09$ partial $\eta^2 = .02$	$F(1,122) = 3.92$ , $p = .05$ partial $\eta^2 = .03$
Non-conflict Direction & Conflict Direction	$F(1,122) = 7.03$ , $p < .01$ partial $\eta^2 = .05$	$F(1,122) = .66$ , $p = .42$ partial $\eta^2 = .005$	$F(1,122) = .263$ , $p = .61$ partial $\eta^2 = .002$
Non-conflict Direction & Conflict- Congruent & Conflict-Incongruent	$F(2,121) = 8.92$ , $p < .001$ partial $\eta^2 = .13$	$F(1,122) = .23$ , $p = .64$ partial $\eta^2 = .002$	$F(2,121) = .58$ , $p = .56$ partial $\eta^2 = .01$

Figure 10a: Mother RCT: Number of Correct Responses: Non-Conflict Location and Conflict Location Conditions

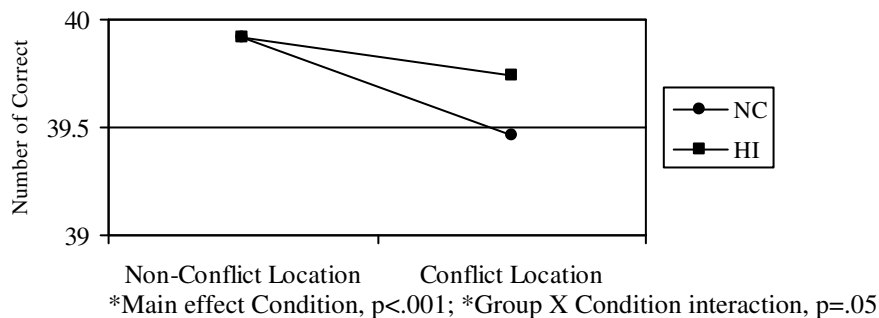


Figure 10b: Mother RCT: Number of Correct Responses: Non-Conflict Direction and Conflict Direction Conditions

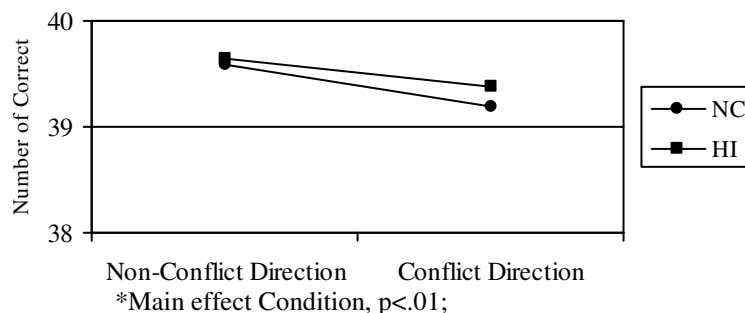
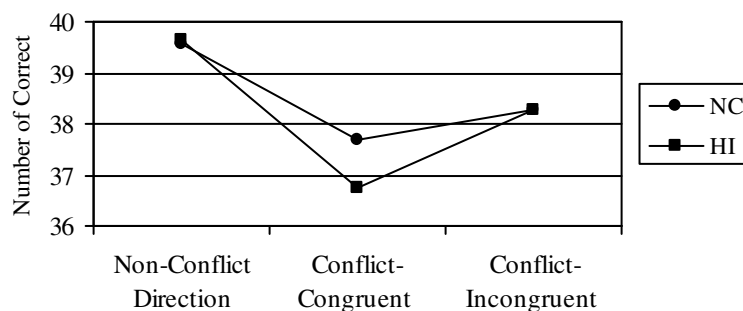


Figure 10c: Mother RCT: Number of Correct Responses: Non-Conflict Direction and Conflict-Congruent and Conflict-Incongruent Conditions



\*Main effect Condition,  $p < .001$

*Median RT:* Separate two-way (Group X Condition) mixed ANOVAs for RCT median RT were conducted for each pair of control and experimental conditions of the RCT: i) *location no-conflict* and *location conflict* condition, ii) *direction no-conflict* and *direction conflict* condition, and iii) *direction no-conflict* and *direction-location conflict* condition (i.e., *conflict-congruent* and *conflict-incongruent*). Again, each ANOVA revealed that there were significant main effects of Condition for each paired comparison but no significant main effects of Group or Group X Condition interactions. These results suggest that participants had more difficulty performing the conflict conditions; however, the performance difference across the conditions did not vary as a function of group. Tables 15 and 16, and Figures 11a, 11b, and 11c depict the F-values and the performance across conditions, respectively.

Table 15  
Mean (SD) of Median RT of the Mother RCT

Condition	Median RT (ms) Mean (SD)	
	NC-M (n=47)	HI-M (n=69)
Non-Conflict Location	386.76 (64.86)	388.89 (77.80)
Conflict Location	488.24 (97.01)	480.78 (105.67)
Non-conflict Direction	422.99 (61.63)	429.80 (74.00)
Conflict Direction	526.04 (101.04)	516.23 (101.20)
Conflict-Congruent	690.11 (168.95)	676.41 (171.03)
Conflict-Incongruent	644.14 (149.76)	643.77 (174.07)

Table 16  
Mother RCT: Median RT

Paired Conditions	Main Effect of Condition	Main Effect of Group	Interaction
Non-conflict Location & Conflict Location	F(1,114) = 207.31, p < .001; partial $\eta^2$ = .65	F(1,114) = .03, p = .86 partial $\eta^2$ = .00	F(1,114) = .51, p = .48 partial $\eta^2$ = .004
Non-conflict Direction & Conflict Direction	F(1,114) = 241.41, p < .001; partial $\eta^2$ = .68	F(1,114) = .01, p = .92; partial $\eta^2$ = .00	F(1,114) = 1.86, p = .18 partial $\eta^2$ = .016
Non-conflict Direction & Conflict- congruent & Conflict- Incongruent	F(2,113) = 209.02, p < .001; partial $\eta^2$ = .79	F(1,114) = .01, p = .92 partial $\eta^2$ = .00	F(2,113) = .58, p = .56 partial $\eta^2$ = .01

Figure 11a: Mother RCT: Median RT: Non-Conflict Location and Conflict Location

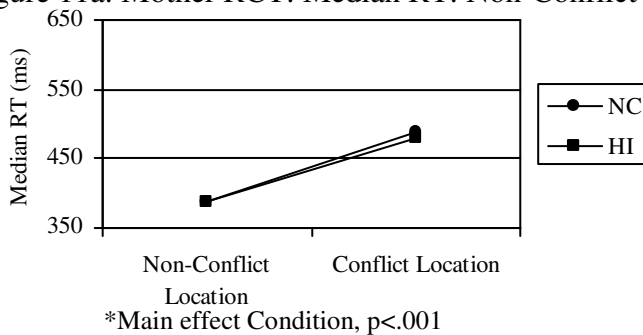


Figure 11b. Mother RCT: Median RT: Non-Conflict Direction and Conflict Direction Conditions

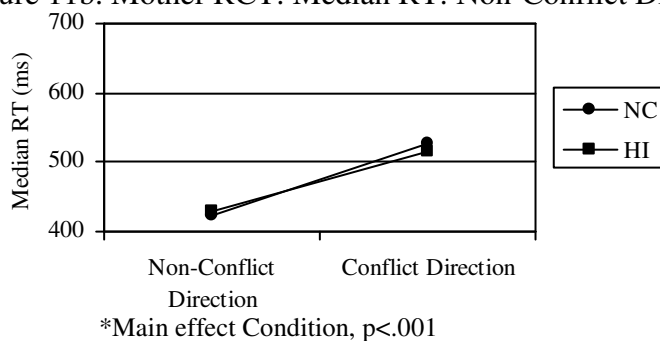
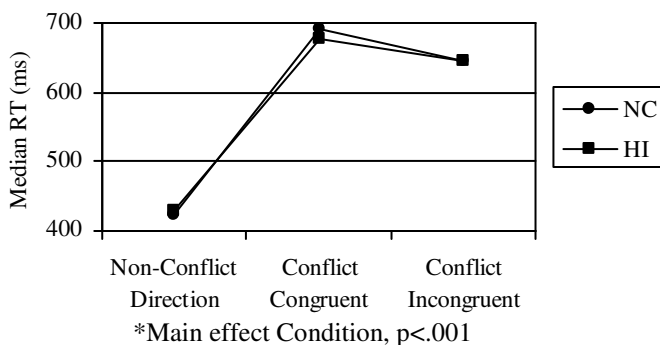


Figure 11c. Mother RCT: Median RT: Non-Conflict Direction and Conflict-Congruent and Conflict-Incongruent Conditions



In sum, there were virtually no significant Group x Condition interactions across paired comparisons for number correct and median RT of RCT. The only significant interaction was for number correct between non-conflict & conflict location conditions. The nature of this interaction suggests that the NC-M group had poorer accuracy relative to the HI-M group, while reaction time between these groups was comparable. The overall lack of significant Group X

Condition interactions for both the number of correct response and median RT suggest that HI-M do not have specific deficit in motor inhibition.

### **Fathers:**

#### 1. Perceptual Inhibition (SCT)

*Number of correct responses:* The two-way (Group X Condition) mixed ANOVA for number of correct responses was conducted for the paired control (*non-conflict direction*) and experimental (*conflict-congruent* and *conflict-incongruent*) conditions. Similar to the findings with mothers, the two-way (Group X Condition) mixed ANOVA for number of correct responses for father participants indicated that there was a significant main effect of Condition [ $F(2,70) = 8.75, p < .001; \text{partial } \eta^2 = .20$ ], suggesting that the participants committed more errors on the conflict condition compared to the non-conflict condition. However, there was no significant main effect of Group [ $F(1,71) = .857, p = .358; \text{partial } \eta^2 = .012$ ] or Group X Condition interaction [ $F(2, 70) = .054, p = .95; \text{partial } \eta^2 = .002$ ].

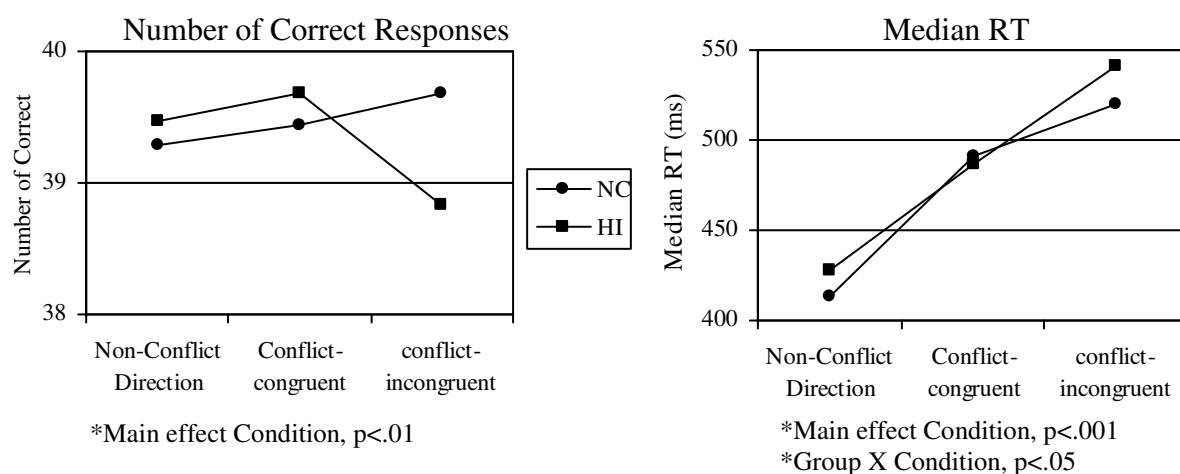
*Median RT:* Similarly, the two-way (Group X Condition) mixed ANOVA for median reaction time was conducted for the paired control (*non-conflict direction*) and experimental (*conflict-congruent* and *conflict-incongruent*) conditions. The results revealed a significant main effect of Condition [ $F(2,70) = 166.97, p < .001; \text{partial } \eta^2 = .83$ ], suggesting that participants had a significantly longer reaction time on the conflict condition compared to the non-conflict condition. There was no significant main effect of Group [ $F(1,71) = .396, p = .53; \text{partial } \eta^2 = .006$ ]. However, there was a significant Group X Condition interaction [ $F(2, 70) = 3.4, p < .05; \text{partial } \eta^2 = .89$ ], such that NC-F and HI-F groups did not differ in RT on the non-conflict condition, but HI-F had significantly longer reaction times on the conflict condition.

In sum, the lack of significant Group X Condition interaction for number correct suggests that the HI-F had comparable accuracy as the NC-F across conditions. Furthermore, the significant Group X Condition interaction for Median RT suggests that the HI-F group took significantly longer time to produce this similar accuracy as NC-F participants. Hence, the performance of fathers on the SCT is consistent with a specific deficit in perceptual inhibition/interference control among HI-F participants. Table 17 and Figure 12 depict the findings based on the number of correct responses and the median RT.

Table 17  
Mean (SD) of Dependent Measures of the Father SCT

Condition	Number Correct Mean (SD)		Median RT (ms) Mean (SD)	
	NC-F (n=32)	HI-F (n=41)	NC-F (n=32)	HI-F (n=41)
Non-Conflict Direction	39.28 (1.14)	39.46 (.84)	413.58 (56.63)	427.29 (84.06)
Conflict-Congruent	39.44 (.75)	39.68 (.57)	490.84 (75.44)	486.52 (73.68)
Conflict-Incongruent	38.69 (1.94)	38.83 (1.47)	520.08 (64.15)	540.57 (80.03)

Figure 12. Father SCT



## 2. Motor Inhibition (RCT)

*Number of correct responses:* The two-way (Group X Condition) mixed ANOVAs for number of correct responses were conducted for each paired control and experimental condition of the RCT: i) *location no-conflict* and *location conflict* condition, ii) *direction no-conflict* and *direction conflict* condition, and iii) *direction no-conflict* and *direction-location conflict* condition (i.e., *conflict-congruent* and *conflict-incongruent*). The separate analyses revealed a significant main effect of Condition only for the paired *non-conflict location & conflict location*. All remaining main effects and interactions were not significant. Tables 18 and 19, and Figures 13a, 13b, and 13c illustrate the results of this dependent measure.

Table 18  
Mean (SD) of Number Correct of the Father RCT

Condition	Number Correct Mean (SD)	
	NC-F (n=32)	HI-F (n=42)
Non-Conflict Location	39.97 (.18)	39.86 (.35)
Conflict Location	39.69 (.69)	39.67 (.61)
Non-conflict Direction	39.28 (.92)	39.43 (.74)
Conflict Direction	39.28 (1.46)	39.57 (.73)
Conflict-Congruent	39.06 (1.32)	39.02 (1.8)
Conflict-Incongruent	39.42 (.84)	39.48 (.74)

Table 19  
Father RCT: Number of Correct Responses

Paired Conditions	Main Effect of Condition	Main Effect of Group	Interaction
Non-conflict Location & Conflict Location,	$F(1,72) = 8.83, p < .01$ partial $\eta^2 = .109$	$F(1) = .58, p = .45$ partial $\eta^2 = .008$	$F(1,72) = .327, p = .57$ partial $\eta^2 = .005$
Non-conflict Direction & Conflict Direction	$F(1,72) = .321, p = .57$ partial $\eta^2 = .004$	$F(1,72) = 1.30, p = .26$ partial $\eta^2 = .02$	$F(1,72) = .321, p = .57$ partial $\eta^2 = .004$
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	$F(2,70) = 1.8, p = .17$ partial $\eta^2 = .05$	$F(1,71) = .13, p = .73$ partial $\eta^2 = .002$	$F(2,70) = .27, p = .78$ partial $\eta^2 = .007$

Figure 13a. Father RCT: Number of Correct Responses: Non-Conflict Location and Conflict Location Conditions

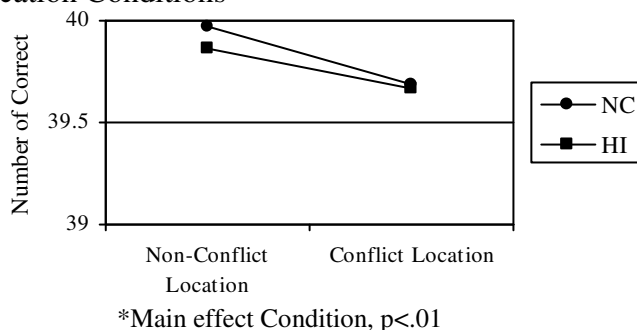


Figure 13b. Father RCT: Number of Correct Responses: Non-Conflict Direction & Conflict Direction Conditions

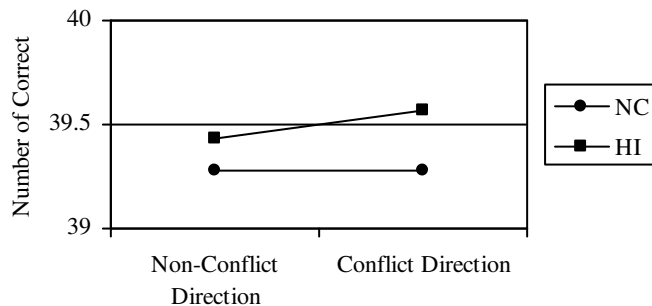
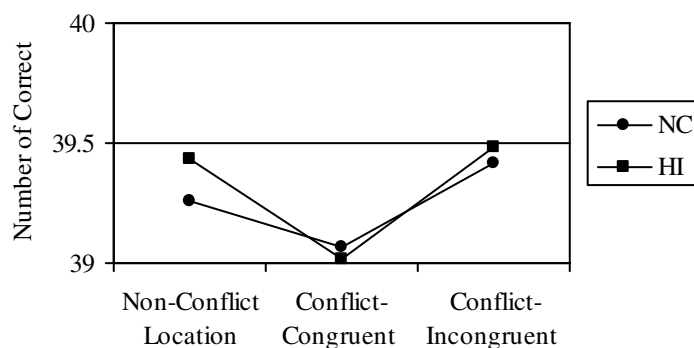


Figure 13c. Father RCT- Number of Correct Responses: Non-Conflict Direction and Conflict-congruent & conflict-incongruent Condition



*Median RT:* Similar to the findings from mothers, separate two-way (Group X Condition) mixed ANOVAs for median RT were conducted for each paired control and experimental condition of the RCT: i) *location no-conflict* and *location conflict* condition, ii) *direction no-conflict* and *direction conflict* condition, and iii) *direction no-conflict* and *direction-location conflict* condition (i.e., *conflict-congruent* and *conflict-incongruent*). The results revealed significant main effects of Condition for each ANOVA, indicating that the participants had longer reaction times on the conflict condition compared to the non-conflict condition. There was no significant main effect of Group for any paired analysis. There was one significant Group X Condition interaction for the non-conflict location vs. conflict location analysis such that HI-F had a shorter reaction time on the non-conflict condition and a longer reaction time on the conflict condition compared to NC-F. Tables 20 and 21, and Figures 14a, 14b, and 14c depict the performance across conditions of the RCT for NC-F and HI-F.

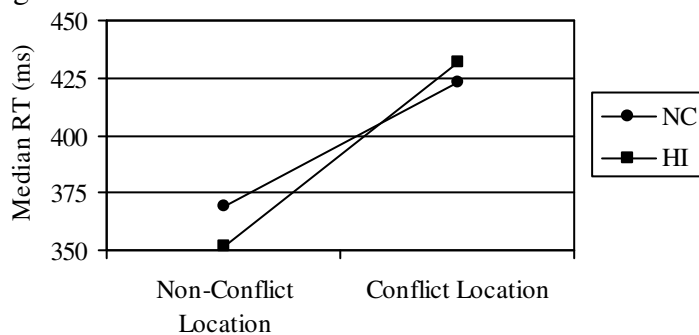
Table 20  
Mean (SD) of Median RT of the Father RCT

Condition	Median RT (ms) Mean (SD)	
	NC-F (n=32)	HI-F (n=42)
Non-Conflict Location	368.70 (83.34)	351.87 (63.05)
Conflict Location	423.19 (83.97)	431.54 (99.77)
Non-conflict Direction	389.23 (48.00)	397.70 (63.44)
Conflict Direction	440.55 (62.37)	458.64 (87.74)
Conflict-Congruent	547.32 (101.94)	578.86 (109.57)
Conflict- Incongruent	518.66 (86.48)	560.81 (113.44)

Table 21  
Father RCT: Median RT

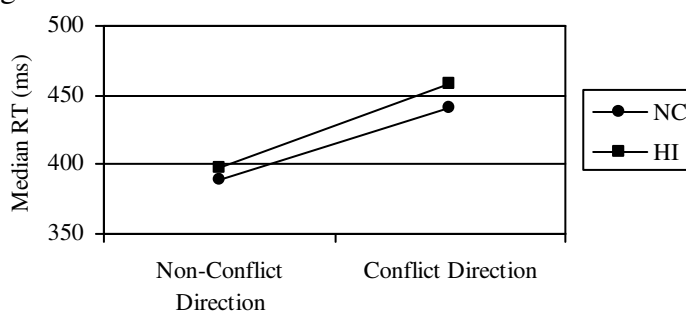
Paired Conditions	Main Effect of Condition	Main Effect of Group	Interaction
Non-conflict Location & Conflict Location	F(1,72) = 109.24, p < .001; partial $\eta^2$ = .60	F(1,72) = .05, p = .81 partial $\eta^2$ = .001	F(1,71) = 3.71, p = .05 partial $\eta^2$ = .05
Non-conflict Direction & Conflict Direction	F(1,72) = 91.93, p < .001 partial $\eta^2$ = .56	F(1,72) = .68, p = .41 partial $\eta^2$ = .01	F(1,71) = .68, p = .41 partial $\eta^2$ = .01
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	F(2,70) = 159.10, p < .001; partial $\eta^2$ = .82	F(1,71) = 1.94, p = .17 partial $\eta^2$ = .03	F(1,71) = 1.87, p = .16 partial $\eta^2$ = .05

Figure 14a. Father RCT: Median RT: Non-Conflict Location and Conflict Location Conditions



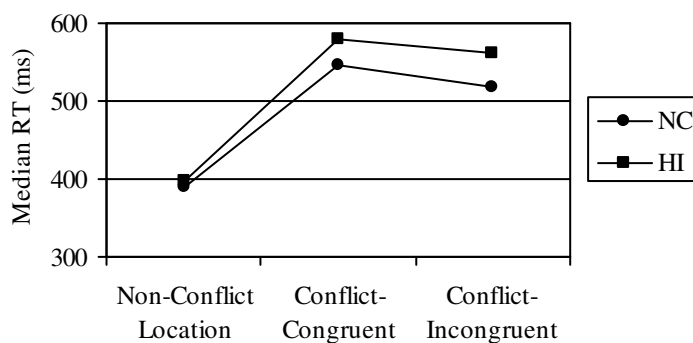
\*Main effect Condition,  $p < .001$ ; \*Group X Condition,  $p = .05$

Figure 14b. Father RCT: Median RT: Non-Conflict Direction &amp; Conflict Direction Conditions



\*Main effect Condition,  $p < .001$

Figure 14c. Father RCT Median RT: Non-Conflict Direction and Conflict-Congruent and Conflict-Incongruent Conditions



\*Main effect Condition,  $p < .001$

In sum, there were virtually no accuracy differences across conditions or groups.

However, significantly longer reaction time was observed on the conflict conditions across all paired comparisons. In addition, the significant Group X Condition interaction (non-conflict location and conflict location) on the median RT of RCT suggests that, as the task demands

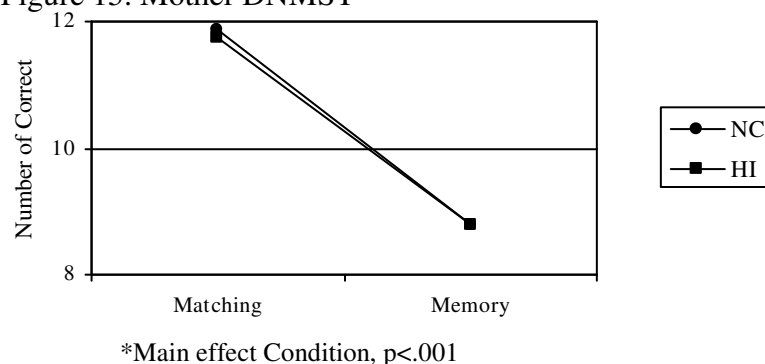
increased, HI-F took longer to respond than NC-F. This pattern of performance is consistent with a specific deficit in motor inhibition among HI-fathers.

### Working Memory: DNMST

#### **Mothers:**

*Number of correct responses:* Two-way (Group X Condition) mixed ANOVA for DNMST revealed a significant main effect of Condition [ $F(1,125) = 331.81, p < .001$ ; partial  $\eta^2 = .73$ ] indicating that participants performed significantly more poorly on the experimental condition than the control condition. However, there was no significant main effect of Group [ $F(1,125) = .071, p = .79$ ; partial  $\eta^2 = .00$ ] or Group X Condition interaction [ $F(1, 125) = .157, p = .69$ ; partial  $\eta^2 = .001$ ], which suggests that HI-M do not have a specific working memory deficit as measured by the DNMST. Figure 15 depicts the performance of mother participants on the DNMST.

Figure 15. Mother DNMST

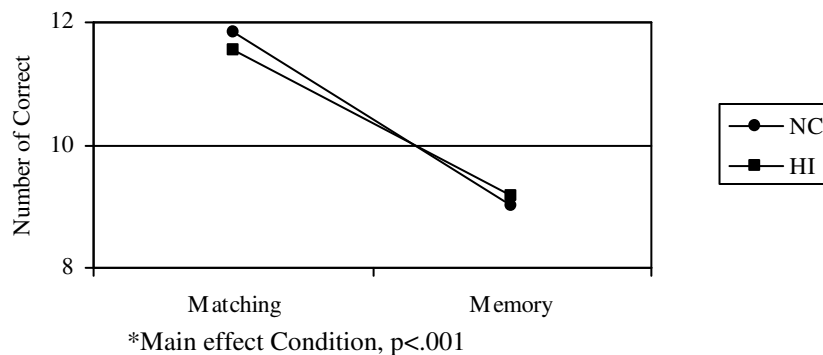


#### **Fathers:**

*Number of correct responses:* Consistent with the results obtained for mothers, the two-way (Group X Condition) mixed ANOVA for father DNMST data revealed a significant main effect of Condition [ $F(1,70) = 95.69, p < .001$ ; partial  $\eta^2 = .58$ ] but no significant main effect of

Group [F (1,70) = .04,  $p = .84$ ; partial  $\eta^2 = .00$ ] or Group X Condition interaction [F (1, 70) = .72,  $p = .40$ ; partial  $\eta^2 = .01$ ]. The findings therefore do not provide support for specific working memory deficits among HI-fathers as measured by the DNMST. Figure 16 depicts the performance of father participants on the DNMST.

Figure 16. Father DNMST



### State Regulation

#### **Mothers:**

*RT variability (SCT):* Independent-samples t-tests did not yield any significant group difference between HI-M and NC-M for RT variability on any condition of the SCT.

*RT variability (RCT):* Independent-samples t-tests did not yield any significant group difference in RT variability between HI-M and NC-M for any condition of the RCT. Table 22a and 22b, and Figure 17 illustrate the mean RT variability for each condition of the mother's SCT and RCT.

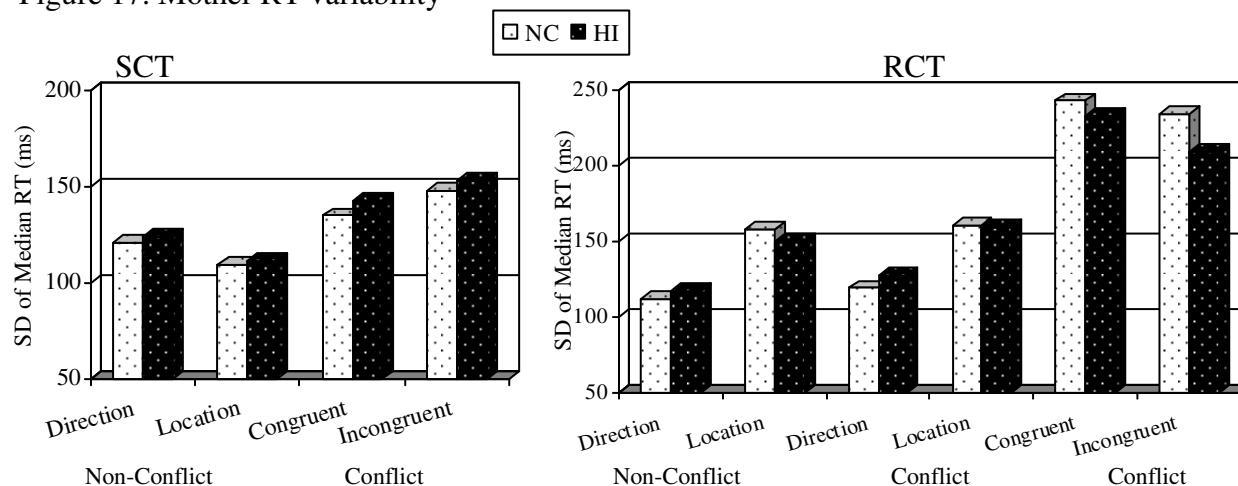
Table 22a  
Mean (SD) of RT Variability of the Mother SCT

	<b>SCT</b> : SD of Median RT (ms) Mean (SD)	
Condition	NC-M (n=46)	HI-M (n=72)
Non-Conflict Direction	120.47 (50.70)	123.88 (48.79)
Non-Conflict Location	109.33 (46.54)	111.21 (33.75)
Conflict-Congruent	134.90 (43.04)	142.96 (46.84)
Conflict-Incongruent	148.08 (63.88)	153.22 (58.63)

Table 22b  
Mean (SD) of RT Variability of the Mother RCT

	<b>RCT</b> : SD of Median RT (ms) Mean (SD)	
Condition	NC-M (n=47)	HI-M (n=69)
Non-Conflict Location	111.71 (46.10)	117.35 (45.42)
Conflict Location	158.03 (67.54)	149.88 (66.06)
Non-conflict Direction	119.12 (44.48)	127.71 (44.65)
Conflict Direction	160.01 (73.34)	159.17 (73.97)
Conflict-Congruent	242.77 (87.22)	233.03 (90.81)
Conflict-Incongruent	233.68 (111.03)	209.14 (97.11)

Figure 17. Mother RT variability



### Fathers:

*RT variability (SCT):* Independent-samples t-tests did not yield any significant group differences in RT variability for any condition of the SCT. However, there was a trend ( $p=.07$ ) for the conflict incongruent condition, such that HI-F had relatively greater RT variability compared to NC-F.

*RT variability (RCT):* Independent-samples t-tests revealed a significant group difference on the *conflict location* condition of the RCT ( $p<.05$ ), suggesting that HI-F had significantly more variability in their performance than NC-F. A trend was also observed for the *conflict congruent* condition ( $p = .08$ ), indicating more variability among HI-F than NC-F. Tables 23a and 23b, and Figure 18 illustrate the mean RT variability for each condition of the father's SCT and RCT.

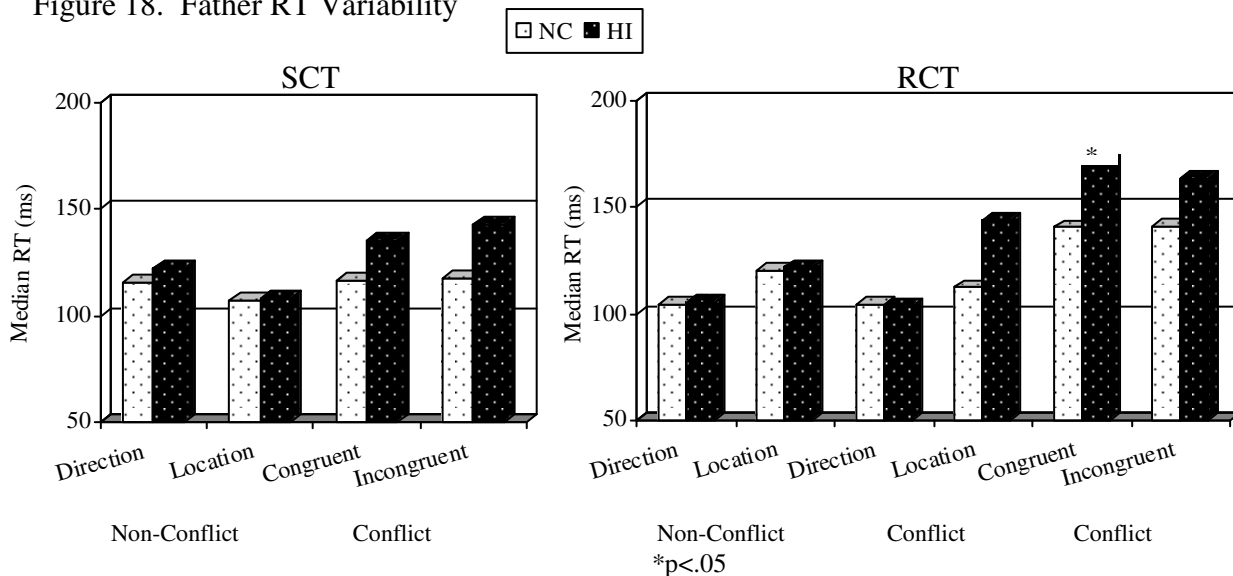
Table 23a  
Mean (SD) of RT Variability of the Father SCT

	<b>SCT</b> : SD of Median RT (ms) Mean (SD)	
Condition	NC-F (n=32)	HI-F (n=41)
Non-Conflict Direction	115.33 (39.37)	122.16 (62.59)
Non-Conflict Location	107.23 (46.70)	108.24 (44.62)
Conflict-Congruent	116.70 (56.00)	134.87 (53.87)
Conflict-Incongruent	117.36 (54.81)	142.65 (63.24)

Table 23b  
Mean (SD) of RT Variability of the Father RCT

	<b>RCT</b> : SD of Median RT (ms) Mean (SD)	
Condition	NC-F (n=32)	HI-F (n=42)
Non-Conflict Location	104.55 (42.37)	105.08 (36.23)
Conflict Location	120.45 (56.91)	121.83 (47.25)
Non-conflict Direction	104.33 (43.37)	103.18 (44.02)
Conflict Direction	112.38 (40.12)	143.48 (75.68)
Conflict-Congruent	140.47 (61.54)	171.06 (81.99)
Conflict-Incongruent	140.84 (66.87)	163.16 (88.37)

Figure 18. Father RT Variability



Overall, the results suggest that, unlike the hyperactive/inattentive children who had greater variability on non-conflict conditions, their fathers had more variable reaction time on the challenging (conflict) conditions relative to fathers of normal controls. This finding is partially supportive of state regulation deficit among HI-F. Such findings were not evident among the mothers of hyperactive/inattentive children. The summary table below (Table 24) compares performance of child, mother, and father on activity level and neurocognitive measures.

Table 24  
Summary of Findings Across Tasks and Participants

Activity Level				
Task	Dependent Measure	Child	Mother	Father
Actigraph	Ankle	Group*	Group	Group*
	Waist	Group*	Group	Group
Neurocognitive Functions: Perceptual Inhibition				
SCT	Number	ME of Condition*	ME of Condition*	ME of Condition*
	Correct	ME of Group*	ME of Group	ME of Group
		Group X Condition	Group X Condition	Group X Condition

	Median RT	ME of Condition* ME of Group Group X Condition	ME of Condition* ME of Group Group X Condition*	ME of Condition* ME of Group Group X Condition*
<b>Neurocognitive Functions: Motor Inhibition</b>				
<b>RCT</b>	Number Correct	ME of Condition* ME of Group* Group X Condition	ME of Condition* ME of Group Group X Condition* (location condition <i>only</i> )	ME of Condition* (location condition <i>only</i> ) ME of Group Group X Condition
	Median RT	ME of Condition* ME of Group Group X Condition	ME of Condition* ME of Group Group X Condition	ME of Condition* ME of Group Group X Condition* (location condition <i>only</i> )
<b>Neurocognitive Functions: State Regulation</b>				
<b>SCT</b>	SD RT	Group*; <i>only</i> on non-conflict condition	Group	Group; trend (p=.07); Conflict condition <i>only</i>
<b>RCT</b>	SD RT	Group*; <i>only</i> non-conflict conditions	Group	Group*; Conflict location <i>only</i> . Trend (p=.08); Conflict congruent
<b>Neurocognitive Functions: Working Memory</b>				
<b>DNMST</b>	Number Correct	ME of Condition* ME of Group* Group X Condition (Trend, p = .058)	ME of Condition* ME of Group Group X Condition	ME of Condition* ME of Group Group X Condition

ME = Main Effect;

\*p&lt;.05

## **Hypothesis II: Part 2**

To assess whether parents of hyperactive-inattentive children with (HI+SX-P) and without current behavioral symptoms (HI-SX-P) differ from normal control parents (NC-P) on neurocognitive functions, the performance of these three groups of parents on the SCT and RCT (median RT) was compared separately for mothers and fathers. Since group differences were not evident on other neurocognitive measures, further analyses were not done using those tasks.

### **1. Perceptual Inhibition (SCT)**

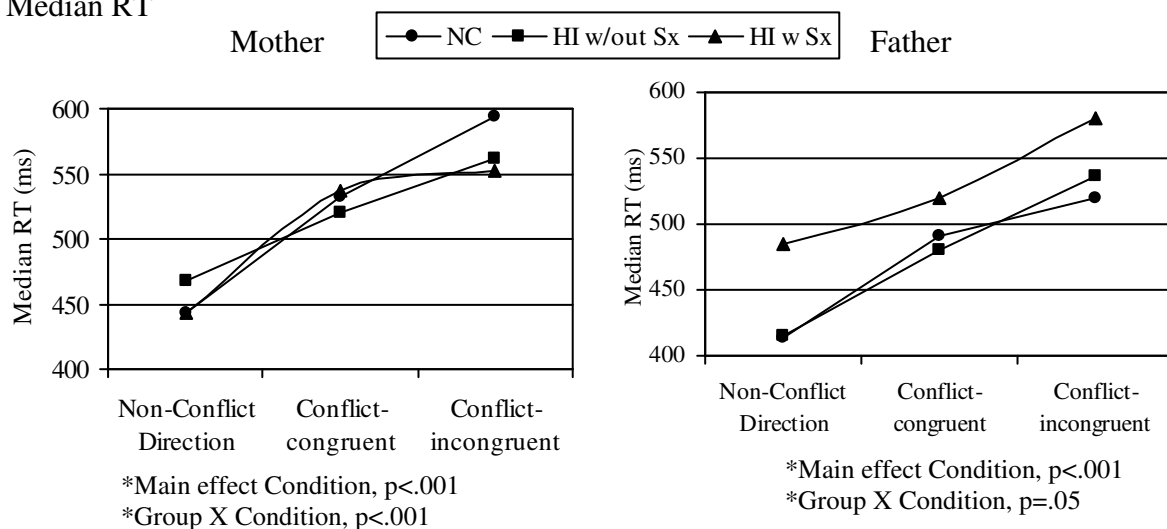
On the measure of perceptual inhibition (SCT), the two-way (Group X Condition) mixed ANOVA for median reaction time between the paired control (*non-conflict direction*) and experimental (*conflict-congruent* and *conflict-incongruent*) conditions yielded significant main effects of Condition and significant Group X Condition interactions for both mothers' and fathers' data. There was no significant main effect of Group for either parent data [Mother:  $F(2,104) = .13, p = .87$ ; partial  $\eta^2 = .003$ ; Father:  $F(2,66) = 1.97, p = .15$ ; partial  $\eta^2 = .06$ ]. The significant main effects of Condition [Mother:  $F(2,103) = 108.09, p < .001$ ; partial  $\eta^2 = .68$ ; Father:  $F(2,65) = 105.30, p < .001$ ; partial  $\eta^2 = .76$ ] indicated that participants had slower reaction times on the conflict conditions compared to non-conflict conditions. The significant interaction for the mother data [ $F(4, 208) = 5.80, p < .001$ ; partial  $\eta^2 = .10$ ] indicated that, while all mothers had a similar reaction time on the non-conflict condition, as the complexity of the task increased, NC-M had significantly longer reaction times than HI+SX-M or HI-SX-M. The follow-up Tukey HSD post-hoc test did not reveal any individual group differences. However, when the change scores (the median RT on Experimental condition minus the median RT on Control condition) were compared using a multivariate analysis of variance, the HI-SX-M performed significantly better than the other two groups ( $p < .05$ ). On the other hand, the nature of the significant Group X Condition interaction for the father data [ $F(4,130) = 2.41, p = .053$ ; partial  $\eta^2$

= .07] indicated that the HI+SX-F had longer reaction times on the non-conflict as well as conflict conditions compared to NC-F and HI-SX-F. Furthermore, NC-F and HI-SX-F had a similar pattern of performance across conditions. Neither the follow-up Tukey HSD post hoc test nor the multivariate analysis of variance on the change score revealed any individual group differences. Therefore, the current findings based on the father SCT data partially support this part of Hypothesis II that indicates that HI-SX-F performed somewhat in between HI + SX-F and NC-F, especially on the conflict condition. Table 25 shows the mean (SD) performance of NC, HI+SX, and HI-SX parents. Figure 19 depicts the significant interactions of 3 (Group: NC, HI+SX, and HI-SX) X 2 (Condition) mixed ANOVAs using median RT as the dependent measure.

Table 25  
Mean (SD) Performance of Normal Control, Symptomatic, and Non-symptomatic Parents on Median RT of SCT

Conditions	Mother Median RT (ms)			Father Median RT (ms)		
	NC (n=46)	HI-SX (n=49)	HI+SX (n=12)	NC (n=32)	HI-SX (N=30)	HI+SX (n=7)
Non-Conflict	443.72	467.18	442.50	413.58	414.45	485.50
Direction	(83.89)	(103.63)	(96.90)	(56.63)	(71.96)	(122.28)
Conflict- Congruent	531.84	519.28	536.58	490.84	481.05	519.00
	(83.91)	(84.39)	(105.52)	(75.44)	(74.76)	(68.85)
Conflict- Incongruent	593.18	561.42	552.83	520.08	536.75	580.14
	(100.38)	(91.29)	(98.95)	(64.15)	(77.53)	(81.68)

Figure 19. Performance of Normal Control, Symptomatic and Non-symptomatic Parents on SCT Median RT



Although, both HI-M and HI-F with current behavioral symptoms committed more errors than NC and HI parents without current symptoms on the SCT, such group differences did not reach statistical significance. There was also no significant Group X Condition interaction; however, there were significant main effects of Condition such that the participants committed significantly more errors during the conflict conditions than the non-conflict conditions. Table 26 depicts these results.

Table 26  
Performance of Normal Control, Symptomatic, and Non-symptomatic Parents on Number Correct of SCT

<b>Paired Conditions</b>	<b>Main Effect of Condition</b>	<b>Main Effect of Group</b>	<b>Interaction</b>
<i>Mother</i>			
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	F(2,107) = 3.63, p<.05; partial $\eta^2$ = .06	F(2,108) =.58, p=.56  Partial $\eta^2$ = .01	F(4,214) =1.17, p=.32  partial $\eta^2$ = .02
<i>Father</i>			
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	F(2,65) = 9.97, p<.001 partial $\eta^2$ = .24	F(2,66) = 1.36,p=.26  partial $\eta^2$ = .02	F(4,130) =.51, p=.73  partial $\eta^2$ = .04

## 2. Motor Inhibition

Similar two-way Group X Condition mixed ANOVAs for number correct and median RT of RCT for both sets of parent data revealed that there were significant main effects of Condition, such that the participants committed significantly more errors during the conflict conditions than the non-conflict conditions, but no significant main effect of Group or Group X Condition interaction. Tables 27 and 28 depict the results of the RCT using median RT and accuracy as dependent measures to compare NC and HI parents (symptomatic and non-symptomatic groups).

Table 27

Performance of Normal Control, Symptomatic, and Non-symptomatic Parents on RCT Median RT

<b>Paired Conditions</b>	<b>Main effect of Condition</b>	<b>Main effect of Group</b>	<b>Interaction</b>
<i>Mother</i>			
Non-conflict Location & Conflict Location	F(1,103) = 112.32, p < .001 partial $\eta^2$ = .52	F(2,103) = .04, p = .96 partial $\eta^2$ = .001	F(2,103) = .43, p = .65 partial $\eta^2$ = .008
Non-conflict Direction & Conflict Direction	F(1,103) = 119.48, p < .001; partial $\eta^2$ = .54	F(2,103) = .08, p = .92; partial $\eta^2$ = .002	F(2,103) = 2.22, p = .11 partial $\eta^2$ = .04
Non-conflict Direction & Conflict-congruent & Conflict-Incongruent	F(2,102) = 131.73, p < .001; partial $\eta^2$ = .72	F(2,103) = .08, p = .92 partial $\eta^2$ = .002	F(4,204) = .47, p = .75 partial $\eta^2$ = .009
<i>Father</i>			
Non-conflict Location & Conflict Location	F(1,66) = 74.71, p < .001 partial $\eta^2$ = .53	F(2,66) = .15, p = .86 partial $\eta^2$ = .004	F(2,66) = 1.93, p = .15 partial $\eta^2$ = .05
Non-conflict Direction & Conflict Direction	F(1,66) = 43.98, p < .001; partial $\eta^2$ = .40	F(2,66) = 1.02, p = .36; partial $\eta^2$ = .03	F(2,66) = 1.01, p = .37 partial $\eta^2$ = .03
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	F(2,65) = 99.55, p < .001; partial $\eta^2$ = .75	F(2,66) = 1.006, p = .37; partial $\eta^2$ = .03	F(4,132) = 1.30, p = .27 partial $\eta^2$ = .04

Table 28  
Performance of Normal Control, Symptomatic, and Non-symptomatic Parents on RCT Number Correct

Paired Conditions	Main effect of Condition	Main effect of Group	Interaction
<i>Mother</i>			
Non-conflict Location & Conflict Location	F(1,111) = 7.82, p<.05 partial $\eta^2$ = .06	F(2,111) = 2.20, p = .12; partial $\eta^2$ = .04	F(2,111) = 2.10, p = .13 partial $\eta^2$ = .04
Non-conflict Direction & Conflict Direction	F(1,111) = 5.14, p<.05; partial $\eta^2$ = .04	F(2,111) = 2.20, p = .12; partial $\eta^2$ = .04	F(2,111) = .78, p = .46 partial $\eta^2$ = .01
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	F(2,110) = 7.27, p<.001; partial $\eta^2$ = .12	F(2,111) = .20, p = .81 partial $\eta^2$ = .004	F(4,220) = .78, p = .54 partial $\eta^2$ = .01
<i>Father</i>			
Non-conflict Location & conflict Location	F(1,67) = .21, p<.64 partial $\eta^2$ = .003	F(2,67) = .36, p = .70 partial $\eta^2$ = .01	F(2,67) = 2.70, p = .07 partial $\eta^2$ = .07
Non-conflict Direction & Conflict Direction	F(1,67) = .40, p<.53; partial $\eta^2$ = .006	F(2,67) = .71, p = .49; partial $\eta^2$ = .02	F(2,67) = .19, p = .82 partial $\eta^2$ = .006
Non-conflict Direction & Conflict-Congruent & Conflict-Incongruent	F(2,65) = 2.68, p<.08; partial $\eta^2$ = .08	F(2,66) = .26, p = .77; partial $\eta^2$ = .008	F(4,130) = 1.02, p = .40; partial $\eta^2$ = .03

### **Hypothesis III**

Pearson product-moment correlations were used to examine the relationships between parent's and children's ADHD symptom levels. Parent and teacher ratings of the child, obtained

using the ADHD-RS, were positively correlated with ratings of both the mother and the father that were obtained from their significant other (see Table 29a). This means that greater levels of child ADHD symptoms were associated with elevated levels parental symptoms as rated by their significant other. However, parent self-reports on the CAARS were not associated with measures of children's behavior.

Tables 29b and 29c illustrate the relationships between children's and parents' performance on the SCT and RCT, respectively. For the location and conflict incongruent conditions of the SCT, child median RT was positively correlated with father's median RT. Similar associations in the latency to respond were also observed for both the non-conflict and conflict conditions of the RCT. No significant correlations emerged for measures of accuracy on the SCT, RCT, or DNMST. Finally, with the exception of the SCT non conflict condition, no significant associations were observed between mother and child performance.

Table 29a  
Correlations Between Parent and Child Behavioral Ratings

	Child ADHD-RS		Mother CAARS: ADHD Index		Father CAARS: ADHD Index	
	Home	School	Self	Observer	Self	Observer
<b>Child ADHD-RS</b>						
Home	1	.588**	.166	.272**	.130	.383**
School	.588**	1	-.042	.224*	.110	.241*

\*  $p < 0.05$  (2-tailed)

\*\*  $p < 0.01$  (2-tailed)

Table 29b  
Correlations Between Parent and Child Performance on the SCT

<i>Number Correct</i>						
	<b>Mother</b>			<b>Father</b>		
<b>Child</b>	Non-Conflict	Conflict Congruent	Conflict Incongruent	Non-Conflict	Conflict Congruent	Conflict Incongruent
Non-conflict	.20*	.04	-.005	-.05	-.04	-.02
Conflict Congruent	.08	.03	.00	-.16	.01	.09
Conflict Incongruent	-.02	-.07	-.17	-.18	.01	-.02
<i>Median RT</i>						
Non-conflict	.12	.04	.06	.30*	.18	.31*
Conflict Congruent	.11	.09	.13	.09	-.11	-.01
Conflict Incongruent	-.03	-.11	.03	.24	.12	.29*

\*  $p < 0.05$  (2-tailed)

\*\*  $p < 0.01$  (2-tailed)

Table 29c  
Correlations Between Parent and Child Performance on the RCT

<u>Number Correct</u>				
	<b>Mother</b>		<b>Father</b>	
<b>Child</b>	Non-Conflict	Conflict	Non-Conflict	Conflict
Non-conflict	-.02	-.08	-.09	.16
Conflict	-.01	.12	-.10	-.20
<u>Median RT</u>				
Non-conflict	.02	.05	.26*	.26*
Conflict	-.06	.08	.24*	.22

\*  $p < 0.05$  (2-tailed)

\*\*  $p < 0.01$  (2-tailed)

### **Simon Effect**

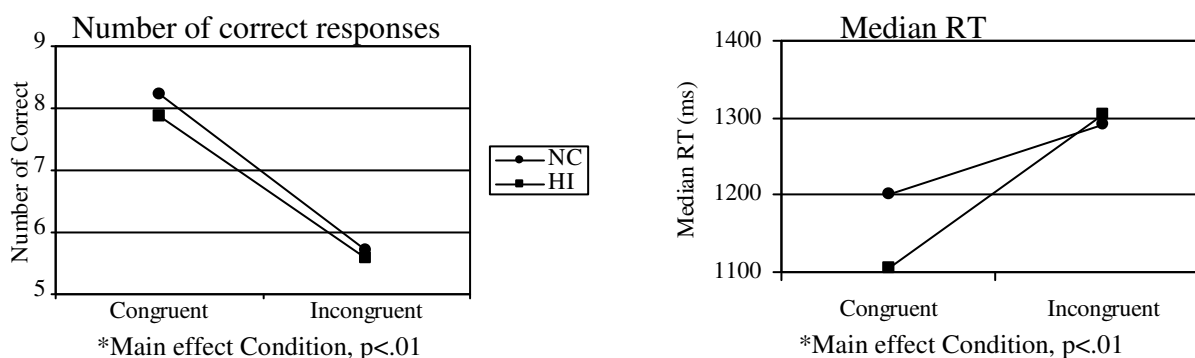
The data from the child and parent SCT were analyzed to assess the ‘Simon Effect’.

*Child Simon Effect (SCT):* The two-way (Group X Condition) mixed ANOVAs for number of correct responses and median RT on the *direction-location conflict* condition assessing the ‘Simon Effect’ indicated that there were significant main effects of Condition for each of these dependent measures. In contrast, there was no significant main effect for Group and no Group X Condition interactions. This pattern of finding suggests that children committed more errors when the required response was incongruent with the location of the stimulus. However, NC and HI children did not exhibit the Simon Effect differentially as a function of condition. Table 30 and Figure 20 depict the findings for the child SCT Simon Effect analyses.

Table 30  
Child SCT: Simon Effect

Paired Conditions	Main effect of Condition	Main effect of Group	Interaction
<u>Number correct</u> Congruent-Conflict & Incongruent-Conflict	F(1,160) = 107.54, p < .001 partial $\eta^2$ = .40	F(1) = 1.11, p = .29 partial $\eta^2$ = .007	F(1, 160) = .24, p = .63 partial $\eta^2$ = .001
<u>Median RT</u> Congruent-Conflict & Incongruent-Conflict	F(1,148) = 19.35, p < .01 partial $\eta^2$ = .02	F(1,160) = .65, p = .42 partial $\eta^2$ = .004	F(1, 148) = 2.77, p = .09 partial $\eta^2$ = .02

Figure 20. Child SCT: Simon Effect



### Mothers:

*Simon Effect (SCT)*: The two-way (Group X Condition) mixed ANOVA for number of correct responses on the *direction-location conflict* condition assessing the Simon Effect revealed that there was a significant main effect of Condition [ $F(1,120) = 15.53, p < .001$ ; partial  $\eta^2 = .12$ ] indicating that participants from both groups displayed poorer accuracy on the *incongruent-conflict* condition relative to the *congruent-conflict* condition. In contrast, there was no significant main effect of Group [ $F(1,20) = 1.09, p = .30$ ; partial  $\eta^2 = .009$ ]. However, a

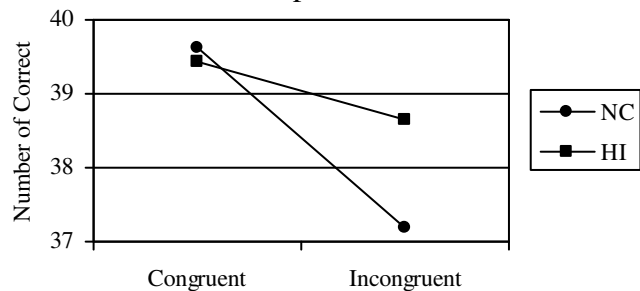
significant Group X Condition interaction was observed [ $F(1, 120) = 4.04, p < .05$ ; partial  $\eta^2 = .03$ ] such that indicating that NC-M were significantly less accurate than HI-M on the incongruent vs. congruent conditions.

The two-way (Group X Condition) mixed ANOVA for median RT on the *direction-conflict* condition revealed a significant main effect of Condition [ $F(1,120) = 125.39, p < .001$ ; partial  $\eta^2 = .51$ ] but not Group ( $F(1,120) = .50, p = .48$ ; partial  $\eta^2 = .004$ ), indicating that participants from both groups had longer reaction times on the *incongruent-conflict* vs. *congruent-conflict* condition. A significant Group X Condition interaction was observed [ $F(1,120) = 10.39, p < .01$ , partial  $\eta^2 = .80$ ] indicating that the group difference in median RT was significantly greater for the conflict condition relative to the the non-conflict condition. Compared to HI-M, NC-M had longer RT's on the *congruent-conflict* condition and even longer RT on the *incongruent-conflict* condition. Thus, mothers of HI children appear to be exhibiting a diminished Simon Effect relative to the mothers of controls. Table 31 and Figure 21 depict the findings for the mother SCT Simon Effect analyses

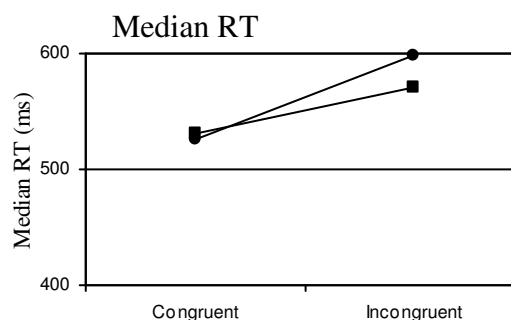
Table 31  
Mother SCT: Simon Effect

<b>Dependent Measures</b>	<b>Main effect of Condition</b>	<b>Main effect of Group</b>	<b>Interaction</b>
Number of correct Responses	$F(1,120) = 15.53,$ $p < .001$ ; partial $\eta^2 = .12$	$F(1,20) = 1.09, p =$ .30; partial $\eta^2 = .009$	$F(1, 120) = 4.04,$ $p < .05$ ; partial $\eta^2 = .03$
Median RT	$F(1,120) = 125.39,$ $p < .001$ ; partial $\eta^2 = .51$	$F(1,120) = .50, p =$ .48; partial $\eta^2 = .004$	$F(1,120) = 10.39,$ $p < .01$ , partial $\eta^2 = .80$

Figure 21. Mother SCT: Simon Effect  
Number of correct responses



\*Main effect Condition,  $p < .001$   
Group X Condition interaction,  $p = .05$



\*Main effect Condition,  $p < .001$ ;  
Group X Condition interaction,  $p < .01$

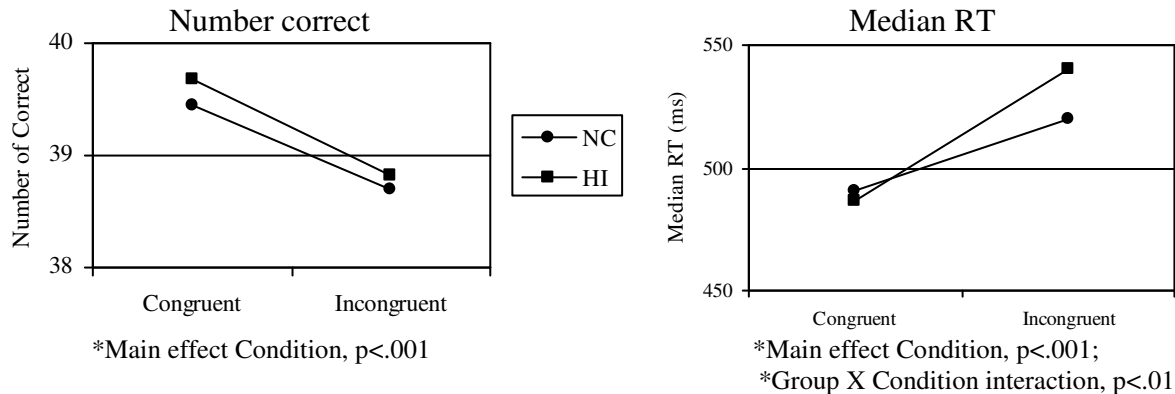
### Fathers:

*Simon Effect (SCT):* Similar to mothers, fathers were significantly less accurate and slower on the *incongruent conflict* condition than the *congruent conflict* condition, as evidenced by significant main effects for Condition for both number of correct responses and median RT on the SCT. A significant Group x Condition interaction [ $F(1, 71) = 6.87, p < .05$  partial  $\eta^2 = .09$ ] was also found for SCT median RT such that HI-F were faster than NC-F on the *congruent conflict* condition but slower on the *incongruent conflict* condition. There were no other significant main effects or interaction. Table 32 and Figure 22 depict the findings for the father SCT Simon Effect analyses

Table 32  
Father SCT: Simon Effect

Dependent Measures	Main effect of Condition	Main effect of Group	Interaction
Number of correct Responses	$F(1,71) = 17.73,$ $p < .001$ ; partial $\eta^2 = .20$	$F(1,71) = .679, p = .41$ partial $\eta^2 = .009$	$F(1,71) = .074, p = .79$ partial $\eta^2 = .001$
Median RT	$F(1,71) = 77.36,$ $p < .001$ ; partial $\eta^2 = .52$	$F(1,71) = .23, p = .63$ partial $\eta^2 = .003$	$F(1, 71) = 6.87,$ $p < .05$ partial $\eta^2 = .09$

Figure 22. Father SCT: Simon Effect



### Summary

In sum, the findings from the child measures indicate that HI children were significantly more active as measured by solid-state actigraphs, which corroborates the parent and teacher ratings as well as their grouping status. With regard to neurocognitive measures, HI children performed more poorly than NC participants on most measures. However, the absence of significant Group X Condition interactions suggests that their relatively poor performance is not due to specific deficits in interference control, response inhibition, or visual working memory, as assessed by the SCT, RCT, and DNMTS, respectively. Significant group differences in reaction time variability for both RCT and SCT are consistent with the hypothesis that the poor performance by the HI children may be attributable to inadequate state regulation that is most evident when the task is less demanding.

Parents of preschoolers did not differ with regard to activity level as measured by waist and ankle actigraphs. Consistent with the child findings, mothers of HI children did not exhibit specific neuropsychological deficits on cognitive measures (i.e., response inhibition and working memory). In addition, HI-M did not show any state regulation deficits. The performance of HI-

M also did not correlate with their children's performance on the neurocognitive measures under investigation.

On the other hand, HI-F, especially those with current behavioral symptoms, had significant difficulty across the conditions of the SCT and RCT, as they required longer reaction time than NC-F. State regulatory deficits were also evident among HI-F during the more challenging conditions. Furthermore, there were significant correlations between father and child performance on the SCT and RCT (median RT). Hence, the findings based on the father data suggest that fathers of HI children, especially those with current behavioral symptoms possess neurocognitive profiles suggestive of response inhibition and state regulation deficits.

## DISCUSSION

ADHD is a highly heritable heterogeneous disorder that likely involves multiple genes with small effect sizes that interact with each other and a host of environmental factors to create a complex clinical presentation. In light of such etiological complexities, efforts to precisely elucidate specific genes that underlie the disorder have been quite limited. One approach to at least partially circumventing these issues is to use more narrowly-defined and, when possible, objectively-measured characteristics, or endophenotypes, to shed light on the genetic basis of ADHD. It is believed that endophenotypes may be more closely linked to the genetic underpinnings of the disorder because they are more narrowly-defined than the clinical features; hence, the number of genes involved in *their* manifestation is likely more restricted relative to the number required to produce the entire syndrome. Ultimately, the identification of neurocognitive endophenotypes may bolster efforts to identify the genetic basis of ADHD.

This dissertation was designed to examine, in preschool children and their parents, several specific neurocognitive characteristics (i.e., response inhibition, working memory, and state regulation) that may serve as potential candidate endophenotypes for ADHD by determining whether such characteristics run in families of children with the disorder. These specific neurocognitive functions were selected because they meet the essential characteristic criteria for endophenotypes (Doyle et al., 2005): 1) measures of these characteristics consistently differentiate probands with ADHD from normal controls; 2) they appear to have a neural basis; and 3) they appear to show some specificity to ADHD but are not direct symptoms of the disorder. Of particular interest for the purpose of the current study was whether impairments in these domains could be detected in preschoolers with ADHD symptoms and their parents.

Ratings of both child and parent behavior were obtained, and their activity level, as measured by solid-state actigraphs, was ascertained to provide objective measures of this closely related construct (i.e., hyperactivity). On the basis of behavioral ratings, children were categorized into two groups: Hyperactive/Inattentive (HI) and Normal Control (NC).

HI and NC groups of children and their parents (HI-P; NC-P) were compared on experimental measures designed with built-in control conditions to isolate the specific neurocognitive processes of interest. Further, efforts were undertaken to investigate whether HI-P who exhibit elevated ADHD symptoms as adults were more likely to have specific neurocognitive deficits relative to those HI-P who did not exhibit such symptoms and NC-P. Finally, the relationships between the performance of children and their parents on these measures were examined to shed additional light on whether such neurocognitive profiles may be genetically mediated.

It was noted that parents of HI preschoolers were less likely to participate in the study than parents of NC children. Although, not certain about the reason(s) for this, parents of HI children were more likely to have been single parents, and in several instances, their time during the [child] assessment was spent caring for another child. It is also conceivable that parents of HI children may have been more reluctant to participate due to reservations about disclosing information about their own behavioral difficulties. However, the lack of significant group differences among child measures as a function of parental participation suggests that those children whose parents participated were not any different than those whose parents did not participate. Hence, the current results pertaining to child data were not an artifact of participation bias.

## **Summary of Findings**

*Behavioral Measures:* Results indicated that HI preschoolers were more active than NC participants as measured by actigraph readings. Hence, the actigraph counts support the validity of the behavioral ratings completed by parents and teachers, which were used to classify participants. Although parents of HI children were rated as more symptomatic than parents of NC children by collateral informants, they did not differ from the parents of control participants with respect to self-reports or activity level as measured by waist and ankle actigraph counts.

*Support for Test Validity:* A significant discrepancy in performance across conditions of all dependent measures of parent and child versions of the SCT, RCT, and DNMST indicated that participants experienced more difficulty, evident in increased errors and response latency, on the experimental conditions relative to the control conditions. Such increases in error rates and reaction times on the experimental conditions are supportive of the built-in “additional” requirement of response inhibition and working memory required by these novel experimental measures.

The experimental measures that were used for this study are developmentally flexible, making them appropriate, with only minor modifications, for a wide age range. Thus, we were able to use virtually identical tasks to presumably assess the same constructs in preschoolers and their parents. Floor and ceiling effects were minimally evident especially in the child version, as very few children received the minimum or maximum score on either the control or experimental conditions of the tasks.

*Specific Deficits in the Proposed Neurocognitive Constructs:* The results from the neurocognitive measures suggest that, despite their relatively poor performance overall (reflected in increased error rates), children with elevated ADHD symptoms did not perform differentially

worse as a function of condition on the SCT, RCT, or DNMST. Thus, according to the additive factors model (Sergeant, 1996; Sternberg, 1969), the lack of significant Group x Condition interactions for accuracy and reaction time suggest that, at this age, HI preschoolers do not exhibit specific deficits in response inhibition and working memory as measured by these tasks. However, the fact that HI children committed significantly more errors across all conditions and had more varied reaction time than controls on the paired control conditions points to possible impairments in state regulation.

Among the parents, the mothers of these HI preschoolers did not exhibit deficits in any of the measured neurocognitive domains. If anything, mothers of HI participants actually performed better than the mothers of NC preschoolers on measures of response inhibition. In contrast, fathers of HI children, relative to those of control participants, had disproportionately longer reaction times on the experimental vs. control conditions of the SCT and RCT. According to the additive factors model, this pattern of performance suggests specific deficits in perceptual inhibition and motor inhibition. These deficits were especially prominent among HI-F who exhibited ADHD features at the time of the assessment. The fathers of HI children also exhibited state regulation deficits, as measured by reaction time variability, but only when executive function demands were present. Significant positive correlations were also observed between the performance of HI children and that of their fathers' on the SCT and RCT; fathers' median reaction time was positively associated with their child's median reaction time. In this way, the data obtained from fathers of HI participants provides partial support for the genetic transmission of response inhibition and state regulation deficits, as well as their candidacy as ADHD endophenotypes.

Taken together, the current data do not provide support for Hypothesis I, which posited that HI children would exhibit specific deficiencies in response inhibition, interference control and working memory; equally poor performance on the control and experimental conditions of the various tasks fails to provide support for executive function deficiencies. Nonetheless, data from the fathers of HI participants provide partial support for Hypothesis II, as HI-F performed significantly worse on measures of response inhibition especially in the presence of current behavioral symptoms. The present data also provide partial support for Hypothesis III, as positive associations were identified between child and father interference control and motor inhibition.

### **Current Findings Relative to the Extant Literature**

#### **Response inhibition**

The viability of response inhibition as an endophenotype was assessed in this dissertation because it has been posited to be the core deficit among individuals with ADHD (Barkley, 1997). In his model of ADHD, Barkley (1997) suggested that response inhibition is comprised of three interrelated processes: 1) inhibition of prepotent responses, 2) cessation of ongoing responses, and 3) interference control.

*Inhibition of prepotent responses:* In this dissertation, inhibition of prepotent responses was measured by the RCT. Previous studies have documented increased commission errors among ADHD probands on Go-no/Go tasks (Banaschewski, 2008; Rodriguez, 2007; Rubia 2007; Wodka et al., 2007), which the investigators have interpreted as a deficiency in the inhibition of prepotent response tendencies. Consistent with this literature, children with ADHD, in the present study, committed significantly more errors on the RCT (designed to inhibition of

prepotent responses). However, after accounting for performance on the paired control condition, no specific deficits were observed in the ability of preschoolers with ADHD to inhibit prepotent response tendencies. It is therefore possible that previous findings, by not using an additive factors design, may have inaccurately concluded the presence of deficits in this aspect of response inhibition. On the other hand, fathers of HI children exhibited specific deficits inhibiting prepotent responses (as reflected in longer reaction time), especially in the presence of increased inhibitory demands.

*Cessation of ongoing responses:* This aspect of Barkley's response inhibition model has conventionally been measured by the Stop Signal Task (Logan, 1994), and has been reported to be deficient among children with ADHD compared to normal controls (Casey et al., 1997; Crosbie and Schachar 2001; Durston et al., 2004; Oosterlaan et al., 1998; Schachar et al., 2000; Vaidya et al., 1998). In contrast, such patterns have been only inconsistently reported in adults with ADHD, with some investigators reporting slower stop signal reaction time compared to controls (Bekker et al., 2005; Murphy 2002; Ossmann & Mulligan 2003) and others failing to observe such differences (Clark et al., In Press; Epstein, 2001). In addition to longer stop signal reaction times, most studies have also reported slower and more variable responses to "Go" signals on the task. The idea that the Stop Signal data are indicative of a specific inability to discontinue ongoing responses was recently challenged by Nigg (2004), who reasoned that, if ADHD probands have slower and more variable reaction times to Go signals, slow responses to the stop signal cannot be considered to represent a specific deficit in inhibition, but instead point to slower and more variable processing speed. Furthermore, the Stop Signal Task lacks a control condition to distinguish specific cognitive process(es) of interest. This aspect of response

inhibition was not studied in this dissertation as the SCT and RCT were not designed to assess this construct.

*Interference control:* Perceptual interference control was assessed in the current study by the SCT, which measures a construct similar to the Stroop Test, but unlike the Stroop, does not require reading, and can therefore be administered to young children. A recent meta-analysis, based on seventeen independent studies, reported that studies that have employed the Stroop Task fail to support the presence of a specific interference control deficit in ADHD probands (Van Mourik et al., 2005). In fact, this study indicated that effect size differences between probands with ADHD and controls were greatest for the control (i.e., word reading and color naming) conditions of the Stroop as opposed to the more critical Interference score. Consistent with the results of this meta-analysis, the present study provided no evidence to support a specific deficiency in interference control among preschool children with ADHD. In contrast, such deficits were observed in fathers of hyperactive/inattentive preschoolers.

Thus, consistent with the prior literature, the present findings indicate that HI children perform relatively poorly on response inhibition tasks compared to normal controls. However, after employing process specific experimental manipulations, it is clear that the poor performance of HI preschoolers cannot be attributed to the process specific deficits in response inhibition. When juxtaposed with the negative findings in the literature, especially those who employed rigorous control conditions (Marks et al., 2005; Rommelse et al. 2007), the present study provides no support for specific deficits in interference control among preschool children with ADHD. The parent data, on the other hand, especially data obtained from fathers, provide support for response inhibition deficits among fathers of HI children, particularly among HI-F with elevated behavioral symptoms. This finding also provides partial support for the heritability

of response inhibition deficits, as fathers of those children who were rated highly on an ADHD rating scale, exhibited response inhibition deficits. This finding is consistent with those of Biederman and colleagues (2002), who indicated that parental ADHD serves as a risk factor for their children regardless of symptom persistence.

The lack of such deficits among preschool children may be attributed to the fact that preschoolers are yet to master (fully develop) executive functions. The lack of differential performance across control and experimental conditions suggests that response inhibition may not have undergone sufficient development during the preschool period after accounting for growth in rudimentary processes. To the extent that this construct has not undergone sufficient maturational growth, it may not be reasonable to expect deficits in this still underdeveloped domain. Hence, based on these data it can be tentatively concluded that response inhibition may be considered a viable endophenotype for ADHD after sufficient maturation of executive functions.

### Working Memory

Overall, HI children performed more poorly than NC participants on measures of working memory (WM); however, the lack of Group x Condition interaction suggests that preschoolers with elevated ADHD symptoms do not exhibit specific WM deficits. Similarly the parents of HI children also did not show such deficits. The findings of working memory impairments among ADHD probands in the extant literature have been somewhat inconsistent, with some investigators reporting such deficits (Cohen et al., 2000; Martinussen & Hayden, 2005; Martinussen & Tannock, 2006; McInnes, 2003; Pasini et al., 2007; Williams et al., 2000), and others not observing such patterns (Marks et al., 2005; Pennington & Ozonoff, 1996; Wu ,

2006). Most of positive findings have been observed using measures of visual spatial working memory that required manipulation of the to-be-remembered information. In contrast, the current investigation employed a visual working memory task which did not require spatial manipulation(s), and failed to identify a specific WM deficit among HI preschool children. Nevertheless, as was reported above, the vast majority of studies that have documented WM deficits in ADHD have not employed a control condition designed to isolate working memory from other non-specific deficits. As such, it is difficult to know the extent to which positive findings reported in prior studies may be better accounted for by attention or state regulation deficits rather than impairments in working memory per se.

In sum, the present findings suggest that working memory deficits do not co-occur universally with ADHD, and fail to provide support for a genetically mediated working memory deficit. Hence, based on these data, it appears as though working memory is not a suitable candidate endophenotype for ADHD.

### State regulation

The possibility of a state regulation deficit being an endophenotype for ADHD was assessed in this dissertation because increased response variability, a purported indicator of poor state regulation, is perhaps the most ubiquitous finding in the recent ADHD literature. For the purpose of the current study, response variability was assessed by examining variability in reaction time (i.e., consistency of response) on the SCT and RCT. Consistent with prior reports (Borger and van der Meere, 2000; Castellanos et al., 2005; Kuntsi et al., 2001; Pasini et al., 2007; Sergeant, 2000; Wiersema et al., 2005), HI children in the present study showed greater variability in their reaction time, especially on the less challenging non-conflict conditions of the

SCT and RCT. Elevations in reaction time variability were not observed during the conflict conditions of the SCT and RCT.

The reason(s) for this discrepancy in group differences in reaction time variability across conditions is not clear. However, it may be attributable to the fact that high rates of errors during the conflict conditions precluded us from obtaining reaction time data from a sufficient number of trials to obtain a reliable measure of reaction time variability. Alternatively, it is possible that the more challenging aspects of the conflict conditions resulted in increased effort and a tonic alerting response in the children, which would be reflected in fewer lapses of attention and more consistent RTs. Hence these results provide partial support for Hypothesis I, which posited that HI children would exhibit state regulation deficits, at least under low effort conditions.

Despite the strong association established in the literature between ADHD and neurocognitive impairments, the heterogeneity of these impairments and low statistical power have led investigators to suggest that the neurocognitive deficits are not universally present in all children with ADHD (Nigg et al., 2005). Nonetheless, deficient state regulation, which is a presumed measure of non-executive mental state and response preparation, appears to be ubiquitous, as it differentiates ADHD probands from controls more consistently than executive function deficits (e.g., response inhibition, working memory, etc.) (Kuntsi et al., 2001). The consistent findings of increased variability in reaction time among children with ADHD vs. controls have shifted the focus of many investigators towards lower level cognitive functions and bottom-up state regulation process as distinct from executive control per se. State regulation figures prominently in Sergeant's (2005) Cognitive Energetic Model (CEM), which attempts to characterize the nature of the deficits associated with ADHD. According to Sergeant (2005), the CEM encompasses the interplay of three cognitive elements: 1) computational mechanisms of

attention, 2) state regulation, and 3) executive functions; the first two levels of this model represent basic cognitive functions, while the third involves executive control. According to this model, variations in the initiation of responses among ADHD probands are likely due to deficiencies in lower level cognitive functions (e.g., activation and arousal and/or inappropriate regulation of mental state; Sergeant, 2005).

In support of the notion that poor state regulation underlies inconsistent response initiation, investigators have reported that increased reaction time variability among ADHD probands is only apparent during slow presentation of stimuli, but not when the presentation of stimuli is more rapid (Borger and van der Meere 2000; Wiersema et al., 2005). According to these researchers, slow rates of stimulus presentation produce non-optimal cognitive activation, which then leads to poor motor preparation and response initiation among children with ADHD. Consistent with these findings, the current study revealed state regulation deficits when minimal response inhibition requirement was present. It is possible that the demand of response inhibition induced a more optimal state in those with ADHD, thus obfuscating differences that are normally apparent.

According to Leth-Steensen and colleagues (2000), reductions in mean reaction time among ADHD probands, which has been reported by other investigators (Casey et al., 1997; Crosbie and Schachar 2001; Durston et al., 2004; Oosterlaan et al., 1998; Schachar et al., 2000; Vaidya et al., 1998) using Stop Signal Tasks and Go no/Go Tasks, is due to their variability in reaction time rather than response inhibition deficits per se. In support of their claim, the investigators reported that the fast correct responses by boys with ADHD in their sample were almost as fast as those of controls; however, their slower responses were much slower than those of controls. Similar to the studies alluded to above (i.e., Borger and van der Meere 2000;

Wiersema et al., 2005) Leth-Steensen and colleagues also concluded that the slower response condition created an inappropriate mental state, which led to an effortful, slower response pattern, which in turn, gave rise to reaction time slowing. Hence increasing evidence suggests that response inhibition, which has been characterized as the core deficit in Barkley's 'top down' model of ADHD, may occur secondary to deficiencies in state regulation, at least for younger children.

Consistent with the literature indicating the persistence of state regulatory deficits into adulthood (Wiersema et al., 2006), the present study found that fathers of HI children had significantly more variable reaction times than NC-F, particularly in the context of response incompatibility. It is important to note that children exhibited state regulation deficits during the control condition (i.e., in the absence of a response inhibition demand), while fathers of HI children exhibited analogous deficits during the conflict condition (i.e., in the presence of a response inhibition demand). One possible explanation for this discrepancy between child and adult data is that adults, in general, may possess relatively better self-control than children and may be capable of executing response patterns that are appropriate to the situational demands. However, demands for response inhibition, which is apparently impaired in these fathers, may set them in a non-optimal mental state, resulting in more variable reactions. Thus as the data suggest, fathers of HI children may, under conflict conditions, show deficits in effortful control or top-down processing that partially, but do not fully compensate (as reflected in their more variable reaction time) for bottom-up deficits that may have been present earlier in ontogeny. Establishing a causal association between response inhibition and state regulation is beyond the scope of the current study. However, some association between top down and bottom up control

is suggested by the present data as the state regulation deficits were only evident in HI-F who also had response inhibition deficit.

In sum, since state regulation deficits have been consistently implicated in ADHD and shown to differentiate probands from controls in the present study, it is a neurocognitive construct that may serve as a candidate endophenotype for ADHD.

### **Familial Aggregation of the Proposed Neurocognitive Constructs**

Although not a direct criterion for a candidate endophenotype, many investigators have suggested that the performance of non-symptomatic first degree relatives of ADHD probands should fall between that of symptomatic first-degree relatives of ADHD probands and relatives of controls on the measured trait (Slaats-Willemse et al., 2003). This was assessed in the current study as part of Hypothesis II, which posited that parents of HI children who themselves do not exhibit current ADHD symptoms would demonstrate a neurocognitive profile that falls between the parents of NC children and the symptomatic parents of HI participants. This hypothesis was partially supported by the present data, as the performance of HI-F with current behavioral symptoms was significantly worse (longer median RT) relative to the performance of the non-symptomatic HI-F and that of NC-F on the SCT and RCT. However, the performance of the non-symptomatic parents was better than that of the symptomatic parents but worse than that of parents of NC children. Therefore, as postulated by Hypothesis II, the present data provide partial support for the familial aggregation of response inhibition. The familial aggregation of the proposed neurocognitive constructs (Hypothesis III) was also examined by determining whether the performance of parents and their offspring on measures of inhibitory control, working memory, and state regulation was significantly correlated. Overall, child performance

on the SCT and RCT were significantly correlated with that of their fathers, such that a child's latency to respond was positively associated with his/her father's latency to respond on the analogous task condition. This pattern is consistent with emerging literature suggesting that neurocognitive functions and ADHD psychopathology are highly heritable (Crosbie and Schachar, 2001; Slaats-Willemse et al., 2003), and thus provide partial support for the familial aggregation of response inhibition. Data would also seem to suggest that such deficits appear to be primarily aggregated through males, as the associations were only observed between child and father's performance, though this may not be surprising given the commonly reported prevalence discrepancy between males and females. Although, this would lead to the expectation of observing sex-specific familial patterns of neurocognitive functioning, the current data, consistent with Faraone and colleagues (2000), provide no such relationship between the performance of mothers and girl participants and fathers and boy participants on these tasks. In addition, parent and child behavioral ratings were directly compared. Results indicated that parent and child symptoms were significantly correlated, a finding that is consistent with the widely held belief that the behavioral features of ADHD are genetically mediated.

### **Summary and Implications**

In sum, the findings from the present study suggest that preschool children with elevated levels of ADHD symptoms present with a global state regulation deficit that likely impacts functioning across a wide array of domains. When appropriate matched control conditions were utilized to control lower-level processes there was no evidence to suggest the presence of specific deficits in executive functioning. It is possible that the executive functions under investigation are not well enough developed during the preschool period, which in turn would

preclude the detection of deficits in these still-emerging functions. Yet, as the fathers of HI preschoolers did exhibit specific neurocognitive deficits in response inhibition (as well as in state regulation), it is possible that this trait is inherited from their parents, but does not emerge until a developmentally later period. In this way, data from the father of HI participants provide support for response inhibition and state regulatory deficits among ADHD probands as well as the genetic liability of response inhibition. The findings also provide partial support for response inhibition and state regulation as candidate endophenotypes for ADHD.

In this study the Simon Effect was observed in both child's and parents' performance as assessed by the SCT. However, a significant group difference was only evident among parent participants. The fathers of HI children seemed to experience more difficulty with task performance than fathers of NC as they required significantly longer time to respond in the incongruent condition. Conversely, the mothers of HI children seemed to have a diminished Simon Effect relative to the NC-M.

It is important to note that, in the present study, group differences between child participants were observed for accuracy, while differences in parent data emerged using reaction time as the dependent measure. This difference is not surprising. Due to the immaturity of cognitive and motor systems in preschool children, it is oftentimes difficult to get consistency in response speed, and investigators have generally preferred to gauge performance via accuracy measures (Diamond et al. 2005). Furthermore, very young children tend to make high numbers of errors on cognitive tasks, which raise questions as to what reaction time findings actually indicate. In contrast, reaction time is generally considered to be a more sensitive measure of cognitive processing in adults, particularly on tasks such as the SCT and RCT where accuracy is quite high and even approaching ceiling levels.

It is also notable that mothers of HI preschoolers in the present study did not exhibit any regulatory or inhibitory control deficits, and on some measures performed better than mothers of controls. Although the precise reason(s) for this is unclear, it is conceivable that fathers of HI children, particularly those who have their own difficulties with organization and self-regulation, seek partners who are more structured and self-regulated to assist them through life.

Over the past decade several theories have been proposed to explain the underlying determinants of ADHD. Barkley's inhibition model (1997) emphasizes poor behavioral inhibition as the central deficit of ADHD, with neural representation subserved by regions of the prefrontal cortex and neural connections of the thalamus and basal ganglia. Sergeant (2000) proposed a cognitive energetic model, which emphasizes state regulatory deficits and low cortical arousal. Sonuga-Barke (2002) suggested a dual pathway model, in which he described deficient inhibition (associated with the meso-cortical branch of the dopamine system projecting to the prefrontal cortex) and delay aversion (associated with the meso-limbic dopamine system linked to the reward circuit of the nucleus accumbens) as co-existing, independent pathways. In each theory, the proposed deficit(s) is believed to be the causal pathway to ADHD. However, the lack of a universal deficit that is present in all individuals with ADHD suggests that any of these theories (i.e., neuropsychological, motivational, or cognitive) may only partially account for the psychopathology of ADHD. In view of the well-known heterogeneity among individuals with ADHD, the identification of subgroups with distinct phenotypes may improve diagnostic practices, facilitate research, and help to tailor interventions.

Nigg and colleagues (2005) reported that only a subgroup of children clinically diagnosed with ADHD exhibit executive function deficits, and suggested that this group of children be considered a separate subgroup. Nigg and Casey (2005) also reported that children with ADHD

primarily have difficulties with the prediction of “what” (mediated by frontostriatal loop) and “when” (the temporal cue mediated by frontocerebellar loop) to expect things in different contexts, as well as a limited ability to deal with the violation of such expectations (mediated by a frontothalamic loop) and the emotional significance of such events/situations (involves a frontolimbic circuit). Therefore, these investigators suggested that several neural processes are causally associated with the behavioral phenotypes of ADHD, a phenomenon commonly referred to as equifinality. They also suggested that, in addition to equifinality, multiple pathways (i.e., prefrontal cortex, nucleus accumbens, and amygdala circuits) with somewhat diverse phenotypic outcomes may be involved. Although different theories of ADHD pathophysiology have emphasized different core cognitive deficits, almost all have implicated neural circuits that involve the PFC (Castellanos, 2001; Schneider, 2006; Schneider et al., 2006; Todd, 2001; Zang, 2006; Zang, 2007). An implication of these theories is that damage to PFC is causally associated with the manifestations of ADHD (Faraone, 1998; Konrad et al., 2006; Todd & Botteron, 2001). Although such explanation is plausible, it is not consistent with neurodevelopmental data which indicates that myelination, dendritic arborization, and pruning of synapses of PFC, continues throughout childhood and adolescence (Case, 1992; Klinberg et al., 1999). Hence the temporal association between the late-neurodevelopment of PFC and the childhood onset of ADHD do not coincide. Consequently, PFC mediated executive function deficits do not appear to be temporally associated with the onset of symptoms of the disorder. This pattern was also evident in the present study, in that the HI preschoolers more clearly demonstrated state regulatory deficits rather than the executive function deficiencies per se. Thus, the current findings are more consistent with recent literature (Sergeant, 2005) which characterizes the emergent manifestations of ADHD as a byproduct of non-cortically mediated, bottom-up state regulatory

deficits. As the PFC matures and executive functions unfold, it is conceivable that ADHD probands may acquire increasing levels of top-down executive control, which in turn, may coincide with the well-documented reduction in behavioral symptoms with age (Brown & Gammon, 1995; Achenbach et al., 1995; Hart et al., 1995). In support of this hypothesis, fathers of the HI children in the current study, although exhibiting neurocognitive deficits in effortful top down control, did not exhibit hyperactivity as measured by solid state actigraphs. Halperin and Schulz (2006) have also suggested that early manifestations of ADHD may be associated with non-cortical dysfunction, while symptom recovery may be more closely related to the development and maturation of executive functions.

## **Conclusions**

Overall, data suggest that ADHD is not a unitary disorder with a single cause, but rather a complex behavioral phenotype that results from an array of etiological factors. It is often associated with multiple comorbid conditions (e.g., Conduct Disorder, Depression, etc.) as well as cognitive dysfunctions (i.e., lower IQ). Several recent reviews (Nigg et al., 2005) have suggested that individuals with ADHD can be further subdivided based on their profile of cognitive deficits. Consequently, in searching for candidate endophenotypes, it is necessary to define distinct subtypes based on specific cognitive, neuropsychological, or motivational deficits as distinct from subdivisions outlined in DSM-IV. Since such grouping criteria may produce multiple small groups, it may require a very large sample size to compensate for reductions in statistical power. However, it is also possible that different clinical/neuropsychological manifestations become more prominent at different stages of development. The present data indicate some support for the notion that state regulatory deficits underlie the reported cognitive

and behavioral deficits characteristic of ADHD, especially during the preschool years. In contrast, findings from adults in the current study support a role for response inhibition deficits in addition to state regulation difficulties in ADHD and its familial aggregation; such a pattern may be associated with the emergence of top-down executive control and may be associated with the remission of the symptoms (Halperin and Schulz, 2006). Therefore, it is important to further assess the relationship between the bottom-up and top-down processes from a developmental perspective.

### **Limitations and Strengths**

The results of the current study should be interpreted within the context of several limitations including difficulties associated with identifying true ADHD probands among preschoolers in light of the complexities in differentiating normative vs. atypical behavioral at this age. In addition, several of the measures under investigation are novel experimental tasks that have yet to be normed and examined for reliability and validity.

The probands in this sample were not with formal clinical diagnosis of ADHD; rather they were grouped based on their parents' and teachers' subjective ratings on a behavioral scale. The hyperactivity and inattentiveness among some of the preschoolers in this sample may be attributable to immaturity rather than manifestations of ADHD. Many of these children who were rated as having ADHD-like symptoms during the preschool period may outgrow these behavioral difficulties later in life. Hence these parents, who were defined as "parents of ADHD" were probably not all parents of preschoolers with 'true' ADHD and may not possess ADHD traits.

Overall, the effect sizes were quite small, suggesting that the lack of significant findings is unlikely the result of limited power. However, due to the high degree of heterogeneity among individuals with ADHD and the notion that the behavioral features of the disorder are related to a confluence of genes with small effect sizes, it is possible that much larger samples will be needed to detect endophenotypes.

Despite the abovementioned limitations, the present study has several unique strengths. The fact that most studies have neglected to utilize experimental manipulations might have led investigators to over-interpret group differences and conclude specific deficits among children with ADHD. However, in this study the measures were designed with built-in control conditions to distill out the process-specific cognitive constructs after accounting for rudimentary cognitive growth in preschool children. Using a process-specific experimental manipulation, no selective deficits in perceptual inhibition/interference control, response inhibition control, and working memory were observed among preschool children. It is conceivable that these constructs might not have adequately developed to detect group wise differences during the preschool period. This lack of specific deficits within these domains does not appear to be an artifact of methodological limitations, as very few children received the minimum or the maximum score on either the control or experimental conditions; this indicates that the results are not due to floor or ceiling effects within this age range.

The fact that these tasks were designed to be developmentally flexible to incorporate increases in difficulty level makes them particularly useful for assessing neurocognitive correlates in preschoolers and their parents simultaneously. This characteristic of the tasks is critical to assessing similar constructs in a wide age range of participants without confounding the results by employing different age-appropriate tasks. This is a particularly unique strength

for this study, as virtually no other studies have compared preschool children and their parents simultaneously on similar measures.

### **Future Directions**

With regard to the emergence of ADHD, the literature mostly emphasizes the development of emotion, motivation, and temperament in very young children (Calkins & Fox, 2002) rather than neurocognitive functions (i.e., state regulation or inhibitory control) as these are more difficult constructs to assess in young children. Such uneven emphasis precludes us from having a unique developmental account for the emergence of ADHD. The next generation of studies focusing on the development of emotion and affect in conjunction with neurocognitive constructs will allow us to understand individual variability in the emergence of ADHD.

The less than 100% concordance between MZ twins suggests that along with genes, non-genetic environmental factors also play important roles in the emergence of ADHD (Plomin, 1994; 2001). Therefore, developmental data integrating the complex interplay between maturation of cognitive function, socialization, and interpersonal process, is necessary to examine individual differences in the realm of early precursors of ADHD.

The development of more psychometrically valid, process specific measures with built-in control conditions will help to disentangle the intertwined neurocognitive functions under investigation, isolate the psychopathology of ADHD from that of comorbid conditions, and ultimately help to uncover potential endophenotypes.

Finally, the extant literature has reported deficits in neurocognitive functions among ADHD probands and their families (Alberty-Cornish et al., 1986; Crosbie & Schachar, 2001; Kuntsi & Stevenson, 2001; Nigg et al., 1997; Nigg et al., 2004; Seidman et al., 2000; Slaats-

Willemse et al., 2003; Stins et al., 2005). However, modest effect sizes of these findings suggest that no particular neurocognitive deficit or gene can explain the complex presentation of the disorder. Additionally, the presence of such neurocognitive deficits may vary as a function of the tasks that are used to collect the data or the age of probands. Thus, at this point, profiles of neurocognitive functioning and associated genetic liability may not be used independently as diagnostic tools for ADHD. However, identifying children based upon specific neurocognitive endophenotypes (e.g., RT variability) and then integrating genetic and neuroimaging techniques to determine underlying characteristics will be of value to understand early precursors of ADHD in relation to a multi-component self-regulatory system.

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